Health Evidence Review Commission and Value-based Benefits Subcommittee Combined Meeting Materials for May 14, 2026

8:00 AM - 5:00 PM

Portland State Office Building, 800 NE Oregon, Room 1D, Portland, OR 97232 and Online

Join online meeting here

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Section 1.0

Call to Order

Agenda

Value-based Benefits Subcommittee (VbBS)

May 14, 2026

8:00 am–1:00pm

Online

All agenda items are subject to change and times listed are approximate.
Public comment will be taken on each topic per HERC policy at the time
at which that topic is discussed.

8:00 AM Call to Order, Roll Call, Approval of Minutes

8:05 AM Staff report

8:25 AM Straightforward/Consent Agenda

1. Consent table
2. Straightforward guideline note modifications

8:30 AM Previous discussion items

1. **Septoplasty for breathing issues** Surgery to straighten the divider inside the nose when the person has difficulty breathing
2. **Septoplasty for CPAP tolerance** Surgery to straighten the divider inside the nose so someone can use a machine for sleep apnea
3. **PE tubes for adults** Tiny tubes placed in the eardrum to help air and fluid move more freely in the middle ear, for adults

9:00 AM New discussion items

1. **Low level laser therapy** A therapy that may help with muscle or joint pain
2. **Transcutaneous neuromodulation** Low-level electrical signals to reduce the brain's pain response
3. **Tumor treatment fields for locally advanced pancreatic cancer** Using electric signals to slow cancer growth

4. **PET for cardiac ischemia evaluation** Heart scans that use radioactive dye to take detailed pictures of the heart when people have blockages in the heart might cause damage to the heart muscle

10:00 AM BREAK

10:15 AM 2027 CPT code review

1. **Microsurgical management of lymphedema** A type of surgery to help with unusual swelling of the arms or legs

10:45 AM Previous discussion items

1. **Hydrophilic urinary catheters** Urinary catheters with a special coating
2. **Acupuncture for depression**

11:30 AM Changes based on coverage guidances

1. **Coverage Guidance: Hypoglossal Nerve Stimulator (HGNS)** This is a small device placed inside the body for people with certain types of sleep apnea. It is meant to work with the airway and breathing during sleep. The device is one option that may be considered for people with this condition

12:25 PM Public comment on topics not on the agenda

1:00 PM Adjournment—Next meeting August 6, 2026

Agenda

Health Evidence Review Commission (HERC)

May 14, 2026

1:30 pm–4:30pm

Online and Portland State Office Building, Room 1D
29373 SW Town Center Loop E
Wilsonville, Oregon 97070

All agenda items are subject to change and times listed are approximate.
Public comment will be taken on each topic per HERC policy at the time
at which that topic is discussed.

1:30 PM Call to Order, Roll Call, Approval of Minutes

1:35 PM Director's report

1:45 PM Public comment on items not on the agenda

1:50 PM Value-based Benefits Subcommittee report

3:15 PM EbGS Report:
Coverage guidance –Hypoglossal Nerve Stimulation for Obstructive Sleep Apnea Small devices to open the airway to help breathing during sleep.

4:30 PM Adjournment -- Next meeting 8/6/2026

If you need help during the meeting, please contact Tracy Hulett at 503-569-9545.

Minutes

Health Evidence Review Commission (HERC)

Portland State Office Building (PSOB), 800 NE Oregon Street, Room 1D and Online

3/19/2026

Members present: Devan Kansagara, MD (HERC Chair); Mark Buchholz, MD; Mike Collins; Max Kaiser, DO; Lisa Kouzes, DC, MPH; Cynthia Levesque LPC, CADC III, Cristina Pinzon, RN, MPH; Matt Serres, JD; Jeff Fortner, PharmD.

Members absent: Ben Hoffman, MD (HERC Vice-Chair); Stacy Geisler, DDS;

OHA Staff present: Ariel Smits, MD, MPH; Heidi Gullett, MD; Jason Gingerich; Liz Walker, PhD; Daphne Peck; Tracy Hulett; Lewis Backus; Dawn Mautner, MD

Others present: Valerie King, MD; Marcus Bachhuber, MD; Courtney Cooper MPH; Shauna Durbin, MPH; Jami Hoffman; Jean Economen; Laura Briggs; Laurie Stuebing, Theresa Gorman-Steward; Mackenzie Bangs; Michelle Heid; Siobhan Hess; Wendy Machalicek; Chris Andrews; Melissa Wood; Maggie Klein

Call to Order

Devan Kansagara, Chair of the Health Evidence Review Commission (HERC), called the meeting to order; roll was called. A quorum of members was present at the meeting.

Minutes Approval

MOTION: To approve the minutes of the January 22, 2026, meeting as presented.
AYES: Devan Kansagara; Mark Buchholz; Max Kaiser; Lisa Kouzes; Matt Serres; Jeff Fortner
ABSTAIN: Cynthia Levesque; Cristina Pinzon
CARRIES 6-0-2

Director's Report

Gingerich provided the director's report.

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Membership Updates

- Recruitment is underway for commission vacancies
- Cynthia Levesque was introduced as HERC's newest member
- Larry Lyon resigned from the HERC Commission

Legislative updates

- HB 4040 passed, modifying public comment timelines and requiring future rulemaking on comment processes
- HB 4003 did not pass, affecting the planned Benefit Update Project. The Prioritized List will continue to exist, but it will serve in the role envisioned in the Benefit Update Project, as medical necessity policy. Services from the 2026 unfunded region which were identified as medically necessary will need to be covered. In addition, prescription medications for currently-unfunded conditions will need to be covered, though step therapy and preferred agents will be used to manage utilization.
- Consequent federal changes will shift the prioritized list toward serving primarily as medical-necessity policy starting in 2026. OHA will issue updated guidance and a transition plan for CMS by July 1.

March HERC Staff Listening Session Report

Staff summarized recent listening sessions. Community members requested re-review of acupuncture as adjunct therapy for behavioral health conditions (anxiety, depression, PTSD). The commission concluded that no additional review is needed but agreed to further examine study subsets.

Errata

In January, HERC removed coverage for COVID antibody testing; however, older COVID guidance still referenced antibody testing.

Web Accessibility Compliance

Meeting packets will increase in size due to federal web accessibility requirements. These changes will include larger fonts, wider line spacing, and will improve content for those that require screen readers. Let us know if you run in to any issues with the new format. Your feedback is always welcome.

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MOTION: To approve the appointment of Cynthia Levesques to the VBBS subcommittee.

AYES: Devan Kansagara; Mark Buchholz; Mike Collins; Max Kaiser; Lisa Kouzes; Cris Pinzon; Matt Serres; Jeff Fortner
Abstain: Cynthia Levesque
CARRIES 8-0-1

Value-based Benefits Subcommittee (VbBS) Report on Prioritized List Changes

Ariel Smits reported that the (VbBS) met earlier in the day. She summarized the subcommittee's recommendations; points of discussion and changes to what was approved at VbBS are noted below the summary. For specific coding recommendations and guideline wording, please see the text of the 3/19/2026 VbBS minutes.

Recommended Code Movement

(Changes to the 10/1/2026 Prioritized List unless otherwise noted):

- Place the April 2026 HCPCS codes on various covered and non-covered lines
- Recommend placing the procedure codes for cardiac PET scans on the diagnostic file
- Make other straightforward coding corrections

Item Considered but No Recommendations for Changes Made:

- Do not add coverage for resorbable intravascular scaffolds for peripheral arterial disease
- Do not add coverage for permanent carotid artery filters
- Do not add coverage for gastric alimetry
- Do not add coverage for low frequency ultrasound for wound healing
- Do not add coverage for vagus nerve stimulation to the covered stroke line
- Do not add coverage for cell free high risk HPV DNA testing for oropharyngeal cancer
- Do not add coverage for transcatheter tricuspid valve replacement or edge to edge repair
- Do not add coverage for aragonite scaffold knee arthritis

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Recommended Guideline Changes

(Changes to the 10/1/2026 Prioritized List unless otherwise noted):

1. Modify the PET scan guideline with criteria for cardiac PET scans for sarcoidosis
2. Modify the physical and occupational therapy guideline note to specify noncoverage of vagus nerve stimulation for post-stroke upper extremity weakness

Make other straightforward guideline changes

DISCUSSION:

Buchholz about coverage of services associated with experimental procedures such as tricuspid value replacement. Gingerich referred him to the administrative rule. Kansagara said he has an additional question about this.

There was additional discussion about hydrophilic urinary catheters. Gingerich said in general, only the least costly alternative service is covered under the Oregon Health Plan. Hydrophilic catheters are more convenient for patients, but OHP doesn't pay for convenience. In the past, hydrophilic catheters were billed with the same procedure code. Now there will be a new code. While it's initially the same price, Medicare may raise the price in the future, which would affect OHP prices in the future. Pinzon asked if it might not be a convenience item for some populations. If the cost is the same, there wouldn't be a reason to end coverage. Smits said she has not found data supporting the use of hydrophilic catheters for any particular population. Kansagara said a coverage might not be the right way to address this issue. He asked if there would be a way to cover it until the cost becomes greater. Gingerich said it would be important to know whether HERC believes it should be covered so that the policy is clear when and if the cost becomes different. There was additional discussion about the code and what would be required to remove coverage if it were to become covered. Kansagara recommended holding off on a decision with the hope of getting more clarity on cost in the coming months. Smits said this will come back to VBBS before August.

MOTION: To accept the VbBS recommendations on Prioritized List changes as amended. See the VbBS minutes of 3/19/2026 for a full description.

AYES: Devan Kansagara; Mark Buchholz; Mike Collins; Max Kaiser; Lisa Kouzes; Cynthia Levesque;Cris Pinzon; Matt Serres; Jeff Fortner

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CARRIES 9-0-0

Decision Standards

Heidi presented the final draft of the decision standard document that was first introduced in October. There were a few edits:

1. Change certain numbered lists to bullet points (to avoid implying hierarchy).
2. Add wording that states HERC may weigh the above listed factors and different sources/types of information differently based on clinical context.

MOTION: To approve the decision standards document with edits as stated above.
AYES: Devan Kansagara; Mark Buchholz; Mike Collins; Max Kaiser; Lisa Kouzes; Cynthia Levesque;Cris Pinzon; Matt Serres; Jeff Fortner
CARRIES 9-0-0

Public Comment

Mackenzie Bangs, Representing the Oregon Association for Behavior Analysis, urged expanding ABA therapy coverage to individuals with intellectual disabilities (ID). She emphasized that people with ID often lack adequate services beyond special education, OT, and speech, and that ABA helps build independence, life skills, and engagement. She argued that ABA is effective across diagnoses and encouraged the commission to re-examine single-case research and engage directly with ABA providers and families.

Michelle Heid, a parent, described how ABA helped her son who has autism develop independence, communication, and daily living skills—leading to a successful adult life. She advocated for ABA coverage for individuals with intellectual and developmental disabilities (IDD), not only autism, noting that ABA procedures are not diagnosis-specific and can reduce behavioral challenges and improve quality of life. She raised concern that restricting ABA based on diagnosis creates mental health parity issues.

Wendy Machalicek, a professor and board-certified behavior analyst, Wendy highlighted serious harms that can result when individuals with intellectual disabilities lack behavioral supports—such as self-injury, aggression, elopement, and pica. She noted increased ER visits among this population and barriers to inpatient placement. Drawing on decades of clinical experience and research (including single-case designs), she stated ABA is an

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effective, evidence-supported intervention for communication, adaptive skills, and reducing dangerous behaviors. She urged timely action, noting that waiting for large RCTs is unrealistic.

Therese Gorman-Steward, a parent and former clinical psychotherapist, advocated expanding ABA to people with behavioral needs outside autism. She described her son's combined disabilities (blindness, autism, intellectual and communication disabilities) and how ABA's individualized, data-driven methods supported his development. She argued that many behavioral challenges are not specific to autism, and that ABA is well-suited to address functional needs regardless of diagnosis. She emphasized that denying ABA based on diagnosis creates inequity and can lead to more restrictive, higher-cost care later.

Laurie Stuebing, mother and legal guardian of a 33-year-old man with autism and intellectual disability, urged expanding ABA coverage to individuals with ID who show significant behavioral or adaptive needs. She argued that tying access to an autism diagnosis creates arbitrary disparities, since many dangerous or disruptive behaviors (self-injury, aggression, elopement) occur across diagnoses. She stressed that untreated behavioral needs can result in injury, crisis situations, ER visits, and loss of stable community placement. ABA, she said, can prevent crises and support safety, communication, and independence.

Adjournment

Meeting adjourned at 4:08 p.m. Next meeting will be from 1:30 p.m.-4:30 p.m. on Thursday, May 14, 2026, at Portland State Office Building and Online

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Value-based Benefits Subcommittee (VbBS) Summary

Recommendations presented to the
Health Evidence Review Commission on 3/19/2026

For specific coding recommendations and guideline wording, please see the text of the 3/19/2026 VbBS minutes.

Recommended Code Movement

(Changes to the 10/1/2026 Prioritized List unless otherwise noted):

- Place the April 2026 HCPCS codes on various covered and non-covered lines
- Recommend placing the procedure codes for cardiac PET scans on the diagnostic file
- Make other straightforward coding corrections

Item Considered but No Recommendations for Changes Made:

- Do not add coverage for resorbable intravascular scaffolds for peripheral arterial disease
- Do not add coverage for permanent carotid artery filters
- Do not add coverage for gastric alimetry
- Do not add coverage for low frequency ultrasound for wound healing
- Do not add coverage for vagus nerve stimulation to the covered stroke line
- Do not add coverage for cell free high risk HPV DNA testing for oropharyngeal cancer
- Do not add coverage for transcatheter tricuspid valve replacement or edge to edge repair
- Do not add coverage for aragonite scaffold knee arthritis

Recommended Guideline Changes

(Changes to the 10/1/2026 Prioritized List unless otherwise noted):

1. Modify the PET scan guideline with criteria for cardiac PET scans for sarcoidosis

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2. Modify the physical and occupational therapy guideline note to specify noncoverage of vagus nerve stimulation for post-stroke upper extremity weakness
3. Make other straightforward guideline changes

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Minutes

Value-based Benefits Subcommittee (VbBS)

Portland State Office Building (PSOB), Room 1D

3/19/2026

Members present: Holly Jo Hodges (VBBS Chair); Brian Duty (VBBS Vice-Chair); Mary Engrav, MD; Adriane Irwin, PharmD, MS; Max Kaiser, DO; Sara Love, ND; Cristina Pinzon, RN, MPH

Members absent: Ben Hoffman, MD, Antoinette Awuakye, JD; Abilgail Khan, MD; Lucy Langer, MD, Mike Collins

OHA Staff present: Ariel Smits, MD, MPH; Heidi Gullett, MD; Jason Gingerich; Liz Walker, PhD; Daphne Peck; Tracy Hulett; Lewis Backus; Dawn Mautner, MD; Hyejin Yu

Others present: Valerie King, MD; Courtney Cooper MPH; Shauna Durbin, MPH; Chris Andrews; Melissa Wood; Anna Markiewicz; Brian Carlson; Carolyn Graziano; Diane Weaver; Jean Economen; Jonathan Kim; Julia Brennan, Kathryn Vaughn; Kelly Seeger; Kent Keyser; Kristin Cortez; Laura Briggs; Laura Williard; Maggie Klein; Mendy Maccabee; Michael Kennelly; Mirella Petersen; Sabah Gerges; Siobhan Hess; West Livaudais

Call to Order

Holly Jo Hodges, Value-based Benefits Subcommittee (VbBS) called the meeting to order at 8:38 a.m.; roll was called. A quorum of members was present at the meeting.

Minutes Approval

MOTION: To approve the minutes of the 1/22/2026 VBBS meeting as presented.
AYES: Brian Duty, Mary Engrav; Adriane Irwin; Max Kaiser; Sara Love
ABSTAIN: Holly Jo Hodges; Cris Pinzon
CARRIES 5-0-2

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Director's Report

Gingerich provided the director's report.

Membership Updates

- Recruitment is underway for commission vacancies
- Cynthia Levesque was introduced as HERC's newest member
- Larry Lyon resigned from the HERC Commission and Evidence-based Guidelines Subcommittee.

Legislative updates

- HB 4040 passed, modifying public comment timelines and requiring future rulemaking on comment processes
- HB 4003 did not pass, affecting the planned Benefit Update Project
- Consequent federal changes will shift the prioritized list toward serving primarily as medical-necessity policy starting in 2026. OHA will issue updated guidance and a transition plan for CMS by July 1.

March HERC Staff Listening Session Report

Staff summarized recent listening sessions. Community members requested re-review of acupuncture as adjunct therapy for behavioral health conditions (anxiety, depression, PTSD). The commission concluded that no additional review is needed but agreed to further examine study subsets.

Errata

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Administrative Reminders

- Draft meeting materials are posted 2 weeks in advance and final materials are posted 1 week in advance
- Public comment closes 2 days before each meeting
- Committee members are encouraged to continue using Q&A for logistical items during virtual meetings.

Straightforward/Consent Agenda

Discussion**:** Smits presented the consent agenda items. There was no discussion on items except:

- The Multisector Intervention Statement 1 recommendations were not accepted. Subcommittee members wanted the diagram to be incorporated into a modified guideline with the content in outline or simple table form that meets accessibility standards but also contains the information in the current MSI. The revised links were considered appropriate. Staff will bring this topic back to the May meeting.
- The Guideline Note 1 change recommendations were not accepted. Subcommittee members requested that the guideline be deleted but left with a reference to Guideline Note 106. Guideline Note 106 should be updated with reference to the ASCCP guidelines for follow up of abnormal pap results as well as a reference to the USPSTF/HRSA recommendations on cervical cancer screening. Staff will bring this topic back to the May meeting.

Recommended Actions:

1. Add **D5934 (Mandibular guidance prosthesis with guide flange) and D5935 (Mandibular guidance prosthesis without guide flange) to lines 285 CANCER OF ORAL CAVITY, PHARYNX, NOSE AND LARYNX 399 BENIGN CONDITIONS OF BONE AND JOINTS AT HIGH RISK FOR COMPLICATIONS, and 545 BENIGN NEOPLASM OF BONE AND ARTICULAR CARTILAGE INCLUDING OSTEOID OSTEOMAS; BENIGN NEOPLASM OF CONNECTIVE AND OTHER SOFT TISSUE
2. Add *43266 (Esophagogastroduodenoscopy, flexible, transoral; with placement of endoscopic stent (includes pre- and post-dilation and guide wire passage, when performed)) and *43247 (Esophagogastroduodenoscopy, flexible, transoral; with removal of foreign body(s)) to line 225 RUPTURED VISCUS

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3. Add 99417 Prolonged outpatient evaluation and management service(s) time with or without direct patient contact beyond the required time of the primary service when the primary service level has been selected using total time, each 15 minutes of total time) to line 309 GENDER AFFIRMING TREATMENT
4. Advise Medicaid to move CPT 81232 (DPYD (dihydropyrimidine dehydrogenase) (eg, 5-fluorouracil/5-FU and capecitabine drug metabolism), gene analysis, common variant(s) (eg, *2A, *4, *5, *6)) to the Diagnostic Procedures file
5. Delete the entry in Excluded Services Guideline E2 for CPT *81232 as shown in Appendix A.
6. Modify Diagnostic Guideline D4 as shown in Appendix A

MOTION: To approve the recommendations as modified.
AYES: Brian Duty, Mary Engrav; Adriane Irwin; Max Kaiser; Sara Love; Holly Jo Hodges; Cris Pinzon
CARRIES 7-0

April 2026 HCPCS Code Placement
Discussion: Smits presented the meeting materials. There was minimal discussion.

Recommended Actions:

- Place HCPCS G0681-G0684 (Application of a premarket approval (pma), 510(k), 361 human cells, tissues or cellular and tissue-based products (hct/p) non-sheet form skin substitute) on lines 57 SEVERE BURNS, 127 MODERATE BURNS 180 CONDITIONS INVOLVING EXPOSURE TO NATURAL ELEMENTS (E.G., LIGHTNING STRIKE, HEATSTROKE), 376 CHRONIC ULCER OF SKIN; VARICOSE VEINS WITH MAJOR COMPLICATIONS, and 416 MODERATE TO SEVERE HIDRADENITIS SUPPURATIVA
- Modify various entries in Excluded Services Guideline E2 as shown in Appendix A.

MOTION: To approve the recommendations as presented.
AYES: Brian Duty, Mary Engrav; Adriane Irwin; Max Kaiser; Sara Love; Holly Jo Hodges; Cris Pinzon

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CARRIES 7-0

New Discussion Items

Gastric Alimetry

Discussion: Smits reviewed the meeting materials. There was minimal discussion.

Public testimony

Christopher Andrews MD, CMO of Alimetry and a gastroenterologist in Canada provided testimony, he said many common and disabling gastrointestinal conditions such as gastroparesis are difficult to diagnose and patients with these conditions are highly symptomatic with high medical costs. Alimetry fills a clinical need as current diagnostic testing is not effective in many cases. Alimetry is not the same as older EEG testing. This test is covered by multiple payers in the US

Recommended Actions:

1. Add gastric alimetry to Excluded Services Guideline E2 as shown in Appendix A

MOTION: To approve the addition to Excluded Services Guideline E2.

AYES: Brian Duty, Mary Engrav; Adriane Irwin; Max Kaiser; Sara Love; Holly Jo Hodges; Cris Pinzon

CARRIES 7-0

Low Frequency Ultrasound for Wound Healing

Discussion: Smits reviewed the meeting materials. There was minimal discussion.

Recommended Actions:

1. Modify Excluded Services Guideline E2 entry for low frequency ultrasound as shown in Appendix A

MOTION: To approve the recommendations as presented.

AYES: Brian Duty, Mary Engrav; Adriane Irwin; Max Kaiser; Sara Love; Holly Jo Hodges; Cris Pinzon

CARRIES 7-0

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Vagal Nerve Stimulation for Upper Extremity Rehabilitation After Stroke

Discussion: Smits reviewed the summary document. There was minimal discussion.

Public testimony

Brian Carlson VP of Marketing for Transponder, Inc in Minnesota: The HERC staff statement that there is a lack of evidence of efficacy for this procedure does not reflect the data from randomized control trials. Many of the studies included in the staff review included transcutaneous vagus nerve stimulation, which is much less effective than implanted VNS. The include meta-analysis had flawed methodology. The main study included in the meta-analysis found clinically meaningful improvement over standard rehabilitation. Carlson objected to proposed explicit non coverage language in the proposed guideline

Recommended Actions:

1. Do not add CPT *64568 (Open implantation of cranial nerve (eg, vagus nerve) neurostimulator electrode array and pulse generator) to line 314 STROKE or any of the dysfunction lines
2. Modify Guideline Note 6 as shown in Appendix

MOTION: To approve the recommendations as presented.

AYES: Brian Duty, Mary Engrav; Adriane Irwin; Max Kaiser; Sara Love; Holly Jo Hodges; Cris Pinzon

CARRIES 7-0

PET Scan for Cardiac Sarcoidosis

Discussion: Smits reviewed in the meeting materials. Members asked for clarification on coverage guidelines for cardiac MRI; currently there are no guidelines for this diagnostic test.

Recommended Actions:

1. Remove CPT *78429-78434, 78459, 78491-78492 (Myocardial imaging, positron emission tomography (PET)) from Excluded Services Guideline E2
2. Advise Medicaid to add CPT *78429-78434, 78459, 78491-78492 to the Diagnostic Procedures file

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3. Delete the entry for cardiac PET from Excluded Services Guideline E2 as shown in Appendix A
4. Modify Diagnostic Guideline D22 as shown in Appendix A

MOTION: To approve the recommendations as presented.
AYES: Brian Duty, Mary Engrav; Adriane Irwin; Max Kaiser; Sara Love; Holly Jo Hodges; Cris Pinzon
CARRIES 7-0

Cell Free High Risk HPV DNA Testing for Oropharyngeal Cancer
Discussion**:** Smits reviewed the summary document. There was minimal discussion.

Recommended Actions:

1. Add an entry to Excluded Services Guideline E2 as shown in Appendix A

MOTION: To approve the recommendations as presented.
AYES: Brian Duty, Mary Engrav; Adriane Irwin; Max Kaiser; Sara Love; Holly Jo Hodges; Cris Pinzon
CARRIES 7-0

2027 CPT Code Early Review
Transcatheter Tricuspid Valve Replacement
Discussion: Smits reviewed the summary document. There was minimal discussion.

Recommended Actions:

1. Add an entry to Excluded Services Guideline E2 regarding transcatheter tricuspid valve replacement as shown in Appendix A

MOTION: To approve the recommendations as presented.
AYES: Brian Duty, Mary Engrav; Adriane Irwin; Max Kaiser; Sara Love; Holly Jo Hodges; Cris Pinzon
CARRIES 7-0

Tricuspid Edge to Edge Repair
Discussion**:** Smits reviewed the summary document. There was minimal discussion.

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Recommended Actions:

1. Add an entry to Excluded Services Guideline E2 regarding transcatheter tricuspid valve edge to edge repair as shown in Appendix A

MOTION: To approve the recommendations as presented.
AYES: Brian Duty, Mary Engrav; Adriane Irwin; Max Kaiser; Sara Love; Holly Jo Hodges; Cris Pinzon
CARRIES 7-0

Aragonite Scaffold For Knee Cartilage Injury
Smits reviewed the meeting materials.
Dr. Carolyn Graziano from Smith and Nephew: Aragonite scaffold treatment addresses an unmet clinical need for patients with cartilage damage without significant arthritis. Other treatments such as microfracture have complications and frequently leads to osteoarthritis and the need for additional procedures. This procedure is superior to alternatives such as MACI or OATS. This procedure has a level one study of 251 patients, while these other interventions have only cohort studies. NICE recommends single step therapy such as this and the AAOS recommends coverage. Numerous national cartilage surgeons submitted written testimony.

Discussion: The discussion in the subcommittee centered around the covered alternatives. It was pointed out that OATS is not covered under OHP (see Guideline Note 220). There was a question about the evidence for MACI and HERC staff were directed to look into this. Hodges noted that the population of patients with cartilage injury is large, making persuasive evidence from large studies necessary for coverage.

The subcommittee agreed with the staff recommendation to not cover the aragonite scaffold treatment. HERC staff were directed to look at the alternative procedures and report back on whether they are covered and if yes, then look at the evidence of effectiveness for possible removal from coverage.

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Recommended Actions:

1. Modify Guideline Note 104 as shown below to specify non-coverage of aragonite scaffold treatments for knee conditions as shown in Appendix A
2. Add it as an entry in Excluded Services Guideline E2 for this procedure to specify noncoverage for diagnoses not included on line 430 as shown in Appendix A

MOTION: To approve the recommendations as presented. Non-coverage: add to Guideline Note 4 (clarifying arthritis vs. non-arthritis indications) and list CPT in E2
AYES: Brian Duty, Mary Engrav; Adriane Irwin; Max Kaiser; Sara Love; Holly Jo Hodges; Cris Pinzon
CARRIES 7-0

Microsurgical Management of Lymphedema
Tabled until May 2026

2027 CPT Code Review: Transcutaneous Neuromodulation
Tabled until May 2026

Previous Discussion Items
Septoplasty/Rhinoplasty
Discussion: Smits reviewed the meeting materials. Dr. Maccabee and Dr. Brennan, ENT physicians in Hood River, gave a presentation on septoplasty. Dr. Brennan said that structural nasal obstruction results from cartilage or bony blockages in the nose (not mucosal inflammation). It does not respond to medications. Septoplasty addresses the majority of the septum, but not the weight-bearing strut. Septo-rhinoplasty addresses the entirety of the septum as well as other bony and cartilagenous nasal structures. Though it's sometimes considered cosmetic, it's a functional surgery. Chronic nasal obstruction affects physical and psychological health, sleep and social relationships. There is a high prevalence of mood disorders among people experiencing nasal blockage. Data supports long-term improvements in objective and patient reported symptoms. It also improves CPAP compliance.

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Dr. Maccabee expressed concern about the conclusions drawn from the evidence. No other payers fail to cover surgery for nasal obstruction due to a fixed deviation in the septum. She suggested members tape their nose closed if they doubt there is an impact. The nose is the body's air cleaner and humidifier. She does not see a lack of data supporting improvement in outcomes and quality of life scores. She asked the committee to address the discrepancy with coverage by other payers.

The discussion first centered around coverage of septoplasty for breathing issues alone. Smits noted that there are frequent discrepancies between coverage on the Prioritized List compared with other health plans. Pinzon asked for clarification around current coverage; septoplasty and rhinoplasty are currently covered in very limited circumstances but not for nasal obstruction or to facilitate CPAP usage. Duty pointed out that Oregon experts recommend coverage for this indication. Kaiser said that quality of life surveys are difficult. For instance, if you ask people what would be the impact of losing a limb on quality of life, they report that it would be worse than people who have actually lost a limb report. Irwin asked for a summary of the EBGS/HERC discussions from June 2025. Engrav noted that the literature in this area is complicated. The group decided that there was a need for more time to review previous discussions and the presented evidence and recommended tabling this topic until May.

After being asked a question, Maccabee said she strenuously disagreed that septoplasty does not improve quality of life for patients with nasal obstruction. She also said that septoplasty is not a treatment for chronic sinusitis.

The discussion then moved on to septoplasty for improving CPAP compliance. Kaiser stated that the Academy of Sleep medicine does not discuss nasal surgery in their recommendations for improving CPAP compliance. They do mention education, mask fitting, etc. Engrav recommended that staff review the literature again. This portion of the topic was also tabled until May.

Tabled until May 2026

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PE Tubes for Adults

Tabled until May 2026

January 2026 HCPCS Code Review: Hydrophilic Catheters

Discussion**:** Smits reviewed the meeting materials. Duty noted that his OHSU group uses standard (non-hydrophilic) catheters. He supported the staff recommendation.

Testimony

Keely Seeger from the American Associated of Homecare, Pacific Association for Medical Equipment Services, the American Association of Medical Equipment, and Coloplast: This is a coding clarification, not new technology. Oregon Medicaid has long covered these types of catheters. Hydrophilic catheters avoid the need for separate lubricant, reduce costs, reduce complications such as UTIs. Hydrophilic catheters are of similar cost to other types of catheters. Not covering these new HCPCS codes disrupts continuity of care. Other state Medicaid programs are covering these new HCPCs codes. Oregon Medicaid can crosswalk reimbursement from the legacy catheter codes.

Keely Seeger from the American Associated of Homecare, Pacific Association for Medical Equipment Services, the American Association of Medical Equipment, and Coloplast. Declared no conflict of Interest.

Oregon Medicaid has long covered these types of catheters. Hydrophilic catheters avoid the need for separate lubricant, reduce costs, reduce complications such as UTIs. Hydrophilic catheters are of similar cost to other types of catheters. Not covering these new HCPCS codes disrupts continuity of care. Other state Medicaid programs are covering these new HCPCs codes. Oregon Medicaid can crosswalk reimbursement from the legacy catheter codes.

Michael Kennelly, MD: from the American Spine Injury Association and other associations, Coloplast consultant. Professor of Urology at Wake Forest University. Declared no conflict of Interest.

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Spinal cord injury patients use these catheters. They have reduced friction which helps with reduced hand function making them a safety issue. Hydrophilic catheter maintains lubrication further into the urethra than other types of catheters which reduces complications. There is a significant reduction in UTI risk. OHP should cover the catheter that is appropriate for the population. There is a need for flexibility to provide this catheter when clinically necessary

Laura Willard: American Association for Homecare VP. Declared no conflict of Interest.

OHP is eliminating a benefit for patients who are already receiving this catheter type which disrupts continuity of care. Other Medicaid programs are covering the new HCPCS codes. The new HCPCS codes have the same cost based on CMS pricing as applied to the legacy code.

Kathryn Vaugn: Coloplast Declared no conflict of Interest.

The meta-analysis found a reduced UTI risk. The presented Ye study was problematic because the included studies used outdated comparison studies and products with limited relevance to US market. The meta-analysis by Claudette with 9 studies found Hydrophile catheter found 22% lower risk of UTI.

Kent Keyser: United Spinal Association and a spinal cord injury pt. Declared no conflict of Interest.

Mr. Keyser uses catheters occasionally although he never used a hydrophilic catheter. These catheters reduce UTI rates. The administrative HCPCS change by CMS should not result in consumers being penalized.

West Livaudais: Oregon spinal cord injury connection group and previous Health Policy Board member. Declared no conflict of Interest.

Mr. Livaudais uses hydrophilic catheters which he found has reduced UTIs and hospitalization personally. There are many patients in Oregon with spinal cord injuries who

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need urinary catheters. He feels that proper lubrication is needed to prevent microabrasion.

There was minimal discussion among the subcommittee due to time limitations. This topic was tabled to a future meeting.

Tabled until May 2026

Public Comment

No additional public comment was received.

Issues for next meeting

- Guideline Note 1 modifications
- Multisector Intervention on Tobacco Cessation modifications
- 2027 CPT Code Review: microsurgical management of lymphedema
- 2027 CPT Code Review: Transcutaneous neuromodulation
- Septoplasty
- PE tubes for adults
- Hydrophilic urinary catheters
- Evidence review for various treatments for chondral defects in the knee

Adjournment

Meeting adjourned at 1:06 p.m. Next meeting will be from 8:00 a.m.-1:00 p.m. on Thursday, May 14, 2026, Portland State Office Building (PSOB), Room 1D and Online.

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Appendix A: Modified guideline notes

[Note: the only changes to Diagnostic Guideline D4 are formatting and are not shown in track changes]

DIAGNOSTIC GUIDELINE D4, ADVANCED IMAGING FOR LOW BACK PAIN

In patients with non-specific low back pain and no "red flag" conditions [see Table D4], imaging is not a covered service; otherwise work up is covered as shown in the table. Repeat imaging is only covered when there is a substantial clinical change (e.g. progressive neurological deficit) or new clinical indication for imaging (i.e. development of a new red flag condition). Repeat imaging for acute exacerbations of chronic radiculopathic pain is not covered.

Electromyelography (CPT *96002-4) is not covered for non-specific low back pain.

Single photon emission computed tomography (SPECT) (CPT *78830-78832) is not covered for routine pre-operative evaluation of neck or back pain. SPECT of the spine may be covered in certain clinical situations (for example, evaluation for possible spinal infection when MRI is contraindicated or for evaluation of spinal stress fractures not visualized on x-ray in adolescents).

Table D4: Low Back Pain - Potentially Serious Conditions ("Red Flags") and Recommendations for Initial Diagnostic Work-up

Possible cause	Key features on history or physical examination	Imaging[1]	Additional studies[1]
Cancer	History of cancer with new onset of LBP	MRI	ESR

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Appendix A: Modified guideline notes

Possible cause	Key features on history or physical examination	Imaging[1]	Additional studies[1]
Cancer	Unexplained weight loss Failure to improve after 1 month Age >50 years Symptoms such as painless neurologic deficit, night pain or pain increased in supine position	Lumbosacral plain radiography	ESR
Cancer	Multiple risk factors for cancer present	Plain radiography or MRI	ESR
Spinal column infection	Fever Intravenous drug use Recent infection	MRI	ESR and/or CRP
Cauda equina syndrome	Urinary retention Motor deficits at multiple levels Fecal incontinence Saddle anesthesia	MRI	None
Vertebral compression fracture	History of osteoporosis Use of corticosteroids Older age	Lumbosacral plain radiography	None

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Appendix A: Modified guideline notes

Possible cause	Key features on history or physical examination	Imaging[1]	Additional studies[1]
Ankylosing spondylitis	Morning stiffness Improvement with exercise Alternating buttock pain Awakening due to back pain during the second part of the night Younger age	Anterior-posterior pelvis plain radiography	ESR and/or CRP, HLA-B27
Nerve compression/ disorders (e.g. herniated disc with radiculopathy)	Back pain with leg pain in an L4, L5, or S1 nerve root distribution present < 1 month Positive straight-leg-raise test or crossed straight-leg-raise test	None	None
Nerve compression/ disorders (e.g. herniated disc with radiculopathy	Radiculopathic signs[2] present >1 month Severe/progressive neurologic deficits (such as foot drop), progressive motor weakness	MRI[3]	Consider EMG/NCV

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Appendix A: Modified guideline notes

Possible cause	Key features on history or physical examination	Imaging[1]	Additional studies[1]
Spinal stenosis	Radiating leg pain Older age Pain usually relieved with sitting (Pseudoclaudication a weak predictor)	None	None
Spinal stenosis	Radiculopathic signs[2] present >1 month Severe/progressive neurologic deficits (such as foot drop), progressive motor weakness	MRI[3]	Consider EMG/NCV

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Appendix A: Modified guideline notes

[1]Level of evidence for diagnostic evaluation is variable

[2]Radiculopathic signs are defined for the purposes of this guideline as the presence of any of the following:

A) Markedly abnormal reflexes
B) Segmental muscle weakness
C) Segmental sensory loss
D) EMG or NCV evidence of nerve root impingement
E) Cauda equina syndrome,
F) Neurogenic bowel or bladder
G) Long tract abnormalities

[3]Only if patient is a potential candidate for surgery

Red Flag: Red flags are findings from the history and physical examination that may be associated with a higher risk of serious disorders.

CRP = C-reactive protein; EMG = electromyography; ESR = erythrocyte sedimentation rate; MRI = magnetic resonance imaging; NCV = nerve conduction velocity.

Extracted and modified from Chou R, Qaseem A, Snow V, et al: Diagnosis and Treatment of Low Back Pain: A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society. Ann Intern Med. 2007; 147:478-491.

The development of this guideline note was informed by a HERC coverage guidance. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx

DIAGNOSTIC GUIDELINE D22, PET SCANS

Diagnosis:

PET Scans are covered for diagnosis only when:

The PET scan is for evaluation of either:

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- Solitary pulmonary nodules, small cell lung cancer and non-small cell lung cancer, OR
- Evaluation of cervical lymph node metastases when CT or MRI do not demonstrate an obvious primary tumor, AND

The PET scan will

Avoid an invasive diagnostic procedure, OR

Assist in determining the optimal anatomic location to perform an invasive diagnostic procedure.

Initial staging:

PET scans are covered for the initial staging when:

A) The staging is for one of the following cancers/situations:
   1) Cervical cancer only when initial MRI or CT is negative for extra-pelvic metastasis
   2) Head and neck cancer when initial MRI or CT is equivocal
   3) Colon cancer
   4) Esophageal cancer
   5) Solitary pulmonary nodule
   6) Non-small cell lung cancer
   7) Lymphoma
   8) Melanoma
   9) Breast cancer ONLY when metastatic disease is suspected AND standard imaging results are equivocal or suspicious
   10) Small cell lung cancer
   11) Neuroendocrine tumors
   12) Multiple myeloma
   13) Thyroid cancers
   14) PSMA PET for unfavorable intermediate, high-risk, or very-high-risk prostate cancer, AND

B) Clinical management of the patient will differ depending on the stage of the cancer identified and either:

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1) the stage of the cancer remains in doubt after standard diagnostic work up, OR
2) PET replaces one or more conventional imaging studies when they are insufficient for clinical management of the patient.

Monitoring:

A) For monitoring tumor response during active therapy for purposes of treatment planning, PET is covered for classic Hodgkin's lymphoma treatment
B) metastatic breast cancer ONLY when a change in therapy is contemplated AND PET scan was the imaging modality initially used to find the neoplasm being monitored.

Restaging:

Restaging is covered only when:

A) the cancer has staging covered above, AND
B) initial therapy has been completed, AND
C) the PET scan is conducted for
    1) detecting residual disease, or
    2) detecting suspected recurrence, or
    3) determining the extent of a known recurrence.

Other indications:

PET scans are covered for preoperative evaluation of the brain in patients who have intractable seizures and are candidates for focal surgery. PET scans are covered for patients being considered for treatment with aducanumab or similar FDA approved medications for treatment of Alzheimer's disease.

Non-covered conditions/situations:

A) PET scans are NOT covered to monitor tumor response during the planned course of therapy for any cancer other than classic Hodgkin's lymphoma or the limited indication described above for metastatic breast cancer.

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B) PET scans are NOT covered for routine follow up of cancer treatment or routine surveillance in asymptomatic patients.

C) ~~PET scans are NOT covered for cardiac evaluation.~~

Cardiac PET

1) Cardiac Sarcoidosis
    a. For evaluation of suspected cardiac sarcoidosis:
        i. Cardiac PET is covered if cardiac MRI is contraindicated, is normal but high clinical suspicion for cardiac sarcoidosis remains, or if cardiac MRI is inconclusive
    a. For monitoring of treatment of established cardiac sarcoidosis
        i. Cardiac PET is covered every 3-6 months while on active immunosuppression
        ii. Cardiac PET is covered every 6 months once there is minimal residual or resolved inflammation
    b. Routine cardiac surveillance of asymptomatic individuals with extracardiac sarcoidosis is not covered after the initial diagnostic work up
    c. NOTE: full body PET/CT (CPT *78815) is not indicated for the diagnosis or monitoring response to therapy of cardiac sarcoid

GUIDELINE NOTE 104, NEWER INTERVENTIONS FOR OSTEOARTHRITIS OF THE KNEE

Lines 430,462

The following treatments are not included on this line for osteoarthritis of the knee:

- Whole body vibration
- Glucosamine/chondroitin (alone, or in combination)
- Platelet rich plasma
- Viscosupplementation
- Transcutaneous electrical stimulation (TENS)
- Genicular artery embolization
- Aragonite scaffold implantation

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CPT * 20610 and 20611 are included on these lines only for interventions other than viscosupplementation for osteoarthritis of the knee.

The development of this guideline note was informed by a HERC coverage guidance. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx

GUIDELINE NOTE 6, REHABILITATIVE AND HABILITATIVE THERAPIES

Lines 31,46,57,68,71,73,80,90,91,127,131,132,136,150,153,160,177,182,183,195,199,200, 206,252,254,270,283,285,290,298,299,306,314,338,342,345,352,353,356,373,374,396, 399,400,406,414,415,420,422,430,441,455,462,465,466,474,480,488,498,542,545,557, 574,591

The quantitative limits in this guideline note do not apply to mental health or substance abuse conditions.

A total of 30 visits per year of rehabilitative therapy and a total of 30 visits per year of habilitative therapy (physical, occupational and speech therapy) are included on these lines when medically appropriate. Additional visits, not to exceed 30 visits per year of rehabilitative therapy and 30 visits per year of habilitative therapy, may be authorized in cases of a new acute injury, surgery, or other significant change in functional status. Children under age 21 may have additional visits authorized beyond these limits if medically appropriate. Massage therapy (CPT * 97124) is included in these service limits. When billing CPT * 97124, there must be a minimum of 8 minutes of massage provided. Massage is limited to no more than one session per week.

Physical, occupational and speech therapy are only included on these lines when the following criteria are met:

A) therapy is provided by a licensed physical therapist, occupational therapist, speech language pathologist, physician, or other practitioner licensed to provide the therapy,

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B) there is objective, measurable documentation of clinically significant progress toward the therapy plan of care goals and objectives,
C) the therapy plan of care requires the skills of a medical provider, and
D) the client and/or caregiver cannot be taught to carry out the therapy regimen independently.

No limits apply while in a skilled nursing facility for the primary purpose of rehabilitation, an inpatient hospital or an inpatient rehabilitation unit.

Spinal cord injuries, traumatic brain injuries, or cerebral vascular accidents are not subject to the visit limitations during the first year after an acute injury.

Implantable vagus nerve stimulation therapy (CPT *64568) is not covered for the treatment of post stroke upper extremity weakness or any other rehabilitation indication.

EXCLUDED SERVICES GUIDELINE E2, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

The following Interventions are unproven, have no clinically important benefit or have harms that outweigh benefits and should be excluded from coverage

Procedure Code	Intervention Description	Rationale	Last Review
*0356U *0470U	Cell-free HPV DNA testing	Insufficient evidence of effectiveness	March 2026
*0569T *0570T	Transcatheter tricuspid valve repair	Insufficient evidence of effectiveness	May 2026
* 0737T	Xenograft implantation into the articular surface	Insufficient evidence of effectiveness	March 2026

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Appendix A: Modified guideline notes

Procedure Code	Intervention Description	Rationale	Last Review
*0868T	High-resolution gastric electrophysiology mapping	Insufficient evidence of effectiveness	March 2026
A9291, A9292, A9293, A9294, G0552, G0553, G0554	Digital prescription therapeutics	Insufficient evidence of effectiveness	November, 2024
C1743	Scaffold, endovascular non-coronary, resorbable drug eluting	Insufficient evidence of effectiveness	March 2026
C8010	Percutaneous placement of permanent common carotid embolic protection device, including all system components and imaging guidance; bilateral	Insufficient evidence of effectiveness	March 2026
* 64582, 64583 C8007-C8009, C8011-C8013	Implantation, revision or replacement of hypoglossal nerve neurostimulator array	Insufficient evidence of effectiveness	October, 2024
* 75571 G0680	CT coronary calcium scoring	Insufficient evidence of benefit	August 2023 Coverage guidance

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Appendix A: Modified guideline notes

Procedure Code	Intervention Description	Rationale	Last Review
~~* 78429-78434, 78459, 78491-78492~~	~~Myocardial imaging, positron emission tomography (PET), metabolic evaluation and/or perfusion~~	~~Insufficient evidence of benefit, unclear harms of radiation exposure~~	~~November 2019~~ ~~Coverage Guidance~~
~~* 81232~~	~~5-fluorouracil/5-FU and capecitabine drug metabolism~~	~~Insufficient evidence of effectiveness~~	~~November, 2017~~
*97610	Low frequency, non-contact, non-thermal ultrasound	No clinically important benefit	March 2026 ~~October, 2013~~

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Minutes

Evidence-based Guidelines Subcommittee (EbGS)

Online meeting

4/16/2026

Members present: Mark Buchholz, MD; Deb Espesete MAcOM, MPH, Lac; Devan Kansagara, MD; Lynnea Lindsey PhD (Chair); Cat Livingston MD, MPH; Mimi McDonell, MD (Vice-Chair), Mathew Serres, JD

Members absent: Jeff Fortner, PharmD

OHA Staff present: Heidi Gullett, MD; Jason Gingerich; Tracy Hulett; Lewis Backus; Sarah Servid, PharmD; Roger Citron, B.S. Pharm; Lacy John

Others present: Marcus Bachhuber, MD; Courtney Cooper MPH; Shauna Durbin, MPH; Derek Lam, MD; Bruce Boston, MD; Jacqueline Espinosa; Michelle Tori; Sabah Gerges; Stephanie Asher; Heather Walz; Holly Jo Hodges, MD; Jean Economen; Tara Chowdhury; Kimberly Terry; Eric Gibson; Elizabeth Levy; Jennifer Olson; Rebecca Reese; Maggie Klein; Cindy Mulholland; Sarah Like; Paula Demaris; Katie Barr; Wendy Stephens; Melissa Wood; Nancy Wood; Jonathan Kim; Felicity Woebkenberg; Carolyn Otey; Laura Briggs, Leah Wilson

Call to Order

Lynnea Lindsay, Chair of the Evidence-based Guidelines Subcommittee (EbGS), called the meeting to order at 2:01 p.m.; roll was called. A quorum of members was present at the meeting.

Minutes Approval

MOTION: To approve the minutes of the 2/5/2026 meeting as presented.
AYES: Mark Buchholz; Deb Espesete; Devan Kansagara; Cat Livingston; Mimi McDonell; Mathew Serres
ABSTAIN: Lynnea Lindsey

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CARRIES 6-0-1

Director's Report

The meeting opened with a request for members to declare any actual or potential conflicts of interest related to the agenda; no conflicts were reported.

Jason Gingerich gave the director's report. He noted that Larry Lyon resigned his position on EbGS and HERC and Katie Schabel resigned her position last fall. New nominees are expected in June. Additional members may also be added to the EbGS subcommittee given the smaller number of current members. Cynthia Levesque was appointed to HERC and VbBS. Gingerich reviewed several legislative updates. The House Bill 4003 for the Benefit Update Project did not pass, so the Prioritized List will continue to exist, but the federal waiver still ends, so its role will need to change. In addition, House Bill 4040 made changes regarding public comment processes that affect VBBS and HERC, but should not affect EbGS; rulemaking is planned for later this year.

Review of public comment and updated Coverage Guidances:

Disposable (Tubeless or Patch) Insulin Pumps for Type 1 Diabetes

Disposable or tubeless insulin pumps are small wearable devices that stick to the skin and give insulin when the body needs it. They don't use tubing and sit directly on the skin. These are one tool to help people with diabetes manage their blood sugar throughout the day.

Heidi Gullett (HERC staff) introduced subject matter expert (Bruce Boston) and OHA colleagues attending to answer questions (Sarah Servid, Roger Citron and Lacy John). Gullett reviewed the summary table for the public comment disposition for disposable insulin pumps. Gullett reviewed updates to the recommendations in the coverage guidance as a result of public comment received.

Members of the committee discussed the proposed recommendations, including clarifying language if disposable pumps are the least costly alternative based on multiple factors, including manufacturer rebates, as well as clinical considerations and challenges with

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tubed pumps for some populations. Bruce Boston shared information about step therapy for insulin pumps and patient/family education in clinical practice. Sarah Servid provided input on the recommendation language from the perspective of pharmacy.

Michelle Tori from Insulet provided public testimony about cost considerations between disposable and traditional insulin pumps as well as clarification of automated insulin delivery (AID) systems (detailed below). Marcus Bachhuber (CEbP evidence contractor) provided clarification about AID systems and current coverage.

Following public comment further discussed the proposed recommendation and approved the motion below.

MOTION: Refer Disposable (Tubeless/Patch) Insulin Pumps — Coverage Guidance Language with updates listed below to HERC.

- Change framing to "tubeless insulin pumps" (remove "disposable"/"patch" in question headers/titles for clarity).
- Add explicit language that specified subpopulations may receive tubeless pumps even if they are not the least costly option from the health plan's perspective.
- Subparagraph G: Add "or is not expected to benefit" and clarify "because they cannot tolerate the tube"; align singular grammar to match A–F.
- Maintain "least costly and clinically appropriate" standard for the general population and clarify plan-level discretion on cost assessment.

AYES: Mark Buchholz; Deb Espesete; Devan Kansagara; Lynnea Lindsey; Cat Livingston; Mimi McDonell; Mathew Serres
CARRIES: 7

Hypoglossal Nerve Stimulation (HGNS) for Obstructive Sleep Apnea

Hypoglossal Nerve Stimulators (HGNS) are small devices placed inside the body for people with certain types of sleep apnea. It is meant to work with the airway and breathing during sleep. The device is one option that may be considered to treat people with this condition.

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Heidi Gullett (HERC staff) reviewed the HGNS topic and the prior reviews before EbGS. She then reviewed the current public comment disposition. Gullett passed the discussion to Bachhuber to review of additional information requested by the committee at the February meeting about body mass index (BMI) and apnea-hypopnea index (AHI). Bachhuber reviewed this information in slides. Gullett then reviewed the coverage guidance recommendations which the committee discussed with input from the subject matter expert (Lam). The committee discussed changing the parameters for both BMI and AHI and the motions below were passed.

MOTION: Refer Hypoglossal Nerve Stimulation (HGNS) — Coverage Guidance with edits listed below to HERC.

- BMI threshold: Increase upper limit to ≤ 35 kg/m^2 (from 32), aligning with Medicare LCD and reflecting real-world registry evidence.
- AHI range: Expand upper limit to 15–100 events/hour (from 15–65), based on FDA supplemental data analysis indicating comparable safety and patient-reported outcomes for higher baseline AHI ranges.
- Rationale text: Update to note that criteria are informed by reported RCT/cohort studies, Medicare criteria, and supplemental data used in FDA approvals.

AYES: Deb Espesete; Devan Kansagara; Lynnea Lindsey; Cat Livingston; Mimi McDonell; Mathew Serres
NOT PRESENT: Mark Buchholz
CARRIES: 6-0

MOTION: Hypoglossal Nerve Stimulation (HGNS) Coverage Guidance Amendment to include the summary table(s) from the slides summarizing FDA supplemental data (BMI and AHI expansion evidence) within the coverage guidance packet provided to HERC/VBBS.

AYES: Deb Espesete; Devan Kansagara; Lynnea Lindsey; Cat Livingston; Mimi McDonell; Mathew Serres
CARRIES: 6-0

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Public Comment

Michelle Tori (public testimony – insulin pumps): Michelle thanked the committee for its detailed responses to public comments. She specifically appreciated the committee's consideration of language changes allowing plans to conduct cost analyses, emphasizing that cost competitiveness is central to coverage decisions. Michelle asked one clarification question regarding page 195, section E4, about the statement that no restrictions exist on AID (Automated Insulin Delivery) systems when insulin pump coverage criteria are met. She sought to understand how this applied to Omnipod 5. Clarification was provided that if a member is eligible for an insulin pump, they are eligible for an AID system.

Additional discussion

Livingston requested that staff formalize a plan to include additional Medicaid policies from additional states beyond Washington. She said with budget pressures in Medicaid, it may be good to look at some less-resourced states. She suggested including states that have readily available policies. Lindsay asked that staff propose 2-3 other states to add. Other members expressed support and acknowledged the difficulties of comparing different states, as there economic, policy and demographic differences among states, along with the robustness of the evidence-based decision process. Staff agreed to discuss it with HERC leadership and do some analysis in preparation for the next scope statement for a future topic.

Next meeting

Next meeting will be from 2:00 p.m.-5:00 p.m. on Thursday, June 4, 2026, Online.

Adjournment

Meeting adjourned at 4:24 p.m.

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Section 2.0

Plain language Summaries

Value-based Benefits Subcommittee (VbBS)
Plain Language Summary of Topics
May 14, 2026

This plain-language summary provides a short, non-technical explanation of the topics to be discussed at the meeting, along with the staff recommendations. Decisions are not final unless approved by the Health Evidence Review Commission (which usually meets later the same day). The Commission may approve, modify, or not approve staff recommendations.

Note: References to Medical Necessity in these materials correspond to the definitions in rule at OAR 410-120-0000, which includes both Medical Necessity and Medical Appropriateness

Low Level Laser Therapy

Low level laser therapy (LLLT) uses gentle, near infrared light that doesn't heat the skin. This treatment might help with some muscle or joint pain.

Transcutaneous Neuromodulation

Nerve stimulation treatment (transcutaneous neuromodulation) uses low-level electrical signals applied to a painful area to reduce the brain's pain response.

Tumor Treating Fields (TTFields) for Pancreatic Cancer (LAPC)

Tumor Treating Fields is a device that uses electric signals to slow cancer growth. The device is approved by the FDA for a certain kind of advanced pancreas cancer.

2026 Cardiac PET Review

Cardiac sarcoidosis is a poorly understood condition where inflammation harms the heart. It can lead to serious heart problems or even death. A cardiac PET scan is an imaging study that uses radioactive dye to take detailed pictures of the heart.

2027 CPT Code Review Microsurgical Management Lymphedema

Lymphedema is an unusual swelling of the arms or legs, sometimes caused by surgery. Lymphovenous surgery is a procedure done with a microscope to reconnect tiny lymph vessels, helping drain extra fluid out of the limb.

Septoplasty for Breathing Issues

A surgery to straighten the divider inside the nose (nasal septum) may help with breathing problems.

Septoplasty for CPAP Tolerance

A surgery to straighten the divider inside the nose (nasal septum) may help people who use a breathing machine to help with sleep apnea, called a Continuous Positive Airway Pressure (CPAP) device.

Adult PE tube clarification

Tympanostomy tubes are tiny tubes placed in the eardrum to help air and fluid move more freely in the middle ear, among other conditions.

Hydrophilic Urinary Catheters

Intermittent urinary catheters drain urine when the bladder cannot empty on its own because of nerve damage or other disease or injury. Some catheters have a hydrophilic coating that becomes slippery in water.

Acupuncture for Depression

Depression is treatable. Many people get better with talk therapy, medication, or both. Acupuncture is proposed as a therapy to help other treatments for depression work better.

CG Hypoglossal Nerve Stimulation (HGNS) for Sleep Apnea (OSA)

This is a small device placed inside the body for people with certain types of sleep apnea. It is meant to work with the airway and breathing during sleep.

Reproductive Health Equity Act (RHEA) – 2026 Review

Every 2 years the Health Evidence Review Commission reviews clinical practice recommendations related to providing preventive care and ensures that these services remain covered per Oregon law.

Section 3.0

Errata

Errata
May 2026

Errata – May 2026

1) On April 1, 2026, staff made the following corrections:
   a) Added CPT 70471-70473 to the Diagnostic Procedures file. This decision was approved at the October 2025 meeting in relation to new CPT codes.
   b) Revised the rationale entry for PLA codes related to upper respiratory panels. It had erroneously contained the date of the decision, whereas the rationale is: Uncertain clinical utility.
   c) Revised line placement for Guideline Note 180 MEDICALLY INDUCED CIRCUMCISION. The guideline formerly paired with Line 410 SCHIZOTYPAL PERSONALITY DISORDERS, where it now correctly pairs with Line 411 BALANOPOSTHITIS AND OTHER DISORDERS OF PENIS.

Section 4.0

Consent Agenda-

Straightforward Items

Consent Agenda Issues—May 2026

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
G45.4 G46.3 G46.4 G46.5 G46.6 G46.7 G46.8	Transient global amnesia Brain stem stroke syndrome Cerebellar stroke syndrome Pure motor lacunar syndrome Pure sensory lacunar syndrome Other lacunar syndromes Other vascular syndromes of brain in cerebrovascular diseases	413 TRANSIENT CEREBRAL ISCHEMIA; OCCLUSION/STENOSIS OF PRECEREBRAL ARTERIES WITHOUT OCCLUSION 630 INTRACRANIAL CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY	HERC staff are reviewing the BUP diagnoses on Evaluation and Management and determined that these codes are considered types of TIA. Other codes in the G45 and G46 families are on line 413	Add G45.3, G46.3-G46.8 to line 413 and delete from line 630 for 10/1/2026 and for the BUP Prioritized List

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Consent Agenda Issues—May 2026

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
90616 90639	Influenza virus vaccine, trivalent (tIRV), mRNA, 37.5 mcg/0.38 mL dosage, for intramuscular use 50 mcg/0.5 mL dosage	3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS Exempt	The AMA released two new codes for mRNA influenza vaccine, effective 7/1/2026. Vaccine codes typically are placed on line 3 for visibility and on the Exempt file to always pay regardless of visit type.	Add 90616 and 90639 to line 3 and the Exempt file

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Straightforward Guideline Notes Changes May 2026

Issue: Broken links, accessibility

Links in the Multisector Intervention Statement 1 are no longer working. The first link just requires an update. The second link appears to no longer exist on the CDC website. The replacement link is to a more extensive document by the same Task Force.
In addition, the graphic does not meet OHA's accessibility standards, is no longer available online. At the March 2026 VBBS meeting, staff recommended removing it. However, members felt that the material in the graphic is useful and requested that staff include the material in a table or outline.

HERC staff recommendations:

1) Modify Multisector Intervention Statement 1 as shown below
    a. Alternative: rather than adding the outline below, add the link to the Community Guide Page with all of this information: https://thecommunityguide.org/pages/task-force-findings-tobacco.html

MULTISECTOR INTERVENTION STATEMENT 1: TOBACCO PREVENTION AND CESSATION, INCLUDING DURING PREGNANCY

Benefit coverage for smoking cessation on Line 5 and in Guideline Note 4 TOBACCO DEPENDENCE, INCLUDING DURING PREGNANCY is intended to be offered with minimal barriers, in order to encourage utilization. To further prevent tobacco use and help people quit, additional evidence-based policy and programmatic interventions from a population perspective are available here:

- Oregon Public Health Division's Health Promotion and Chronic Disease Prevention Section: Evidence-Based Strategies for Reducing Tobacco Use A Guide for CCOs ~~https://www.oregon.gov/oha/PH/PREVENTIONWELLNESS/TOBACCOPREVENTION/Documents/evidence-based_strategies_reduce_tob_use_guide_cco.pdf~~https://www.oregon.gov/oha/HPA/ANALYTICS/CCOMetrics/Strategies-for-Reducing-Tobacco-Use.pdf
- Community Preventive Services Task Force (supported by the CDC) - ~~What Works: Tobacco Use~~ ~~http://www.thecommunityguide.org/about/What-Works-Tobacco-~~

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~~factsheet-and-insert.pdf~~ https://www.thecommunityguide.org/findings/tobacco-use-comprehensive-tobacco-control-programs.html

The Community Preventive Services Task Force identified the following evidence-based strategies:

A) Recommended
   1) Increasing the unit price of tobacco products to reduce tobacco use initiation and increase tobacco use cessation
   2) Mass media campaigns when combined with other interventions to reduce tobacco use initiation and increase tobacco use cessation
   3) Smoke-free policies for reducing tobacco use initiation, increasing tobacco use cessation, reducing exposure to environmental tobacco smoke and decreasing tobacco use among workers
   4) To increase tobacco use cessation
      a) Mass-reach health communication interventions, mobile phone-based interventions
      b) Multi-component interventions that include client telephone support
      c) Provider reminders when used alone
      d) Provider reminders with provider education
      e) Reducing client out-of-pocket costs for cessation therapies
      f) Community mobilization with additional interventions to restrict minors access to tobacco products
      g) Incentives and competitions to increase smoking cessation combined with additional interventions to decreased tobacco use among workers

B) Insufficient evidence
   1) To increase tobacco use cessation
      a) Internet-based interventions
      b) Mass medial cessation contests
      c) Mass media cessation series
      d) Provider assessment and feedback
      e) Provider education when used alone
   2) To reduce exposure to environmental tobacco smoke
      a) Community education to reduce exposure in the home
   3) For reducing minors access to tobacco products
      a) Sales laws directed at retailers when used alone

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b) Active enforcement of sales laws directed at retailers when used alone
c) Community education about youth's access to tobacco products when used alone
d) Retailer education with reinforcement and information on health consequences when used alone
e) Retailer education without reinforcement when used alone
f) Laws directed at minor's purchase, possession, or use of tobacco products when used alone

4) To decrease tobacco use among workers
   a) Incentives and competitions to increase smoking cessation when used alone

[DELETE THIS FIGURE]

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TASK FORCE FINDINGS ON TOBACCO USE

The Community Preventive Services Task Force (Task Force) has released the following findings on what works in public health to prevent tobacco use. These findings are compiled in The Guide to Community Preventive Services (The Community Guide) and listed in the table below. Use the findings to identify strategies and interventions you could use for your community.

Legend for Task Force Findings: ● Recommended ◆ Insufficient Evidence ▲ Recommended Against (See reverse for detailed descriptions.)

Intervention	Task Force Finding
Reducing Tobacco Use Initiation	
Increasing the unit price of tobacco products	●
Mass media campaigns when combined with other interventions	●
Smoke-free policies	●
Increasing Tobacco Use Cessation	
Increasing the unit price of tobacco products	●
Mass media campaigns when combined with other interventions	●
Mass-reach health communication interventions	●
Mobile phone-based interventions	●
Multicomponent interventions that include client telephone support	●
Smoke-free policies	●
Provider reminders when used alone	●
Provider reminders with provider education	●
Reducing client out-of-pocket costs for cessation therapies	●
Internet-based interventions	◆
Mass media – cessation contests	◆
Mass media – cessation series	◆
Provider assessment and feedback	◆
Provider education when used alone	◆

Intervention	Task Force Finding
Reducing Exposure to Environmental Tobacco Smoke	
Smoke-free policies	●
Community education to reduce exposure in the home	◆
Restricting Minors' Access to Tobacco Products	
Community mobilization with additional interventions	●
Sales laws directed at retailers when used alone	◆
Active enforcement of sales laws directed at retailers when used alone	◆
Community education about youth's access to tobacco products when used alone	◆
Retailer education with reinforcement and information on health consequences when used alone	◆
Retailer education without reinforcement when used alone	◆
Laws directed at minors' purchase, possession, or use of tobacco products when used alone	◆
Decreasing Tobacco Use Among Workers	
Smoke-free policies	●
Incentives and competitions to increase smoking cessation combined with additional interventions	●
Incentives and competitions to increase smoking cessation when used alone	◆

Visit the "Tobacco Use" page of The Community Guide website at www.thecommunityguide.org/tobacco to find summaries of Task Force findings and recommendations on tobacco use. Click on each topic area to find results from the systematic reviews, included studies, evidence gaps, and journal publications.

The Centers for Disease Control and Prevention provides administrative, research, and technical support for the Community Preventive Services Task Force.

To reduce the use of tobacco during pregnancy and improve associated outcomes, the evidence supports the following interventions:

- Financial incentives (incentives contingent upon laboratory tests confirming tobacco abstinence are the most effective)
- Smoke-free legislation
- Tobacco excise taxes

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HPV Testing:

The CPT codes in Guideline Note 1 for HPV testing are not correct. CPT 87620 and 87621 are no longer valid codes. At the March 2026 meetings, VBBS members recommended deleting the table in Guideline Note 1 and replacing with a reference to Guideline Note 106. GN106 should be modified to include all required references to cervical cancer screening. On review, the HRSA women's preventive services guidelines includes all the information previously included in Guideline Note 1.

HERC staff recommendations:

1) Modify Guideline Note 1 as shown below for 10/1/2025
    a. For 1/1/2027, delete this guideline
2) Modify Guideline Note 106 as shown below

GUIDELINE NOTE 1, ROUTINE CERVICAL CANCER SCREENING

Line 3

Cervical cancer screening is covered on Line 3 as indicated in Guideline Note 106. ~~for women~~:

~~Age group in years~~	~~Type of screening covered~~	~~Frequency~~
~~<21~~	~~None~~	~~Never~~
~~21-29~~	~~Cytology alone~~ ~~Mandatory HPV testing (87620-87621 87624-87625) is not covered for women age 21-29~~	~~Every 3 years~~
~~30-65~~	~~High-risk human papillomavirus (hrHPV) testing alone, co-testing (hrHPV and cytology) or cytology alone~~	~~Co-testing every 5 years~~ ~~hrHPV testing alone every 5 years~~ ~~Cytology alone every 3 years~~
~~>65~~	~~None~~ ~~Unless adequate screening* has not been achieved, or it is <20 years after regression or appropriate management of a high-grade precancerous lesion~~	~~Never~~

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~~Women who have had a hysterectomy with removal of cervix for non cervical cancer related reasons (i.e., other than high grade precancerous lesion, CIN 2 or 3, or cervical cancer)~~	~~None~~	~~Never~~
~~Women who have abnormal testing~~	~~Per ASCCP** Guideline, until indicated to resume routine screening~~	~~Per ASCCP Guideline, until indicated to resume routine screening~~

~~* Adequate screening is defined as 3 consecutive negative cytology results or 2 consecutive negative HPV results within 10 years of the cessation of screening, with the most recent test occurring within 5 years.~~

~~** American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology guideline (Perkins, 2020)~~

~~Women who have received a diagnosis of a high-grade precancerous cervical lesion or cervical cancer, women with in-utero exposure to diethylstilbestrol, or women who are immunocompromised (such as those who are HIV positive) are intended to have screening more frequently than delineated in this guideline.~~

GUIDELINE NOTE 106, PREVENTIVE SERVICES

Lines 3,604

Included on Line 3 are the following preventive services:

A) US Preventive Services Task Force (USPSTF) “A” and “B” Recommendations in effect and issued prior to January 1, 2025.

   1) https://www.uspreventiveservicestaskforce.org/uspstf/recommendation-topics/uspstf-a-and-b-recommendations/

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2) USPSTF "D" recommendations are not included on this line or any other line of the Prioritized List.

B) American Academy of Pediatrics (AAP) Bright Futures Guidelines:

1) http://brightfutures.aap.org. Periodicity schedule available at https://downloads.aap.org/AAP/PDF/periodicity_schedule.pdf

a) Bright Futures is the periodicity schedule for screening for EPSDT for the Oregon Health Plan.

2) Screening for lead levels is defined as blood lead level testing and is indicated for Medicaid populations at 12 and 24 months. In addition, blood lead level screening of any child between ages 24 and 72 months with no record of a previous blood lead screening test is indicated.

C) Health Resources and Services Administration (HRSA) Women's Preventive Services-Required Health Plan Coverage Guidelines (revised October 2025). Available at https://www.hrsa.gov/womens-guidelines as of October 27, 2025.

1) Note: these guidelines include cervical cancer screening previously outlined in Guideline Note 1. Abnormal cervical cancer screening results should be evaluated and follow up on as indicated by the American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology guideline (Perkins, 2020)

D) Immunizations as recommended by the Advisory Committee on Immunization Practices (ACIP): https://www.cdc.gov/vaccines/hcp/imz-schedules/?CDC_AAref_Val=https://www.cdc.gov/vaccines/schedules/hcp/index.html or approved for the Oregon Immunization Program: https://www.oregon.gov/oha/ph/preventionwellness/vaccinesimmunization/immunizationproviderresources/pages/payor.aspx

1) COVID-19 vaccines are intended to be included on this line even if the specific administration code(s) do not yet appear on the line when the vaccine has both 1) FDA approval or FDA emergency use authorization (EUA) and 2) ACIP recommendation.
2) Other ACIP recommended vaccines not on the routine vaccine schedule are included on Line 3 when administered according to recommendations specified in the Morbidity and Mortality Weekly Review (MMWR) as required by federal

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law: https://www.cdc.gov/acip-recs/hcp/vaccine-specific/?CDC_AAref_Val=https://www.cdc.gov/vaccines/hcp/acip-recs/index.html (retrieved 10/27/25).

Colorectal cancer screening is included on Line 3 for average-risk adults aged 45 to 75, using one of the following screening programs:

A) Colonoscopy every 10 years
B) Flexible sigmoidoscopy every 5 years
C) Fecal immunochemical test (FIT) every year (CPT * 82274)
D) Guaiac-based fecal occult blood test (gFOBT) every year

Screening CT colonography (CPT * 74263) is only covered for patients who are unable to complete a screening colonoscopy due to colon structural problems (for example, colonic obstruction, stricture, or compression or tortuous or redundant colon).

FIT-DNA (CPT * 81528) and blood-based colorectal cancer screening tests (HCPCS G0327) are included on Excluded Services Guideline 1.

Colorectal cancer screening for average-risk adults aged 76 to 85 is covered after informed decision making between patients and clinicians which includes consideration of the patient's overall health, prior screening history, and preferences.

Supervised evidence-based exercise programs for fall prevention for persons aged 65 or older OR younger patients who are at increased risk of falls are included on Line 3 using CPT * 98961 or 98962 or HCPCS S9451. HCPCS S9451 is only included on Line 3 for the provision of supervised exercise therapy for fall prevention. Programs should be culturally tailored/culturally appropriate when feasible.

Note: CPT * 96110 (Developmental screening (e.g., developmental milestone survey, speech and language delay screen), with scoring and documentation, per standardized instrument) can be billed in addition to other CPT codes, such as evaluation and management (E&M) codes or preventive visit codes.

The development of this guideline note was informed by a HERC coverage guidance. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx

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Issue: Revised CMS NCD

The guideline regarding wearable cardiac defibrillators has a reference to the 2005 CMS NCD for implantable cardiac defibrillators. The NCD has been updated, most recently in 2023. There are no substantial coverage differences between the 2003 and 2023 versions.

HERC staff recommendations:

1) Modify GN 49 as shown below

GUIDELINE NOTE 49, WEARABLE CARDIAC DEFIBRILLATORS

Lines 69,98,110,188,279,344

Wearable cardiac defibrillators (WCDs; CPT * 93745, HCPCS K0606-K0609) are included on these lines for patients at high risk for sudden cardiac death who meet the medical necessity criteria for an implantable cardioverter defibrillator (ICD) as defined by the CMS ~~2005~~ 2023 National Coverage Determination but are unable to have an ICD implanted due to medical condition (e.g. ICD explanted due to infection with waiting period before ICD reinsertion or current medical condition contraindicates surgery). WCDs are not included on these lines for use during the waiting period for ICD implantation after myocardial infarction, coronary bypass surgery, or coronary artery stenting.

Issue: Clarification of non-coverage of cancer detection blood tests

Blood based colorectal cancer screening tests were reviewed in August 2025 and reaffirmed for non-coverage. The GN106 test and the Excluded Services Guideline Note E1 entry only list one HCPCS code for this type of test. The Shield test as a PLA code that was released in April 2025 that needs to be added to the GN106 and the Excluded Services E1 entries for this type of testing. PLA 0537U DNA next-generation sequencing of more than 2500 differentiated methylated regions (DMRs), reported as positive or negative in colorectal cancer.

An updated Cologuard stool test, the Cologuard Plus, has been released and has a PLA code: PLA 0464U Oncology (colorectal) screening, quantitative real-time target and signal amplification, methylated DNA markers, including LASS4, LRRC4 and PPP2R5C, a reference marker ZDHHC1, and a protein marker (fecal hemoglobin), utilizing stool,

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algorithm reported as a positive or negative result. This code should be added to the Cologuard entry in Excluded Services Guideline E1.

HERC staff recommendations:

1) Modify GN106 as shown below
    a. Note: other modifications are proposed in another straightforward entry above and are noted in purple below
2) Modify Excluded Services E1 as shown below

GUIDELINE NOTE 106, PREVENTIVE SERVICES

Lines 3,604

Included on Line 3 are the following preventive services:

A) US Preventive Services Task Force (USPSTF) "A" and "B" Recommendations in effect and issued prior to January 1, 2025.
    1) https://www.uspreventiveservicestaskforce.org/uspstf/recommendation-topics/uspstf-a-and-b-recommendations/
    2) USPSTF "D" recommendations are not included on this line or any other line of the Prioritized List.
B) American Academy of Pediatrics (AAP) Bright Futures Guidelines:
    1) http://brightfutures.aap.org. Periodicity schedule available at https://downloads.aap.org/AAP/PDF/periodicity_schedule.pdf
        a) Bright Futures is the periodicity schedule for screening for EPSDT for the Oregon Health Plan.
    2) Screening for lead levels is defined as blood lead level testing and is indicated for Medicaid populations at 12 and 24 months. In addition, blood lead level screening of any child between ages 24 and 72 months with no record of a previous blood lead screening test is indicated.
C) Health Resources and Services Administration (HRSA) Women's Preventive Services-Required Health Plan Coverage Guidelines (revised October 2025). Available at https://www.hrsa.gov/womens-guidelines as of October 27, 2025.
    1) Note: these guidelines include cervical cancer screening previously outlined in Guideline Note 1. Abnormal cervical cancer screening results should be evaluated and follow up on as indicated by the American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology guideline (Perkins, 2020)
D) Immunizations as recommended by the Advisory Committee on Immunization Practices (ACIP): https://www.cdc.gov/vaccines/hcp/imz-

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schedules/?CDC_AAref_Val=https://www.cdc.gov/vaccines/schedules/hcp/index.html or approved for the Oregon Immunization Program: https://www.oregon.gov/oha/ph/preventionwellness/vaccinesimmunization/immunizationproviderresources/pages/payor.aspx

1) COVID-19 vaccines are intended to be included on this line even if the specific administration code(s) do not yet appear on the line when the vaccine has both 1) FDA approval or FDA emergency use authorization (EUA) and 2) ACIP recommendation.
2) Other ACIP recommended vaccines not on the routine vaccine schedule are included on Line 3 when administered according to recommendations specified in the Morbidity and Mortality Weekly Review (MMWR) as required by federal law: https://www.cdc.gov/acip-recs/hcp/vaccine-specific/?CDC_AAref_Val=https://www.cdc.gov/vaccines/hcp/acip-recs/index.html (retrieved 10/27/25).

Colorectal cancer screening is included on Line 3 for average-risk adults aged 45 to 75, using one of the following screening programs:

A) Colonoscopy every 10 years
B) Flexible sigmoidoscopy every 5 years
C) Fecal immunochemical test (FIT) every year (CPT * 82274)
D) Guaiac-based fecal occult blood test (gFOBT) every year

Screening CT colonography (CPT * 74263) is only covered for patients who are unable to complete a screening colonoscopy due to colon structural problems (for example, colonic obstruction, stricture, or compression or tortuous or redundant colon).

FIT-DNA (CPT * 81528) and blood-based colorectal cancer screening tests (for example, HCPCS G0327 and PLA 0537U) are included on Excluded Services Guideline 1.

Colorectal cancer screening for average-risk adults aged 76 to 85 is covered after informed decision making between patients and clinicians which includes consideration of the patient's overall health, prior screening history, and preferences.

Supervised evidence-based exercise programs for fall prevention for persons aged 65 or older OR younger patients who are at increased risk of falls are included on Line 3 using CPT * 98961 or 98962 or HCPCS S9451. HCPCS S9451 is only included on Line 3 for the provision of supervised exercise therapy for fall prevention. Programs should be culturally tailored/culturally appropriate when feasible.

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Note: CPT * 96110 (Developmental screening (e.g., developmental milestone survey, speech and language delay screen), with scoring and documentation, per standardized instrument) can be billed in addition to other CPT codes, such as evaluation and management (E&M) codes or preventive visit codes.

The development of this guideline note was informed by a HERC coverage guidance. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx

EXCLUDED SERVICES GUIDELINE E1, INTERVENTIONS WITH MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS FOR CERTAIN CONDITIONS

The following interventions result in marginal clinical benefit or have low cost-effectiveness and should be excluded from coverage:

Procedure Code	Intervention Description	Rationale	Last Review
* 81528; 81327; 0421U; 0464U	FIT-DNA (Cologuard); Chromoscopy; Colosense	Insufficient evidence for use in population screening	August, 2021
G0327; 0537U	Blood based colorectal cancer screening tests	Insufficient evidence for use in population screening	August, 2025

Issue: Broken Link

The link to the Oregon Vaccine Schedule (informed by the West Coast Health Alliance) is not correct in GN106

HERC staff recommendations:

1) Modify GN106 as shown below
    a. Note: other modifications are proposed in other straightforward entries above and are noted in purple below

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GUIDELINE NOTE 106, PREVENTIVE SERVICES

Lines 3,604

Included on Line 3 are the following preventive services:

A) US Preventive Services Task Force (USPSTF) "A" and "B" Recommendations in effect and issued prior to January 1, 2025.
   1) https://www.uspreventiveservicestaskforce.org/uspstf/recommendation-topics/uspstf-a-and-b-recommendations/
   2) USPSTF "D" recommendations are not included on this line or any other line of the Prioritized List.
B) American Academy of Pediatrics (AAP) Bright Futures Guidelines:
   1) http://brightfutures.aap.org. Periodicity schedule available at https://downloads.aap.org/AAP/PDF/periodicity_schedule.pdf
      a) Bright Futures is the periodicity schedule for screening for EPSDT for the Oregon Health Plan.
   2) Screening for lead levels is defined as blood lead level testing and is indicated for Medicaid populations at 12 and 24 months. In addition, blood lead level screening of any child between ages 24 and 72 months with no record of a previous blood lead screening test is indicated.
C) Health Resources and Services Administration (HRSA) Women's Preventive Services-Required Health Plan Coverage Guidelines (revised October 2025). Available at https://www.hrsa.gov/womens-guidelines as of October 27, 2025.
   1) Note: these guidelines include cervical cancer screening previously outlined in Guideline Note 1. Abnormal cervical cancer screening results should be evaluated and follow up on as indicated by the American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology guideline (Perkins, 2020)
D) Immunizations as recommended by the Advisory Committee on Immunization Practices (ACIP): https://www.cdc.gov/vaccines/hcp/imz-schedules/?CDC_AAref_Val=https://www.cdc.gov/vaccines/schedules/hcp/index.html or approved for the Oregon Immunization Program: ~~https://www.oregon.gov/oha/ph/preventionwellness/vaccinesimmunization/immunizationproviderresources/pages/payor.aspx~~ https://www.oregon.gov/oha/PH/PREVENTIONWELLNESS/VACCINESIMMUNIZATION/IMMUNIZATIONPROVIDERRESOURCES/Documents/DMAPvactable.pdf
   1) COVID-19 vaccines are intended to be included on this line even if the specific administration code(s) do not yet appear on the line when the vaccine has both 1) FDA approval or FDA emergency use authorization (EUA) and 2) ACIP recommendation.
   2) Other ACIP recommended vaccines not on the routine vaccine schedule are included on Line 3 when administered according to recommendations specified

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in the Morbidity and Mortality Weekly Review (MMWR) as required by federal law: https://www.cdc.gov/acip-recs/hcp/vaccine-specific/?CDC_AAref_Val=https://www.cdc.gov/vaccines/hcp/acip-recs/index.html (retrieved 10/27/25).

Colorectal cancer screening is included on Line 3 for average-risk adults aged 45 to 75, using one of the following screening programs:

A) Colonoscopy every 10 years
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D) Guaiac-based fecal occult blood test (gFOBT) every year

Screening CT colonography (CPT * 74263) is only covered for patients who are unable to complete a screening colonoscopy due to colon structural problems (for example, colonic obstruction, stricture, or compression or tortuous or redundant colon).

FIT-DNA (CPT * 81528) and blood-based colorectal cancer screening tests (for example, HCPCS G0327 and PLA 0537U) are included on Excluded Services Guideline 1.

Colorectal cancer screening for average-risk adults aged 76 to 85 is covered after informed decision making between patients and clinicians which includes consideration of the patient's overall health, prior screening history, and preferences.

Supervised evidence-based exercise programs for fall prevention for persons aged 65 or older OR younger patients who are at increased risk of falls are included on Line 3 using CPT * 98961 or 98962 or HCPCS S9451. HCPCS S9451 is only included on Line 3 for the provision of supervised exercise therapy for fall prevention. Programs should be culturally tailored/culturally appropriate when feasible.

Note: CPT * 96110 (Developmental screening (e.g., developmental milestone survey, speech and language delay screen), with scoring and documentation, per standardized instrument) can be billed in addition to other CPT codes, such as evaluation and management (E&M) codes or preventive visit codes.

The development of this guideline note was informed by a HERC coverage guidance. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx

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Section 5.0

New Discussion Items

Low Level Laser Therapy 2026

Plain Language Summary:

Low-level laser therapy (LLLT) uses gentle, near-infrared light that doesn't heat the skin. This treatment might help with some muscle or joint pain.

Because there isn't enough strong evidence that it helps with pain or daily function, staff recommend not covering this treatment.

Staff Analysis Summary:

No significant change to current coverage:

1. Do not add any additional indications for low level laser therapy

No changes were made from the advance packet (no comments received)

Changes after public comment period

No public comments were received on this topic. Since the advanced packet, HERC staff became aware of another LLLT related billing code on the Prioritized List and is recommending removal from the list.

Coverage Question:

Should coverage for low level laser therapy (LLLT) be expanded to additional indications?

Question source:

Natasha Ruegsegger, DC

Background:

Low level laser therapy (LLLT) uses near infrared nonthermal lasers has been promoted as an effective way to produce analgesia and accelerate healing of a variety of clinical

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conditions. LLLT may be administered by a physician, physical therapist, occupational therapist or Doctor of Chiropractic (DC) in a physician's office or other outpatient setting and requires no sedation or anesthesia. It is theorized that LLLT may cause a biostimulatory healing effect for the treatment of a range of conditions, including arthritis, chronic pain commonly associated with carpal tunnel syndrome, tissue injuries, tendinopathy, plantar fasciitis, low back pain, radiculopathy and a variety of other conditions.

Dr. Ruegsegger is requesting re-review of lack of coverage for LLLT for "neuromusculoskeletal, neurologic, degenerative, and pain-related conditions."

Previous HSC/HERC reviews:

LLLT was last reviewed for multiple conditions in 2019-2020. That review included a 2020 Systematic review by AHRQ on non-invasive treatments for pain that found that low level evidence from 3 trials that LLLT was associated with a small improvement in low back pain in the short term, but not intermediate or long term. The AHRQ review found moderate certainty evidence based on 2 trials that LLLT had a moderate improvement in short term function with chronic neck pain, but no change in long term function. The Washington State Bureau of Labor and Industry 2018 review found low or very low quality evidence that LLLT may provide a clinically uncertain improvement in pain in the short term for a variety of musculoskeletal conditions, but not in the long term. A 2010 Cochrane review found LLLT provided short term relieve of pain in the short term for rheumatoid arthritis patients. Inconclusive results were found in a systematic review looking at LLLT for tennis elbow. Based on this review, LLLT was added to what is now Excluded Services Guideline E2.

In November 2023, the HCPCS code for LLLT was added to various lines for prevention of oral mucositis for patients undergoing cancer therapy based on a new systematic review and meta-analysis of effectiveness.

Current Prioritized List/Coverage status:

CPT 97037 (Application of a modality to 1 or more areas; low-level laser therapy (ie, nonthermal and non-ablative) for post-operative pain reduction) is excluded

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HCPCS S8948 (Application of a modality (requiring constant provider attendance) to one or more areas; low-level laser; each 15 minutes): on all cancer therapy lines
CPT D9128 and D9129 (photobiomodulation therapy): on all cancer therapy lines
CPT 0552T (Low-level laser therapy, dynamic photonic and dynamic thermokinetic energies, provided by a physician or other qualified health care professional): on 50+ lines
[note: in general, category III CPT codes ("T") codes are excluded by rule if level 1 CPT or HCPCS codes are available]

GUIDELINE NOTE 231, LOW LEVEL LASER THERAPY

Lines 92,111,112,114,115,124,125,129,133,135,157,163,190, 198, 199, 207, 209, 213,214,216,228,233, 236,237,239,256,257,259-261,269,274,283-285,292,311-313,326,339,369,393-395,399,417,433,440,459,545,557

Low level laser therapy (HCPCS S8948; CDT ** D9128 and D9129) is included on these lines only for prevention of oral mucositis for members undergoing cancer treatment associated with increased risk of oral mucositis, including chemotherapy, radiotherapy, and/or hematopoietic stem cell transplantation.

EXCLUDED SERVICES GUIDELINE E2, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

The following Interventions are unproven, have no clinically important benefit or have harms that outweigh benefits and should be excluded from coverage

Procedure Code	Intervention Description	Rationale	Last Review
97037	Application of a modality to 1 or more areas; low-level laser therapy (ie, nonthermal and non-ablative) for post-operative pain reduction	Insufficient evidence of effectiveness	November 2023

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Evidence:

Chronic pain

1) **NICE 2021** Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain; Evidence review for electrical physical modalities for chronic primary pain
    a. Laser therapy vs sham laser therapy (N=14 studies)
        i. Quality of life
            1. Very low quality evidence from 6 studies with 276 participants showed a clinically important benefit of laser therapy compared to sham laser therapy at ≤3 months. Low to moderate quality evidence from 2 studies with 110 participants showed both a clinically important benefit of laser therapy (physical subscale) and no clinically important difference (mental subscale) compared to sham laser therapy at ≤3 months. Low quality evidence from 2 studies with 117 participants showed no clinically important difference compared to sham laser therapy at >3 months
        ii. Pain reduction
            1. Very low quality evidence from 13 studies with 558 participants showed a clinically important benefit of laser therapy compared to sham laser therapy at ≤3 months. Moderate quality evidence from 2 studies with 71 participants showed a clinically important benefit of laser therapy compared to sham laser therapy at >3 months.
        iii. Physical function No evidence identified.
    b. Discussion: Evidence for laser therapy versus sham was based on 14 studies and showed a benefit of treatment in terms of pain and quality of life at short term follow up, although there was serious uncertainty around the effect estimates. The long-term data showing a benefit of laser therapy for pain was based on much smaller sample sizes. Contrastingly, evidence from 2 studies showed no clinically important difference (with some uncertainty) between laser therapy and sham for quality of life at less than 3 months, as measured by the mental component summary of the SF-36 questionnaire, but there was evidence to suggest a benefit on the physical component summary of the SF-36. At longer-term follow up, evidence from 2 studies also showed no clinically important difference. The committee noted that they would expect to see a consistent benefit across more domains, if an intervention were to be interpreted as being generally effective. This therefore raised questions about the effectiveness of the intervention for all critical outcomes being assessed. The committee agreed that although there was some evidence of benefit for quality of life and pain, they could not make a recommendation for laser therapy. The evidence from clinical trials was heterogeneous.

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Comparisons were against sham laser therapy, rather than usual care, which is the comparison of greatest interest for implementation in the NHS. Taking all of this into account, the committee agreed they could not make a recommendation for the use of laser therapy in clinical practice. However, they agreed that this preliminary evidence looked promising, and as a result made a recommendation for further research.

Low back pain/lumbar disc herniation

1) **Lee 2023**: Effectiveness and Safety of Low-Level Laser Treatment for Lumbar Disc Herniation: A Systematic Review and Meta-Analysis
    a. N=5 RCTs of LLLT for LBP (845 patients)
        i. N=1 with sham laser comparator (Ay 2010)
        ii. N=1 with sham laser and with usual care (De Carvalho 2016)
        iii. N=1 with sham laser and with usual care + nimesulide (Konstantinovic 2010)
        iv. N=1 with usual care (Unlu 2008)
        v. N=1 with usual care + physical therapy (Ahmed 2022)
        vi. Studies lasted 3 weeks to 8 weeks
    b. LLT vs sham: The meta-analysis on the VAS for leg pain confirmed a significant difference in outcome with an MD of -1.90 [95% confidence interval (CI): -2.01, -1.80]; however, substantial heterogeneity was identified (I2 of 80%).
    c. LLT vs usual care: As a result of the meta-analysis on the VAS for leg pain, no significant difference in outcome was confirmed with an MD of 0.61 (95% CI: -0.35, 1.56). As a result of the meta-analysis on the VAS for LBP, no significant difference in outcome was confirmed with an MD of 0.51 (95% CI: -0.34, 1.36)
    d. LLT vs usual care + PT or nimesulide: The meta-analysis on the VAS for leg pain, a significant difference in the outcome of pain reduction was confirmed with an MD of -2.52 (95% CI: -2.65, -2.40). However, considerable heterogeneity was identified (I2 of 97%). As a result of the meta-analysis on the VAS for LBP, the MD was -1.47 (95% CI: -1.58, -1.36); however, only one study reported on this outcome. Meta-analysis of the ODI showed an MD of-4.10 (95% CI: -4.55, -3.65), confirming a significant difference in the outcome of improvement in functional disability
    e. Authors conclusions: The outcomes of using LLLT as monotherapy did not significantly differ from that using usual care. When LLLT was employed as an add-on therapy with usual care, the studies reported the possibility of significant differences in outcomes. There is limited data regarding safety assessments. As there have been few published studies on the effectiveness and safety of LLLT, we also emphasize the need to establish relevant evidence through well-designed large-scale RCTs in the future

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2) **Huang 2015** The effectiveness of low-level laser therapy for nonspecific chronic low back pain: a systematic review and meta-analysis
    a. N=7 RCTs (202 patients in LLLT group; 192 patients in placebo group)
        i. Treatment lengths not reported. Timing of outcome not reported; assumed to be short term
        ii. 3 studies used exercise therapy as control group; 4 studies did not have their control group modality reported
        iii. "Heterogeneous laser schedules and parameters"
    b. The mean VAS pain score after treatment was lower in the LLLT compared with the placebo group (WMD = -13.57 [95 % CI = -17.42, -9.72], I2 = 0 %).
        i. MCID in VAS is 10-14 mm
    c. Disability data measured by ODI after treatment were provided by four studies. The combined results showed no significant difference between LLLT and placebo groups (WMD = -2.89 [95 % CI = -7.88, 2.29], I2 = 88 %)
    d. Author conclusions: Our findings indicate that LLLT is an effective method for relieving pain in NSCLBP patients. However, there is still a lack of evidence supporting its effect on function

Arthritis

1) **Stausholm 2019**: Efficacy of low-level laser therapy on pain and disability in knee osteoarthritis: systematic review and meta-analysis of randomised placebo-controlled trials
    a. N=22 trials (N=1063 patients)
        i. 1 trial was unpublished
        ii. Mean treatment duration 3.53 weeks
        iii. Non-recommended LLLT doses applied in 9 of the trials
        iv. Comparison groups were sham laser, exercise therapy, heat packs, advice, TENS, therapeutic ultrasound
    b. Overall, pain was significantly reduced by LLLT compared with the placebo control at the end of therapy (14.23 mm VAS (95% CI 7.31 to 21.14); I2 =93%; n=816) and during follow-ups 1–12 weeks later (15.92 mm VAS (95% CI 6.47 to 25.37); I2 =93%; n=581)
        i. MCID in VAS is 10-14 mm
    c. Overall, disability was significantly reduced by LLLT compared with placebo at the end of therapy (SMD=0.59 (95% CI 0.33 to 0.86); I2 =57%; n=617) and during follow-ups 1–12 weeks later (SMD=0.66 (95% CI 0.23 to 1.09); I2 =67%; n=289)
        i. Used WOMAC disability scale, MCID 16-22%
        ii. Actual reduction in score not reported
    d. Authors conclusions: LLLT reduces pain and disability in knee osteoarthritis at 4–8 J with 785–860 nm wavelength and at 1–3 J with 904 nm wavelength per treatment spot.
2) **Lourinho 2023**: Effects of low-level laser therapy in adults with rheumatoid arthritis (RA): A systematic review and meta-analysis of controlled trials

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a. N=18 RCTs (793 patients)
    i. Comparisons included sham, laser acupuncture, reflexology, teletherapy, methotrexate, naproxen, NSAIDs
    ii. 17 studies at high risk of bias
b. LLLT vs sham
    i. Pain. Two studies, Walker et al. and Bliddal et al., evaluated pain outcome after red laser. These studies were not sufficiently homogeneous to be pooled. Walker et al. [35] observed no difference between groups for the pain outcome. According to Bliddal et al., red laser treatment is better than placebo in terms of pain relief. The quality of evidence for this outcome is very low.
    ii. Morning stiffness. Bliddal et al. evaluated morning stiffness after 10 weeks of red laser. In this study, it was not possible to detect differences between red laser and sham treatment regarding relief of morning stiffness. The quality of evidence for this outcome is very low.
    iii. Adverse events. For Bliddal et al., adverse effects were observed in 3 patients, who complained of a burning sensation in the irradiated joints—all in the laser-treated group. In these cases, the sensation disappeared within a few hours and none of the patients withdrew from the study. The quality of evidence for this outcome is very low
c. LLLT vs sham + naproxen
    i. N=1 study (24 pts)
    ii. Very uncertain evidence for pain, stiffness, or disease activity
d. LLLT vs naproxen
    i. N=1 study (22 patients)
    ii. Very uncertain evidence for pain, stiffness, or disease activity
e. Authors conclusions: Infrared laser may not be superior to sham in RA patients. There is insufficient information to support or refute the effectiveness of red laser, laser acupuncture and reflexology for treating patients with RA

Frozen shoulder/adhesive capsulitis/shoulder impingement syndrome

1) **Challoumas 2020** Comparison of Treatments for Frozen Shoulder A Systematic Review and Meta-analysis
    a. No study of LLLT met inclusion criteria

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Tendonitis/Patellar tendonitis/Achilles tendonitis/Lateral epicondylitis/plantar fasciitis

1) **Naterstad 2023** Efficacy of low-level laser therapy in patients with lower extremity tendinopathy or plantar fasciitis: systematic review and meta-analysis of randomised controlled trials
    a. N=18 RCTs
        i. N=2 patellar teniopathy
        ii. N=5 Achilles tendoinopathy
        iii. N=11 plantar faciitis
        iv. LLLT was compared with placebo in 10 trials, other interventions in 5 trials and as an adjunct intervention in 3 trials
    b. Overall, pain was significantly reduced by LLLT over any control immediately after completed therapy (13.15mm VAS (95%CI 7.82 to 18.48), I 2 =65%, n=784) and at follow-ups 4–12 weeks later (12.56mm VAS (95%CI 5.69 to 19.42), I 2 =48%, n=556)
        i. Majority of studies used VAS scale; some used the NRS scale. Unclear how these two scales were aggregated for meta-analysis
        ii. MCID in VAS is 10-14 mm
    c. Overall, the disability results immediately after completed therapy significantly favoured LLLT over any control (SMD=0.39 (95% CI 0.09 to 0.7), I 2 =30%, n=260). A disability reduction by LLLT remained significant at follow-ups 4–9 weeks after completed therapy (SMD=0.32 (95% CI 0.05 to 0.59), I 2 =4%, n=222)
        i. Variety of scales used. Unclear how authors meta-analyzed these various scales together
    d. Authors' conclusions: LLLT significantly reduces pain and disability in lower extremity tendinopathy and plantar fasciitis in the short and medium terms. Long-term data were not available. Some uncertainty about the effect size remains due to wide CIs and lack of larger trials

Submitted literature:

1) Multiple links to article abstracts
2) Clijsen 2017: included in the Washington State Department of Labor and Industries systematic review that was included in the 2019/2020 LLLT review
3) Huang 2015: included in evidence review above
4) Ince 2024: study of high intensity laser therapy
5) Simunovic 1998: >20 years since publication
6) Naeser 2011: case reports, N=2
7) Chang 2008
    a. RCT of LLLT vs sham for carpal tunnel syndrome (N=36 patients)
    b. The VAS scores were significantly lower in the laser group than the placebo group after treatment and at follow-up ($p < 0.05$). After 2 wk of treatment, no

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significant differences were found in grip strengths or for symptoms and functional assessments
    i. Actual VAS score change not reported

8) Hegedus 2009: included in Stausholm 2019 above
9) Gur 2003: >20 years since publication
10) Basaran 2025
    a. RCT of LLLT vs neuromuscular electrical nerve stimulation (NMES) vs PT for stroke patients with hemiplegic shoulder pain
    b. After treatment, statistically significant improvements were found in Brunnstrom (BRS) upper extremity, BRS Hand, BRS Hand, Barthel index, Shoulder Pain and Disability Index (SPADI), Fugl Meyer and VAS in all three groups (all $p<0.005$)
    c. Actual score ranges appear to overlap for all groups for all measurements
11) Ordahan 2023: included in de la Barra Ortiz above
12) Mahmoud 2024: cohort study of LLLT on trigger points, currently a non-covered condition under OHP. After 1/1/2027 these conditions will be on the evaluation and management only group. Cohort studies are not generally relied on by HERC due to the lack of a control group.
13) Ahmed 2022:
    a. RCT of LLLT for cervical radiculopathy (N=110).
    b. Statistically significant reduction in pain for LLLT + PT group vs PT group but actual pain measurements missing and therefore unable to determine clinical significance of change
    c. Included in Lee 2023 above
14) Larkin-Kaiser 2015: study of infrared light
15) Luo 2022: study of LLLT for athletic recovery which is not a covered condition under OHP
16) Bjordal 2008: included in Naterstad 2022 above
17) Tumilty 2010: included in Naterstad 2022 above
18) Haslerud 2015: included in Naterstad 2022 above
19) De Re Guerra 2016: studied cytokine levels with LLLT
20) Oliveira 2009: studied tissue repair processes with LLLT
21) Fillipin 2005: non-human study
22) De Jesus 2014: non-human study
23) Tsai 2014: studied protein upregulation with LLLT
24) Tsai 2012: studied protein upregulation with LLLT
25) Guerra 2013: studied protein upregulation with LLLT
26) Neves 2011: power setting study
27) Guerra 2014: non-human study
28) Casalechi 2014: non-human study
29) Ohshiro 1993: outcomes of plastic surgery
30) Simunovic: abstract only
31) Simunovic 1998: more than 20 years since publication

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Expert guidelines:

1) **American Academy of Orthopaedic Surgeons 2021** Management of Osteoarthritis of the Knee (Non-Arthroplasty) Evidence-Based Clinical Practice Guideline
    a. FDA-approved laser treatment may be used to improve pain and function in patients with knee osteoarthritis
        i. Strength of recommendation: limited
        ii. Studies were all of high intensity laser treatment, not LLLT
2) **American Academy of Orthopaedic Surgeons 2024** Management of Carpal Tunnel Syndrome Evidence-Based Clinical Practice Guideline
    a. Evidence suggests the following non-operative treatments do not improve long-term patient reported outcomes for carpal tunnel syndrome: oral corticosteroid, hyaluronic acid injection, hydro dissection, kinesiotaping, laser therapy, peloid therapy, perineural injection therapy, topical treatment, shockwave therapy, exercise, ozone injection, massage therapy, manual therapy, pulsed radiofrequency
        i. Quality of evidence: high, strength of option: limited

Other payer policies:

1) Aetna 2025: only covers LLLT for prevention of oral mucositis in patients undergoing cancer treatment
2) Cigna 2025: only covers LLLT for prevention of oral mucositis in patients undergoing cancer treatment
3) Providence 2025: only covers LLLT for prevention of oral mucositis in patients undergoing cancer treatment
4) UHC 2025: LLLT is experimental
5) Capital BCBS 2026: only covers LLLT for prevention of oral mucositis in patients undergoing cancer treatment
6) Kaiser Permanente 2020: There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies

Expert input:

None received to date

HERC staff summary:

A recent high quality evidence review by a highly trusted evidence source (NICE) found mixed evidence that LLLT was beneficial for chronic pain in terms of pain level or quality of life. Evidence was found to be insufficient to add coverage for the NHS. The NICE review

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also noted that RCTs compared LLLT to sham laser rather than standard of care (physical therapy, etc.) A recent meta-analysis of LLLT for low back pain compared to usual care did not find a significant difference in pain. Similarly, a recent systematic review and meta-analysis for LLT for frozen shoulder found no difference in comparison to standard physical therapy. The literature on LLLT for arthritis conditions generally found short term, if any decrease in pain or disability with LLT compared to any comparison. A poorly conducted meta-analysis of LLLT for various tendinopathies found short term clinically significant improvement in pain and an improvement in function of unclear clinical significance.

No private payer surveyed is covering LLLT for any indication other than prevention of oral mucositis in patients undergoing cancer treatment. Expert guidelines do not recommend LLLT for knee osteoarthritis and carpal tunnel syndrome.

Based on the literature that finds at most small, short-term improvements in pain but not function with LLLT for a range of painful conditions compared to currently covered treatments such as physical therapy, HERC staff does not recommend adding any additional indications for LLLT beyond the current coverage in cancer treatment and recommends removing 0552T, since this service now has a HCPCS code.

HERC staff recommendation:

1) Remove CPT 0552T (Low-level laser therapy, dynamic photonic and dynamic thermokinetic energies, provided by a physician or other qualified health care professional) from all lines on the Prioritized List
    a. Advise Medicaid to place on the Excluded file
        i. in general, category III CPT codes (“T”) codes are excluded by rule if level 1 CPT or HCPCS codes are available
2) Make no other changes to the Prioritized List

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National Institute for Health and Care Excellence

Final

Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain

[H] Evidence review for electrical physical modalities for chronic primary pain

NICE guideline NG193

Intervention evidence review underpinning recommendation 1.2.6 and the research recommendations in the NICE guideline

April 2021

This evidence review was developed by the National Guideline Centre based at the Royal College of Physicians

NICE accredited
www.nice.org.uk/accreditation

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and, where appropriate, their carer or guardian.

Local commissioners and providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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ISBN
978-1-4731-4066-0

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1 Electrical physical modalities for chronic primary pain

1.1 Review question: What is the clinical and cost effectiveness of electrical physical modalities for the management of chronic primary pain?

1.2 Introduction

Electrical physical modalities of treatment have been used therapeutically for many centuries. Reports of their use have been found in ancient writings, and include techniques still in use today, such as use of heat, cold and electricity.

Contemporary electrical physical modalities are diverse and include treatments regularly used for pain management and self-management. The list below is not exhaustive:

- Thermal modalities, often in the form of reusable hot or cold packs applied to the skin.
- Therapeutic ultrasound, using a probe that generates ultrasonic waves from electricity and delivers them into the tissues.
- Interferential therapy, using medium frequency electrical currents delivered with multiple electrodes over the affected areas.
- Pulsed Shortwave Diathermy, using high frequency electromagnetic energy delivered using electrical coils, to heat the tissues.
- Low level laser therapy (LLLT), involving the non-invasive application of a single wavelength of light to the skin over the injured area using a probe.
- Neuromuscular Electrical Stimulation (NMES), using superficial electrodes to target motor fibres.

For many of these techniques, a mechanism of action is currently unclear. Mechanisms may include activation of pain gate mechanisms, stimulation of cellular activity related to healing and repair, delivery of mechanical forces to alter the physical properties of tissues, alteration of blood flow and reduction of inflammation.

While many of these interventions are popular choices for the self-management of painful conditions, their role in clinical practice is much less clear. This evidence review therefore intends to explore the effectiveness of these interventions for chronic primary pain.

1.3 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	People, aged 16 years and over, with chronic primary pain (whose pain management is not addressed by existing NICE guidance) (chronic widespread pain, complex regional pain syndrome, chronic visceral pain, chronic orofacial pain, chronic primary musculoskeletal pain other than orofacial) Chronic pain in one or more anatomical regions that is characterized by significant emotional distress (anxiety, anger/frustration or depressed mood) and functional disability (interference in daily life activities and reduced participation in social roles). The diagnosis is appropriate independently of identified biological or psychological contributors unless another diagnosis would better account for the presenting symptoms.

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Interventions	Interventions: • Transcutaneous electrical nerve stimulation (TENS) • Percutaneous electrical nerve stimulation (PENS) • Interferential therapy • Laser therapy • Therapeutic ultrasound • Transcranial magnetic stimulation (TMS) • Transcranial direct current stimulation (TDCS).
Comparisons	Comparators: • Each other • Placebo/sham • Usual care • Physical therapies in this guideline.
Outcomes	Outcomes will be extracted at the longest time point up to 3 months and at the longest time point after 3 months. CRITICAL: • Pain reduction (any validated scale) • Health related quality of life (including meaningful activity) • Physical function (5 minute walk, sit to stand, Roland Morris Disability Questionnaire, Oswestry Disability Index, Canadian Occupational Performance Measure) • Psychological distress (depression/anxiety) (preferably Hospital Anxiety and Depression Scale) • Pain interference (brief pain inventory interference subscale) • Pain self-efficacy (pain self-efficacy questionnaire). IMPORTANT: • Use of healthcare services • Sleep • Discontinuation.
Study design	Randomised controlled trials (RCTs) and systematic reviews of RCTs. Cross-over RCTs will be considered if no non-cross-over RCT evidence is identified.

1.4 Clinical evidence

1.4.1 Included studies

34 studies were included in the review; [19, 28, 31, 37, 53, 61, 77, 78, 92, 94, 96, 101, 117, 120, 129, 137, 147, 167, 176, 185, 205, 241, 250, 274, 289, 314, 325, 329, 339, 345, 346, 354, 375] these are summarised in Table 2 below.

Evidence from these studies is summarised in the clinical evidence summary tables below (Table 3, Table 4, Table 5, Table 6, Table 7, Table 8, Table 9). See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix F.

1.4.2 Excluded studies

A Cochrane review of TENS for fibromyalgia was identified (Johnson 2017 [174]), and references were cross-checked with this review. However, the review was not included because it deviated from the protocol of this review as it included crossover studies and studies that compared to other interventions, for example pharmacological.

See the excluded studies list in appendix I.

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1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Altan 2005[19]	2 week interventions **Intervention 1: Laser therapy (n=26)** **Number of sessions**: 10 (over 2 weeks) **Duration of sessions**: Not reported (2mins per trigger point) **Delivered by**: Not reported **Details**: Laser applied over each trigger point for 2 minutes, frequency 1000Hz frequency, 904nm wavelength, maximum power 50W. Participants instructed to perform daily isometric exercises and stretching at home **Intervention 2: Sham laser therapy (n=27)** Details: identical treatment but laser not turned on.	Myofascial pain (n=53) Mean age: 43.4 (2.26) years Duration of pain: 4.56 (1.26) years	At 2 weeks post-intervention and 3 months (follow up, including 2-week intervention): • Pain reduction	Myofascial pain definition: localised pain and taut bands in the neck for a minimum of the previous 3 months, tenderness in the cervical trigger points.
Arbabi-Kalati 2015[28]	2 week interventions **Intervention 1: Laser therapy (n=10)** **Number of sessions**: 4 (over 2 weeks) **Duration**: Estimated 1.5 minutes (laser applied for 10s to 10 areas) **Delivered by:** Not reported **Details**: 630nm wavelength, 30mW power, low level laser therapy applied to oral mucosa. **Intervention 2: Sham laser therapy (n=10)** **Details**: Identical treatment but laser not turned on.	Burning mouth syndrome (n=20) Mean age: 46.9 (4.95) years Duration of pain: 14.45 (6-36) years	At 2 weeks (post-intervention): • Quality of life • Pain reduction	Burning mouth syndrome defined as burning sensation in the oral cavity for at least 4 months without any identified causes.

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Study	Intervention and comparison	Population	Outcomes	Comments
Armagan 2006[31]	10 days interventions **Intervention 1: Laser therapy (n=16)** **Number of sessions:** 10 (over 10 days) **Duration:** 1 minute per tender point **Delivered by:** Physician **Details**: 830nm wavelength, 50mW power, laser diameter 1mm, 1 minute per tender point at 2 joules per tender point. **Intervention 2: Sham laser therapy (n=16)** **Details:** Identical treatment but laser not turned on.	Fibromyalgia (n=32) Mean age: 38.25 (5.36) years Duration of pain: 5.8 (3.2) years All women	At 10 days (post-intervention) and 6 months (follow up, including 10 day intervention): • Quality of life	
Bardellini 2019[37]	10 weeks interventions **Intervention 1: Laser therapy (n=45)** **Number of sessions:** 10 (over 10 weeks) **Duration:** unclear **Delivered by:** Dentist **Details:** K Laser Cube 3® irradiated the most painful areas in the oral cavity, with discontinuous combined wavelengths between 660-970 nm, medium power 3.2 W (6.4 W pulsed at 50%), treatment time 3'51", frequency 1-20000Hz, spot size 1cm². **Intervention 2:** Sham laser therapy (n=45) **Details:** The device was turned on but the hand piece did not work.	Burning mouth syndrome (n=90) Mean age: laser group: 60.31 (9.78) years Duration of pain: inclusion criteria specified >6 months, mean duration not reported All female	At 10 weeks (post-intervention) and 14 weeks (1 month follow up): • Quality of life	
Boyer 2014[53]	10 week interventions **Intervention 1: TMS (n=19)** **Number of sessions:** 14 (over 10 weeks) **Duration:** Not reported	Fibromyalgia (n=38) Mean age: 48.5 (10.5) years	At 10 weeks (post-intervention): • Quality of life • Psychological distress	Inclusion criteria: score of at least 4 on the BPI average pain intensity scale

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Study	Intervention and comparison	Population	Outcomes	Comments
	Delivered by: Not reported **Details:** No further details available **Intervention 2: Sham TMS (n=19)** **Details:** Identical treatment but a sham coil used that emitted a similar sound to the active coil	Duration of pain: 3.7 (4.2) years		
Brietzke 2019 [54]	3 month interventions **Intervention 1: TDCS (n=10)** **Number of sessions:** 60 sessions over 12 weeks **Duration: approx.** 30 minutes **Delivered by:** Self-administered **Details:** 2mA current applied through electrodes over the left dorsolateral prefrontal cortex (DLPFC) attached to cap (caps individually fitted to each participant). **Intervention 2: Sham TDCS (n=10)** **Details:** Identical treatment but no electrical stimulation	Fibromyalgia (n=40) Mean age 49.1 years Duration of pain: 6.2 years	At 3 months (post-intervention) • Psychological distress • Sleep	Intervention self-administered at home. The electrode position was accurate for the subjects. To avoid incorrect placement of the electrodes, the anode was painted red and cathode black (although equipment was already set up – participant could not change any part of it).
Carretero 2009 [61]	4 week interventions **Intervention 1: TMS (n=14)** **Number of sessions:** 20 sessions over 4 weeks **Duration: approx.** 30 minutes **Delivered by:** Not reported **Details:** Butterfly coil used, 20 trains at 110% of motor threshold for 60s at 1Hz and a 45s interval between trains. Stimulation area right dorsolateral prefrontal area (total of 1,200 pulses per session) **Intervention 2: Sham TMS (n=12)**	Fibromyalgia (n=26) Mean age: 51.2 (5.3) years Duration of pain not stated	At 3 months (follow up, including 4 week intervention): • Pain reduction	

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Study	Intervention and comparison	Population	Outcomes	Comments
	Details: Identical treatment but coil placed perpendicular to the cranium (the magnetic field did not significantly penetrate the brain)			
Chow 2004[77]	7 week interventions **Intervention 1: Laser therapy (n=10)** **Number of sessions: 7** (over 7 weeks) **Duration:** 30 minutes **Delivered by:** Not reported **Details:** 830nm, 15mm laser length and 3mm width, 300mW power, applied 30s per point or until area became less tender **Intervention 2: Sham laser therapy (n=10)** **Details:** Identical treatment but laser did not emit a beam	Chronic neck pain (n=20) Mean age: 57.7(10.9) years Duration of pain: 13.3 years (SE 2.48)	At 3 months (follow up, including 7 week intervention): • Quality of life • Pain reduction	Participants that had previously received laser therapy were excluded (other than laser acupuncture). People with work related or third party injuries in which litigation or compensation were still current were excluded.
Chow 2006[78]	7 week interventions **Intervention 1: Laser therapy (n=45)** **Number of sessions:** 7 (over 7 weeks) **Duration:** 30 minutes **Delivered by:** Not reported **Details:** 830nm wavelength, 300mW, each tender point treated for 30 seconds, up to 50 points treated **Intervention 2: Sham laser (n=45)** **Details:** Identical treatment but device did not emit laser (although did emit sound)	Chronic neck pain (n=90) Mean age: 56 (12.8) years Duration of pain: 15 (12.6) years	At 3 months (follow up, including 7 week intervention): • Quality of life • Pain reduction • Discontinuation	People with work related or third party injuries in which litigation or compensation were still current were excluded.
da Cunha 2008[92]	4 week interventions **Intervention 1: Laser therapy (n=20)** **Number of sessions:** 4 (over 4 weeks)	Temporomandibular disorder (n=40)	At 4 weeks (post-intervention) • Pain reduction	Temporomandibular disorder diagnosed based on complete clinical examination, including patient's

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Study	Intervention and comparison	Population	Outcomes	Comments
	Duration: Not reported (each area irradiated for 20s) **Delivered by:** Not reported **Details:** 830nm wavelength, 500mW output, each area irradiated for 20s **Intervention 2: Sham laser (n=20)** **Details:** Identical treatment but without energy output	Mean age: 43.3 years Duration of pain: Not stated		history, at the Center of Occlusion and Temporomandibular Disorder of the Dental School of Sao Paulo State University (UNESP).
Dailey 2019 [94]	4 week interventions **Intervention 1: TENS (n=103)** **Number of sessions:** Not reported **Duration:** at least 2 hours/day during activity **Delivered by:** self-administered (first application delivered in clinic) **Details:** EMPI-Select TENS (DJO Global, Vista, CA) delivered through butterfly electrodes placed at the cervicothoracic junction and lower back. Active-TENS parameters were asymmetrical, biphasic waveform with a modulating frequency (2-125 Hz), pulse duration 200µ sec, and highest tolerable stimulation intensity. Active-TENS was sent home with participants with an instruction manual developed by study personnel. **Intervention 2: sham TENS (n=99)** **Details:** delivered current for 45s ramping down to 0 in the last 15s and the appearance was identical to the active unit. **Intervention 3: Usual care (n=99)** **Details:** used a mock-TENS during visits to blind Outcome-Assessors with electrodes that were attached to a TENS unit that provided no current intensity.	Fibromyalgia (n=301) Mean age: 46.8 (13.06) years Duration of pain median (range): 7 (2-15) years All female	At 4 weeks (post intervention): • Quality of life • Pain reduction • Physical function • Psychological distress • Pain interference • Pain self-efficacy	All participants continued current treatments prescribed by their health care provider and were asked not to change medications during the study.

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Study	Intervention and comparison	Population	Outcomes	Comments
Dall'Agnol 2014[96]	10 day interventions **Intervention 1: TMS (n=12)** **Number of sessions:** 10 (over 10 days) **Duration:** Not reported **Delivered by:** Not reported **Details:** Figure 8 coil placed over left motor cortex, trains consisted of 16 series of 10-s pulses at 10Hz, interval of 26s between trains. Intensity was 80% of resting motor threshold **Intervention 2: sham TMS (n=12)** **Details:** Identical treatment but inactive sham coil used (identical sounds and sensations but no brain stimulation)	Myofascial pain (n=24) Mean age: 45.43 (12.86) years Duration of pain: Not stated All women	At 3 months (follow up, including 10 day intervention): • Pain reduction	Number of sessions stated to be 10, but duration of study not specified. Myofascial pain defined as reduced quality of life due to regional pain, decreased range of motion, stiffness in muscles, presence of trigger points, taut bands, tender points, palpable nodules and pain. Must have score of more than 4 on the neuropathic pain diagnostic questionnaire.
Del Vecchio 2019 [101]	1 week interventions **Laser therapy (n=30)** **Number of sessions:** 14 (over 7 days; delivered at home) **Duration:** 1 week **Delivered by:** Self-administered (first application delivered in clinic) **Details:** Laser with 808nm wavelength, 5J/min, 250mW and 15KHz for 8 minutes, for a total of 40J applied directly to each painful area. **Sham laser therapy (n=30)** **Details:** identical device with beam and sound but devoid of therapeutic diode source.	Temporomandibular joint disorder-related pain (n=60) Mean age: 42.55 (14.842) years Duration of pain not specified (minimum duration 6 months)	At 1 week (post-intervention): • Pain reduction	The inclusion criteria were: presence of pain in the joint area and/or radiating to the face, jaw, or neck for at least six months; reduced mouth opening or jaw locks; painful clicking, popping or grating when opening or closing the mouth; occlusal changes; no muscle

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Study	Intervention and comparison	Population	Outcomes	Comments
				tenderness at palpation; and no drug consumption for at least three weeks before treatment. The disorder was diagnosed by clinical and radiological examinations and according to the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) Axis I and Axis II
Esenyel 2000[117]	10 day interventions **Intervention 1: Ultrasound (n=36)** **Number of sessions:** 10 (over 10 days) **Duration:** 6 mins per trigger point **Delivered by:** Not reported **Details:** 1.5Wcm^2 applied to each trigger point for 6 minutes. Neck exercises also advised **Intervention 2: Usual care (n=40)** **Details:** Usual care as well as advice on neck stretching exercises	Myofascial pain (n=76) Mean age: 30 (7.7) years Duration of pain: ranged 6 months to 7 years	At 3 months (follow up, including 10 day intervention): • Pain reduction	Myofascial pain followed Travel and Simons criteria for active myofascial trigger points in the upper trapezius muscles
Fagerlund 2015[120]	5 day interventions **Intervention 1: TDCS (n=25)** **Number of sessions:** 5 (over 5 days) **Duration:** 20 minutes	Fibromyalgia (n=50) Mean age: 48.6 (9.4) years	At 4 weeks (follow up, including 5 day intervention): • Quality of life • Pain reduction	

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Study	Intervention and comparison	Population	Outcomes	Comments
	Delivered by: Not reported **Details:** Intensity 2mA, anode placed on C3 and cathode placed on contralateral supraorbital area **Intervention 2: Sham TDCS (n=25)** **Details:** Identical treatment but stimulation faded in for 30s, then terminated by 5s fade out (to mimic skin sensation of active treatment with insufficient duration to induce cortical excitability)	Duration of pain: 18.1 (9) years	• Psychological distress	
Fregni 2006[129]	1 week interventions *Note: interventions 1 and 2 pooled in the analysis.* **Intervention 1: TDCS (DLPFC) (n=11)** **Number of sessions:** 5 (over 5 days) **Duration:** 20mins **Delivered by:** Not reported **Details:** Current transferred by pair of saline soaked sponge electrodes, max output 10mA, anode on left DLPFC brain area, constant current of 2mA applied for 20mins **Intervention 2: TDCS (motor cortex [M1]) (n=11)** **Number of sessions:** 5 (over 5 days) **Duration:** 20mins **Delivered by:** Not reported **Details:** Current transferred by pair of saline soaked sponge electrodes, max output 10mA, anode on primary motor cortex brain area, constant current of 2mA applied for 20mins **Intervention 3: Sham TDCS (n=10)** **Details:** Identical treatment but with sham stimulation of the primary motor cortex (stimulator turned off after	Fibromyalgia (n=32) Mean age: 53.2 (8.97) years Duration of pain: 8.4 (9.3) years All women	At 3 weeks (follow up, including 1 week intervention): • Psychological distress	Inclusion criteria: score of at least 4 on the VAS and at least 30 on the total tender point score.

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Study	Intervention and comparison	Population	Outcomes	Comments
	30s to mimic sensation but no current received after this)			
Gokyildiz 2012[137]	12 week interventions **Intervention 1: PENS (n=13)** **Number of sessions:** 12 (over 3 months) **Duration:** 30mins **Delivered by:** Not reported **Details:** Percutaneous tibial nerve stimulation, applied using a needle set and stimulator with 9-volt batteries and current between 0.5-10mA, 20Hz frequency. Needle inserted 3-4cm above inner malleolus and electrode placed on inner side of the heel. Current adjusted based on tolerance **Intervention 2: Usual care (n=13)** **Details:** Routine usual care, no further details	Chronic pelvic pain (n=26) Mean age: Not reported Duration of pain: Not reported (minimum duration 6 months)	At 3 months (post-intervention): • Quality of life • Pain reduction	Score of at least 5 on VAS. Cessation of analgesics at least 2 weeks before treatment, and physiotherapy or electrotherapy at least 3 months before treatment.
Gur 2002[147]	2 week interventions **Intervention 1: Laser therapy (n=25)** **Number of sessions:** 14 (over 2 weeks) **Duration:** Not reported (3 mins per tender point) **Delivered by:** Physical therapists **Details:** 904nm wavelength, 20W max per pulse, 200ns max pulse duration, 2.8Hz pulse frequency, 11.2mW average power, 3 mins at each tender point **Intervention 2: Sham laser therapy (n=25)** **Details:** Identical treatment but no laser beam emitted	Fibromyalgia (n=50) Mean age: 29.44 (6.6) years Duration of pain: 4.74 (3.98) years	At 2 weeks (post-intervention): • Pain reduction	All participants discontinued medications at least 1 month prior to treatment
Jales 2015[167]	10 week interventions **Intervention 1: TDCS (n=10)**	Fibromyalgia (n=20)	At 10 weeks (post-intervention): • Quality of life	

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Study	Intervention and comparison	Population	Outcomes	Comments
	Number of sessions: 10 (over 10 weeks) **Duration:** 20 minutes **Delivered by:** Not reported **Details:** 2 electrodes placed on scalp, 1mA impulse applied (anode over m1, cathode over contralateral supraorbital region). Applied for 20 mins **Intervention 2: Sham TDCS (n=10)** **Details:** Identical treatment but device not turned on	Mean age: 46.4 (10.615) years Duration of pain: Not reported All women	• Pain reduction	
Kabay 2009[176]	12 week interventions **Intervention 1: PENS (n=45)** **Number of sessions:** 12 (over 3 months) **Duration:** 30 mins **Delivered by:** Not reported **Details:** Percutaneous posterior tibial nerve stimulation, needle inserted 5cm from medial malleolus and electrode placed on same leg. Electrical stimulation applied with 200us pulses, rate of Hz, intensity level just below motor threshold. Amplitude set at maximum tolerable (using 1.5x threshold for evoking plantar flexion) **Intervention 2: Sham PENS (n=44)** **Details:** Identical treatment but electrical stimulation not applied.	Pelvic pain (n=89) Mean age: 37.7(7.4) years Duration of pain: 4.5 (6.1) years	At 3 months (post-intervention): • Quality of life • Pain reduction	Diagnosis of category IIIB CP/CPPS
Khedr 2017[185]	2 week interventions **Intervention 1: TDCS (n=20)** **Number of sessions:** 10 (over 2 weeks) **Duration:** 20mins **Delivered by:** Not reported	Fibromyalgia (n=40) Mean age: 32.3 (10.9) years Duration of pain: 6.1 (2.5) years	At 8 weeks (follow up, including 2 week intervention): • Pain reduction • Psychological distress	Score of at least 4 on VAS pain scale

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Study	Intervention and comparison	Population	Outcomes	Comments
	Details: 2mA, anodal electrode on left M1 over C3, reference electrode over contralateral arm. **Intervention 2: Sham TDCS (n=20)** **Details:** Identical treatment but current applied for 30s only at the beginning and at the end of the session.			
Lee 2012[205]	10 day interventions Note: intervention 1 and 2 pooled in the analysis **Intervention 1: TMS (low frequency) (n=7)** **Number of sessions:** 10 (over 10 days) **Duration:** Not reported **Delivered by:** Physiatrist **Details:** Figure 8 coil, applied to right M1 (at the DLPFC), 1Hz, 110% intensity of resting motor threshold, 800 stimuli of each train and 2 trains with 60s of inter-train interval and a total of 1600 stimuli per session. **Intervention 2: TMS (high frequency) (n=8)** **Details:** Identical treatment to intervention 2 but 80% of resting motor threshold, 2000 stimuli per session. **Intervention 3: Sham TMS (n=7)** **Details:** Identical treatment but coil angle was 90% perpendicular to skull (magnetic field did not penetrate the brain).	Fibromyalgia (n=22) Mean age: 47.2(6.2) years Duration of pain: 44.7(10.3) years All women	At 6 weeks (follow up, including 10 day intervention): • Quality of life • Pain reduction • Psychological distress • Discontinuation	Inclusion criteria: pain for at least 24 months
Mhalla 2011[241]	21 week interventions **Intervention 1: TMS (n=20)** **Number of sessions:** 14 (over 21 weeks) **Duration:** Not reported **Delivered by:** Not reported	Fibromyalgia (n=40) Mean age: 50.2 (10.8) years	At 25 weeks (follow up, including 21 week intervention): • Quality of life • Psychological distress • Pain interference	Score of at least 4 on BPI pain scale.

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Study	Intervention and comparison	Population	Outcomes	Comments
	Details: figure 8 coil, positioned to induce current in the anterior posterior direction, 15 series of 10s pulses, frequency 10Hz, interval of 50s between each train, total of 1500 pulses per session (stimulation intensity 80% of resting motor threshold) **Intervention 2: Sham TMS (n=20)** **Details:** Identical treatment but sham coil used	Duration of pain: 13.55 (12.4) years All women		
Murina 2008[250]	10 week interventions **Intervention 1: TENS (n=20)** **Number of sessions:** 20 (over 10 weeks) **Duration:** 15-30 mins **Delivered by:** Not reported **Details:** Electrical stimulation via vaginal probe 20mm in diameter, 110mm in length. Frequencies of 10 and 50Hz at 15min intervals. **Intervention 2: Sham TENS (n=20)** **Details:** Identical treatment but nonactive stimulation (2Hz, pulse duration 2ms followed by 15min pause).	Vestibulodynia (n=40) Mean age: 28 (21-44) years Duration of pain: 15 month (range 7-48 months) All women	At 10 weeks (post-intervention): • Pain reduction • Discontinuation At 22 weeks (including 10 week intervention) • Pain reduction	
Panton 2013[274]	4 week interventions **Intervention 1: Laser therapy (n=23)** **Number of sessions:** 8 (over 4 weeks) **Duration:** 15 mins **Delivered by:** Not reported **Details:** Laser applied to 7 tender points with dual wavelength laser (20% 810nm and 80% 980nm), heat also applied via warm air, each point treated for 60s for total of 600J per point **Intervention 2: Sham laser (n=18)**	Fibromyalgia (n=41) Mean age: 53 (11.5) years Duration of pain: 10.5 (7.5) years All women	At 4 weeks (post-intervention): • Quality of life • Pain reduction • Discontinuation	Participants received $100 for participating in the study.

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Study	Intervention and comparison	Population	Outcomes	Comments
	Details: Identical treatment but laser not turned on			
Rohlig 2011[289]	3 week interventions **Intervention 1: Laser therapy (n=20)** **Number of sessions:** 10 (over 3 weeks) **Duration:** Not reported (10s per tender point) **Delivered by:** Not reported **Details:** 820nm wavelength, beam diameter 6mm, 8J/cm2 to each tender point **Intervention 2: Sham laser therapy (n=20)** **Details:** Identical treatment but laser not turned on	Temporomandibular disorder (n=40) Mean age: 42.5 (2.3) years Duration of pain: 10.75 (2.9) years	At 3 weeks (post-intervention): • Pain reduction	Presence of signs and symptoms of TMD of myogenic origin according to the research diagnostic criteria for TMD.
Short 2011[314]	2 week interventions **Intervention 1: TMS (n=10)** **Number of sessions:** 10 (over 2 weeks) **Duration:** 20 mins **Delivered by:** Not reported **Details:** Applied to left prefrontal cortex, 10Hz, 5s train duration, intensity 120% resting motor threshold **Intervention 2: Sham TMS (n=10)** **Details:** Identical treatment but sham TMS coil used	Fibromyalgia (n=20) Mean age: 53 (13.53) years Duration of pain: 11.1 (10.36) years	At 4 weeks (follow up, including 2 week intervention): • Quality of life • Pain reduction • Physical function • Psychological distress	
Spanemberg 2015[325]	3 week interventions *Note: intervention 1 and 2 pooled in analysis* **Intervention 1: Laser therapy (infrared) (n=20)** **Number of sessions:** 9 (over 3 weeks) **Duration:** M50s per point **Delivered by:** Not reported	Burning mouth syndrome (n=58) Mean age: 61.9 (8.76) years	At 8 weeks (follow up, including 3 week intervention): • Quality of life • Pain reduction	Burning or pain in the oral mucosa for at least 6 months with clinically normal mucosa.

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Study	Intervention and comparison	Population	Outcomes	Comments
	Details: 830nm wavelength, 100mW output, continuous emissions, 5J energy per point, 50s per point. **Intervention 2: Laser therapy (red laser) (n=19)** **Details:** Identical treatment but red laser at 685nm wavelength, 2J per point, 35mQ output power **Intervention 3: Sham laser therapy (n=19)** **Details:** Identical treatment but sham laser	Duration of pain: Not reported (minimum 6 months)		
Sugaya 2016[329]	2 week interventions **Intervention 1: Laser therapy (n=15)** **Number of sessions:** 4 (over 2 weeks) **Duration:** Not reported **Delivered by:** Not reported **Details:** 6J/cm2, applied to entire area affected by burning sensation. No further details. **Intervention 2: Sham laser therapy (n=15)** **Details:** Identical treatment but no laser energy delivered (machine still appeared active)	Burning mouth syndrome (n=30) Mean age: 59.7(29-83) years Duration of pain: 31.7 months (range 6 to 192)	At 3 months and 16 weeks (follow up, including 2 week intervention): • Pain reduction	Exclusion criteria: Clinical alterations in the oral mucosa potentially associated with the burning symptoms
Tekin 2014[339]	10 day interventions **Intervention 1: TMS (n=27)** **Number of sessions:** 10 (over 10 days) **Duration:** Not reported **Delivered by:** Psychiatry physician **Details:** Figure 8 coil, 30 sequential series each for 5s at 10Hz, at 100% of motor threshold, 12s interval between series	Fibromyalgia (n=52) Mean age: 44.4 (8.1) years Duration of pain: 12.1 (6.47) years	At 10 weeks (post-intervention): • Quality of life • Pain reduction • Psychological distress • Discontinuation	No analgesic use for at least 1 month prior to treatment

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Study	Intervention and comparison	Population	Outcomes	Comments
	Intervention 2: Sham TMS (n=25) **Details:** Identical treatment but placebo sham coil used.			
Umezaki 2016[345]	10 day interventions **Intervention 1: TMS (n=14)** **Number of sessions:** 10 (over 10 days) **Duration:** Not reported **Delivered by:** Not reported **Details:** Figure 8 coil, positioned around primary motor cortex, 10Hz frequency, 5s pulse train duration, intensity 110% of resting motor threshold, total 30,000 pulses **Intervention 2: Sham TMS (n=12)** **Details:** Identical treatment but coil was shielded so actual stimulation did not occur.	Burning mouth syndrome (n=26) Mean age: 63.85 (9.56) years Duration of pain: 63.42 (65.51) years	At 8 weeks (follow up, including 10 day intervention): • Pain reduction • Discontinuation (at 1 week)	Diagnosis of BMS confirmed by (1) daily and deep bilateral burning sensation of the oral mucosa, burning sensation for at least 4-56 months, constant intensity or increasing intensity during the day, no worsening but possible improvement on eating or drinking, no interference with sleep and normal appearing oral mucosa.
Valenzuela 2017[346]	4 week interventions *Note: intervention 1 and 2 pooled in the analysis* **Intervention 1: Laser therapy (low intensity) (n=16)** **Number of sessions:** 4 (over 4 weeks) **Duration:** Not reported **Delivered by:** Not reported **Details:** 815nm wavelength, 1W output, 4s per point, 4J, applied intra-orally and spot sizes of 0.03cm^3. **Intervention 2: Laser therapy (high intensity) (n=16)** **Details:** Identical treatment but 6J energy over 6s **Intervention 3: Sham laser therapy (n=12)**	Burning mouth syndrome (n=44) Mean age: 65.5 (10.6) years Duration of pain: Not reported	At 4 weeks (post-intervention): • Quality of life • Pain reduction • Psychological distress	Burning mouth syndrome diagnosis according to international classification of headaches

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Study	Intervention and comparison	Population	Outcomes	Comments
	Details: Identical treatment but laser turned off			
Venancio 2005[354]	3 week interventions **Intervention 1: Laser therapy (n=15)** **Number of sessions:** 6 (over 3 weeks) **Duration:** Not reported **Delivered by:** Not reported **Details:** 780nm wavelength, 30mW output, 10s duration at each point **Intervention 2: Sham laser therapy (n=15)** **Details:** Identical treatment but laser device not turned on	Temporomandibular disorder (n=30) Mean age: 36.25 (13-63) years Duration of pain: 44.8 months (range 6-120 months)	At 8 weeks (follow up, including 3 week intervention): • Pain reduction	TMD diagnosis according to criteria of the American Academy of Orofacial pain
Yagci 2014[375]	2 week interventions **Intervention 1: TMS (n=14)** **Number of sessions:** 10 (over 2 weeks) **Duration:** Not reported **Delivered by:** Not reported **Details:** Stimulation of motor cortex area, applied stimulation at 90% of motor threshold for 60s at 1Hz and 45s intervals between trains (1200 pulses in total each session) **Intervention 2: Sham TMS (n=14)** **Details:** Identical treatment but sham coil used	Fibromyalgia (n=28) Mean age: 44.9(8.6) years Duration of pain: 53.5 (29.8) months All women	At 3 months (follow up, including 2 week intervention): • Quality of life • Pain reduction • Psychological distress	

See appendix D for full evidence tables.

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1.4.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: Laser therapy versus sham laser therapy

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Laser therapy versus sham laser therapy (95% CI)
Quality of life at ≤3 months (Oral health impact profile, FIQ, high is poor outcome, final values)	276 (6 studies) 2 weeks-3 months	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, inconsistency, imprecision		-	The mean quality of life score in the intervention groups was 0.68 standard deviations lower (1.1 to 0.25 lower)
Quality of life at ≤3 months (SF-36 physical component summary score, 0-100, high is good outcome, change scores)	110 (2 studies) 3 months	⊕⊕⊕⊖ MODERATE1 due to imprecision		The mean quality of life change score in the control groups was 1.26	The mean quality of life score in the intervention groups was 2.09 higher (0.91 lower to 5.09 higher)
Quality of life at ≤3 months (SF-36 mental component summary score, 0-100, high is good outcome, change scores)	110 (2 studies) 3 months	⊕⊕⊖⊖ LOW1,2 due to inconsistency, imprecision		The mean quality of life change score in the control groups was 2.7	The mean quality of life score in the intervention groups was 0.74 lower (5.35 lower to 3.87 higher)
Quality of life at >3 months (FIQ, Oral health impact profile, high is poor outcome, final values)	117 (2 studies) 14-24 weeks	⊕⊕⊖⊖ LOW1,3 due to risk of bias, imprecision		-	The mean quality of life score in the intervention groups was 0.78 standard deviations lower (1.16 to 0.4 lower)
Pain reduction at ≤3 months (VAS, NRS, FIQ pain scale, high is poor outcome, 0-10, final values and change scores)	558 (13 studies) 1 week-3 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, inconsistency, imprecision		The mean pain reduction score in the control groups was 4.97	The mean pain reduction score in the intervention groups was 1.42 lower (2.12 to 0.73 lower)
Pain reduction at >3 months (VAS, high is poor outcome, 0-10, final values)	71 (2 studies) 14-16 weeks	⊕⊕⊕⊖ MODERATE1 due to imprecision		The mean pain reduction score in the control groups was 2.8	The mean pain reduction score in the intervention groups was 0.6 lower (0.91 to 0.3 lower)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Laser therapy versus sham laser therapy (95% CI)
Psychological distress at ≤3 months (Hospital anxiety and depression rating scale, anxiety subscale, 0-21, high is poor outcome, final values)	44 (1 study) 4 weeks	⊕⊕⊖⊖ LOW1,3 due to risk of bias, imprecision		The mean psychological distress score in the control groups was 10.33	The mean psychological score in the intervention groups was 0.83 higher (1.52 lower to 3.18 higher)
Psychological distress at ≤3 months (Hospital anxiety and depression rating scale, depression subscale, 0-21, high is poor outcome, final values)	48 (1 study) 4 weeks	⊕⊕⊖⊖ LOW1,3 due to risk of bias, imprecision		The mean psychological distress score in the control groups was 7.25	The mean psychological distress score in the intervention groups was 1.29 higher (1.39 lower to 3.96 higher)
Discontinuation at ≤3 months	90 (1 study) 3 months	⊕⊕⊕⊖ LOW1 due to imprecision	RR 0.67 (0.12 to 3.8)	67 per 1000	22 fewer per 1000 (from 59 fewer to 188 more)

1 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
2 Downgraded for heterogeneity, unexplained by subgroup analysis
3 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 4: Clinical evidence summary: TMS versus sham TMS

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with TMS versus sham TMS (95% CI)
Quality of life at ≤3 months (SF-36 physical summary score, 0-100, high is good outcome, change scores)	29 (1 study) 10 weeks	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean quality of life change score in the control groups was 0.4	The mean quality of life score in the intervention groups was 1 higher (4.12 lower to 6.12 higher)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with TMS versus sham TMS (95% CI)
Quality of life at ≤3 months (SF-36 mental summary score, 0-100, high is good outcome, change scores)	29 (1 study) 10 weeks	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean quality of life change score in the control groups was -1.6	The mean quality of score in the intervention groups was 6.6 higher (1.26 to 11.94 higher)
Quality of life at ≤3 months (WHOQOL-BREF physical domain, 4-20, high is good outcome, final values)	51 (1 study) 2 weeks	⊕⊕⊕⊕ HIGH		The mean quality of life score in the control groups was 11.33	The mean quality of score in the intervention groups was 3.27 higher (1.79 to 4.75 higher)
Quality of life at ≤3 months (WHOQOL-BREF psychological domain, 4-20, high is good outcome, final values)	51 (1 study) 2 weeks	⊕⊕⊕⊖ MODERATE2 due to imprecision		The mean quality of score in the control groups was 12.71	The mean quality of score in the intervention groups was 1.18 higher (0.18 lower to 2.54 higher)
Quality of life at ≤3 months (FIQ, 0-100, high is poor outcome, final values)	60 (3 studies) 4 weeks-3 months	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean quality of life score in the control groups was 49.92	The mean score in the intervention groups was 8.69 lower (18.83 lower to 1.46 higher)
Quality of life at >3 months (FIQ, 0-100, high is poor outcome, final values)	30 (1 study) 25 weeks	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean quality of life score in the control groups was 63.3	The mean quality of life score in the intervention groups was 7.3 lower (19.04 lower to 4.44 higher)
Pain reduction at ≤3 months (VAS, McGill Pain questionnaire, 0-10, high is poor outcome, final values)	181 (7 studies) 2 weeks-3 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, inconsistency, imprecision		The mean pain reduction score in the control groups was 5.68	The mean pain reduction score in the intervention groups was 1.17 lower (2.1 to 0.24 lower)
Physical function at ≤3 months (BPI functional impairment subscale, 0-10, high is poor outcome, final values)	20 (1 study) 4 weeks	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean physical function score in the control groups was 3.79	The mean physical function score in the intervention groups was 0.19 lower (2.34 lower to 1.96 higher)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with TMS versus sham TMS (95% CI)
Psychological distress at ≤3 months (Beck depression inventory, 0-61, high is poor outcome, final values and change scores)	44 (2 studies) 6-10 weeks	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		-	The mean psychological score in the intervention groups was 1.59 lower (4.13 lower to 0.94 higher)
Psychological distress at ≤3 months (Hamilton depression rating scale, MADRS, BDI, high is poor outcome, final values)	96 (3 studies) 2 weeks-3 months	⊕⊕⊕⊖ MODERATE1 due to risk of bias		-	The mean psychological distress score in the intervention groups was 0.01 standard deviations higher (0.39 lower to 0.41 higher)
Psychological distress at ≤3 months (HADS anxiety, 0-21, high is poor outcome, change scores)	29 (1 study) 10 weeks	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean psychological distress change score in the control groups was 0.5	The mean psychological distress score in the intervention groups was 0.1 lower (1.6 lower to 1.4 higher)
Psychological distress at >3 months (HADS anxiety, 0-21, high is poor outcome, change scores)	30 (1 study) 25 weeks	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean psychological distress change score in the control groups was 9.4	The mean psychological score in the intervention groups was 0.2 lower (4 lower to 3.6 higher)
Psychological distress at >3 months (HADS depression, 0-21, high is poor outcome, change scores)	30 (1 study) 25 weeks	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean psychological distress change score in the control groups was 7.4	The mean psychological score in the intervention groups was 1.2 higher (1.92 lower to 4.32 higher)
Pain interference at >3 months (BPI pain interference, 0-10, high is poor outcome, final values)	30 (1 study) 25 weeks	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean pain interference score in the control groups was 6	The mean pain interference score in the intervention groups was 1.9 lower (3.05 to 0.75 lower)
Discontinuation at ≤3 months	141 (4 studies) 2-6 weeks	⊕⊕⊖⊖ LOW2 due to imprecision	RD 0.03 (-0.06 to 0.12)	20 per 1000	30 more per 1000 (from 60 fewer to 120 more)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with TMS versus sham TMS (95% CI)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
3 Downgraded for heterogeneity, unexplained by subgroup analysis

Table 5: Clinical evidence summary: TDCS versus sham TDCS

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with TDCS versus sham TDCS (95% CI)
Quality of life at ≤3 months (SF-36 mental summary score, 0-100, high is good outcome, final values)	48 (1 study) 4 weeks	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean quality of life in the control groups was 45.4	The mean quality of life score in the intervention groups was 2.8 higher (4.72 lower to 10.32 higher)
Quality of life at ≤3 months (SF-36 physical summary score, 0-100, high is good outcome, final values)	48 (1 study) 4 weeks	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean quality of life in the control groups was 35.92	The mean quality of life score in the intervention groups was 1.14 lower (5.92 lower to 3.64 higher)
Quality of life at ≤3 months (SF-36 physical function subscale, 0-100, high is good outcome, final values)	20 (1 study) 10 weeks	⊕⊕⊕⊖ MODERATE1 due to risk of bias		The mean quality of life score in the control groups was 38	The mean quality of score in the intervention groups was 30.5 higher (12.47 to 48.53 higher)
Quality of life at ≤3 months (SF-36 physical role subscale, 0-100, high is good outcome, final values)	20 (1 study) 10 weeks	⊕⊖⊖⊖ VERY LOW1,2 due to risk of		The mean quality of score in the control groups was 47.5	The mean quality of life score in the intervention groups was 27.5 higher (4.71 lower to 59.71 higher)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with TDCS versus sham TDCS (95% CI)
		bias, imprecision			
Quality of life at ≤3 months (SF-36 bodily pain subscale, 0-100, high is good outcome, final values)	20 (1 study) 10 weeks	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean quality of life score in the control groups was 50	The mean quality of life score in the intervention groups was 7 lower (25.49 lower to 11.49 higher)
Quality of life at ≤3 months (SF-36 general health subscale, 0-100, high is good outcome, final values)	20 (1 study) 10 weeks	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean quality of life score in the control groups was 63.5	The mean quality of life score in the intervention groups was 5.5 lower (14.54 lower to 3.54 higher)
Quality of life at ≤3 months (SF-36 vitality subscale, 0-100, high is good outcome, final values)	20 (1 study) 10 weeks	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean quality of life score in the control groups was 58	The mean quality of life score in the intervention groups was 4.5 lower (12.92 lower to 3.92 higher)
Quality of life at ≤3 months (SF-36 general aspects subscale, 0-100, high is good outcome, final values)	20 (1 study) 10 weeks	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean quality of life score in the control groups was 50	The mean quality of life score in the intervention groups was 2.5 lower (16.55 lower to 11.55 higher)
Quality of life at ≤3 months (SF-36 emotional role subscale, 0-100, high is good outcome, final values)	20 (1 study) 10 weeks	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean quality of score in the control groups was 60	The mean quality of life score in the intervention groups was 20 higher (15.04 lower to 55.04 higher)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with TDCS versus sham TDCS (95% CI)
Quality of life at ≤3 months (SF-36 mental health subscale, 0-100, high is good outcome, final values)	20 (1 study) 10 weeks	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean quality of score in the control groups was 54	The mean quality of life score in the intervention groups was 4.4 higher (5.82 lower to 14.62 higher)
Pain reduction at ≤3 months (NRS, VAS, 0-10, high is poor outcome, final values)	104 (3 studies) 4-10 weeks	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, inconsistency, imprecision		The mean pain reduction score in the control groups was 6.04	The mean pain reduction score in the intervention groups was 2.12 lower (3.82 to 0.43 lower)
Psychological distress at ≤3 months (Hospital anxiety and depression scale, HAM-A, anxiety subscales, high is poor outcome, final values)	84 (2 studies) 4-8 weeks	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, inconsistency, imprecision		-	The mean psychological distress score in the intervention groups was 0.55 standard deviations lower (1.49 lower to 0.39 higher)
Psychological distress at ≤3 months (Hospital anxiety and depression scale, BDI, HAM-D, depression subscales, high is poor outcome, final values)	136 (4 studies) 3-12 weeks	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, imprecision, inconsistency		-	The mean psychological distress score in the intervention groups was 0.39 standard deviations lower (1.06 lower to 0.28 higher)
Sleep at ≤3 months (PSQI, scale range not reported, high is poor outcome, final values)	20 (1 study) 12 weeks	⊕⊕⊕⊖ MODERATE2 due to risk of bias		The mean sleep in the control groups was 16.7	The mean psychological distress score in the intervention groups was 8.8 lower (13.96 to 3.64 lower)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with TDCS versus sham TDCS (95% CI)
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias 2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs. 3 Downgraded for heterogeneity, unexplained by subgroup analysis					

Table 6: Clinical evidence summary: TENS versus sham TENS

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with TENS versus sham TENS (95% CI)
Quality of life at ≤3 months (SF36 physical component T scores, high is good outcome, change scores)	202 (1 study) 4 weeks	⊕⊕⊕⊖ MODERATE1 due to risk of bias		The mean change in quality of life score in the control groups was 1.2	The mean change in quality of life score in the intervention groups was 1.2 higher (0.7 lower to 3.1 higher)
Quality of life at ≤3 months (SF36 mental component T scores, high is good outcome, change scores)	202 (1 study) 4 weeks	⊕⊕⊕⊖ MODERATE1 due to risk of bias		The mean change in quality of life score in the control groups was 1.2	The mean change in quality of life score in the intervention groups was 1.1 higher (1.9 lower to 4.1 higher)
Pain reduction at ≤3 months (VAS, BPI intensity, 0-10, high is poor outcome, final values and change scores)	242 (2 studies) 4-10 weeks	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, inconsistency, imprecision		The mean pain score in the control groups was 5.7	The mean pain reduction score in the intervention groups was 1.96 lower (5.00 lower to 1.07 higher)
Pain reduction >3 months (VAS, 0-10, high is poor outcome, final values)	40 (1 study) 22 weeks	⊕⊕⊕⊖ **MODERATE**[1] due to risk of bias		The mean pain score in the control group was 5.6	The mean pain reduction at 22 weeks in the intervention group was 2.8 lower (4.23 to 1.37 lower)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with TENS versus sham TENS (95% CI)
Physical function at ≤3 months (6 minute walk test, feet walked, change scores)	202 (1 study) 4 weeks	⊕⊕⊕⊕ HIGH		The mean change physical function in the control groups was -20	The mean change in physical function in the intervention groups was 19 higher (58 lower to 96 higher)
Psychological distress at ≤3 months (PROMIS depression T scores, high is poor outcome, change scores)	202 (1 study) 4 weeks	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean change in psychological distress in the control groups was -0.1	The mean change in psychological distress in the intervention groups was 2.7 lower (4.7 to 0.7 lower)
Psychological distress at ≤3 months (PROMIS anxiety T scores, high is poor outcome, change scores)	202 (1 study) 4 weeks	⊕⊕⊕⊖ MODERATE1 due to risk of bias		The mean change in psychological distress in the control groups was -0.6	The mean change in psychological distress in the intervention groups was 0.5 lower (2.7 lower to 1.7 higher)
Pain interference at ≤3 months (BPI interference 0-10, high is poor outcome, change scores)	202 (1 study) 4 weeks	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean change in pain interference in the control groups was -0.3	The mean change in pain interference in the intervention groups was 0.7 lower (1.3 to 0.1 lower)
Pain self-efficacy at ≤3 months (PSEQ 0-60, high is good outcome, change scores)	202 (1 study) 4 weeks	⊕⊕⊕⊕ HIGH		The mean change in pain self-efficacy in the control groups was 1.5	The mean change in pain self-efficacy in the intervention groups was 1.6 higher (1.8 lower to 5 higher)
Discontinuation at ≤3 months	40 (1 study) 10 weeks	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision	RD 0 (-0.09 to 0.09)	0 per 1000	0 fewer per 1000 (from 90 fewer to 90 more)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with TENS versus sham TENS (95% CI)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
3 Downgraded for heterogeneity, unexplained by subgroup analysis

Table 7: Clinical evidence summary: TENS versus usual care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with TENS versus sham TENS (95% CI)
Quality of life at ≤3 months (SF36 physical component T scores, high is good outcome, change scores)	202 (1 study) 4 weeks	⊕⊕⊕⊖ MODERATE1 due to risk of bias		The mean change in quality of life score in the control groups was 1.4	The mean change in quality of life score in the intervention groups was 1 higher (0.8 lower to 2.8 higher)
Quality of life at ≤3 months (SF36 mental component T scores, high is good outcome, change scores)	202 (1 study) 4 weeks	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean change in quality of life score in the control groups was 0.04	The mean change in quality of life score in the intervention groups was 2.4 higher (0.6 lower to 5.4 higher)
Pain reduction at ≤3 months (BPI intensity, 0-10, high is poor outcome, change scores)	242 (2 studies) 4-10 weeks	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean change in pain score in the control groups was 0.15	The mean pain reduction score in the intervention groups was 0.9 lower (1.4 to 0.4 lower)
Physical function at ≤3 months (6 minute walk test, feet walked, change scores)	202 (1 study) 4 weeks	⊕⊕⊕⊕ HIGH		The mean change physical function in the control groups was -42.1	The mean change in physical function in the intervention groups was 42 higher (34 lower to 118 higher)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with TENS versus sham TENS (95% CI)
Psychological distress at ≤3 months (PROMIS depression T scores, high is poor outcome, change scores)	202 (1 study) 4 weeks	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean change in psychological distress in the control groups was 0.4	The mean change in psychological distress in the intervention groups was 3.2 lower (5.1 to 1.3 lower)
Psychological distress at ≤3 months (PROMIS anxiety T scores, high is poor outcome, change scores)	202 (1 study) 4 weeks	⊕⊕⊕⊖ MODERATE1 due to risk of bias		The mean change in psychological distress in the control groups was -0.7	The mean change in psychological distress in the intervention groups was 0.4 lower (2.5 lower to 1.7 higher)
Pain interference at ≤3 months (BPI interference 0-10, high is poor outcome, change scores)	202 (1 study) 4 weeks	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean change in pain interference in the control groups was -0.3	The mean change in pain interference in the intervention groups was 0.6 lower (1.3 lower to 0.1 higher)
Pain self-efficacy at ≤3 months (PSEQ 0-60, high is good outcome, change scores)	202 (1 study) 4 weeks	⊕⊕⊕⊕ HIGH		The mean change in pain self-efficacy in the control groups was 0.8	The mean change in pain self-efficacy in the intervention groups was 2.3 higher (1 lower to 5.6 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

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Table 8: Clinical evidence summary: PENS versus sham PENS

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with PENS versus sham PENS (95% CI)
Quality of life at ≤3 months (NIH-CPSI, 0-12, high is poor outcome, final values)	89 (1 study) 3 months	⊕⊕⊖⊖ LOW1 due to risk of bias		The mean quality of life score in the control groups was 6.7	The mean quality of life score in the intervention groups was 4.6 lower (5.27 to 3.93 lower)
Pain reduction at ≤3 months (VAS, 0-10, high is poor outcome, final values)	89 (1 study) 3 months	⊕⊕⊖⊖ LOW1 due to risk of bias		The mean pain reduction score in the control groups was 7.2	The mean pain reduction score in the intervention groups was 2.9 lower (3.11 to 2.69 lower)
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias					

Table 9: Clinical evidence summary: PENS versus usual care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with PENS versus usual care (95% CI)
Quality of life at ≤3 months (SF-36 physical function, 0-100, high is good outcome, final values)	24 (1 study) 3 months	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean quality of life score in the control groups was 52.91	The mean quality of life score in the intervention groups was 21.25 higher (0.64 lower to 43.14 higher)
Quality of life at ≤3 months (SF-36 physical role, 0-100, high is good outcome, final values)	24 (1 study) 3 months	⊕⊕⊖⊖ LOW1 due to risk of bias		The mean quality of life score in the control groups was 14.58	The mean quality of life score in the intervention groups was 52.08 higher (23.29 to 80.87 higher)
Quality of life at ≤3 months (SF-36 fatigue, 0-100, high is good outcome, final values)	24 (1 study) 3 months	⊕⊖⊖⊖ VERY LOW1,2 due to risk of		The mean quality of life score in the control groups	The mean quality of life score in the intervention groups was

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with PENS versus usual care (95% CI)
		bias, imprecision		was 45	17.91 higher (0.58 to 35.24 higher)
Quality of life at ≤3 months (SF-36 emotional role, 0-100, high is good outcome, final values)	24 (1 study) 3 months	⊕⊕⊖⊖ LOW1 due to risk of bias		The mean quality of life score in the control groups was 13.87	The mean quality of life score in the intervention groups was 47.24 higher (17.93 to 76.55 higher)
Quality of life at ≤3 months (SF-36 mental health, 0-100, high is good outcome, final values)	24 (1 study) 3 months	⊕⊕⊖⊖ LOW1 due to risk of bias		The mean quality of life score in the control groups was 40.33	The mean quality of life score in the intervention groups was 20.33 higher (6.31 to 34.35 higher)
Quality of life at ≤3 months (SF-36 social functioning, 0-100, high is good outcome, final values)	24 (1 study) 3 months	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean quality of life score in the control groups was 50	The mean quality of life score in the intervention groups was 21.87 higher (1.84 to 41.9 higher)
Quality of life at ≤3 months (SF-36 bodily pain, 0-100, high is good outcome, final values)	24 (1 study) 3 months	⊕⊕⊖⊖ LOW1 due to risk of bias		The mean quality of life score in the control groups was 23.33	The mean quality of life score in the intervention groups was 36.67 higher (20.25 to 53.09 higher)
Pain reduction at ≤3 months (VAS, 0-10, high is poor outcome, final values)	24 (1 study) 3 months	⊕⊕⊖⊖ LOW1 due to risk of bias		The mean pain reduction score in the control groups was 7.87	The mean pain reduction score in the intervention groups was 5.25 lower (6.86 to 3.64 lower)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

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Table 10: Clinical evidence summary: Therapeutic ultrasound versus usual care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Therapeutic ultrasound versus usual care (95% CI)
Pain reduction at ≤3 months (VAS, 0-10, high is poor outcome, final values)	76 (1 study) 3 months	⊕⊕⊖⊖ LOW1 due to risk of bias		The mean pain score in the control groups was 5.78	The mean pain reduction score in the intervention groups was 2.7 lower (3.54 to 1.86 lower)
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias					

See appendix F for full GRADE tables.

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1.5 Economic evidence

1.5.1 Included studies

No relevant health economic studies were included.

1.5.2 Excluded studies

No health economic studies that were relevant to this question were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in appendix G.

1.5.3 Unit costs

Unit costs of the devices that could be sourced are illustrated below in Table 12.

For some of the interventions it is possible that the equipment can be provided to the patient (or purchased by the patient) and the patient can undertake the intervention themselves (such as TENS). Other types of intervention require that a healthcare professional provides the treatment.

Table 11 demonstrates the costs of staff per hour.

It is common that some interventions such as interferential therapy, laser therapy and ultrasound therapy, are a shared resource that would be available in most physiotherapy departments, and are counted as part of a physiotherapist's appointment.

Table 11: staff costs

Healthcare professional	Cost (per hour)
Community physiotherapist (band 5/6/7)	£52 / £64 / £78

Source: PSSRU 2018[91]

Note: These costs include the ratio of direct to indirect time with patients of 1.37 from the PSSRU. And qualification costs.

Table 12: Electrical physical modalities costs

Intervention	Cost	Source
TENS	£18 - £50	NHS supply chain 2018[261]
Interferential therapy unit (a)	£1128.	NHS supply chain 2014 (based on costs used in the low back pain guideline (NG59))[259]
Laser therapy unit (a)	£955 and £1609	
Ultrasound therapy unit (a)	£853 and £2159	

(a) These interventions were no longer available from the latest version of the NHS supply chain (at the time of writing), however some costs sources are demonstrated in the table taken from the NICE guideline on low back pain. Note these have not been inflated from 2014 as it is not clear if prices of the machines would have increased or decreased since 2014:

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1.6 Evidence statements

1.6.1 Clinical evidence statements

1.6.1.1 Laser therapy versus sham laser therapy

Quality of life

Very low quality evidence from 6 studies with 276 participants showed a clinically important benefit of laser therapy compared to sham laser therapy at ≤3 months. Low to moderate quality evidence from 2 studies with 110 participants showed both a clinically important benefit of laser therapy (physical subscale) and no clinically important difference (mental subscale) compared to sham laser therapy at ≤3 months. Low quality evidence from 2 studies with 117 participants showed no clinically important difference compared to sham laser therapy at >3 months.

Pain reduction

Very low quality evidence from 13 studies with 558 participants showed a clinically important benefit of laser therapy compared to sham laser therapy at ≤3 months. Moderate quality evidence from 2 studies with 71 participants showed a clinically important benefit of laser therapy compared to sham laser therapy at >3 months.

Physical function

No evidence identified.

Psychological distress

Low to moderate quality evidence from 1 study with 44 participants showed no clinically important difference between laser therapy and sham laser therapy at ≤3 months.

Pain interference

No evidence identified.

Pain self-efficacy

No evidence identified.

Use of healthcare services

No evidence identified.

Sleep

No evidence identified.

Discontinuation

Low quality evidence from 1 study with 90 participants showed no clinically important difference between laser therapy and sham laser therapy at ≤3 months.

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1.6.1.2 TMS versus sham TMS

Quality of life

Very low quality evidence from 1 study with 29 participants showed no clinically important difference between TMS and sham TMS at ≤3 months. Low quality evidence from 1 study with 29 participants showed a clinically important benefit of TMS compared to sham TMS at ≤3 months. High quality evidence from 1 study with 51 participants showed a clinically important benefit of TMS compared to sham TMS at ≤3 months. Moderate quality evidence from 1 study with 51 participants showed no clinically important difference between TMS and sham TMS at ≤3 months. Very low quality evidence from 3 studies with 60 participants showed no clinically important difference between TMS and sham TMS at ≤3 months. Very low quality evidence from 1 study with 30 participants showed no clinically important difference between TMS and sham TMS at >3 months.

Pain reduction

Very low quality evidence from 7 studies with 181 participants showed a clinically important benefit of TMS compared to sham TMS at ≤3 months.

Physical function

Very low to moderate quality evidence from 1 study with 20 participants showed no clinically important difference between TMS and sham TMS at ≤3 months.

Psychological distress

Very low quality evidence from 2 studies with 44 participants showed no clinically important difference between TMS and sham TMS at ≤3 months. Moderate quality evidence from 3 studies with 96 participants showed no clinically important difference between TMS and sham TMS at ≤3 months. Very low quality evidence from 1 study with 29 participants showed no clinically important difference between TMS and sham TMS at ≤3 months. Very low quality evidence from 1 study with 30 participants showed no clinically important difference between TMS and sham TMS at >3 months.

Pain interference

Very low quality evidence from 1 study with 30 participants showed a clinically important benefit of TMS compared to sham TMS at >3 months.

Pain self-efficacy

No evidence identified.

Use of healthcare services

No evidence identified.

Sleep

No evidence identified.

Discontinuation

Low quality evidence from 4 studies with 141 participants showed no clinically important difference between TMS and sham TMS at ≤3 months.

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1.6.1.3 TDCS versus sham TDCS

Quality of life

Very quality evidence from 1 study with 48 participants showed no clinically important difference between TDCS and sham TDCS at ≤3 months. Moderate to low quality evidence from 1 study with 20 participants showed a clinically important benefit, clinically important harm and no clinically important difference (various subscales) of TDCS compared to sham TDCS at ≤3 months.

Pain reduction

Very low quality evidence from 3 studies with 104 participants showed a clinically important benefit of TDCS compared to sham TDCS at ≤3 months.

Physical function

No evidence identified.

Psychological distress

Very low quality evidence from 2 studies with 84 participants showed a clinically important benefit of TDCS compared to sham TDCS at ≤3 months. Very low quality evidence from 4 studies with 136 participants showed no clinically important difference between TDCS and sham TDCS at ≤3 months.

Pain interference

No evidence identified.

Pain self-efficacy

No evidence identified.

Use of healthcare services

No evidence identified.

Sleep

Moderate quality evidence from 1 study with 20 participants showed a clinically important benefit of TDCS compared to sham TDCS at ≤3 months.

Discontinuation

No evidence identified.

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1.6.1.4 TENS versus sham TENS

Quality of life

Moderate quality evidence from 1 study with 202 participants showed no clinically important difference between TENS and sham TENS at ≤3 months.

Pain reduction

Very low quality evidence from 2 studies with 242 participants showed a clinically important difference for TENS compared to sham TENS at ≤3 months. Moderate quality evidence from 1 study with 40 participants showed a clinically important difference for TENS at >3 months.

Physical function

High quality evidence from 1 study with 202 participants showed no clinically important difference between TENS and sham TENS at ≤3 months.

Psychological distress

Moderate to low quality evidence from 1 study with 202 participants showed no clinically important difference between TENS and sham TENS at ≤3 months.

Pain interference

Low quality evidence from 1 study with 202 participants showed no clinically important difference between TENS and sham TENS at ≤3 months.

Pain self-efficacy

High quality evidence from 1 study with 202 participants showed no clinically important difference between TENS and sham TENS at ≤3 months.

Discontinuation

Low quality evidence from 1 study with 40 participants showed no clinically important difference between TENS and sham TENS at ≤3 months.

No other evidence identified for TENS versus sham TENS.

1.6.1.5 TENS versus usual care

Quality of life

Moderate to low quality evidence from 1 study with 202 participants showed no clinically important difference between TENS and usual care at ≤3 months.

Pain reduction

Low quality evidence from 1 study with 202 participants showed no clinically important difference between TENS and usual care at ≤3 months.

Physical function

High quality evidence from 1 study with 202 participants showed no clinically important difference between TENS and usual care at ≤3 months.

Psychological distress

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Moderate to low quality evidence from 1 study with 202 participants showed no clinically important difference between TENS and usual care at ≤3 months.

Pain interference

Low quality evidence from 1 study with 202 participants showed no clinically important difference between TENS and usual care at ≤3 months.

Pain self-efficacy

High quality evidence from 1 study with 202 participants showed no clinically important difference between TENS and usual care at ≤3 months.

No other evidence identified for TENS versus usual care.

1.6.1.6 PENS versus sham PENS

Quality of life

Low quality evidence from 1 study with 89 participants showed a clinically important benefit of PENS compared to sham PENS at ≤3 months.

Pain reduction

Low quality evidence from 1 study with 89 participants showed a clinically important benefit of PENS compared to sham PENS at ≤3 months.

No other evidence identified for PENS versus sham PENS.

1.6.1.7 PENS versus usual care

Quality of life

Very low to low quality evidence from 1 study with 24 participants showed a clinically important benefit of PENS compared to usual care at ≤3 months.

Pain reduction

Low quality evidence from 1 study with 24 participants showed a clinically important benefit of PENS compared to usual care at ≤3 months.

No other evidence identified for PENS versus usual care.

1.6.1.8 Therapeutic ultrasound versus usual care

Pain reduction

Low quality evidence from 1 study with 76 participants showed a clinically important benefit of therapeutic ultrasound compared to usual care at ≤3 months.

No other evidence identified for therapeutic ultrasound versus usual care.

1.6.2 Health economic evidence statements

- No relevant economic evaluations were identified.

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1.7 The committee's discussion of the evidence

1.7.1 Interpreting the evidence

1.7.1.1 The outcomes that matter most

The committee considered health-related quality of life, pain reduction, physical function, psychological distress, pain interference and pain self-efficacy to be critical outcomes for decision-making. Use of healthcare services, sleep and discontinuation were also considered to be important outcomes. The critical and important outcomes agreed by the committee were adapted by consensus from relevant core outcome sets registered under the Core Outcome Measures in Effectiveness Trials (COMET) Initiative. This included the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations.

Evidence was identified for all critical outcomes, other than pain interference and pain self-efficacy. Evidence for important outcomes was limited; no evidence was identified for sleep or use of healthcare services, and evidence for discontinuation was limited.

1.7.1.2 The quality of the evidence

Evidence from 34 randomised controlled trials was identified for 8 different comparisons. The comparison with the most evidence was laser therapy versus sham laser therapy. No head-to-head comparisons of different electrical therapies were identified and no evidence was identified for interferential therapy. There was little evidence comparing interventions to usual care.

The majority of the evidence was of low to very low quality. The main reasons for downgrading were risk of bias, inconsistency and imprecision. A large number of studies had small sample sizes, which increased the uncertainty around the point estimates. The evidence for many outcomes included studies that looked at heterogeneous populations, and used different electrical parameters (such as wavelength and voltage) and intervention durations. Where there was heterogeneity in the evidence for an outcome, pre-specified subgroup analyses did not explain the variation in effect sizes. As a result, many outcomes were downgraded for inconsistency.

The committee took into account the low to very low quality of evidence in their discussions, particularly when considering the small amount of evidence for comparisons of TENS, PENS and ultrasound versus sham or usual care.

1.7.1.3 Benefits and harms

Evidence for laser therapy versus sham was based on 14 studies and showed a benefit of treatment in terms of pain and quality of life at short term follow up, although there was serious uncertainty around the effect estimates. The long-term data showing a benefit of laser therapy for pain was based on much smaller sample sizes. Contrastingly, evidence from 2 studies showed no clinically important difference (with some uncertainty) between laser therapy and sham for quality of life at less than 3 months, as measured by the mental component summary of the SF-36 questionnaire, but there was evidence to suggest a benefit on the physical component summary of the SF-36. At longer-term follow up, evidence from 2 studies also showed no clinically important difference. The committee noted that they would expect to see a consistent benefit across more domains, if an intervention were to be interpreted as being generally effective. This therefore raised questions about the effectiveness of the intervention for all critical outcomes being assessed. Evidence for psychological distress and discontinuation was limited at less than 3 months, with some low to moderate quality evidence suggesting there was no clinically important benefit of laser

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therapy, again based on small sample sizes and with serious uncertainty. No evidence was identified for physical function, pain interference or sleep either in the short or long term. The only long-term evidence was for outcomes of pain and quality of life.

The committee agreed that although there was some evidence of benefit for quality of life and pain, they could not make a recommendation for laser therapy. The evidence from clinical trials was heterogeneous. The physical parameters of the laser light used, the duration of treatment and the time the laser was applied to each painful point varied widely. It was also unclear whether these parameters affected the size, quality and duration of clinical benefit seen within the evidence. This made it difficult for the committee to be confident about the benefits of laser therapy in routine practice, or to make specific recommendations. No cost-effectiveness evidence or evidence assessing longer-term benefit was available. Comparisons were against sham laser therapy, rather than usual care, which is the comparison of greatest interest for implementation in the NHS. Taking all of this into account, the committee agreed they could not make a recommendation for the use of laser therapy in clinical practice. However, they agreed that this preliminary evidence looked promising, and as a result made a recommendation for further research.

Evidence for transcranial magnetic stimulation (TMS) showed a benefit for pain at less than 3 months. This was based on 7 studies, although it was very low quality evidence with serious uncertainty. Evidence for other outcomes, including quality of life, physical function and psychological distress showed no clinical benefit of TMS. Furthermore, the long-term benefit of TMS was unclear with limited evidence. As a result, the committee agreed it could not base a recommendation on pain reduction alone, particularly taking into account the relatively small sample size and low quality of the evidence. The committee instead agreed that the short-term benefit for pain was promising, and that further long-term evidence is needed to determine the effectiveness of TMS. As a result the committee made a recommendation for future research.

Evidence for TENS showed no clinically important difference compared with sham TENS, nor with usual care for quality of life, physical function, psychological distress, pain interference, pain self-efficacy or discontinuation at less than 3 months. For pain, benefits were seen for TENS compared to sham at both time points, but not compared to usual care. The committee noted that there was significant heterogeneity between the two studies in the meta-analysis at less than 3 months compared to sham and the effect was only demonstrated in the smaller of the 2 studies (given more influence in the meta-analysis due to random effects being used in the meta-analysis). The evidence for longer term follow up was only from this single small study. They discussed that in the absence of evidence of benefit in any other outcome or compared to usual care, the significant heterogeneity and the small sample size, they could not place too much weight on this finding. The committee noted that the majority of the evidence came from 1 larger study and the quality of the evidence ranged from high to very low. No longer term evidence was identified with the exception of 1 pain outcome. No evidence was identified for ultrasound or interferential therapy. The committee also noted that these technologies have existed for some time and are being used by some in the NHS without evidence of benefit. The committee agreed that resources should be re-allocated to areas with more evidence of clinical and cost effectiveness. Therefore, the committee decided to make a recommendation against the use of TENS, ultrasound and interferential therapy.

The committee also considered the limited evidence identified for TDCS and PENS. Evidence was limited to a small number of studies with small sample sizes. Both interventions showed a benefit for pain, although TDCS showed mixed results for quality of life and psychological distress. PENS on the other hand also showed a benefit for quality of life. However, the evidence was low to very low quality, with uncertainty around the effect sizes. The committee agreed that this evidence was insufficient to determine the effectiveness of each intervention. However, the committee decided not to recommend against these interventions because neither intervention is commonly used in current

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practice. The committee also decided not to make a research recommendation due to this, and agreed that other areas reviewed across the guideline showed more promising results for future research to be warranted.

1.7.2 Cost effectiveness and resource use

No economic evidence was identified for this question.

It is common that some interventions such as interferential therapy, laser therapy and ultrasound therapy are a shared resource that would be available in most physiotherapy departments, as they might be used for a variety of conditions, and are counted as part of a physiotherapist's appointment. Costs of physiotherapist time were presented to the committee. Some interventions such as TMS are specialist and are not used clinically in the NHS for chronic pain.

There is also a distinction between interventions that the person could self-administer, and do not necessarily require appointments with NHS clinical staff to undertake the intervention. Examples of this would include TENS and TDCS.

If the use of these interventions in general is not widespread across the NHS for people with chronic primary pain, then a positive recommendation in favour of any interventions will require capital outlay to purchase more units to allow the interventions to be more widely available. TENS is relatively cheap and the cheapest of all the interventions to purchase. Costs of the devices for interferential therapy, laser therapy, and ultrasound therapy are not currently available on the NHS supply chain, but the costs of such units that were quoted in the low back pain guideline were presented to the committee as an illustration, which were sourced from the NHS supply chain in 2014.

The committee view of the clinical evidence was that there was considerable uncertainty in the data, with little long-term evidence. Additionally, data on who delivered the intervention was lacking and treatments were relatively short term with a wide range in the number of treatment sessions provided. The intervention which had the largest signal of benefit was laser therapy. This is not widely used in the NHS, and, because of a lack of cost effectiveness evidence of laser therapy, the committee decided to make a research recommendation for laser therapy.

The committee also made some recommendations to not offer some types of electrical physical modalities. This was because there was no or very little evidence, and the committee opinion was that as these are technologies that have been around for some time, no new research was likely to be undertaken. Additionally, they were also aware that as those treatments are being used by some people in the NHS, resources should be re-allocated to areas with more evidence of clinical and cost effectiveness.

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Appendices

Appendix A: Review protocols

Review protocol for electrical physical modalities

ID	Field	Content
0.	PROSPERO registration number	Not registered.
1.	Review title	What is the clinical and cost effectiveness of electrical physical modalities for the management of chronic primary pain?
2.	Review question	What is the clinical and cost effectiveness of electrical physical modalities for the management of chronic primary pain?
3.	Objective	To determine the clinical and cost effectiveness of electrical physical modalities for the management of chronic primary pain.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • CINAHL, Current Nursing and Allied Health Literature Searches will be restricted by: • English language • Human studies • Letters and comments are excluded. Other searches:

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		• Inclusion lists of relevant systematic reviews will be checked by the reviewer. The searches may be re-run 6 weeks before final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	Chronic pain in one or more anatomical regions that is characterized by significant emotional distress (anxiety, anger/frustration or depressed mood) and functional disability (interference in daily life activities and reduced participation in social roles). The diagnosis is appropriate independently of identified biological or psychological contributors unless another diagnosis would better account for the presenting symptoms.
6.	Population	Inclusion: People, aged 16 years and over, with chronic primary pain (whose pain management is not addressed by existing NICE guidance) (chronic widespread pain, complex regional pain syndrome, chronic visceral pain, chronic orofacial pain, chronic primary musculoskeletal pain other than orofacial) Exclusion: Those whose pain management is addressed by existing NICE guidance.
7.	Intervention/Exposure/Test	Interventions: • transcutaneous electrical nerve stimulation (TENS) • percutaneous electrical nerve stimulation (PENS) • interferential therapy • laser therapy • therapeutic ultrasound • transcranial magnetic stimulation (TMS) • transcranial direct current stimulation (TDCS)
8.	Comparator/Reference standard/Confounding factors	Comparators: • each other • placebo/sham • usual care • physical therapies in this guideline.
9.	Types of study to be included	Randomised controlled trials (RCTs) and systematic reviews of RCTs

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		Cross-over RCTs will be considered if no non-cross-over RCT evidence is identified.
10.	Other exclusion criteria	Non-English language studies. Studies comparing combinations of interventions.
11.	Context	A clear understanding of the evidence for the effectiveness of chronic primary pain treatments: • improves the confidence of healthcare professionals in their conversations about pain, and • helps healthcare professionals and patients to have realistic expectations about outcomes of treatment.
12.	Primary outcomes (critical outcomes)	• Pain reduction (any validated scale) • health related quality of life (including meaningful activity) • physical function (5 minute walk, sit to stand, Roland Morris Disability Questionnaire, Oswestry Disability Index, Canadian Occupational Performance Measure) • psychological distress (depression/anxiety) (preferably Hospital Anxiety and Depression Scale) • pain interference (brief pain inventory interference subscale) • pain self-efficacy (pain self-efficacy questionnaire). Outcomes will be extracted at the longest time point up to 3 months and at the longest time point after 3 months.
13.	Secondary outcomes (important outcomes)	• Use of healthcare services • sleep • discontinuation. Outcomes will be extracted at the longest time point up to 3 months and at the longest time point after 3 months.
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two

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		reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. EviBASE will be used for data extraction. Study investigators may be contacted for missing data where time and resources allow.	
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the Cochrane Risk of Bias (2.0) tool. Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.	
16.	Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome.	
17.	Analysis of sub-groups	Proposed sensitivity / subgroup analysis to be explored where there is heterogeneity: • chronic widespread pain • complex regional pain syndrome • chronic visceral pain • chronic orofacial pain • chronic primary musculoskeletal pain • cognitive impairment • learning difficulties • first language not English • sensory impairment • homeless	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic

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		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
19.	Language	English	
20.	Country	England	
21.	Anticipated or actual start date	NA – not registered on PROSPERO	
22.	Anticipated completion date	19/08/2020	
23.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail Chronicpain@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre	
24.	Review team members	From the National Guideline Centre: Serena Carville, Guideline Lead Maria Smyth, Senior Systematic Reviewer Rebecca Boffa, Senior Systematic Reviewer	

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		Margaret Constanti, Senior Health Economist Joseph Runicles, Information Specialist Katie Broomfield, Project Manager
25.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
26.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
27.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10069
28.	Other registration details	NA
29.	Reference/URL for published protocol	NA
30.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.

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31.	Keywords	-
32.	Details of existing review of same topic by same authors	NA
33.	Additional information	-
34.	Details of final publication	www.nice.org.uk

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Table 13: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2002. Abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[258] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).

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	• OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2002 or later but that depend on unit costs and resource data entirely or predominantly from before 2002 will be rated as 'Not applicable'. • Studies published before 2002 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

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Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[258]

For more information, please see the Methods Report published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 20 May 2020	Exclusions Randomised controlled trials Systematic review studies
Embase (OVID)	1974 – 20 May 2020	Exclusions Randomised controlled trials Systematic review studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2020 Issue 5 of 12 CENTRAL to 2020 Issue 5 of 12	None

Medline (Ovid) search terms

1.	Chronic pain/
2.	((chronic or persist* or idiopathic or atypical or a-typical) adj4 pain).ti,ab.
3.	exp Complex Regional Pain Syndromes/
4.	(complex regional pain syndrome* or CRPS or causalgia).ti,ab.
5.	((reflex or sympathetic) adj2 dystroph*).ti,ab.
6.	fibromyalgia/
7.	(fibromyalgia* or fibrositis or myofascial pain syndrome).ti,ab.
8.	vulvodynia/
9.	(vulvodynia or vestibulodynia or dyspareunia or vulvar vestibulitis or vulvitis).ti,ab.
10.	interstitial cystitis/
11.	(interstitial adj2 cystitis).ti,ab.
12.	algodystrophy/
13.	(algodystroph* or sudek or sudeck*).ti,ab.
14.	exp myofascial pain syndromes/
15.	cystitis, interstitial/
16.	(loin pain adj (haematuria or hematuria) adj syndrome*).ti,ab.
17.	(LPHS or prostatodynia or CPPS or atypic* odontalgia or a-typic* odontalgia or burning mouth syndrome* or phantom tooth pain or neuropathic orofacial pain or "myofascial pain" or MPS).ti,ab.

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18.	((pelvic or pelvis) adj pain syndrome*).ti,ab.
19.	((non-cardiac or noncardiac) adj3 chest adj3 pain).ti,ab.
20.	(temporomandibular adj3 joint adj3 pain).ti,ab.
21.	((prostate or vulv* or bladder or perineal) adj3 pain).ti,ab.
22.	(functional pain syndrome* or non-cancer pain or noncancer pain).ti,ab.
23.	((pelvic or pelvis or abdominal) adj3 pain adj3 (unknown or un-known or idiopathic or atypic* or a-typic*)).ti,ab.
24.	or/1-23
25.	letter/
26.	editorial/
27.	news/
28.	exp historical article/
29.	Anecdotes as Topic/
30.	comment/
31.	case report/
32.	(letter or comment*).ti.
33.	or/25-32
34.	randomized controlled trial/ or random*.ti,ab.
35.	33 not 34
36.	animals/ not humans/
37.	exp Animals, Laboratory/
38.	exp Animal Experimentation/
39.	exp Models, Animal/
40.	exp Rodentia/
41.	(rat or rats or mouse or mice).ti.
42.	or/35-41
43.	24 not 42
44.	limit 43 to English language
45.	Transcutaneous Electric Nerve Stimulation/
46.	(TENS or PENS or ALTENS or TNS or TENMS or TMS or TDCS).ti,ab.
47.	(electroanalges* or electro analges*).ti,ab.
48.	Electric Stimulation Therapy/
49.	electrotherap*.ti,ab.
50.	((transcutaneous or transcranial or percutaneous or cutaneous or transderm* or peripheral or microamperage) adj3 (stimulat* or electr*)).ti,ab.
51.	electrostimulat*.ti,ab.
52.	(interferential adj2 current*).ti,ab.
53.	((electric* or electro or interferential) adj2 (stimulat* or therap* or acupuncture)).ti,ab.
54.	Laser Therapy, Low-Level/
55.	(laser adj2 (therap* or treat* or phototherap* or irradiat* or biostimulat* or stimulat*)).ti,ab.
56.	Ultrasonic Therapy/ or Extracorporeal Shockwave Therapy/
57.	((ultrasound or ultra sound or ultrasonic or ultra sonic) adj3 (contin* or therap* or treat* or stimulat* or intervention*)).ti,ab.
58.	or/45-57
59.	randomized controlled trial.pt.
60.	controlled clinical trial.pt.
61.	randomi#ed.ti,ab.

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62.	placebo.ab.
63.	randomly.ti,ab.
64.	Clinical Trials as topic.sh.
65.	trial.ti.
66.	or/59-65
67.	Meta-Analysis/
68.	exp Meta-Analysis as Topic/
69.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
70.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
71.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
72.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
73.	(search* adj4 literature).ab.
74.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
75.	cochrane.jw.
76.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
77.	or/67-76
78.	44 and 58 and (66 or 77)

Embase (Ovid) search terms

1.	Chronic pain/
2.	((chronic or persist* or idiopathic or atypical or a-typical) adj4 pain).ti,ab.
3.	exp Complex regional pain syndrome/
4.	(complex regional pain syndrome* or CRPS or causalgia).ti,ab.
5.	((reflex or sympathetic) adj2 dystroph*).ti,ab.
6.	fibromyalgia/
7.	(fibromyalgia* or fibrositis or myofascial pain syndrome).ti,ab.
8.	vulvodynia/
9.	(vulvodynia or vestibulodynia or dyspareunia or vulvar vestibulitis or vulvitis).ti,ab.
10.	interstitial cystitis/
11.	(interstitial adj2 cystitis).ti,ab.
12.	algodystrophy/
13.	(algodystroph* or sudek or sudeck*).ti,ab.
14.	myofascial pain/
15.	noncardiac chest pain/
16.	cystalgia/
17.	Pelvis pain syndrome/
18.	(loin pain adj (haematuria or hematuria) adj syndrome*).ti,ab.
19.	(LPHS or prostatodynia or CPPS or atypic* odontalgia or a-typic* odontalgia or burning mouth syndrome* or phantom tooth pain or neuropathic orofacial pain or "myofascial pain" or MPS).ti,ab.
20.	((pelvic or pelvis) adj pain syndrome*).ti,ab.
21.	((non-cardiac or noncardiac) adj3 chest adj3 pain).ti,ab.
22.	(temporomandibular adj3 joint adj3 pain).ti,ab.
23.	((prostate or vulv* or bladder or perineal) adj3 pain).ti,ab.
24.	(functional pain syndrome* or non-cancer pain or noncancer pain).ti,ab.

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25.	((pelvic or pelvis or abdominal) adj3 pain adj3 (unknown or un-known or idiopathic or atypic* or a-typic*)).ti,ab.
26.	or/1-25
27.	letter.pt. or letter/
28.	note.pt.
29.	editorial.pt.
30.	case report/ or case study/
31.	(letter or comment*).ti.
32.	or/27-31
33.	randomized controlled trial/ or random*.ti,ab.
34.	32 not 33
35.	animal/ not human/
36.	nonhuman/
37.	exp Animal Experiment/
38.	exp Experimental Animal/
39.	animal model/
40.	exp Rodent/
41.	(rat or rats or mouse or mice).ti.
42.	or/34-41
43.	26 not 42
44.	limit 43 to English language
45.	transcutaneous nerve stimulation/
46.	electrostimulation therapy/
47.	(TENS or PENS or ALTENS or TNS or TENMS or TMS or TDCS).ti,ab.
48.	(electroanalges* or electro analges*).ti,ab.
49.	electrotherap*.ti,ab.
50.	((transcutaneous or transcranial or percutaneous or cutaneous or transderm* or peripheral or microamperage) adj3 (stimulat* or electr*)).ti,ab.
51.	electrostimulat*.ti,ab.
52.	(interferential adj2 current*).ti,ab.
53.	((electric* or electro or interferential) adj2 (stimulat* or therap* or acupuncture)).ti,ab.
54.	(laser adj2 (therap* or treat* or phototherap* or irradiat* or biostimulat* or stimulat*)).ti,ab.
55.	Ultrasonic Therapy/
56.	((ultrasound or ultra sound or ultrasonic or ultra sonic) adj3 (contin* or therap* or treat* or stimulat* or intervention*)).ti,ab.
57.	low level laser therapy/
58.	electroanalgesia/
59.	or/45-58
60.	44 and 59
61.	random*.ti,ab.
62.	factorial*.ti,ab.
63.	(crossover* or cross over*).ti,ab.
64.	((doubl* or singl*) adj blind*).ti,ab.
65.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
66.	crossover procedure/
67.	single blind procedure/
68.	randomized controlled trial/

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69.	double blind procedure/
70.	or/61-69
71.	systematic review/
72.	meta-analysis/
73.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
74.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
75.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
76.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
77.	(search* adj4 literature).ab.
78.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
79.	cochrane.jw.
80.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
81.	or/71-80
82.	60 and (70 or 81)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Chronic Pain] explode all trees
#2.	((chronic or persist* or idiopathic or atypical or a-typical) near/4 pain):ti,ab
#3.	MeSH descriptor: [Complex Regional Pain Syndromes] explode all trees
#4.	(complex regional pain syndrome* or CRPS or causalgia):ti,ab
#5.	((reflex or sympathetic) near/2 dystroph*):ti,ab
#6.	MeSH descriptor: [Fibromyalgia] explode all trees
#7.	(fibromyalgia* or fibrositis or myofascial pain syndrome):ti,ab
#8.	MeSH descriptor: [Vulvodynia] explode all trees
#9.	(vulvodynia or vestibulodynia or dyspareunia or vulvar vestibulitis or vulvitis):ti,ab
#10.	MeSH descriptor: [Cystitis, Interstitial] explode all trees
#11.	(interstitial near/2 cystitis):ti,ab
#12.	MeSH descriptor: [Reflex Sympathetic Dystrophy] explode all trees
#13.	(algodystroph* or sudek or sudeck*):ti,ab
#14.	MeSH descriptor: [Myofascial Pain Syndromes] explode all trees
#15.	(loin pain near (haematuria or hematuria) near syndrome*):ti,ab
#16.	(LPHS or prostatodynia or CPPS or atypic* odontalgia or a-typic* odontalgia or burning mouth syndrome* or phantom tooth pain or neuropathic orofacial pain or "myofascial pain" or MPS):ti,ab
#17.	((pelvic or pelvis) near pain syndrome*):ti,ab
#18.	((non-cardiac or noncardiac) near/3 chest near/3 pain):ti,ab
#19.	(temporomandibular near/3 joint near/3 pain):ti,ab
#20.	((prostate or vulv* or bladder or perineal) near/3 pain):ti,ab
#21.	(functional pain syndrome* or non-cancer pain or noncancer pain):ti,ab
#22.	((pelvic or pelvis or abdominal) near/3 pain near/3 (unknown or un-known or idiopathic or atypic* or a-typic*)):ti,ab
#23.	(or #1-#22)
#24.	MeSH descriptor: [Transcutaneous Electric Nerve Stimulation] explode all trees
#25.	(TENS or PENS or ALTENS or TNS or TENMS or TMS or TDCS):ti,ab
#26.	(electroanalges* or electro analges*):ti,ab
#27.	MeSH descriptor: [Electric Stimulation Therapy] explode all trees

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#28.	electrotherap*:ti,ab
#29.	((transcutaneous or transcranial or percutaneous or cutaneous or transderm* or peripheral or microamperage) near/3 (stimulat* or electr*)):ti,ab
#30.	electrostimulat*:ti,ab
#31.	(interferential near/2 current*):ti,ab
#32.	((electric* or electro or interferential) near/2 (stimulat* or therap* or acupuncture)):ti,ab
#33.	MeSH descriptor: [Laser Therapy] explode all trees
#34.	(laser near/2 (therap* or treat* or phototherap* or irradiat* or biostimulat* or stimulat*)):ti,ab
#35.	MeSH descriptor: [Ultrasonic Therapy] explode all trees
#36.	MeSH descriptor: [Extracorporeal Shockwave Therapy] explode all trees
#37.	((ultrasound or ultra sound or ultrasonic or ultra sonic) near/3 (contin* or therap* or treat* or stimulat* or intervention*)):ti,ab
#38.	(or #24-#37)
#39.	#23 and #38

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to a Chronic Pain population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics and economic modelling.

Table 14: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2014 – 20 May 2020	Exclusions Health economics studies Health economics modelling studies
Embase	2014 – 20 May 2020	Exclusions Health economics studies Health economics modelling studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 20 May 2020 NHSEED - Inception to March 2015	None

Medline search terms

1.	chronic pain/ or pain, intractable/
2.	((persist* or intract* or chronic or longstanding or long standing or longterm or long term or refractory or prolong* or long last* or sustain* or linger* or syndrome*) adj3 pain*).ti,ab.
3.	((chronic or persist* or idiopathic or atypical or a-typical) adj4 pain).ti,ab.
4.	exp Complex Regional Pain Syndromes/
5.	(complex regional pain syndrome* or CRPS or causalgia).ti,ab.

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6.	fibromyalgia/
7.	((reflex or sympathetic) adj2 dystroph*).ti,ab.
8.	vulvodynia/
9.	(vulvodynia or vestibulodynia or dyspareunia or vulvar vestibulitis or vulvitis).ti,ab.
10.	interstitial cystitis/
11.	(interstitial adj2 cystitis).ti,ab.
12.	algodystrophy/
13.	(algodystroph* or sudek or sudeck*).ti,ab.
14.	exp myofascial pain syndromes/
15.	cystitis, interstitial/
16.	(loin pain adj (haematuria or hematuria) adj syndrome*).ti,ab.
17.	(LPHS or prostatodynia or CPPS or atypic* odontalgia or a-typic* odontalgia or burning mouth syndrome* or phantom tooth pain or neuropathic orofacial pain or "myofascial pain" or MPS).ti,ab.
18.	((pelvic or pelvis) adj pain syndrome*).ti,ab.
19.	((non-cardiac or noncardiac) adj3 chest adj3 pain).ti,ab.
20.	(temporomandibular adj3 joint adj3 pain).ti,ab.
21.	((prostate or vulv* or bladder or perineal) adj3 pain).ti,ab.
22.	(functional pain syndrome* or non-cancer pain or noncancer pain).ti,ab.
23.	((pelvic or pelvis or abdominal) adj3 pain adj3 (unknown or un-known or idiopathic or atypic* or a-typic*)).ti,ab.
24.	(fibromyalgia* or fibrositis or myofascial pain syndrome).ti,ab.
25.	or/1-24
26.	letter/
27.	editorial/
28.	news/
29.	exp historical article/
30.	Anecdotes as Topic/
31.	comment/
32.	case report/
33.	(letter or comment*).ti.
34.	or/26-33
35.	randomized controlled trial/ or random*.ti,ab.
36.	34 not 35
37.	animals/ not humans/
38.	exp Animals, Laboratory/
39.	exp Animal Experimentation/
40.	exp Models, Animal/
41.	exp Rodentia/
42.	(rat or rats or mouse or mice).ti.
43.	or/36-42
44.	25 not 43
45.	Economics/
46.	Value of life/
47.	exp "Costs and Cost Analysis"/
48.	exp Economics, Hospital/
49.	exp Economics, Medical/
50.	Economics, Nursing/

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51.	Economics, Pharmaceutical/
52.	exp "Fees and Charges"/
53.	exp Budgets/
54.	budget*.ti,ab.
55.	cost*.ti.
56.	(economic* or pharmaco?economic*).ti.
57.	(price* or pricing*).ti,ab.
58.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
59.	(financ* or fee or fees).ti,ab.
60.	(value adj2 (money or monetary)).ti,ab.
61.	or/45-60
62.	exp models, economic/
63.	*Models, Theoretical/
64.	*Models, Organizational/
65.	markov chains/
66.	monte carlo method/
67.	exp Decision Theory/
68.	(markov* or monte carlo).ti,ab.
69.	econom* model*.ti,ab.
70.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
71.	or/62-70
72.	44 and (61 or 71)

Embase (Ovid) search terms

1.	chronic pain/ or pain, intractable/
2.	((persist* or intract* or chronic or longstanding or long standing or longterm or long term or refractory or prolong* or long last* or sustain* or linger* or syndrome*) adj3 pain*).ti,ab.
3.	((chronic or persist* or idiopathic or atypical or a-typical) adj4 pain).ti,ab.
4.	exp Complex regional pain syndrome/
5.	(complex regional pain syndrome* or CRPS or causalgia).ti,ab.
6.	((reflex or sympatheti) adj2 dystroph*).ti,ab.
7.	fibromyalgia/
8.	(fibromyalgia* or fibrositis or myofascial pain syndrome).ti,ab.
9.	vulvodynia/
10.	(vulvodynia or vestibulodynia or dyspareunia or vulvar vestibulitis or vulvitis).ti,ab.
11.	interstitial cystitis/
12.	(interstitial adj2 cystitis).ti,ab.
13.	algodystrophy/
14.	(algodystroph* or sudek or sudeck*).ti,ab.
15.	myofascial pain/
16.	noncardiac chest pain/
17.	cystalgia/
18.	Pelvis pain syndrome/
19.	(loin pain adj (haematuria or hematuria) adj syndrome*).ti,ab.
20.	(LPHS or prostatodynia or CPPS or atypic* odontalgia or a-typic* odontalgia or burning mouth syndrome* or phantom tooth pain or neuropathic orofacial pain or "myofascial pain" or MPS).ti,ab.

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21.	((pelvic or pelvis) adj pain syndrome*).ti,ab.
22.	((non-cardiac or noncardiac) adj3 chest adj3 pain).ti,ab.
23.	(temporomandibular adj3 joint adj3 pain).ti,ab.
24.	((prostate or vulv* or bladder or perineal) adj3 pain).ti,ab.
25.	(functional pain syndrome* or non-cancer pain or noncancer pain).ti,ab.
26.	((pelvic or pelvis or abdominal) adj3 pain adj3 (unknown or un-known or idiopathic or atypic* or a-typic*)).ti,ab.
27.	or/1-26
28.	letter.pt. or letter/
29.	note.pt.
30.	editorial.pt.
31.	case report/ or case study/
32.	(letter or comment*).ti.
33.	or/28-32
34.	randomized controlled trial/ or random*.ti,ab.
35.	33 not 34
36.	animal/ not human/
37.	nonhuman/
38.	exp Animal Experiment/
39.	exp Experimental Animal/
40.	animal model/
41.	exp Rodent/
42.	(rat or rats or mouse or mice).ti.
43.	or/35-42
44.	27 not 43
45.	health economics/
46.	exp economic evaluation/
47.	exp health care cost/
48.	exp fee/
49.	budget/
50.	funding/
51.	budget*.ti,ab.
52.	cost*.ti.
53.	(economic* or pharmaco?economic*).ti.
54.	(price* or pricing*).ti,ab.
55.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
56.	(financ* or fee or fees).ti,ab.
57.	(value adj2 (money or monetary)).ti,ab.
58.	or/45-57
59.	statistical model/
60.	exp economic aspect/
61.	59 and 60
62.	*theoretical model/
63.	*nonbiological model/
64.	stochastic model/
65.	decision theory/
66.	decision tree/

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67.	monte carlo method/
68.	(markov* or monte carlo).ti,ab.
69.	econom* model*.ti,ab.
70.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
71.	or/61-70
72.	44 and (58 or 71)

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Chronic Pain EXPLODE ALL TREES
#2.	(((persist* or intract* or chronic or longstanding or long standing or longterm or long term or refractory or prolong* or long last* or sustain* or linger* or syndrome*) adj3 pain*))
#3.	(((chronic or persist* or idiopathic or atypical or a-typical) adj4 pain))
#4.	MeSH DESCRIPTOR Complex Regional Pain Syndromes EXPLODE ALL TREES
#5.	((complex regional pain syndrome* or CRPS or causalgia))
#6.	MeSH DESCRIPTOR Fibromyalgia EXPLODE ALL TREES
#7.	(((reflex or sympathetic) adj2 dystroph*))
#8.	MeSH DESCRIPTOR Vulvodynia EXPLODE ALL TREES
#9.	((vulvodynia or vestibulodynia or dyspareunia or vulvar vestibulitis or vulvitis))
#10.	MeSH DESCRIPTOR Cystitis, Interstitial EXPLODE ALL TREES
#11.	((interstitial adj2 cystitis))
#12.	MeSH DESCRIPTOR Reflex Sympathetic Dystrophy EXPLODE ALL TREES
#13.	((algodystroph* or sudek or sudeck*))
#14.	MeSH DESCRIPTOR Myofascial Pain Syndromes EXPLODE ALL TREES
#15.	((loin pain adj (haematuria or hematuria) adj syndrome*))
#16.	((LPHS or prostatodynia or CPPS or atypic* odontalgia or a-typic* odontalgia or burning mouth syndrome* or phantom tooth pain or neuropathic orofacial pain or "myofascial pain" or MPS))
#17.	(((pelvic or pelvis) adj pain syndrome*))
#18.	(((non-cardiac or noncardiac) adj3 chest adj3 pain))
#19.	((temporomandibular adj3 joint adj3 pain))
#20.	(((prostate or vulv* or bladder or perineal) adj3 pain))
#21.	((functional pain syndrome* or non-cancer pain or noncancer pain))
#22.	(((pelvic or pelvis or abdominal) adj3 pain adj3 (unknown or un-known or idiopathic or atypic* or a-typic*)))
#23.	((fibromyalgia* or fibrositis or myofascial pain syndrome))
#24.	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23)

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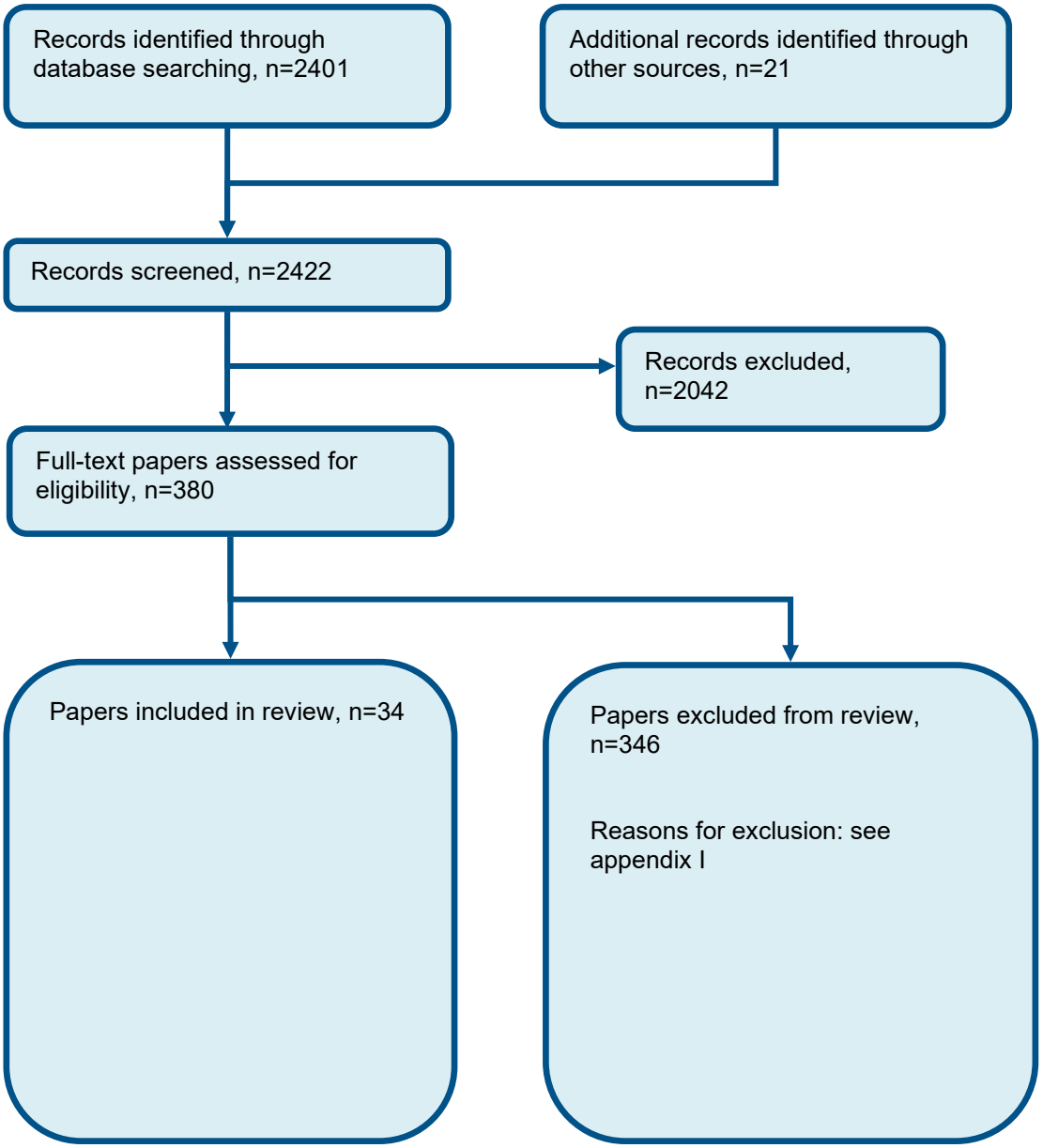
Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of electrical physical modalities



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Appendix D: Clinical evidence tables

Study	Altan 2005[19]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=53)
Countries and setting	Conducted in Turkey; Setting: Not stated
Line of therapy	Unclear
Duration of study	Intervention + follow up: 2 weeks + 3 months
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: Only state inclusion criteria, not assessment method
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	1. Localised pain and taut bands in the neck for a minimum of the previous 3 months; 2. Bilateral and significantly more tenderness in the three cervical trigger points (midpoint and the upper border of the trapezius muscle, origin of the supraspinatus muscle, and insertion of the sub occipital muscle) compared to the control point (a non0tender point over deltoid muscle). These three trigger points are among the 18 described for FMS according to 1990 American College of Rheumatology criteria; 3. Existence of no other criterion for FMS diagnosis; 4. No history or finding of cervical arthrosis, discal hernia, cervical vertebral fracture, radiculopathy, or myelopathy; 5. No pathological finding in blood count, urinalysis, sedimentation or cervical X-ray.
Exclusion criteria	Only inclusion criteria stated.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Laser group 43.48 (2.42) ; Placebo group 43.32 (2.1). Gender (M:F): 16/32. Ethnicity: Not stated
Further population details	Chronic primary musculoskeletal pain

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Extra comments	Duration of symptoms in years, mean (SD): Laser group 4.74 (1.3) Placebo group 4.38 (1.21).
Indirectness of population	No indirectness
Interventions	(n=26) Intervention 1: Electrical Physical Modalities - Laser therapy. GaAs laser treatment was applied over the three trigger points bilaterally and also one point in the taut bands in trapezius muscle bilaterally with a frequency of 1000 Hz for 2 min over each point once a day for 10 weekdays during a period of 2 weeks. The head of the instrument was held perpendicularly to and in slight contact with the skin. The infrared-27 GaAs diode laser instrument (Roland Serie Elettronica Pagani) with a wavelength of 904 nm, frequency range of 5-7000 Hz, and maximum power of 27 W, 50 W, or 27x4 W was used. Duration 2 weeks (10 sessions). Concurrent medication/care: All patients were instructed not to take nonsteroidal anti-inflammatory drugs (NSAID) or any other analgesic during the treatment and control periods. All patients in both groups were instructed to perform daily isometric exercises and stretching just short of pain 2 weeks at home. Indirectness: No indirectness. (n=27) Intervention 2: Placebo/Sham. A placebo laser treatment was given by using the same instrument in the same way over the same points as in the intervention group but not turning it on. Duration 2 weeks (10 sessions). Concurrent medication/care: All patients were instructed not to take nonsteroidal anti-inflammatory drugs (NSAID) or any other analgesic during the treatment and control periods. All patients in both groups were instructed to perform daily isometric exercises and stretching just short of pain 2 weeks at home. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LASER THERAPY versus PLACEBO/SHAM

Protocol outcome 1: Pain reduction
- Actual outcome: Pain intensity (VAS) at 2 weeks (end of treatment); Group 1: mean 4.13 (SD 0.58); n=23, Group 2: mean 3.92 (SD 0.42); n=25; Visual analogue scale (VAS) 0-10 Top=High is poor outcome; Comments: Baselines, mean (SD):
Laser group 6.85 (0.35)
Placebo group 6.24 (0.32)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: VAS baselines, mean (SD):
Laser group 6.85 (0.35)
Placebo group 6.24 (0.32); Group 1 Number missing: 3, Reason: Not available for treatment stage.; Group 2 Number missing: 2, Reason: Not available for

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treatment stage. - Actual outcome: Pain intensity (VAS) at 14 weeks; Group 1: mean 3.17 (SD 0.58); n=23, Group 2: mean 3.8 (SD 0.51); n=25; Visual analogue scale (VAS) 0-10 Top=High is poor outcome; Comments: Baselines, mean (SD): Laser group 6.85 (0.35) Placebo group 6.24 (0.32) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: VAS baselines, mean (SD): Laser group 6.85 (0.35) Placebo group 6.24 (0.32); Group 1 Number missing: 3, Reason: Not available for treatment stage.; Group 2 Number missing: 2, Reason: Not available for treatment stage.	
Protocol outcomes not reported by the study	Quality of life ; Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

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Study	Arbabi-kalati 2015[28]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=20)
Countries and setting	Conducted in Iran; Setting: Zahedan University of Medical Sciences
Line of therapy	Unclear
Duration of study	Intervention time: 2 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Burning mouth patients referred from Zahedan Faculty of Dentistry
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosis criteria: 1) burning sensation in all or a part of the oral cavity with or without symptoms such as a change in taste sensation for at least 4 months; 2) normal oral mucosa without any lesion; 3) absence of any local or systemic factors which produce the same symptoms.
Exclusion criteria	Any known systemic condition; patients under 18; pregnancy; smoking; patients with oral legions; patients not signing the informed consent form.
Recruitment/selection of patients	Referred from Zahedan Faculty of Dentistry
Age, gender and ethnicity	Age - Mean (SD): Laser group 47.2(+-5.3) ; Placebo group 46.6(+-4.6). Gender (M:F): 0/20. Ethnicity: Not reported
Further population details	1. Chronic orofacial pain
Extra comments	Duration of disease in months, mean+-SD: Laser group 13.4+-7.4(6-30) ; 15.5+-0.1(6-36)
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: Electrical Physical Modalities - Laser therapy. Low Level Laser Therapy (LLLT), wavelength 630 nm, power of 30 mW for 10 seconds, using an Iodine-Gallium-Aresnide laser of Mustange laser device (Russia). Laser dose 1 j/cm2. Applied to 10 areas on the oral mucosa, 2 areas on the tongue, 2 areas on the floor of the mouth, 1 area on the soft palate and 1 area on the soft palate. Duration Twice a week for 2 weeks.

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	Concurrent medication/care: None stated. Indirectness: No indirectness. (n=10) Intervention 2: Placebo/Sham. Silent/off laser therapy carried out for the same period and at the same points as the laser treatment group. Participants wore protective glasses, blinding them to the type of treatment modality used. Duration Twice a week for 2 weeks. Concurrent medication/care: None stated. Indirectness: No indirectness
Funding	Academic or government funding (Zahedan University of Medical Sciences)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LASER THERAPY versus PLACEBO/SHAM

Protocol outcome 1: Quality of life
- Actual outcome: Quality of life questionnaire at After treatment (2 weeks); Group 1: mean 12.8 (SD 11.4); n=10, Group 2: mean 28.6 (SD 11.5); n=10; Quality of life questionnaire (Persian version of Oral Health Impact Profile) 0-40 Top=High is poor outcome; Comments: Baseline, mean (SD):
Laser group 27.8 (12)
Placebo group 28.3 (11.9)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Outcome baselines comparable; Group 1 Number missing; Group 2 Number missing

Protocol outcome 2: Pain reduction
- Actual outcome: Pain on numeric rating scale at After treatment (2 weeks); Group 1: mean 3.6 (SD 3); n=10, Group 2: mean 8 (SD 1.5); n=10; Numeric rating scale (for severity of burning sensation) 0-10 Top=High is poor outcome; Comments: Baselines, mean (SD):
Laser group 8 (2.3)
Placebo group 8.2 (1.7)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Outcome baselines comparable.; Group 1 Number missing; Group 2 Number missing

Protocol outcomes not reported by the study	Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

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Study	Armagan 2006[31]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=32)
Countries and setting	Conducted in Turkey; Setting: Physical Therapy and Rehabilitation department of Osmangazi University hospital
Line of therapy	Unclear
Duration of study	Intervention + follow up: 10 day intervention and 6 month follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ACR criteria for fibromyalgia
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Widespread pain for at least 3 months located on both sides of the body and above and below the waist, the presence of at least 11 of 18 tender points on digital palpation
Exclusion criteria	Inflammatory causes of pain, inability to interrupt therapy with medications, presence of other conditions that could influence pain or response to treatment or ability to take part in treatment, pregnancy, major psychiatric disorders.
Recruitment/selection of patients	Not specified
Age, gender and ethnicity	Age - Mean (SD): 38.25 (5.36) years. Gender (M:F): All women. Ethnicity: Not specified
Further population details	Chronic widespread pain
Extra comments	Mean duration of pain 5.8 (3.2) years
Indirectness of population	No indirectness
Interventions	(n=16) Intervention 1: Electrical Physical Modalities - Laser therapy. Gal-Al-As diode laser device used with a power output of 50mW and a wavelength of 830nm. Diameter of laser beam 1mm, and laser was set to deliver a continuous form of energy, for 1 minute periods at each tender point (2 joules per tender joint). Once a day, 5 days a week for a total duration of 10 days and all participants treated by the same physician. Duration 10 days. Concurrent medication/care: Not specified. Indirectness: No indirectness

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	(n=16) Intervention 2: Placebo/Sham. Placebo laser therapy. The same treatment protocol and the laser device appeared to patients to be working, but no laser beam was transferred to the treated area, and all painful points were irradiated. Duration 10 days. Concurrent medication/care: Not specified. Indirectness: No indirectness.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LASER THERAPY versus PLACEBO/SHAM Protocol outcome 1: Quality of life - Actual outcome: FIQ at 10 days; Group 1: mean 58.5 (SD 10.33); n=16, Group 2: mean 63.63 (SD 9.59); n=16; FIQ 0-100 Top=High is poor outcome; Comments: Baseline: 65.5(9.01);65.38(9.44) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing; Group 2 Number missing - Actual outcome: FIQ at 6 months; Group 1: mean 62.06 (SD 8.99); n=16, Group 2: mean 66.94 (SD 8.44); n=16; FIQ 0-100 Top=High is poor outcome; Comments: Baseline: 65.5(9.01);65.38(9.44) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness.	
Protocol outcomes not reported by the study	Pain reduction ; Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

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Study	Bardellini 2019[37]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=90)
Countries and setting	Conducted in Italy; Setting: Department of oral medicine
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 10 weeks + 1 month
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: complaint of oral pain or burning for more than 6 months
Stratum	Overall: NA
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	Patients who had complained of oral pain or burning for more than 6 months
Exclusion criteria	age under 18 years, pregnancy, oral mucosal lesions, systemic disease (hypertension, diabetes, anaemia, vitamin B12 or folic acid deficiency.), gastro-esophageal reflux, Sjogren's syndrome, allergies, and hyposalivation; positivity to Candidida or other microorganisms
Recruitment/selection of patients	consecutive meeting the inclusion criteria
Age, gender and ethnicity	Age - Mean (SD): laser group: 59.76 (9.51) years, sham group: 60.86 (10.02) years . Gender (M:F): all female. Ethnicity: not reported

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Further population details	1. Chronic orofacial pain: Chronic orofacial pain 2. Chronic primary musculoskeletal pain: Pain other than chronic primary musculoskeletal pain 3. Chronic visceral pain: Pain other than chronic visceral pain 4. Chronic widespread pain: Pain other than chronic widespread pain 5. Cognitive impairment: Not stated / Unclear 6. Complex regional pain syndrome: Pain other than complex regional pain syndrome 7. First language not English: Not applicable 8. Homeless: Not stated / Unclear 9. Learning difficulties: Not stated / Unclear 10. Sensory impairment : Not stated / Unclear
Indirectness of population	No indirectness: NA
Interventions	(n=45) Intervention 1: Electrical Physical Modalities - Laser therapy. The laser instrument used for this trial was K Laser Cube 3®. The laser was applied by a trained dentist and irradiated the most painful areas in the oral cavity, with discontinuous combined wavelengths between 660-970 nm, medium power 3.2 W (6.4 W pulsed at 50%), treatment time 3'51", frequency 1-20000Hz, spot size 1cm². Treatment was once a week for 10 weeks. Duration 10 weeks . Concurrent medication/care: Not reported . Indirectness: No indirectness; Indirectness comment: NA Comments: NA (n=45) Intervention 2: Placebo/Sham. The device was turned on but the hand piece did not work. Laser/sham therapy was dispensed once a week for ten weeks. Duration 10 weeks . Concurrent medication/care: Not reported . Indirectness: No indirectness; Indirectness comment: NA Comments: NA
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LASER THERAPY versus PLACEBO/SHAM

Protocol outcome 1: Quality of life
- Actual outcome: Oral Health Impact Profile questionnaire (OHIP-14)
at 10 weeks ; Group 1: mean 7.09 (SD 2.59); n=43, Group 2: mean 10.64 (SD 4.13); n=42; OHIP-14 (Italian version) 0-56 Top=High is poor outcome; Comments: Baseline values: laser group 16.09 (4.2), sham group 15.26 (3.75)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement -

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Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 2, Reason: did not complete therapy; Group 2 Number missing: 3, Reason: did not complete therapy - Actual outcome: Oral Health Impact Profile questionnaire (OHIP-14) at 14 weeks (10 weeks + 1 month follow up); Group 1: mean 7.43 (SD 3.78); n=43, Group 2: mean 10.43 (SD 2.99); n=42; OHIP-14 (Italian version) 0-56 Top=High is poor outcome; Comments: Baseline values: laser group 16.09 (4.2), sham group 15.26 (3.75) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 2, Reason: did not complete therapy; Group 2 Number missing: 3, Reason: did not complete therapy	
Protocol outcomes not reported by the study	Pain reduction; Physical function; Psychological distress; Pain interference; Pain self-efficacy; Use of healthcare services; Sleep; Discontinuation

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Study	Boyer 2014[53]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=38)
Countries and setting	Conducted in France; Setting: La Timone University Hospital pain centre
Line of therapy	Unclear
Duration of study	Intervention time: 10 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ACR FMS criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged >18 years, right handed, diagnosis of FMS according to ACR, score of at least 4 on the BPI average pain intensity scale, pain for more than 6 months, stable treatment for more than 1 month before enrolment, rTMS naive
Exclusion criteria	Other causes of pain such as inflammatory or autoimmune disorders, current primary psychiatric conditions, substance abuse, contraindications for rTMS. Concomitant treatment for pain and sleep were allowed, provided the dose administered had been stable for at least 1 month before enrolment and remained stable throughout the study
Recruitment/selection of patients	Not specified
Age, gender and ethnicity	Age - Mean (SD): 48.5(10.5) years. Gender (M:F): 1:37. Ethnicity: Not reported
Further population details	Chronic widespread pain
Extra comments	Duration of pain 3.7(4.2) years
Indirectness of population	No indirectness
Interventions	(n=19) Intervention 1: Electrical Physical Modalities - Transcranial Magnetic Stimulation (TMS). 14 sessions over 10 weeks (10 sessions over 2 weeks followed by maintenance phase of 4 sessions across 4 weeks). Duration 10 weeks. Concurrent medication/care: Not specified (n=19) Intervention 2: Placebo/Sham. Identical treatment but with a sham coil, that emitted a similar sound to

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	the active coil. Duration 10 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Academic or government funding (Funding from Inserm and AP-HM)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCRANIAL MAGNETIC STIMULATION (TMS) versus PLACEBO/SHAM

Protocol outcome 1: Quality of life
- Actual outcome: SF-36 physical component summary score at 10 weeks; Group 1: mean 1.4 (SD 9); n=16, Group 2: mean 0.4 (SD 4.8); n=13; SF-36 0-100 Top=High is good outcome; Comments: Baseline: 29.9(7.5); 32.4(5.9)
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: NR; Group 2 Number missing: 6, Reason: NR
- Actual outcome: SF-36 mental component summary score at 10 weeks; Group 1: mean 5 (SD 6.9); n=16, Group 2: mean -1.6 (SD 7.6); n=13; SF-36 0-100 Top=High is good outcome; Comments: Baseline:39.6(11.4);34(9.3)
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: NR; Group 2 Number missing: 6, Reason: NR

Protocol outcome 2: Psychological distress
- Actual outcome: BDI at 10 weeks; Group 1: mean -1.9 (SD 2.8); n=16, Group 2: mean -0.1 (SD 4.4); n=16; BDI Not reported Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: NR; Group 2 Number missing: 6, Reason: NR
- Actual outcome: HADS anxiety at 10 weeks; Group 1: mean 0.4 (SD 1.7); n=16, Group 2: mean 0.5 (SD 2.3); n=13; HADS:A Not reported Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: NR; Group 2 Number missing: 6, Reason: NR

Protocol outcomes not reported by the study	Pain reduction ; Physical function ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

Study	**Brietzke 2019 [54]**
Study type	RCT (Patient randomised; Parallel)

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Number of studies (number of participants)	(n=20)
Countries and setting	Conducted in Brazil; Setting: Not specified
Line of therapy	Unclear
Duration of study	Intervention time: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of fibromyalgia (ACR 2011 criteria)
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosis of fibromyalgia according to diagnostic criteria, daily disability present for the routine activities during the 3 months preceding enrolment, a score of at least 50mm on VAS 0-100mm.
Exclusion criteria	Contra-indications of the NIBS stimulation, positive history of other conditions such as rheumatoid arthritis, lupus autoimmune disease, neurological or oncological disease or cardiovascular disease.
Recruitment/selection of patients	2017-2018
Age, gender and ethnicity	Age - Mean (range):48.6 (18-59; 49.7(45-54) years. Gender (M:F): All female. Ethnicity: Not reported
Further population details	Chronic widespread pain
Extra comments	Mean duration of symptoms 5.75(1.48); 6.62(1.64)
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: Electrical Physical Modalities – TDCS The anodal electrode was used over the left DLPFC and the cathode at the right DLPFC. Current applied at 2mA for 30 minutes for 5 consecutive days for 12 weeks. Current was delivered using 35cm2 electrodes coated with a vegetable sponge, which was moistened with saline solution before the start of the stimulation by 2 silicone cannulas coupled to the electrode. Neoprene caps were produced in small, medium and large sizes and cap size selected appropriately for each patients head. The electrode position was then accurate for the subjects to facilitate the identification and avoid incorrect placement of the electrodes, the anode was painted red and cathode black (although equipment already set up – participant could not change any part of it). Duration 3 months. Concurrent medication/care: Not specified (n=10) Intervention 2: Placebo/Sham. Identical treatment but the electrical stimulation was not applied in the

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	sham group. Duration 3 months. Concurrent medication/care: Not specified
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TDCS versus PLACEBO/SHAM

Protocol outcome 1: Psychological distress
- Actual outcome: BDI at 3 months; Group 1: mean 11.8 (SD 5.63); n=10, Group 2: mean 21.5 (SD 6.6); n=10; BDI 0-61 Top=High is poor outcome; Comments: Baseline: 27.1(12.1); 20.5(5.63)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness

Protocol outcome 1: Sleep
- Actual outcome: Pittsburgh sleep quality index at 3 months; Group 1: mean 7.9 (SD 7.44); n=10, Group 2: mean 16.7 (SD 3.74); n=10; PSQI, range not reported, Top=High is poor outcome; Comments: Baseline: 27.5(7.63); 24.6(7.57)
Risk of bias: All domain – High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Quality of life; Pain reduction; Physical function ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Discontinuation

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Study	Carretero 2009[61]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=26)
Countries and setting	Conducted in Spain; Setting: Trial part of wider project investigating the usefulness of LF-RTMS in major depression being carried out by Hospital Son Llatzer, Hospital Son Dureta, and the University of the Balearic Islands, Majorca.
Line of therapy	Unclear
Duration of study	Intervention + follow up: 4 weeks + 8 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Fibromyalgia diagnosed by a rheumatologist according to the criteria of the American College of Rheumatology
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Over 18 and fulfilling the diagnostic criteria for major depression (Diagnostic and Statistical Manual of Mental Disorders-IV Text Revision) and fibromyalgia (criteria of the American College of Rheumatology).
Exclusion criteria	Not stated
Age, gender and ethnicity	Age - Mean (SD): Real TMS group 47.5 (5.7) ; Sham TMS group 54.9 (4.9). Gender (M:F): 2/24. Ethnicity: Not stated
Further population details	Chronic widespread pain
Extra comments	Duration of illness in participants not stated, but assumed from fibromyalgia diagnosis (≥ 3 months).
Indirectness of population	No indirectness
Interventions	(n=14) Intervention 1: Electrical Physical Modalities - Transcranial Magnetic Stimulation (TMS). High-frequency repetitive transcranial magnetic stimulation (HF-rTMS) using DANTEC TMS equipment (Dantec Medical, Medtronic Inc., Minneapolis, MN), MagLite model. A butterfly coil with each wing of 8.5 cm in diameter was used. Stimulation parameters were 20 trains at 110% of motor threshold for 60 seconds at 1 Hz and a 45-second interval between trains. A total of 1,200 pulses was administered at each of the 20 sessions, which each took approximately 30 minutes. The stimulation area was the right dorsolateral prefrontal area, 5 cm in front of the specular point that triggered a more selective right-thumb abduction response in the left motor cortex. Duration 4 weeks (20 sessions). Concurrent medication/care: Pharmacologic therapy remained

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	unchanged during the month before the study and during the study. (n=12) Intervention 2: Placebo/Sham. In the sham sessions, the coil was placed perpendicularly to the cranium at the calculated stimulation point, before being inclined 45° forward on the axis. Thus, the magnetic field did not significantly penetrate the brain, although the patient did hear the sound produced by the apparatus. It was explained to patients that two randomly selected methods for applying magnetic fields were being used, and that the researchers wanted to know which one was more useful for people in their situation. Duration 4 weeks (10 sessions). Concurrent medication/care: Pharmacologic therapy remained unchanged during the month before the study and during the study.
Funding	Academic or government funding (IUNICS Institute, Universitat Illes Balears - grant SEJ2007-62312 (MICINN-FEDER Funds))

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCRANIAL MAGNETIC STIMULATION (TMS) versus PLACEBO/SHAM

Protocol outcome 1: Pain reduction
- Actual outcome: Pain reduction (Likert pain scale) at 3 months; Group 1: mean 8.1 (SD 1); n=14, Group 2: mean 7.5 (SD 2.1); n=12; Likert pain scale 0-10 Top=High is poor outcome; Comments: Baselines, mean (SD):
Real TMS group 8.7 (1.2)
Sham TMS group 8.6 (1.9)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: Small variation in continued background psychopharmacological therapy between patients; Group 1 Number missing: 1, Reason: Did not complete the treatment cycle. Group 2 Number missing: 1, Reason: Did not complete the treatment cycle.

Protocol outcomes not reported by the study	Quality of life ; Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

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Study	Chow 2004[77]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=20)
Countries and setting	Conducted in Australia; Setting: Not specified
Line of therapy	Unclear
Duration of study	Intervention + follow up: 7 week intervention and 3 months follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of chronic neck pain
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Over 18 years old, chronic neck pain, not experienced previous treatment with laser therapy other than laser acupuncture.
Exclusion criteria	Work related or third party injuries in which litigation or compensation was still current, abnormal neurological signs, inability to discontinue activity that exacerbated pain, conditions that could limit effectiveness of laser therapy or cause pain.
Recruitment/selection of patients	Adverts in the practice of the principle author
Age, gender and ethnicity	Age - Mean (SD): 57.7(10.9) years. Gender (M:F): 4:16. Ethnicity: Not specified
Further population details	Chronic primary musculoskeletal pain
Extra comments	Mean duration of pain 13.3 years (SE 2.48)
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: Electrical Physical Modalities - Laser therapy. 830nm laser therapy for 7 weeks. Diolase device, 15mm length laser and 3mm width at widest, 300mW power. Laser applied for 30s per point or until the area became less tender. 30 minute sessions. Duration 7 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=10) Intervention 2: Placebo/Sham. Identical treatment but laser did not emit a beam. Duration 7 weeks.

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	Concurrent medication/care: Not specified. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LASER THERAPY versus PLACEBO/SHAM

Protocol outcome 1: Quality of life
- Actual outcome: SF-36 physical component summary score at 3 months (including 7 week intervention); Group 1: mean 4 (SD 8.22); n=10, Group 2: mean 1.22 (SD 6.32); n=10; SF-36 0-100 Top=High is good outcome; Comments: Baseline mean (SEs): 39(3.6); 41.6(3)
SDs calculated from SDs reported in the study
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: NA, Reason: NR; Group 2 Number missing: NA, Reason: NR
- Actual outcome: SF-36 mental component summary score at 3 months (including 7 week intervention); Group 1: mean 1.71 (SD 3.79); n=10, Group 2: mean 0 (SD 6.01); n=10; SF-36 0-100 Top=High is good outcome; Comments: Baseline mean (SEs): 50.9(3.4);50.1(2.5)
SDs calculated from SDs reported in the study
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: NA, Reason: NR; Group 2 Number missing: NA, Reason: NR

Protocol outcome 2: Pain reduction
- Actual outcome: VAS at 3 months (including 7 week intervention); Group 1: mean 2.1 (SD 2.84); n=10, Group 2: mean 0.7 (SD 1.58); n=10; VAS 0-10 Top=High is poor outcome; Comments: Baseline mean (SEs): 3.9(0.6); 3.2(0.5)
SDs calculated from SDs reported in the study
Note: change scores in study transformed to scale whereby high score is good outcome. Converted back to high score = poor outcome in the analysis
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: NA, Reason: NR; Group 2 Number missing: NA, Reason: NR

Protocol outcomes not reported by the study	Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

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Study	Chow 2006[78]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=90)
Countries and setting	Conducted in Australia; Setting: Large suburban medical centre of 17 GPs in Sydney, Australia
Line of therapy	Unclear
Duration of study	Intervention + follow up: 7 week intervention and 12 week follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Chronic neck pain with unknown cause
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	18 years and over, pain for at least 3 months
Exclusion criteria	Injury with current compensation or litigation, abnormal neurological signs in the upper limbs due to nerve abnormalities, unable to discontinue activities that exacerbate pain, pregnancy, previous surgery on the cervical spine, RA, neck pain part of a widespread pain syndrome involving other areas, known photosensitivity or illnesses unrelated to neck pain which precluded involvement in study.
Recruitment/selection of patients	2002-2003, Posters in waiting room of medical centre and local newspaper adverts.
Age, gender and ethnicity	Age - Mean (SD): 56(12.8) years. Gender (M:F): 31:59. Ethnicity: Not specified
Further population details	Chronic primary musculoskeletal pain
Extra comments	Duration of pain 15(12.6) years
Indirectness of population	No indirectness
Interventions	(n=45) Intervention 1: Electrical Physical Modalities - Laser therapy. Diolase laser devices. 7 week intervention 1 session per week. Subjects treated with laser 15mm in length and 3mm at widest with a wavelength of 830nm and power of 300mW. Subjects seated comfortably and tender points in the next were identified, and each treated for 30 seconds per point with up to 50 points being treated within the maximum half-hour allocated for treatment. Number of points dependent on severity of symptoms. Duration 7 weeks. Concurrent medication/care: Not specified. Indirectness: No indirectness

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	(n=45) Intervention 2: Placebo/Sham. Sham laser therapy. Digital display of machine on and sound emitted identical to active intervention, but device did not emit laser. Duration 7 weeks. Concurrent medication/care: Not specified. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LASER THERAPY versus PLACEBO/SHAM

Protocol outcome 1: Quality of life
- Actual outcome: SF-36 physical component summary score at 3 months (follow up); Group 1: mean 3.2 (SD 10.78); n=45, Group 2: mean 1.3 (SD 4.28); n=45; SF-36 summary score 0-100 Top=High is good outcome; Comments: Baseline not reported
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness; Group 1 Number missing: 2, Reason: Family illness; Group 2 Number missing: 3, Reason: Family illness, asthma requiring steroid treatment, unanticipated work changes
- Actual outcome: SF-36 mental component summary score at 3 months (follow up); Group 1: mean 2.4 (SD 8.99); n=45, Group 2: mean 5.4 (SD 10.98); n=45; SF-36 summary score 0-100 Top=High is good outcome; Comments: Baseline not reported
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness; Group 1 Number missing: 2, Reason: Family illness; Group 2 Number missing: 3, Reason: Family illness, asthma requiring steroid treatment, unanticipated work changes

Protocol outcome 2: Pain reduction
- Actual outcome: VAS at 3 months (follow up); Group 1: mean -2.7 (SD 1.99); n=45, Group 2: mean 0.3 (SD 2.33); n=45,
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: Family illness; Group 2 Number missing: 3, Reason: Family illness, asthma requiring steroid treatment, unanticipated work changes

Protocol outcome 3: Discontinuation
- Actual outcome: Discontinuation of study at 3 months (follow up); Group 1: 2/45, Group 2: 3/45
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness; Group 1 Number missing: 2, Reason: Family illness; Group 2 Number missing: 3, Reason: Family illness, asthma requiring steroid treatment, unanticipated work changes

Protocol outcomes not reported by the study	Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep

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Study	Da cunha 2008[92]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Brazil; Setting: Center of Occlusion and Temporomandibular Disorder of the Dental School of Sao Paulo State University (UNESP), Sao Jose dos Campos.
Line of therapy	Unclear
Duration of study	Intervention time: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Temporomandibular disorder diagnosed based on complete clinical examination, including patient's history, at the Center of Occlusion and Temporomandibular Disorder of the Dental School of Sao Paulo State University (UNESP).
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Sample selection was done based on complete clinical examination, including patients' history, masticatory and cervical muscle palpation, joint palpation and joint noises.
Exclusion criteria	Patients presenting asymptomatic joint clicking, major psychological problems, heart disease, psoriasis, rheumatoid arthritis, pregnancy and patients with pacemakers were not included in this study. Patients presenting myofascial trigger points and fibromyalgia were also excluded because of the particular characteristics of these entities.
Recruitment/selection of patients	One hundred and twenty patients were selected for assessment on a voluntary basis from a waiting list of those who presented for diagnosis and treatment of temporomandibular disorder.
Age, gender and ethnicity	Age - Mean: Laser group 40.15 years; Placebo group 46.6. Gender (M:F): 1/39. Ethnicity: Not stated
Further population details	1. Chronic orofacial pain
Extra comments	Before participating in this study, the selected patients had been waiting for treatment for at least six months, without any form of professional care.
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Electrical Physical Modalities - Laser therapy. The experimental group received laser treatment performed with a Ga-Al-As (Gallium-Aluminium-Arsenide) low level laser (Biolux laser - Bio-Art, Sao

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	Carlos, SP, Brazil) from a probe applied perpendicularly and directly over the painful area. Duration 4 weeks. Concurrent medication/care: Patients had not received treatment or any professional care for 6 months prior to trial. Indirectness: No indirectness (n=20) Intervention 2: Placebo/Sham. The control group received a placebo treatment performed exactly in the same manner, but without energy output. Duration 4 weeks. Concurrent medication/care: Patients had not received treatment or any professional care for 6 months prior to trial. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LASER THERAPY versus PLACEBO/SHAM Protocol outcome 1: Pain reduction - Actual outcome: Level of pain (VAS) at 4 weeks (end of treatment); Group 1: mean 3.62 Visual analogue scale (VAS) (SD 2.45); n=20, Group 2: mean 4.67 Visual analogue scale (VAS) (SD 1.9); n=20; Visual analogue scale (VAS) 0-10 Top=High is poor outcome; Comments: Baselines, mean (SD): Laser group 6.87 (2.12) Placebo group 6.60 (2.57) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Mean pain baseline on VAS comparable between treatment and placebo groups.	
Protocol outcomes not reported by the study	Quality of life ; Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

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Study (subsidiary papers)	Dailey 2019[94] (Dailey 2020[95])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=301)
Countries and setting	Conducted in USA; Setting: dual-site: University and University Medical Center
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: met ACR criteria for FM
Stratum	Overall: NA
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	female sex, age 18–70 years, FM according to the American College of Rheumatology 1990 criteria, on a stable medication regimen during the 4 weeks preceding the study, and projected to be on a stable treatment regimen for the next 2 months
Exclusion criteria	pain level of <4 on a 10-point numerical rating scale (NRS) at the first and second visits, inability to walk 6 minutes without assistance, TENS use in the last 5 years, presence of a pacemaker, history of neuropathic or autoimmune disorder, history of spinal fusion or metal implants in the spine, allergy to adhesive or nickel, pregnancy, epilepsy, and/or a serious or unstable medical or psychiatric condition that would preclude participation
Recruitment/selection of patients	recruited from the Pain Clinic, Rheumatology Clinic, Family Practice Clinic, Orthopedic Clinic, local physician offices, support groups, local physical therapy clinics, and radio and TV interviews, also from UIHC EPIC database for individuals with a diagnosis of myalgia and ResearchMatch (www.researchmatch.org). Specific recruitment strategies included mass email, posting flyers, and discussion of the project with physicians and nurses.

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Age, gender and ethnicity	Age - Mean (SD): active: 44.7 (14.3), placebo: 47.2 (12.6), no TENS: 48.6 (11.8). Gender (M:F): all female . Ethnicity: White: active 92%, placebo 92%, no TENS 92%; not Hispanic: active 95%, placebo 95%, no TENS 95%
Further population details	1. Chronic orofacial pain: Pain other than chronic orofacial pain 2. Chronic primary musculoskeletal pain: Pain other than chronic primary musculoskeletal pain 3. Chronic visceral pain: Pain other than chronic visceral pain 4. Chronic widespread pain: Chronic widespread pain 5. Cognitive impairment: Not stated / Unclear 6. Complex regional pain syndrome: Pain other than complex regional pain syndrome 7. First language not English: Not stated / Unclear 8. Homeless: Not stated / Unclear 9. Learning difficulties: Not stated / Unclear 10. Sensory impairment : Not stated / Unclear
Extra comments	Duration of fibromyalgia, median (range) years: active 7 (3–12), placebo 7 (2–14), no TENS 7 (4–15)
Indirectness of population	No indirectness: NA
Interventions	(n=103) Intervention 1: Electrical Physical Modalities - Transcutaneous Electrical Nerve Stimulation (TENS). EMPI-Select TENS (DJO Global, Vista, CA) delivered through butterfly electrodes placed at the cervicothoracic junction and lower back. Active-TENS parameters were asymmetrical, biphasic waveform with a modulating frequency (2-125 Hz), pulse duration 200u sec, and highest tolerable stimulation intensity. TENS was applied by the TENS-Allocator in the clinic for 30 min prior to the Outcome-Assessor measuring effects on pain, fatigue, and function. Following completion of Visit-2, active-TENS was sent home with participants with an instruction manual developed by study personnel. TENS-Allocators used a standardized script to instruct participants in home use and for weekly contact. Participants were instructed to use TENS at least 2h per day during activity. TENS units monitored number of sessions, number of minutes used, and average intensity per channel. Duration 4 weeks. Concurrent medication/care: All participants continued current treatments prescribed by their health care provider and were asked not to change medications during the study. . Indirectness: No indirectness; Indirectness comment: NA (n=99) Intervention 2: Placebo/Sham. EMPI-Select TENS (DJO Global, Vista, CA) delivered through butterfly electrodes placed at the cervicothoracic junction and lower back. TENS was applied by the TENS-Allocator in the clinic for 30 min prior to the Outcome-Assessor measuring effects on pain, fatigue, and function. The placebo-TENS unit delivered current for 45s ramping down to 0 in the last 15s and the appearance was identical to the active unit. Following completion of Visit-2 placebo-TENS was sent home with participants with an instruction manual developed by study personnel.

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	TENS-Allocators used a standardized script to instruct participants in home use and for weekly contact. Participants were instructed to use TENS at least 2h per day during activity. Placebo-TENS units monitored number of sessions, number of minutes used, and average intensity per channel. Duration 4 weeks . Concurrent medication/care: All participants continued current treatments prescribed by their health care provider and were asked not to change medications during the study.. Indirectness: No indirectness; Indirectness comment: NA (n=99) Intervention 3: Usual care. No TENS - used a mock-TENS during visits to blind Outcome-Assessors with electrodes that were attached to a TENS unit that provided no current intensity Duration 4 weeks . Concurrent medication/care: All participants continued current treatments prescribed by their health care provider and were asked not to change medications during the study. Indirectness: No indirectness; Indirectness comment: NA
Funding	Academic or government funding (NIH. One author received consulting fees from pharmaceutical companies. Active and placebo TENS units and electrodes were provided by DJO, Inc.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION (TENS) versus PLACEBO/SHAM

Protocol outcome 1: Quality of life
- Actual outcome: SF36 mental composite at 4 weeks ; MD; 1.1 (95%CI -1.9 to 4.1) (p value : >0.99) T score SF36 0-100 Top=High is good outcome, Comments: Mean difference in T scores, adjusted for study site differences at baseline. Baseline values: TENS 88.7 (10), placebo 40.2 (10.2);
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: difference in marital status and FIQR, but model adjusted for baseline differences ; Group 1 Number missing: 18, Reason: unclear ; Group 2 Number missing: 18, Reason: unclear
- Actual outcome: SF36 physical composite at 4 weeks ; MD; 1.2 (95%CI -0.7 to 3.1) (p value : 0.36) T scores SF36 0-100 Top=High is good outcome, Comments: Mean difference in T scores, adjusted for study site differences at baseline. Baseline values: TENS 32.7 (6.4), placebo 33.3 (6.2)
;
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: difference in marital status and FIQR, but model adjusted for baseline differences ; Group 1 Number missing: 18, Reason: unclear ; Group 2 Number missing: 18, Reason: unclear

Protocol outcome 2: Pain reduction
- Actual outcome: Brief pain inventory - intensity at 4 weeks ; MD; -0.5 (95%CI -1 to 0) (p value : 0.036) BPI intensity 0-10 Top=High is poor outcome, Comments: Adjusted for study site differences at baseline. Baseline values: not reported ;

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Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: difference in marital status and FIQR, but model adjusted for baseline differences. Outcome values at baseline not reported ; Group 1 Number missing: 18, Reason: unclear ; Group 2 Number missing: 18, Reason: unclear

Protocol outcome 3: Physical function
- Actual outcome: 6 minute walk test at 4 weeks ; MD; 19 (95%CI -58 to 96) (p value : >0.99) number of feet walked , Comments: adjusted for study site differences at baseline. Baseline values: TENS 1386 (323), placebo 1358 (305);
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: difference in marital status and FIQR, but model adjusted for baseline differences ; Group 1 Number missing: 18, Reason: unclear ; Group 2 Number missing: 18, Reason: unclear

Protocol outcome 4: Psychological distress
- Actual outcome: PROMIS depression at 4 weeks ; MD; -2.7 (95%CI -4.7 to -0.8) (p value : 0.002) T scores PROMIS depression 8-40 Top=High is poor outcome, Comments: Mean difference in T scores, adjusted for study site differences at baseline. Baseline values: TENS 58.1 (8.1), placebo 55.7 (8.5)
;
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: difference in marital status and FIQR, but model adjusted for baseline differences ; Group 1 Number missing: 18, Reason: unclear ; Group 2 Number missing: 18, Reason: unclear
- Actual outcome: PROMIS anxiety at 4 weeks ; MD; -0.5 (95%CI -2.7 to 1.7) (p value : >0.99) T scores PROMIS anxiety 7-35 Top=High is poor outcome, Comments: Mean difference in T scores, adjusted for study site differences at baseline. Baseline values: TENS 58.8 (8.7), placebo 58.1 (8)
;
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: difference in marital status and FIQR, but model adjusted for baseline differences ; Group 1 Number missing: 18, Reason: unclear ; Group 2 Number missing: 18, Reason: unclear

Protocol outcome 5: Pain interference
- Actual outcome: Brief pain inventory - interference at 4 weeks ; MD; -0.7 (95%CI -1.3 to 0.01) (p value : 0.043) NA BPI interference 0-10 Top=High is poor outcome, Comments: adjusted for study site differences at baseline. Baseline values: not reported ;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: difference in marital status and FIQR, but model adjusted for baseline differences. Outcome values at baseline not reported ; Group 1 Number missing: 18, Reason: unclear ; Group 2 Number missing: 18, Reason: unclear

Protocol outcome 6: Pain self-efficacy
- Actual outcome: Pain self-efficacy questionnaire at 4 weeks ; MD; 1.6 (95%CI -1.8 to 5.1) (p value : 0.75) NA Pain self-efficacy questionnaire 0-

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60 Top=High is good outcome, Comments: adjusted for study site differences at baseline. Baseline values: TENS 28.2 (13.3), placebo 29.9 (13.1)
;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: difference in marital status and FIQR, but model adjusted for baseline differences ; Group 1 Number missing: 18, Reason: unclear ; Group 2 Number missing: 18, Reason: unclear

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION (TENS) versus USUAL CARE

Protocol outcome 1: Quality of life
- Actual outcome: SF36 mental composite at 4 weeks ; MD; 2.4 (95%CI -0.6 to 5.3) (p value : 0.17) T scores SF36 0-100 Top=High is good outcome, Comments: mean difference in T scores, adjusted for study site differences at baseline. Baseline values: TENS 38.7 (10), no TENS 39.5 (10.6)
;
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: difference in marital status and FIQR, but model adjusted for baseline differences ; Group 1 Number missing: 18, Reason: unclear ; Group 2 Number missing: 8, Reason: unclear
- Actual outcome: SF36 physical composite at 4 weeks ; MD; 1 (95%CI -0.8 to 2.8) (p value : 0.58) T scores SF36 0-100 Top=High is good outcome, Comments: mean difference in T scores, adjusted for study site differences at baseline. Baseline values: TENS 32.7 (6.4), no TENS 32.7 (6.6)
;
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: difference in marital status and FIQR, but model adjusted for baseline differences ; Group 1 Number missing: 18, Reason: unclear ; Group 2 Number missing: 8, Reason: unclear

Protocol outcome 2: Pain reduction
- Actual outcome: Brief pain inventory - intensity at 4 weeks ; MD; -0.9 (95%CI -1.4 to -0.4) (p value : <0.0001) BPI intensity 0-10 Top=High is poor outcome, Comments: adjusted for study site differences at baseline. Baseline values: not reported ;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: difference in marital status and FIQR, but model adjusted for baseline differences. Baseline outcome values not reported ; Group 1 Number missing: 18, Reason: unclear ; Group 2 Number missing: 8, Reason: unclear

Protocol outcome 3: Physical function
- Actual outcome: 6 minute walk test at 4 weeks ; MD; 42 (95%CI -34 to 117) (p value : >0.99) number of feet walked , Comments: adjusted for study site differences at baseline. Baseline values: TENS 1386 (323), no TENS 1316 (318)
;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

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Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: difference in marital status and FIQR, but model adjusted for baseline differences ; Group 1 Number missing: 18, Reason: unclear ; Group 2 Number missing: 8, Reason: unclear

Protocol outcome 4: Psychological distress
- Actual outcome: PROMIS depression at 4 weeks ; MD; -3.2 (95%CI -5.1 to -1.3) (p value : 0.0001) T scores PROMIS depression 8-40 Top=High is poor outcome, Comments: mean difference in T scores, adjusted for study site differences at baseline. Baseline values: TENS 58.1 (8.1), no TENS 56.6 (8.1)
;
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: difference in marital status and FIQR, but model adjusted for baseline differences ; Group 1 Number missing: 18, Reason: unclear ; Group 2 Number missing: 8, Reason: unclear
- Actual outcome: PROMIS anxiety at 4 weeks ; MD; -0.4 (95%CI -2.5 to 1.7) (p value : >0.99) T scores , Comments: mean difference in T scores, adjusted for study site differences at baseline. Baseline values: TENS 58.8 (8.7), no TENS 58.3 (7.8)
;
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: difference in marital status and FIQR, but model adjusted for baseline differences ; Group 1 Number missing: 18, Reason: unclear ; Group 2 Number missing: 8, Reason: unclear

Protocol outcome 5: Pain interference
- Actual outcome: Brief pain inventory - interference at 4 weeks ; MD; -0.6 (95%CI -1.3 to 0) (p value : 0.048) BPI interference 0-10 Top=High is poor outcome, Comments: adjusted for study site differences at baseline. Baseline values: not reported ;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: difference in marital status and FIQR, but model adjusted for baseline differences. Baseline outcome values not reported ; Group 1 Number missing: 18, Reason: unclear ; Group 2 Number missing: 8, Reason: unclear

Protocol outcome 6: Pain self-efficacy
- Actual outcome: Pain self-efficacy questionnaire at 4 weeks ; MD; 2.3 (95%CI -1 to 5.7) (p value : 0.28) Pain self-efficacy questionnaire 0-60 Top=High is good outcome, Comments: adjusted for study site differences at baseline. Baseline values: TENS 28.2 (13.3), no TENS 29 (13.2)
;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: difference in marital status and FIQR, but model adjusted for baseline differences ; Group 1 Number missing: 18, Reason: unclear ; Group 2 Number missing: 8, Reason: unclear

Protocol outcomes not reported by the study	Use of healthcare services; Sleep; Discontinuation

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Study	Dall'agnol 2014[96]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=24)
Countries and setting	Conducted in Brazil
Line of therapy	Unclear
Duration of study	Intervention + follow up: 10 rTMS sessions + 3 months follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Myofascial pain syndrome was diagnosed by two independent examiners with more than 10 years of clinical experience related to chronic pain.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Right-handed females aged 19 to 65 years with a diagnosis of myofascial pain syndrome in an upper body segment for at least 3 months prior to enrolment. Participants were also required to be experiencing limitation in at least one of the following areas of life: work, personal relationships, pleasure of activities, responsibilities at home, personal goals, clear thinking. MPS as defined by regional pain, normal neurologic examination, decreased range of motion, stiffness in the muscles, presence of trigger points, taut bands, tender points, palpable nodules, and pain characterized by dull, hollow, or deep that was exacerbated during stress. Must have scored ≥ 4 on the Neuropathic Pain Diagnostic Questionnaire.
Exclusion criteria	Presence of any other pain disorder, such as rheumatoid arthritis, radiculopathy, and fibromyalgia;
Age, gender and ethnicity	Age: mean (SD): 45.43(12.86) years . Gender (M:F): 0:24. Ethnicity: Not stated
Further population details	Chronic primary musculoskeletal pain
Indirectness of population	No indirectness
Interventions	(n=12) Intervention 1: Electrical Physical Modalities - Transcranial Magnetic Stimulation (TMS). TMS performed with a MagPro X100 and a figure-8 coil. The hot spot was marked on the scalp with a soft-tip pen. The subjects were comfortably seated in a reclining chair with arm rests for relaxing arms and hand positioning. The coil was placed over the left motor cortex (M1), held tangentially to the scalp with the handle pointing back and away from the midline at 45 degrees. All participants underwent rTMS delivered in trains consisting of 16 series of 10-second pulses with a high frequency of 10 Hz of biphasic magnetic stimulator (MagPro X100) and an interval of 26 seconds between each train, giving a total of 1,600 pulses per session. The stimulation intensity used was 80% of resting motor threshold (RMT). Duration 10 sessions. Concurrent

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	medication/care: All of the patients were permitted to use supplementary analgesic medication (acetaminophen, ibuprofen, codeine, or tramadol) to relieve their pain if necessary. Patients were allowed to take 750mgof acetaminophen up to 4 times per day and 200 mg of ibuprofen at maximum 4 times per day as a rescue analgesic. If these drugs were ineffective, patients could use Dorflex (Sanofi Aventis, Sao Paulo, Brazil; 35 mg orphenadrine citrate combined with 300 mg dipyrone and 50 mg caffeine). If their pain persisted, patients were permitted to use 60mgof codeine up to 4 times per day or tramadol 3 times per day. The patients were asked to record their analgesic intake during the treatment period in their pain diaries, and these diaries were reviewed during each intervention session. The total analgesic dose administered during treatment was considered for the analysis. Indirectness: No indirectness (n=12) Intervention 2: Placebo/Sham. During placebo (sham stimulation), an inactive rTMS coil (MagPro X100) was used as a sham coil and was placed in the identical area as the active coil. The patient recorded identical experiences (including sound effects and somatic sensations caused by contraction of the muscles of the scalp) as during active stimulation. Duration 10 sessions. Concurrent medication/care: All of the patients were permitted to use supplementary analgesic medication (acetaminophen, ibuprofen, codeine, or tramadol) to relieve their pain if necessary. Patients were allowed to take 750mgof acetaminophen up to 4 times per day and 200 mg of ibuprofen at maximum 4 times per day as a rescue analgesic. If these drugs were ineffective, patients could use Dorflex (Sanofi Aventis, Sao Paulo, Brazil; 35 mg orphenadrine citrate combined with 300 mg dipyrone and 50 mg caffeine). If their pain persisted, patients were permitted to use 60mgof codeine up to 4 times per day or tramadol 3 times per day. The patients were asked to record their analgesic intake during the treatment period in their pain diaries, and these diaries were reviewed during each intervention session. The total analgesic dose administered during treatment was considered for the analysis. Indirectness: No indirectness
Funding	Academic or government funding (Grants and material from the Brazilian Innovation Agency, Committee for the Development of Higher Education Personnel, National Council for Scientific and Technological Development, Postgraduate Program in Medical Sciences at the School of Medicine of the Federal University of Rio Grande do Sul, Postgraduate Research Group at the Hospital de Clinicas de Porto Alegre and the Foundation for Support of Research at Rio Grande do Sul.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCRANIAL MAGNETIC STIMULATION (TMS) versus PLACEBO/SHAM

Protocol outcome 1: Pain reduction
- Actual outcome: Pain intensity (visual analogue scale) at 3 months after treatment; Group 1: mean 3.57 Pain reported on VAS (SD 2.82); n=12, Group 2: mean 5.29 Pain reported on VAS (SD 2.78); n=12; VAS 0-10 Top=High is poor outcome; Comments: Baselines, mean (SD):
Placebo 6.83 (2.45)

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rTMS 6.94 (1.7) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Treatment inefficacy.; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

Study	**Del vecchio 2019[101]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=60)
Countries and setting	Conducted in Italy; Setting: Department of Dental Sciences and Maxillo-Facial Surgery of Sapienza, University of Rome
Line of therapy	Unclear
Duration of study	Intervention time: 1 week

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Method of assessment of guideline condition	Adequate method of assessment/diagnosis: TMJD diagnosis. The disorder was diagnosed by clinical and radiological examinations and according to the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD)Axis I and Axis II
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	The inclusion criteria to been rolled in the study were: the presence of pain in the joint area and/or radiating to the face, jaw, or neck for at least six months; reduced mouth opening or jaw locks; painful clicking, popping or grating when opening or closing the mouth; occlusal changes; no muscle tenderness at palpation; and no drug consumption for at least three weeks before treatment.
Exclusion criteria	None specified
Recruitment/selection of patients	Not specified
Age, gender and ethnicity	Age - Mean (SD): 42.55 (14.842) years. Gender (M:F): 12:74. Ethnicity: Not specified
Further population details	Chronic orofacial pain
Extra comments	Duration of pain not specified (minimum duration 6 months)
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Electrical Physical Modalities - Laser therapy. Received LLLT through the B-cureDental Pro low-level laser device, provided by BiocareEnterprise Limited (Good Energies, Haifa, Israel). This medical device emits a low-level laser beam with a wavelength of 808 nm; each application was performed at 5 J/min, 250 mW and 15 KHz for 8 m, for a total of40J each, directly over the pain area. The treatment had to be performed twice a day for seven consecutive days. A laser therapy expert examiner performed the first application at the Department of Dental Sciences and Maxillo-Facial Surgery of Sapienza, University of Rome. This first application was used as an instruction to the patients so they could perform the successive applications by themselves at home. The same examiner explained clearly to each patient how to use and safely store the devices. After the instruction, each patient performed the remaining applications at home. Duration 1 week. Concurrent medication/care: Not specified. Indirectness: No indirectness (n=30) Intervention 2: Placebo/Sham. Participants received the same instructions and followed the same protocol as the SG patients but received a sham laser device manufactured also by Biocare Enterprise Limited (Good Energies, Haifa,Israel) with the same exterior characteristics of the effective device, including the guide beam and the working sound, but devoid of the therapeutic diode source. Duration 1 week. Concurrent medication/care: Not specified. Indirectness: No indirectness

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Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LASER THERAPY versus PLACEBO/SHAM Protocol outcome 1: Pain reduction - Actual outcome: VAS pain reduction at 1 week; Group 1: mean 35.17 (SD 22.139); n=29, Group 2: mean 22.14 (SD 16.635); n=28; VAS 0-100 Top=High is poor outcome Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Minimal baseline details; Group 1 Number missing: 1; Group 2 Number missing: 2	
Protocol outcomes not reported by the study	Quality of life ; Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

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Study	Esenyel 2000[117]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=76)
Countries and setting	Conducted in Turkey; Setting: Not specified
Line of therapy	Unclear
Duration of study	Intervention time: 10 days (with 12 week follow up)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of myofascial pain
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Travel and Simons criteria for active myofascial trigger points in the upper trapezius muscle.
Exclusion criteria	Meeting the ACR criteria for fibromyalgia, having myofascial trigger point infections or receiving physical medicine in the year preceding this study, having a history of acute trauma, inflammatory joint or muscle disease, infection or malignancy, or evidence of neurologic deficit.
Recruitment/selection of patients	Consecutively recruited from the outpatient clinic of the physical medicine and rehab department and the pain clinic of a hospital over a 2.3 year period.
Age, gender and ethnicity	Age - Mean (SD): 30(7.7) years. Gender (M:F): 38:64. Ethnicity: Not stated
Further population details	Chronic widespread pain
Extra comments	Pain duration ranged 6 months to 7 years
Indirectness of population	No indirectness
Interventions	(n=36) Intervention 1: Electrical Physical Modalities - Therapeutic Ultrasound. Ultrasound therapy 1.5Wcm2 to trigger points for 6 minute duration for 10 sessions, as well as neck-stretching exercises. Duration 10 days. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=40) Intervention 2: Usual care. Neck stretching exercises only. Duration 10 days. Concurrent medication/care: Not reported. Indirectness: No indirectness

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Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: THERAPEUTIC ULTRASOUND versus USUAL CARE Protocol outcome 1: Pain reduction - Actual outcome: VAS at 3 months; Group 1: mean 3.08 (SD 2.42); n=36, Group 2: mean 5.78 (SD 0.87); n=40; VAS 0-10 Top=High is poor outcome; Comments: Baseline not reported Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life ; Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

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Study	Fagerlund 2015[120]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=50)
Countries and setting	Conducted in Norway; Setting: Pain clinic, university hospital of Northern Norway
Line of therapy	Unclear
Duration of study	Intervention + follow up: 5 day intervention and 1 month follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ACR criteria for fibromyalgia
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Over 18 years old, diagnosed with FMS, and manual examination of patients' tender points confirmed this. If on medication, this needed to be stable for 3 months before inclusion
Exclusion criteria	Severe psychiatric conditions, neurological conditions, developmental disorders, pregnancy and drug abuse.
Recruitment/selection of patients	Commenced September 2011, from Tromso (Northern Norway) - patients treated in pain clinics in the previous 2 years and members of the national FM patient association were contacted by mail, as well as advertisements in local newspapers
Age, gender and ethnicity	Age - Mean (SD): 48.6 (9.4) years. Gender (M:F):3:47. Ethnicity: Not specified
Further population details	Chronic widespread pain
Extra comments	Duration of pain 18.1(9) years
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Electrical Physical Modalities - Transcranial Direct Current Stimulation (TDCS). 5 consecutive days of treatment. Direct current stimulation administered using neuroConn DC stimulator. Stimulation duration 20 minutes, intensity of 2mA. Anodes placed at C3 position and cathode placed on contralateral supraorbital area. Duration 5 days. Concurrent medication/care: Not specified. Indirectness: No indirectness (n=25) Intervention 2: Placebo/Sham. Identical treatment but sham treatment; 8 second fade in period

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	followed by 30 seconds of direct current stimulation that was terminated by a 5 second fade out (mimics skin sensation of active treatment with insufficient duration to induce changes in cortical excitability). Duration 5 days. Concurrent medication/care: Not specified. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS) versus PLACEBO/SHAM

Protocol outcome 1: Quality of life
- Actual outcome: SF-36 physical component at 1 month (follow up); Group 1: mean 34.78 (SD 9.42); n=24, Group 2: mean 35.92 (SD 7.34); n=24; SF-36 summary score 0-100 Top=High is good outcome; Comments: Baseline: 29.83(26.17-33.49); 34.55(31.37-37.74)

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Difference at baseline more than MIDs; Group 1 Number missing: 1, Reason: NR; Group 2 Number missing: 1, Reason: NR
- Actual outcome: SF-36 mental component at 1 month (follow up); Group 1: mean 48.2 (SD 15.35); n=24, Group 2: mean 45.4 (SD 10.85); n=24; SF-36 summary score 0-100 Top=High is good outcome; Comments: Baseline: 48.16(42.54-53.78);45.88(39.92-51.83)

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Difference at baseline more than MIDs; Group 1 Number missing: 1, Reason: NR; Group 2 Number missing: 1, Reason: NR

Protocol outcome 2: Pain reduction
- Actual outcome: Pain intensity (numeric rating scale) at 1 month (follow up); Group 1: mean 4.26 (SD 1.9); n=24, Group 2: mean 5.22 (SD 1.5); n=24; NRS 0-10 Top=High is poor outcome; Comments: Baseline: 4.93(1.58); 5.31(1.59)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Difference at baseline; Group 1 Number missing: 1, Reason: NR; Group 2 Number missing: 1, Reason: NR

Protocol outcome 3: Psychological distress
- Actual outcome: HADS anxiety at 1 month (follow up); Group 1: mean 5.47 (SD 4.16); n=24, Group 2: mean 5.82 (SD 3.36); n=24; HADS:A Not specified Top=High is poor outcome; Comments: Baseline: 6.9(3.99);6.48(3.48)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Difference at baseline; Group 1 Number missing: 1, Reason: NR; Group 2 Number missing: 1, Reason: NR

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- Actual outcome: HADS depression at 1 month (follow up); Group 1: mean 3.76 (SD 2.77); n=24, Group 2: mean 5.41 (SD 3.37); n=24; HADS:D Not specified Top=High is poor outcome; Comments: Baseline: 5.33(3.04); 6.13(3.53) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Difference at baseline; Group 1 Number missing: 1, Reason: NR; Group 2 Number missing: 1, Reason: NR	
Protocol outcomes not reported by the study	Physical function ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

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Study	Fregni 2006[129]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=32)
Countries and setting	Conducted in Brazil; Setting: Not specified
Line of therapy	Unclear
Duration of study	Intervention + follow up: 1 week (and 3 week follow up)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ACR criteria for fibromyalgia
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Met ACR criteria for FMS, score of at least 4 on VAS and at least 20 on the total tender point score. Participants were required to maintain a stable dose of any medications they were on.
Exclusion criteria	Uncontrolled clinical disease such as thyroid or cardiovascular disease, substance abuse, pregnancy, lactation
Recruitment/selection of patients	From a specialised outpatient centre
Age, gender and ethnicity	Age - Mean (SD): 53.2(8.97) years. Gender (M:F): All female. Ethnicity: Not specified
Further population details	Chronic widespread pain
Extra comments	Mean duration of pain 8.4(9.3) years
Indirectness of population	No indirectness
Interventions	(n=11) Intervention 1: Electrical Physical Modalities - Transcranial Direct Current Stimulation (TDCS). Current transferred by a pair of saline soaked surface sponge electrodes and battery driven stimulators with maximum output of 10mA. Anodal stimulation of left DLPFC area. Constant current of 2mA intensity was applied for 20 minutes. Duration 5 days. Concurrent medication/care: Not specified. Indirectness: No indirectness (n=11) Intervention 2: Electrical Physical Modalities - Transcranial Direct Current Stimulation (TDCS). Current transferred by a pair of saline soaked surface sponge electrodes and battery driven stimulators with maximum output of 10mA. Anodal stimulation of primary motor cortex area. Constant current of 2mA intensity was

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	applied for 20 minutes. Duration 5 days. Concurrent medication/care: Not specified. Indirectness: No indirectness (n=10) Intervention 3: Placebo/Sham. Identical treatment with sham stimulation of the primary motor cortex. The stimulator was turned off after 30 seconds of stimulation. The patients therefore felt the initial itching sensation but received no current for the rest of the stimulation period. Duration 5 days. Concurrent medication/care: Not specified. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS) FOR DLPFC versus PLACEBO/SHAM

Protocol outcome 1: Psychological distress
- Actual outcome: BDI at 3 weeks; Group 1: mean 14.6 (SD 5.7); n=11, Group 2: mean 18 (SD 7.7); n=10; Comments: baseline:17.8(8.7); 20.7(8.1)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS) FOR M1 versus PLACEBO/SHAM

Protocol outcome 1: Psychological distress
- Actual outcome: BDI at 3 weeks; Group 1: mean 18.6 (SD 9.1); n=11, Group 2: mean 18 (SD 7.7); n=10; BDI Not reported Top=High is poor outcome; Comments: Baseline: 19.9(8.2); 20.7(8.1)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Quality of life ; Pain reduction ; Physical function ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

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Study	Gokyildiz 2012[137]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=26)
Countries and setting	Conducted in Turkey; Setting: Urogynecology Unit, Istanbul Medical School Department of Obstetrics and Gynecology, Istanbul University.
Line of therapy	Unclear
Duration of study	Intervention time: 3 months
Method of assessment of guideline condition	Method of assessment/diagnosis not stated: All the patients were evaluated through CPP history, physical examination, gynecological examination and ultrasound at Istanbul Medical School Department of Obstetrics and Gynecology, Istanbul University.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosis of CPP; voluntary participation; pain score >5 according to the visual analogue scale (VAS); cessation of analgesic at least 2 weeks before PTNS treatment; cessation of physiotherapy or electrotherapy at least 3 months before PTNS treatment.
Exclusion criteria	Pregnancy or planning a pregnancy; heart disease or cardiac pacing; nerve damage; use of anticoagulant medicine; active or recurrent urinary tract infection (more than five in the last 12 months).
Recruitment/selection of patients	8,872 gynecology patient records in the year 2006, 10,427 in the year 2007 and 500 in the year 2008 were reviewed at Istanbul Medical School Department of Obstetrics and Gynecology, Istanbul University. Sixty-five patients who had pain in the pelvis/lower abdomen for at least 6 months were identified and these patients were called and asked whether they still had pain. Those who still did were invited to the Urogynecology Unit and 52 patients applied to the unit.
Age, gender and ethnicity	Age - Other: Ages not stated, but report that 'no significant difference between the women in the control and experimental groups in terms of age'. Gender (M:F): 0/26. Ethnicity: Not stated
Further population details	Chronic visceral pain
Extra comments	Chronic population: pain in pelvis and lower abdomen for at least 6 months.
Indirectness of population	No indirectness

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Interventions	(n=13) Intervention 1: Electrical Physical Modalities - Percutaneous Electrical Nerve Stimulation (PENS). Percutaneous Tibial Nerve Stimulation (PTNS) was applied using a neuromodulation system composing a needle set and a stimulator that runs with a 9-volt battery and creates an adjustable current between 0.5 and 10 mA, 200s and 20 Hz frequency. The patients lay on their backs in a supine position with the knees abducted and flexed (frog position). The 34-gauge needle was inserted approximately 3–4 cm above the inner malleolus, by entering at the place appropriate to the posterior tibial nerve line with a 60° angle, the adhesive electrode was placed on the inner side of the heel and the set was connected to the stimulator. The stimulator was run and the current was adjusted according to the patient's tolerance. When the current is flowing correctly, if the inserted needle is in the right place, toes should have plantar flexion (moving downwards) and/or 2nd to 5th fingers should release or have plantar flexion. Each session lasted 30 minutes. Duration 3 months (12 sessions). Concurrent medication/care: None. Inclusion required cessation of analgesic at least 2 weeks before treatment and cessation of physiotherapy or electrotherapy at least 3 months before treatment. Indirectness: No indirectness (n=13) Intervention 2: Usual care. Received 'routine intervention' (normal care) for 3 months. Duration 3 months. Concurrent medication/care: None. Inclusion required cessation of analgesic at least 2 weeks before treatment and cessation of physiotherapy or electrotherapy at least 3 months before treatment. Indirectness: No indirectness
Funding	Funding not stated (State no conflict of interest.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PERCUTANEOUS ELECTRICAL NERVE STIMULATION (PENS) versus USUAL CARE

Protocol outcome 1: Quality of life
- Actual outcome: SF-36 Physical function at After treatment (3 months); Group 1: mean 74.16 (SD 31.03); n=12, Group 2: mean 52.91 (SD 23.1); n=12; SF-36 0-100 Top=High is good outcome; Comments: Baselines, mean (SD):
PENS group 56.66 (23.19)
Control group 54.58 (23.88)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Key outcome baselines comparable between experimental and control groups. Differences in baseline for SF-36 Physical role and SF-36 Social functioning. ; Group 1 Number missing: 1, Reason: Unclear ("dropped"); Group 2 Number missing: 1, Reason: Unclear ("dropped")
- Actual outcome: SF-36 Physical role at After treatment (3 months); Group 1: mean 66.66 (SD 45.64); n=12, Group 2: mean 14.58 (SD 22.5); n=12; Sf-36 0-100 Top=High is good outcome; Comments: Baselines, mean (SD):
PENS group 25.00 (35.35)
Control group 12.5 (25.00)

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Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Key outcome baselines comparable between experimental and control groups. Differences in baseline for SF-36 Physical role and SF-36 Social functioning. ; Group 1 Number missing: 1, Reason: Unclear ("dropped"); Group 2 Number missing: 1, Reason: Unclear ("dropped")
- Actual outcome: SF-36 Emotional role at After treatment (3 months); Group 1: mean 61.11 (SD 44.57); n=12, Group 2: mean 13.87 (SD 26.4); n=12; SF-36 0-100 Top=High is good outcome; Comments: Baselines, mean (SD):
PENS group 27.77 (37.15)
Control group 19.42 (29.98)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Key outcome baselines comparable between experimental and control groups. Differences in baseline for SF-36 Physical role and SF-36 Social functioning. ; Group 1 Number missing: 1, Reason: Unclear ("dropped"); Group 2 Number missing: 1, Reason: Unclear ("dropped")
- Actual outcome: SF-36 Energy/fatigue at After treatment (3 months); Group 1: mean 62.91 (SD 25.97); n=12, Group 2: mean 45 (SD 16.23); n=12; SF-36 0-100 Top=High is good outcome; Comments: Baselines, mean (SD):
PENS group 49.16 (14.74)
Control group 46.25 (18.35)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Key outcome baselines comparable between experimental and control groups. Differences in baseline for SF-36 Physical role and SF-36 Social functioning. ; Group 1 Number missing: 1, Reason: Unclear ("dropped"); Group 2 Number missing: 1, Reason: Unclear ("dropped")
- Actual outcome: SF-36 Mental health at After treatment (3 months); Group 1: mean 60.66 (SD 19.35); n=12, Group 2: mean 40.33 (SD 15.48); n=12; SF-36 0-100 Top=High is good outcome; Comments: Baselines, mean (SD):
PENS group 42.00 (17.18)
Control group 42.33 (18.48)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Key outcome baselines comparable between experimental and control groups. Differences in baseline for SF-36 Physical role and SF-36 Social functioning. ; Group 1 Number missing: 1, Reason: Unclear ("dropped"); Group 2 Number missing: 1, Reason: Unclear ("dropped")
- Actual outcome: SF-36 Social functioning at After treatment (3 months); Group 1: mean 71.87 (SD 33.33); n=12, Group 2: mean 50 (SD 11.91); n=12; SF-36 0-100 Top=High is good outcome; Comments: Baselines, mean (SD):
PENS group 43.75 (25.28)
Control group 54.16 (17.94)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Key outcome baselines comparable between experimental and control groups. Differences in baseline for SF-36 Physical role and SF-36 Social functioning. ; Group 1 Number missing: 1, Reason: Unclear ("dropped"); Group 2 Number missing: 1, Reason: Unclear ("dropped")
- Actual outcome: SF-36 Pain at After treatment (3 months); Group 1: mean 60 (SD 27.96); n=12, Group 2: mean 23.33 (SD 7.78); n=12; SF-36 0-100 Top=High is good outcome; Comments: Baselines, mean (SD):

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PENS group 32.5 (23.40) Control group 23.33 (7.78) Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Key outcome baselines comparable between experimental and control groups. Differences in baseline for SF-36 Physical role and SF-36 Social functioning. ; Group 1 Number missing: 1, Reason: Unclear ("dropped"); Group 2 Number missing: 1, Reason: Unclear ("dropped") - Actual outcome: SF-36 General health at After treatment (3 months); Group 1: mean 50.58 (SD 12.84); n=12, Group 2: mean 47.08 (SD 9.4); n=12; SF-36 0-100 Top=High is good outcome; Comments: Baselines, mean (SD): PENS group 48.58 (13.20) Control group 46.83 (10.01) Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Key outcome baselines comparable between experimental and control groups. Differences in baseline for SF-36 Physical role and SF-36 Social functioning. ; Group 1 Number missing: 1, Reason: Unclear ("dropped"); Group 2 Number missing: 1, Reason: Unclear ("dropped") Protocol outcome 2: Pain reduction - Actual outcome: Pain intensity according to VAS at After treatment (3 months); Group 1: mean 2.62 Visual analogue scale (VAS) (SD 2.7); n=12, Group 2: mean 7.87 Visual analogue scale (VAS) (SD 0.88); n=12; Visual analogue scale (VAS) 0-10 Top=High is poor outcome; Comments: Baselines, mean (SD): PENS group 8.08 (1.72) Usual care group 7.95 (1.03) Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Key outcome baselines comparable between experimental and control groups.; Group 1 Number missing: 1, Reason: Unclear ("dropped"); Group 2 Number missing: 1, Reason: Unclear ("dropped")	
Protocol outcomes not reported by the study	Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

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Study	Gur 2002[147]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in Turkey; Setting:
Line of therapy	Unclear
Duration of study	Intervention time: 2 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Fibromyalgia patients diagnosed according to the American College of Rheumatology (ACR) criteria for FM.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Fibromyalgia patients fulfilled the American College of Rheumatology (ACR) criteria for FM. These criteria include (a) a history of widespread pain for at least 3 months, i.e., pain in the left or right side of the body, pain above and below the waist, axial skeletal pain (cervical spine or anterior chest or thoracic spine or low back pain) and (b) the presence of at least 11 tender point sites.
Exclusion criteria	Major clinical conditions other than FM were excluded by physical examinations and routine blood cells and differentials, red blood cells, hematocrit and hemoglobin, baseline thyroid-stimulating hormone, and antinuclear autoantibodies. Furthermore, exclusionary criteria for FM patients and normal controls were (a) a recent or past history of psychiatric disorders, e.g., major depressive disorder, alcohol dependence, substance abuse, schizophrenic or paranoid disorder, personality disorders, and somatoform disorders, (b) immunocompromised subjects, (c) subjects with neurological, inflammatory, endocrine, or clinically significant chronic disease such as diabetes mellitus, rheumatoid arthritis, inflammatory bowel disease, and organic brain disorders, (d) abnormal liver function tests such as serum aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and gamma-glutamyl transpeptidase, and (e) pregnant females.
Recruitment/selection of patients	Recruited from Department of Physical Therapy and Rehabilitation, University Hospital of Dicle, Diyarbakyr, Turkey.
Age, gender and ethnicity	Age - Mean (SD): Laser group 30.36 (6.91) ; Placebo group 28.52 (6.28) years. Gender (M:F): 39/11. Ethnicity: Not stated
Further population details	Chronic widespread pain

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Extra comments	Disease duration in years, mean (SD): Laser group 4.86 (4.67) Placebo group 4.63 (3.28).
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Electrical Physical Modalities - Laser therapy. Low power laser therapy of approximately 2 J/cm2 was used at each tender point, producing an energy density radiant exposure) at each point. Two physical therapist investigators used standard technique with a Ga-As laser (20 W maximum output per pulse, 904 nm, 200 ns maximum pulse duration, 2.8 kHz pulse frequency, 11.2 mW average power, and 1 cm2 surface (class IIIb Laser Product, Frank Line IR 30, Fysiomed, Belgium). The patients were treated for 3 min at each tender point daily for 2 weeks, except weekends, at the same time in the afternoon in a sitting position and at a temperature of 20C. Duration 2 weeks. Concurrent medication/care: All patients were free of any medications for at least 1 month prior to treatment. Indirectness: No indirectness (n=25) Intervention 2: Placebo/Sham. The same unit as used for the laser intervention was used for the placebo treatment, but no laser beam was emitted. Duration 2 weeks. Concurrent medication/care: All patients were free of any medications for at least 1 month prior to treatment. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LASER THERAPY versus PLACEBO/SHAM

Protocol outcome 1: Pain reduction
- Actual outcome: Pain intensity on Likert scale at After treatment (2 weeks); Group 1: mean 1.24 (SD 0.72); n=25, Group 2: mean 2.19 (SD 0.74); n=25; Likert scale for pain (VAS) 0-10 Top=High is poor outcome; Comments: Baselines, mean (SD):
Laser group 3.04 (0.53)
Placebo group 3.19 (0.87)
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing; Group 2 Number missing

Protocol outcomes not reported by the study	Quality of life ; Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

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Study	Jales 2015[167]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=20)
Countries and setting	Conducted in Brazil; Setting: Outpatient setting in the Norte Riogranense Institute of Health Research and Teaching (IPENS), Natal/RN.
Line of therapy	Unclear
Duration of study	Intervention time: 10 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosed according to criteria established by the American College of Rheumatology: 1. Widespread Pain Index (WPI) ≥7 and severity symptoms (SS) in a scale of ≥ 5 or WPI between 3 and 6 and SS with score of ≥9; 2. Symptoms are present at similar level for at least three months; 3. Patients have no other disease which could justify the sensation of widespread pain
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Inclusion criteria were patients with FMS, aged between 25 and 65 years, of both genders and living in the city of Natal/RN.
Exclusion criteria	Exclusion criteria were patients with severe cognitive deficits; illiterate; patients with previous and/or family history of seizures; patients with arrhythmias and pacemaker; pregnant and breastfeeding females.
Recruitment/selection of patients	Not stated.
Age, gender and ethnicity	Age - Mean (SD): 46.4 (10.615) years. Gender (M:F): All female. Ethnicity: Not stated
Further population details	Chronic widespread pain
Extra comments	Over 3 months pain by nature of fibromyalgia diagnosis.
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: Electrical Physical Modalities68.5 - Transcranial Direct Current Stimulation (TDCS). For tDCS procedures, two electrodes were positioned on the scalp of patients without causing discomfort and a 1.0mA electric impulse was applied, supplied by an electronic unit with direct current control from Cerebral

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	Electronic Stimulator equipment (CES). During procedures, patients remained comfortably lying down in beds, with the anodal electrode positioned on the scalp, on the superior-lateral face of the skull, the region corresponding to the left precentral gyrus (M1 or Brodman's area 4) on its medial third. The cathodic electrode was positioned on the contralateral supraorbital region. A rubber sponge was placed between the scalp and the electrode measuring 3x5cm, previously moistened with 0.9% saline. Direct 1.0mA current was applied for 20 minutes. Duration 10 weeks. Concurrent medication/care: For the duration of the treatment patients were permitted to continue their normal pharmacological and non-pharmacological therapies according to individual situations. Indirectness: No indirectness (n=10) Intervention 2: Placebo/Sham. For the sham tDCS group (control), the same procedures were adopted as for the active tDCS treatment, once a week for 20 minutes for 10 consecutive weeks, but the tDCS device was not turned on. Duration 10 weeks. Concurrent medication/care: For the duration of the treatment patients were permitted to continue their normal pharmacological and non-pharmacological therapies according to individual situations. Indirectness: No indirectness
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS) versus PLACEBO/SHAM

Protocol outcome 1: Quality of life
- Actual outcome: SF-36: Functional capacity at 10 weeks (end of treatment); Group 1: mean 68.5 (SD 11.068); n=10, Group 2: mean 38 (SD 26.895); n=10; SF-36 Quality of life questionnaire 0-100 Top=High is good outcome; Comments: Baselines, mean (SD):
tDCS group 48.00 (16.364)
Sham group 31.00 (23.07)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: SF-36 baselines significantly different in some categories
- Actual outcome: SF-36: Physical aspects at 10 weeks (end of treatment); Group 1: mean 75 (SD 31.18); n=10, Group 2: mean 47.5 (SD 41.583); n=10; SF-36 Quality of life questionnaire 0-100 Top=High is good outcome; Comments: Baselines, mean (SD):
tDCS group 17.5 (23.717)
Sham group 22.5 (36.228)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: SF-36 baselines significantly different in some categories
- Actual outcome: SF-36: Pain at 10 weeks (end of treatment); Group 1: mean 43 (SD 18.288); n=10, Group 2: mean 50 (SD 23.57); n=10; SF-36 Quality of life questionnaire 0-100 Top=High is good outcome; Comments: Baseline, mean (SD):
tDCS group 55 (22.73)
Sham group 62 (13.166)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

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- Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: SF-36 baselines significantly different in some categories
- Actual outcome: SF-36: General health status at 10 weeks (end of treatment); Group 1: mean 58 (SD 11.106); n=10, Group 2: mean 63.5 (SD 9.443); n=10; SF-36 Quality of life questionnaire 0-100 Top=High is good outcome; Comments: Baselines, mean (SD):
tDCS group 63.5 (10.554)
Sham group 59 (15.42)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome:. No indirectness ; Baseline details: SF-36 baselines significantly different in some categories
- Actual outcome: SF-36: Vitality at 10 weeks (end of treatment); Group 1: mean 53.5 (SD 9.144); n=10, Group 2: mean 58 (SD 10.055); n=10; SF-36 Quality of life questionnaire 0-100 Top=High is good outcome; Comments: Baselines, mean (SD):
tDCS group 46.5 (10.014)
Sham group 54.5 (6.852)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: SF-36 baselines significantly different in some categories
- Actual outcome: SF-36: General aspects at 10 weeks (end of treatment); Group 1: mean 47.5 (SD 15.366); n=10, Group 2: mean 50 (SD 16.667); n=10; SF-36 Quality of life questionnaire 0-100 Top=High is good outcome; Comments: Baselines, mean (SD):
tDCS group 51.25 (17.129)
Sham group 50 (16.667)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: SF-36 baselines significantly different in some categories
- Actual outcome: SF-36: Emotional aspects at 10 weeks (end of treatment); Group 1: mean 80 (SD 35.633); n=10, Group 2: mean 60 (SD 43.886); n=10; SF-36 Quality of life questionnaire 0-100 Top=High is good outcome; Comments: Baselines, mean (SD):
tDCS group 26.67 (30.633)
Sham group 16.67 (17.566)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: SF-36 baselines significantly different in some categories
- Actual outcome: SF-36: Mental health at 10 weeks (end of treatment); Group 1: mean 58.4 (SD 11.345); n=10, Group 2: mean 54 (SD 11.963); n=10; SF-36 Quality of life questionnaire 0-100 Top=High is good outcome; Comments: Baselines, mean (SD):
tDCS group 53.6 (8.044)
Sham group 51.6 (10.741)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: SF-36 baselines significantly different in some categories

Protocol outcome 2: Pain reduction
- Actual outcome: Pain intensity (VAS) at 10 weeks (end of treatment); Group 1: mean 3.6 (SD 1.838); n=10, Group 2: mean 5.6 (SD 2.503); n=10; Visual analogue scale 0-10 Top=High is poor outcome; Comments: Baselines, mean (SD):
tDCS group 6.05 (2.061)
Sham group 6.70 (2.111)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

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- Low, Subgroups - Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

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Study	Kabay 2009[176]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=89)
Countries and setting	Conducted in Turkey; Setting: Not specified
Line of therapy	Unclear
Duration of study	Intervention time: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Chronic therapy resistant pelvic pain category IIIB pelvic pain
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosis of category IIIB CP/CPPS as confirmed by detailed history, physical examination, ultrasound, urine flow measurement, residual urine volume measurement, and standard microbiologic cultures. CP/CPPS defined as complaints of pain for at least 6 months in the bladder, groin, genitals, or lower abdomen and or perineal or perianal pain without any obvious abnormalities.
Exclusion criteria	Chronic bacterial prostatitis or category IIIA, aged <18 years, symptoms for less than 6 months, active or recurrent UTIs, STIs, or IC. Other diagnoses such as diabetes, cardiopulmonary disease, neurological disease or other conditions that could explain pain or limit ability to take part in treatment were excluded.
Recruitment/selection of patients	May 2006 to March 2008
Age, gender and ethnicity	Age - Mean (SD): 37.7(7.4) years. Gender (M:F): Not specified. Ethnicity: Not reported
Further population details	Chronic visceral pain
Extra comments	Mean duration of symptoms 4.5(6.1) years
Indirectness of population	No indirectness
Interventions	(n=45) Intervention 1: Electrical Physical Modalities - Percutaneous Electrical Nerve Stimulation (PENS). Percutaneous posterior tibial nerve stimulation. 30 minute sessions, one a week. Needles inserted 5cm from medial malleolus and neutral electrode placed on the same leg, both connected to a stimulator. Electrical stimulation was applied unilaterally with 200-us pulses and a pulse rate of 20Hz, and intensity levels were just below the threshold determining motor contraction. Amplitude was set at maximum tolerable level, usually 1.5

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	times the threshold for evoking plantar flexion of toes or toe fanning. Duration 3 months. Concurrent medication/care: Not specified (n=44) Intervention 2: Placebo/Sham. Identical treatment but the electrical stimulation was not applied in the sham group. Duration 3 months. Concurrent medication/care: Not specified
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PERCUTANEOUS ELECTRICAL NERVE STIMULATION (PENS) versus PLACEBO/SHAM Protocol outcome 1: Quality of life - Actual outcome: NIH-CPSI quality of life at 3 months; Group 1: mean 2.1 (SD 0.9); n=45, Group 2: mean 6.7 (SD 2.1); n=44; NIH-CPSI QOL 0-12 Top=High is poor outcome; Comments: Baseline: 6.7(2.2); 6.5(2.8) Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness Protocol outcome 2: Pain reduction - Actual outcome: VAS pain at 3 months; Group 1: mean 4.3 (SD 0.6); n=45, Group 2: mean 7.2 (SD 0.4); n=44; VAS 0-10 Top=High is poor outcome; Comments: Baseline: 7.6(0.8);7.4(0.9) Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

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Study	Khedr 2017[185]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=40)
Countries and setting	Conducted in Egypt; Setting: Assiut university hospital
Line of therapy	Unclear
Duration of study	Intervention + follow up: 2 weeks intervention and 8 weeks follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ACR criteria for fibromyalgia
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Met FMS criteria and had score of at least 4 on VAS pain scale
Exclusion criteria	History of autoimmune or chronic inflammatory disease, substance abuse, neuropsychiatric disorders, pregnancy or lactation.
Recruitment/selection of patients	2015-2016, from outpatient clinic
Age, gender and ethnicity	Age - Mean (SD): 32.3(10.9) years. Gender (M:F): 2:34. Ethnicity: Not specified
Further population details	Chronic widespread pain
Extra comments	Duration of symptoms 6.1(2.5) years
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Electrical Physical Modalities - Transcranial Direct Current Stimulation (TDCS). 10 sessions over 2 weeks (5 days of 5 sessions x2). 2mA for 20 mins in each session. Anodal electrode with a current density of 0.08mA placed on left primary motor area, over C3, and reference electrode fixed over contralateral arm. Duration 2 weeks. Concurrent medication/care: Not specified. Indirectness: No indirectness (n=20) Intervention 2: Placebo/Sham. Identical treatment but the current applied only for 30s at the beginning and at the end of the session (considered reliable sham stimulation as sensations similar but not enough to induce response). Duration 2 weeks. Concurrent medication/care: Not specified. Indirectness: No indirectness

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Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS) versus PLACEBO/SHAM Protocol outcome 1: Pain reduction - Actual outcome: VAS at 8 weeks (follow up); Group 1: mean 3.9 (SD 2.1); n=18, Group 2: mean 7.3 (SD 0.9); n=18; VAS 0-10 Top=High is poor outcome; Comments: Baseline: 7.4(1.1); 8(0.8) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness Protocol outcome 2: Psychological distress - Actual outcome: HAM-A at 8 weeks (follow up); Group 1: mean 11.6 (SD 5.9); n=18, Group 2: mean 17.1 (SD 4.2); n=18; HAM:A Not specified Top=High is poor outcome; Comments: Baseline: 19.3(4.5); 18.7(3.3) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness - Actual outcome: HAM-D at 8 weeks (follow up); Group 1: mean 19.6 (SD 6.3); n=18, Group 2: mean 17.6 (SD 4); n=18; HAM:D Not specified Top=High is poor outcome; Comments: Baseline: 17.5(4.4); 20.3(3.2) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life ; Physical function ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

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Study	Lee 2012[205]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=22)
Countries and setting	Conducted in South Korea
Line of therapy	Unclear
Duration of study	Intervention + follow up: 10 day intervention and 1 month follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ACR criteria for fibromyalgia
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Chronic, persistent pain for more than 24 months
Exclusion criteria	Evidence of other inflammatory rheumatologic disease or auto-immune disease, or psychiatric disorders, or contraindications for TMS
Recruitment/selection of patients	From division of rheumatology to the neuromodulation outpatient clinic at Adan Medical Center between May 2008 and June 2009
Age, gender and ethnicity	Age - Mean (SD): 47.2(6.2) years. Gender (M:F): All women. Ethnicity: Not specified
Further population details	Chronic widespread pain
Extra comments	Duration of pain 44.7(10.3) years
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: Electrical Physical Modalities - Transcranial Magnetic Stimulation (TMS). Randomised to low frequency stimulation (n=7) or high frequency stimulation (n=8). 1Hz or 10 Hz treatment 5 times per week for 2 weeks of TMS, performed by a physiatrist with a 70-mm air cooled figure of eight shaped coil. Applied to the right side motor cortex, approximate location at the DLPFC. Each patient received either: 1Hz, 110% intensity of resting motor threshold, 800 stimuli of each train (2 trains with 60 secs of intertrain interval and a total of 1600 stimuli per session 10Hz, 80% intensity of resting motor threshold, 2000 stimuli per session. Duration 2 weeks. Concurrent medication/care: Not specified (medications remained unchanged throughout study period). Indirectness: No

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	indirectness (n=7) Intervention 2: Placebo/Sham. Identical treatment but coil angle was 90% perpendicular to the skull rather than tangential to it, so the magnetic field could not penetrate the brain, although patients could hear the sound produced. Duration 2 weeks. Concurrent medication/care: Not specified. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCRANIAL MAGNETIC STIMULATION (TMS) versus PLACEBO/SHAM Protocol outcome 1: Quality of life - Actual outcome: FIQ at 6 weeks; Group 1: mean 51.8 (SD 13.51); n=10, Group 2: mean 53.7 (SD 27.3); n=5; FIQ 0-100 Top=High is poor outcome; Comments: Baseline: 59.3(23.4); 67.2(11.1);60.4(21.1) Mean of TMS group: weighted mean and SD calculated from LF and HF groups Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5; Group 2 Number missing: 2 Protocol outcome 2: Pain reduction - Actual outcome: VAS at 6 weeks; Group 1: mean 60.5 (SD 22.23); n=10, Group 2: mean 72.3 (SD 25.3); n=5; VAS 0-100 Top=High is poor outcome; Comments: Baseline: 72.4(10.7); 70(8.5); 78.1(13.1) Mean of TMS group: weighted mean and SD calculated from LF and HF groups Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5; Group 2 Number missing: 2 Protocol outcome 3: Psychological distress - Actual outcome: BDI at 6 weeks; Group 1: mean 17.85 (SD 6.553); n=10, Group 2: mean 18.3 (SD 5.8); n=5; BDI Not reported Top=High is poor outcome; Comments: Baseline: 19.2(4.4); 25.5(6.4); 21.6(5.5) Mean of TMS group calculated from weighted mean and SDs of HF and LF groups Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5; Group 2 Number missing: 2 Protocol outcome 4: Discontinuation - Actual outcome: Discontinuation at 6 weeks; Group 1: 5/15, Group 2: 2/7; Comments: 1 in the intervention group discontinued due to a seizure Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0, Reason: NA; Group 2 Number missing: 0, Reason: NA	
Protocol outcomes not reported by the study	Physical function ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep

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Study	Mhalla 2011[241]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=40)
Countries and setting	Conducted in France; Setting: Not specified
Line of therapy	Unclear
Duration of study	Intervention + follow up: 21 week intervention, follow up at week 25
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ACR criteria for fibromyalgia
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Met ACR criteria, score of at least 4 on BPI, persistent pain for more than 6 months
Exclusion criteria	Inflammatory rheumatic disease, autoimmune disease, or other painful disorders that might confound the assessment of FMS. Any psychiatric condition including major depression or major personality disorders, or history of substance abuse. All women of childbearing age included in this study had negative pregnancy tests at inclusion and were using contraception. Any contraindications for TMS such as seizures or brain trauma. Concomitant medication for pain and sleep allowed provided dose had been stable for at least 1 month before study.
Recruitment/selection of patients	Between 2008 and 2009
Age, gender and ethnicity	Age - Mean (SD): 50.2(10.8) years. Gender (M:F): All female. Ethnicity: Not specified
Further population details	Chronic widespread pain
Extra comments	Pain duration 13.55(12.4) years
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Electrical Physical Modalities - Transcranial Magnetic Stimulation (TMS). 1 session per day for 5 days followed by one weekly session for 3 weeks, 3 fortnightly sessions, and 3 monthly sessions. Patients seated in comfortable chair in relaxed position. MagPROX100 MS device used, using a figure-8 shaped coil oriented at a tangent to the scalp, with the main phase of the induced current in the anterior posterior direction. Resting motor threshold was established in each person, and each session consisted of

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	15 series of 10 second pulses with a frequency of 10Hz and an interval of 50 seconds between each train, giving a total of 1500 pulses per session (and stimulation intensity used was 80% of RMT). Duration 21 weeks. Concurrent medication/care: Not specified. Indirectness: No indirectness (n=20) Intervention 2: Placebo/Sham. Sham TMS, carried out with identical coil that emitted a sound similar to that emitted by the active coil. Duration 21 weeks. Concurrent medication/care: Not specified. Indirectness: No indirectness
Funding	Academic or government funding (Fondation APICIL and the Fondation de France)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCRANIAL MAGNETIC STIMULATION (TMS) versus PLACEBO/SHAM Protocol outcome 1: Quality of life - Actual outcome: FIQ at 25 weeks (follow up); Group 1: mean 56 (SD 17.7); n=15, Group 2: mean 63.3 (SD 15); n=15; FIQ 0-100 Top=High is poor outcome; Comments: Baseline: 66.8(12.5);67.2(14.8) Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness Protocol outcome 2: Psychological distress - Actual outcome: HADS:A at 25 weeks (follow up); Group 1: mean 9.2 (SD 4.9); n=15, Group 2: mean 9.4 (SD 5.7); n=15; HADS:A 0-21 Top=High is good outcome; Comments: Baseline: 11.8(4); 11.4(4.4) Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: HADS:D at 25 weeks (follow up); Group 1: mean 8.6 (SD 4.7); n=15, Group 2: mean 7.4 (SD 4); n=15; HADS:D 0-21 Top=High is poor outcome; Comments: Baseline: 8.4(4.7); 8.7(3.5) Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness Protocol outcome 3: Pain interference - Actual outcome: BPI pain interference at 25 weeks (follow up); Group 1: mean 4.1 (SD 1.7); n=15, Group 2: mean 6 (SD 1.5); n=15; BPI interference Not specified Top=High is poor outcome; Comments: Baseline: 5.8(1.3); 6.1(1.7) Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Pain reduction ; Physical function ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

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Study	Murina 2008[250]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=40)
Countries and setting	Conducted in Italy; Setting: Not specified
Line of therapy	Unclear
Duration of study	Intervention time: 10 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of vestibulodynia (positive cotton-swab test with exclusions)
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	All were diagnosed as having vestibulodynia due to the coexistence of the following conditions: a history of at least 6 months of vulval pain upon tampon insertion or attempted intercourse and a positive cotton-swab test, that is, tenderness at palpation of the vestibular area with a cotton tip applicator,8 in the absence of other causes for these findings
Exclusion criteria	pregnancy, cardiac pacemakers, vaginal infections, neurological or neuromuscular disorders and diabetes
Recruitment/selection of patients	Not specified
Age, gender and ethnicity	Age - Mean (range): 28(21-44) years. Gender (M:F): All women. Ethnicity: Not specified
Further population details	Chronic visceral pain
Extra comments	Duration of symptoms 15 month (range 7-48 months)
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Electrical Physical Modalities - Transcutaneous Electrical Nerve Stimulation (TENS). TENS group received an electrical stimulation in the form of a symmetrical biphasic wave generated via a calibrated dual channel TENS unit, an YSY-EST device. The stimulation was delivered through a commercially available plastic vaginal probe (PERIPROBE VAG2ST), 20 mm in diameter and 110 mm in length, with two gold metallic transversal rings as electrodes. It was inserted into the vagina for 20 mm. Previous studies involving the use of TENS in women with chronic pain syndromes showed that the optimal analgesic effect was achieved by alternating low- and high-frequency stimulation for 15–30 minutes.12 Based

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	on these experiences, frequencies of 10 and 50 Hz at 15-min intervals during each of the active TENS treatment sessions were chosen. The standard protocol for active TENS was 15 minutes of 10-Hz frequency. Duration 10 weeks. Concurrent medication/care: Not specified. Indirectness: No indirectness (n=20) Intervention 2: Placebo/Sham. The placebo group received an electrical stimulation considered to be nonactive, that is, two sets of 3-second stimulation (frequency 2 Hz, pulse duration 2 microseconds) followed by a 15-minute pause. Women of both groups underwent 20 treatment sessions on a twice per week basis. Duration 10 weeks. Concurrent medication/care: Not stated. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION (TENS) versus PLACEBO/SHAM

Protocol outcome 1: Pain reduction
- Actual outcome: VAS at 10 weeks; Group 1: mean 2.1 (SD 2.7); n=20, Group 2: mean 5.7 (SD 2.2); n=20; VAS 0-10 Top=High is poor outcome; Comments: Baseline: 6.1(1.9); 6.7(2)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0, Reason: NA; Group 2 Number missing: 0, Reason: NA
- Actual outcome: VAS at 22 weeks (including 10 week intervention); Group 1: mean 2.8 (SD 2.5); n=20, Group 2: mean 5.6 (SD 2.1); n=20; VAS 0-10 Top=High is poor outcome; Comments: Baseline: 6.1(1.9); 6.7(2)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0, Reason: NA; Group 2 Number missing: 0, Reason: NA

Protocol outcome 2: Discontinuation
- Actual outcome: Discontinuation at 10 weeks; Group 1: 0/20, Group 2: 0/20
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0, Reason: NA; Group 2 Number missing: 0, Reason: NA

Protocol outcomes not reported by the study	Quality of life ; Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep

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Study	Panton 2013[274]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=41)
Countries and setting	Conducted in USA; Setting: Not specified
Line of therapy	Unclear
Duration of study	Intervention time: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ACR criteria for FMS
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	None specified but only women recruited
Exclusion criteria	Participants were excluded if they had uncontrolled hypertension (160/ 100mm Hg or higher), uncontrolled diabetes, active heart disease, known history of cancer, long-term corticosteroid use, pregnant or planning to get pregnant, endocrine disease, anticoagulant therapy, bleeding disorders, history of stroke, a chronic infection, any type of malignancy, if they were taking medications that caused sensitivity to light, if they had a physical examination or radiological findings that would contraindicate the use of light or thermal therapy, and/or currently under the care of a chiropractic physician, acupuncture physician, massage therapist, or other forms of manual therapy.
Recruitment/selection of patients	Participants received $100.00 for participating in the study. Fifty dollars ($50.00) was given after the end of pretesting and another $50.00 was given at the completion of the study.
Age, gender and ethnicity	Age - Mean (SD): 53(11.5) years. Gender (M:F): All women. Ethnicity: Not stated
Further population details	Chronic widespread pain
Extra comments	FMS duration 10.5(7.5) years
Indirectness of population	No indirectness
Interventions	(n=23) Intervention 1: Electrical Physical Modalities - Laser therapy. Delivered by chiropractors. Treatment was designed to be consistent with the laser manufacturer's recommendations and consisted of twice weekly sessions for 4 weeks for a total of 8 sessions. The duration of each session was approximately 15 minutes,

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	while actual treatment time was 7 minutes. During the treatment sessions, the participants were either gowned, or wore a sports bra to expose the skin of the cervical, thoracic, and lumbar regions. Participants were positioned face down on a treatment table or a massage chair, depending upon their comfort and preference. Participants wore eye protection with an optical density rating >5.0 at 810nm and 980nm in order to protect their eyes and further obscure which treatment they received. To ensure consistency between the laser and heat and sham and heat group, the treatment targets consisted of seven tender points used as part of the diagnostic criteria to establish a diagnosis of FM (Fig. 1). Treatment was delivered to an area approximately 2.5 inches·3.5 inches or approximately 56.45cm2 to conform to LiteCure's manual ''Clinical Overview and Application of Class IV Therapy Laser'' written by Riegal and Pryor. For the laser group, treatment was rendered utilizing a LCT-1000 (LiteCure LLC, Newark, DE) solid-state GaAlAs laser delivering a continuous-wave, dual-wavelength laser with 20% 810nm, and 80% 980nm at 10W. Each 56.45cm2 treatment point was treated with laser at 10.63J/cm2 and warm air utilizing a grid scanning technique to avoid overheating tissue. Participants were instructed to expect some warmth but that the treatment should not burn and to provide verbal cues if the treatment spots became excessively warm. Each treatment point was treated for exactly 60 seconds for a total of 600J per point, for a total daily treatment dose of 4200J. The dual wavelength was used for two reasons: (1) this is what is commercially available and (2) two wavelengths allow for treatment in patients with different skin colours since different melanin concentrations will absorb light differently. Both wavelengths are in the accepted therapeutic window. The sham treatment consisted of 60 seconds of warm air alone over the seven tender points. A timer was used to ensure that each area was treated for exactly 60 seconds so that the treatment time was identical for both groups. Duration 4 weeks. Concurrent medication/care: Not specified. Indirectness: No indirectness (n=18) Intervention 2: Placebo/Sham. Delivered by chiropractors. Because of the thermal affects associated with Class IV laser, and because the laser manufacturer's website specifically mentions the ''soothing warmth'' of laser therapy, a sham and heat therapy treatment was designed to disguise true laser treatment from sham treatment. The device for the treatment was designed to force warm air, provided by a commercially available air warmer through a tube. The air warmer was mounted out of view inside a vented cart upon which the laser was mounted so as to appear as a single unit. The air warmer was mounted to a short section of insulated pipe, which was then attached to a T fitting with a gate valve attached to one side and the warm air supply hose attached to the opposite side. The gate valve was used to control the flow of warm air. The warm air supply hose was then bound together with the laser's fiber-optic cable with zip ties, and wound with white elastic tape to obscure both the tube and the fiber-optic cable. The air supply tube was routed through a hole drilled in the laser handpiece so that warm air could be delivered alone for the sham and heat therapy or in tandem with the laser for the laser and heat therapy. The same device was used for both groups, so the treatment group received both laser and warm air, and the sham group received only warm air. Although neither the skin temperature, nor the warm air output of the treatment device was measured, an effort was made to standardize the heat treatment by utilizing the same medium heat setting for each treatment preceded by a warmup period of approximately 5 minutes to provide a consistent application

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	of warm air at approximately the same LASER THERAPY ON FIBROMYALGIA 447 temperature from treatment to treatment. The air flow and temperature were adjusted by way of the gate valve and the air warmer's heat settings in an attempt to mimic the warmth associated with the Class IV laser with sufficient warmth so that participants could not discern whether they received the laser treatment or the sham. Duration 4 weeks. Concurrent medication/care: Not specified. Indirectness: No indirectness
Funding	Study funded by industry (Litecure)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LASER THERAPY versus PLACEBO/SHAM

Protocol outcome 1: Quality of life
- Actual outcome: FIQ at 4 weeks; Group 1: mean 55 (SD 16); n=20, Group 2: mean 55 (SD 12); n=18; FIQ 0-100 Top=High is poor outcome; Comments: Baseline: 62(21); 57(11)
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 3, Reason: Discontinued intervention; Group 2 Number missing: 0, Reason: NA

Protocol outcome 2: Pain reduction
- Actual outcome: FIQ pain at 4 weeks; Group 1: mean 6.2 (SD 2.1); n=20, Group 2: mean 6.1 (SD 1.4); n=18; FIQ pain subscale 0-10 Top=High is poor outcome; Comments: Baseline: 7.1(2.3);5.8(1.3)
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 3, Reason: Discontinued intervention; Group 2 Number missing: 0, Reason: NA

Protocol outcome 3: Discontinuation
- Actual outcome: Discontinuation at 4 weeks; Group 1: 3/23, Group 2: 0/18
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0, Reason: NA; Group 2 Number missing: 0, Reason: NA

Protocol outcomes not reported by the study	Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep

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Study	Rohlig 2011[289]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=40)
Countries and setting	Conducted in Turkey; Setting: Istanbul University
Line of therapy	Unclear
Duration of study	Intervention time: 3 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of TMD
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Presence of signs and symptoms of TMD of myogenic origin according to the research diagnostic criteria for TMD, orofacial pain lasting for more than 6 months, aged between 18 and 60 years.
Exclusion criteria	Exclusion criteria were disk displacements, arthralgia, arthritis, general inflammatory connective tissue diseases, psychiatric disorders, tumours, heart diseases, pacemakers, pregnancy, symptoms which could be referred to other disorders of the orofacial region, any medication use or treatment for TMD within the last six months, high baseline pain intensity, local skin infections over the TM area.
Recruitment/selection of patients	Selected consecutively among patients requesting orofacial pain treatment over a period of 8 months
Age, gender and ethnicity	Age - Mean (SD): 42.5(2.3) years. Gender (M:F): 16:24. Ethnicity: Not specified
Further population details	1. Chronic orofacial pain
Extra comments	Duration of pain: 10.75(2.9) years
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Electrical Physical Modalities - Laser therapy. Active laser applied every other day for 3 weeks, totalling 10 sessions. A continuous low-intensity semiconductor was used for laser irradiation, generating radiation of 820nm wavelength, with a beam diameter of 6mm and a probe angle of 45 degrees. 8J/cm2 applied to each muscle point for 10 seconds. Duration 3 weeks. Concurrent medication/care: Not specified. Indirectness: No indirectness

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	(n=20) Intervention 2: Placebo/Sham. Same equipment but the device was not programmed. No further details. Duration 3 weeks. Concurrent medication/care: Not specified. Indirectness: No indirectness
Funding	Academic or government funding (Research fund of Istanbul university)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LASER THERAPY versus PLACEBO/SHAM Protocol outcome 1: Pain reduction - Actual outcome: VAS at 3 weeks; Group 1: mean 30.05 (SD 7.14); n=20, Group 2: mean 49.75 (SD 9.54); n=20; VAS 0-100 Top=High is poor outcome; Comments: Baseline: 60.05(10.42); 53.3(8.79) Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: NR, Reason: NR; Group 2 Number missing: NR, Reason: NR	
Protocol outcomes not reported by the study	Quality of life ; Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

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Study	Short 2011[314]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=20)
Countries and setting	Conducted in USA; Setting: In the MUSC
Line of therapy	Unclear
Duration of study	Intervention time: 2 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ACR criteria for fibromyalgia
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Subjects could enrol with or without a history of major depressive disorder, but the depression could not be the main reason for their functional impairment or study enrolment. Rather subjects were recruited solely for fibromyalgia pain.
Exclusion criteria	Patients were excluded if they were taking medications known to increase the risk of TMS-induced seizures (e.g., theophylline, Ritalin, high dose thyroid supplementation), if they had medication changes within the 4 weeks of starting the trial or during the trial, or if they had pacemakers, epilepsy, recent head trauma, stroke, bipolar disorder or schizophrenia
Recruitment/selection of patients	2007-2010; Medical University of South Carolina (MUSC) Rheumatology clinics and local newspaper
Age, gender and ethnicity	Age - Mean (SD): 53(13.53) years. Gender (M:F): 4:16. Ethnicity: Not specified
Further population details	Chronic widespread pain
Extra comments	Duration of pain: 11.1(10.36) years
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: Electrical Physical Modalities - Transcranial Magnetic Stimulation (TMS). Both Active and sham groups received the same treatment sessions 5x per week 80 trains × 15 sec = 4000 pulses per

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	session, 5 × per week=20,000 pulses per week, × 2weeks = 40,000 pulses. Time - 1200 sec = 20 minutes/session, all days. Resting motor threshold (rMT) was determined using a NeoPulse Neotonus® Model 3600 (with a solid focal coil) TMS machine by starting with 80% of the machine output and 1Hz stimulus frequency. The coil was positioned over the area of the skull roughly corresponding to the motor cortex and then systematically moved and adjusted until each pulse results in isolated movement of the right thumb at rest (Abductor Pollicis Brevis; APB muscle). As the left prefrontal cortex was the cortical target, a mark was made 6 cm anterior to the motor cortex target. During active and sham stimulation, the TMS coil was aligned in a parasaggital orientation, 6 cm from the area that produced right APB muscle movement for rMT testing. The length of treatment and the number of pulses on the head was the same for all subjects; whether they receive active or sham. The same stimulation frequency was used for all active subjects (chosen as a priori stimulation based on studies showing antidepressant and antinociceptive effects): 10 Hertz - Pulse train duration (on time) 5 seconds, Power (intensity)level 120% of resting motor threshold, Inter-train interval (off time) 10seconds (15 second cycle time). Duration 2 weeks. Concurrent medication/care: No further details. Indirectness: No indirectness (n=10) Intervention 2: Placebo/Sham. Both Active and sham groups received the same treatment sessions 5x per week 80 trains × 15 sec = 4000 pulses per session, 5 × per week=20,000 pulses per week, × 2weeks = 40,000 pulses. A specially designed sham TMS coil was used for all sham conditions that produces auditory signals identical to active coils but is shielded so that actual stimulation does not occur, however subjects do experience sensory stimulation that is difficult to distinguish from real TMS. Participants experienced a brief (~250 μs) electrical pulse every time the sham TMS coil clicked. The intensity of the stimulus was adjustable at the electrical generator (1 to 60 mA) and the time that the gate was let open after each TTL trigger was adjustable on the switch-box as well. Duration 2 weeks. Concurrent medication/care: No further details. Indirectness: No indirectness
Funding	Principal author funded by industry (Glaxo-Smith Kline, Jazz Pharmaceuticals, Brainsway, Cephos, and Force Protection)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCRANIAL MAGNETIC STIMULATION (TMS) versus PLACEBO/SHAM

Protocol outcome 1: Quality of life
- Actual outcome: FIQ at 4 weeks; Group 1: mean 38.99 (SD 19.44); n=10, Group 2: mean 47.93 (SD 14.7); n=10; FIQ 0-100 Top=High is poor outcome; Comments: baseline: 58.79(11.93); 54.38(13.96)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Number of participants on medications differed (e.g., 20% vs 0% of participants were taking muscle relaxants in the real and sham groups respectively); Group 1 Number missing, Reason: NR; Group 2 Number missing, Reason: NR

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Protocol outcome 2: Pain reduction - Actual outcome: VAS at 4 weeks; Group 1: mean 4.41 (SD 1.95); n=10, Group 2: mean 5.37 (SD 2.02); n=10; VAS 0-10 Top=High is poor outcome; Comments: Baseline: 5.6(1.85); 5.34(1.82) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Number of participants on medications differed (e.g., 20% vs 0% of participants were taking muscle relaxants in the real and sham groups respectively); Group 1 Number missing, Reason: NR; Group 2 Number missing, Reason: NR Protocol outcome 3: Physical function - Actual outcome: Brief pain inventory functional impairment at 4 weeks; Group 1: mean 3.6 (SD 2.18); n=10, Group 2: mean 3.79 (SD 2.69); n=10; BPI subscale 0-10 Top=High is poor outcome; Comments: Baseline: 5.57(2.58); 5.44(2.25) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Number of participants on medications differed (e.g., 20% vs 0% of participants were taking muscle relaxants in the real and sham groups respectively); Group 1 Number missing, Reason: NR; Group 2 Number missing, Reason: NR Protocol outcome 4: Psychological distress - Actual outcome: Hamilton depression rating scale at 4 weeks; Group 1: mean 14.1 (SD 9.42); n=10, Group 2: mean 16.4 (SD 8.18); n=10; HDRS 0-52 Top=High is poor outcome; Comments: Baseline:21.8(7.79); 17.6(7.31) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Number of participants on medications differed (e.g., 20% vs 0% of participants were taking muscle relaxants in the real and sham groups respectively); Group 1 Number missing, Reason: NR; Group 2 Number missing, Reason: NR	
Protocol outcomes not reported by the study	Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

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Study	Spanemberg 2015[325]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=58)
Countries and setting	Conducted in Spain; Setting: Not specified
Line of therapy	Unclear
Duration of study	Intervention time: 3 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of burning mouth syndrome
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Above 40 years old, burning or pain in the oral mucosa for at least 6 months with clinically normal mucosa.
Exclusion criteria	Participants who were taking antidepressants, anxiolytic or anticonvulsant drugs or those who had undergone chemotherapy or radiotherapy were excluded. Patients who showed hyposalivation, alterations in blood count, glucose serum levels, iron, folic acid, vitamin b12 were also excluded.
Recruitment/selection of patients	Not specified
Age, gender and ethnicity	Age - Mean (SD): 61.9(8.76) years. Gender (M:F): 8:51. Ethnicity: Not specified
Further population details	1. Chronic orofacial pain: Chronic orofacial pain
Extra comments	Duration of pain not specified (minimum duration 6 months)
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Electrical Physical Modalities - Laser therapy. Infrared laser therapy 3 times a week. GaA1As, 830nm wavelength, 100mW output, continuous emissions, 3.57W/cm2, 5J energy per point, 176J/cm2 radiant exposure, application time 50s per point. Total 9 sessions. Duration 3 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=19) Intervention 2: Electrical Physical Modalities - Laser therapy. Red laser therapy: InGaAlP, 685nm wavelength, 35mW output power, continuous emissions, 1.25W/cm2, 2J energy per point, 72 J/cm2 radiant exposure, application time 58s per point. Total 9 sessions (3 per week). Duration 3 weeks. Concurrent

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	medication/care: Not specified. Indirectness: No indirectness (n=19) Intervention 3: Placebo/Sham. 9 sessions, similar to both laser interventions but the tool received a plastic tip with rubber interior that blocked radiation emissions, checked by means of a power meter prior to the applications. Duration 3 weeks. Concurrent medication/care: Not specified. Indirectness: No indirectness
Funding	Study funded by industry (Coorednacao de Aperfeicoamento de Pesal de Nivel Superior (CAPES) - Brazil)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LASER THERAPY (INFRARED) versus PLACEBO/SHAM Protocol outcome 1: Quality of life - Actual outcome: Oral health impact profile at 3 weeks; Group 1: mean 6.89 (SD 4.05); n=20, Group 1: mean 13.39 (SD 3.62); n=19 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Pain reduction - Actual outcome: VAS at 8 weeks follow up (including 3 week intervention); Group 1: mean 25.9 (SD 19.48); n=20, Group 2: mean 62.84 (SD 26.3); n=19; VAS 0-100 Top=High is poor outcome; Comments: Baseline: 85.26(14.25); 78.9(15.25) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LASER THERAPY (RED) versus PLACEBO/SHAM Protocol outcome 1: Quality of life - Actual outcome: Oral health impact profile at 3 weeks; Group 1: mean 9.77 (SD 4.92); n=19, Group 2: mean 13.39 (SD 3.62); n=19; OHIP Not specified Top=High is poor outcome; Comments: Baseline: 14.46(7.21); 17.8(5.37) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Pain reduction - Actual outcome: VAS at 8 weeks follow up (including 3 week intervention); Group 1: mean 41.11 (SD 27.14); n=19, Group 2: mean 62.84 (SD 26.3); n=19; VAS 0-100 Top=High is poor outcome; Comments: Baseline: 85.26(14.25);80.68(18.63) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

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Study	Sugaya 2016[329]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=30)
Countries and setting	Conducted in Brazil; Setting: Not specified
Line of therapy	Unclear
Duration of study	Intervention time: 2 week intervention plus 90 days follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Met the diagnostic criteria for burning mouth syndrome
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Other diagnoses ruled out (diabetes, anemia, hypovitaminosis).
Exclusion criteria	Clinical alterations in the oral mucosa potentially associated with the burning symptoms, hyposalivation, diabetes, B hypovitaminosis, and anemia. History of malignant of benign head and neck neoplasia, pregnancy, breast feeding
Recruitment/selection of patients	Stomatology Clinic of the Sao Paulo University School of Dentistry
Age, gender and ethnicity	Age - Mean (range): 59.7(29-83) years. Gender (M:F): 2:21. Ethnicity: Not specified
Further population details	1. Chronic orofacial pain: Chronic orofacial pain
Extra comments	Mean duration of symptoms 31.7 months (range 6 to 192)
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: Electrical Physical Modalities - Laser therapy. 4 sessions of irradiation across 2 weeks, with a 3 day interval between each session. Laser irradiation delivered in scanning mode with laser point in contact with the mucosa. The energy released was 6J/cm2, and irradiation was applied on the entire area affected by the burning sensation. Irradiation time was determined by the extension of the affected area, according to a standardised formula. Duration 2 weeks. Concurrent medication/care: Not specified. Indirectness: No indirectness

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	(n=15) Intervention 2: Placebo/Sham. Identical method but no laser energy was delivered. The machine still beeped at regular intervals so it appeared active. Duration 2 weeks. Concurrent medication/care: Not specified. Indirectness: No indirectness
Funding	Academic or government funding (State of Sao Paulo research foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LASER THERAPY versus PLACEBO/SHAM

Protocol outcome 1: Pain reduction
- Actual outcome: VAS (calculated from individual patient data) at 3 months; Group 1: mean 2 (SD 1.89); n=13, Group 2: mean 2.2 (SD 1.94); n=10; VAS 0-10 Top=High is poor outcome; Comments: Baseline not reported
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2; Group 2 Number missing: 5
- Actual outcome: VAS (calculated from individual patient data) at 16 weeks; Group 1: mean 2.08 (SD 2.25); n=13, Group 2: mean 1.8 (SD 1.89); n=10; VAS 0-10 Top=High is poor outcome; Comments: Baseline values not reported
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2; Group 2 Number missing: 5

Protocol outcomes not reported by the study	Quality of life ; Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

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Study	Tekin 2014[339]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=52)
Countries and setting	Conducted in Turkey; Setting: Not specified
Line of therapy	Unclear
Duration of study	Intervention time: 10 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ACR FMS criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Right handed, 18-65 years old, no analgesic use for at least 1 month, suffered persistent pain for longer than 6 months
Exclusion criteria	Causes of pain such as inflammatory or rheumatologic diseases, other pain related diseases, psychiatric disorders other than depression, drug abuse or dependency, or patients contraindicated to electrical therapy (e.g. epilepsy or head trauma).
Recruitment/selection of patients	2012-2013, patients who were evaluated at the Sisli Etfal education and research hospital physical medicine and rehab outpatient unit
Age, gender and ethnicity	Age - Mean (SD): 44.4(8.1) years. Gender (M:F): 4:47. Ethnicity: Not specified
Further population details	Chronic widespread pain
Extra comments	Duration of pain 12.1(6.47) years
Indirectness of population	No indirectness
Interventions	(n=27) Intervention 1: Electrical Physical Modalities - Transcranial Magnetic Stimulation (TMS). Repetitive TMS conducted with Magstim biphasic stimulation device with 8 shaped coil of 70mm. Conducted by a psychiatry physician. Resting motor threshold values determined for each patient using the minimum motor threshold method. Sessions conducted as 30 sequential series, for 5s, frequency 10Hz, application intensity 100%, interval between the series was 12s (total of 1500 stimuli per day given to each patient). Duration 10 days. Concurrent medication/care: Not specified. Indirectness: No indirectness

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	(n=25) Intervention 2: Placebo/Sham. Identical treatment but a placebo coil system was used which produced similar sounds to the real application but without magnetic stimulation. Duration 10 days. Concurrent medication/care: Not specified. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCRANIAL MAGNETIC STIMULATION (TMS) versus PLACEBO/SHAM Protocol outcome 1: Quality of life - Actual outcome: WHOQOL-BREF physical domain at 10 days; Group 1: mean 14.26 (SD 2.52); n=27, Group 2: mean 11.33 (SD 2.84); n=24; WHOQOL-BREF 4-20 Top=High is good outcome; Comments: baseline: 11.07(2.54); 10.83(2.79) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: NA; Group 2 Number missing: 1, Reason: NR - Actual outcome: WHOQOL-BREF psychological domain at 10 days; Group 1: mean 13.89 (SD 2.47); n=27, Group 2: mean 12.71 (SD 2.49); n=24; WHOQOL-BREF 4-20 Top=High is good outcome; Comments: Baseline: 12.15(2.57); 12.29(2.85) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: NA; Group 2 Number missing: 1, Reason: NR Protocol outcome 2: Pain reduction - Actual outcome: VAS at 10 days; Group 1: mean 37.96 (SD 9.83); n=27, Group 2: mean 62.08 (SD 16.68); n=24; VAS 0-100 Top=High is poor outcome; Comments: Baseline: 79.63(12.24); 81.25(12.9) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: NA; Group 2 Number missing: 1, Reason: NR Protocol outcome 3: Psychological distress - Actual outcome: MADRS at 10 days; Group 1: mean 10.14 (SD 3.96); n=27, Group 2: mean 10.24 (SD 6); n=24; MADRS Not specified Top=High is poor outcome; Comments: Baseline: 12.89(4.53); 12.25(6.44) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: NA; Group 2 Number missing: 1, Reason: NR Protocol outcome 4: Discontinuation - Actual outcome: Discontinuation from treatment at 10 days; Group 1: 0/27, Group 2: 1/25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: NA; Group 2 Number missing: 1, Reason: NR	
Protocol outcomes not reported by the study	Physical function ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep

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Study	Umezaki 2016[345]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=26)
Countries and setting	Conducted in USA; Setting: MUSC
Line of therapy	Unclear
Duration of study	Intervention + follow up: 10 day treatment and 8 weeks follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of burning mouth syndrome
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosis of BMS confirmed by (1) daily and deep bilateral burning sensation of the oral mucosa, burning sensation for at least 4-56 months, constant intensity or increasing intensity during the day, no worsening but possible improvement on eating or drinking, no interference with sleep and normal appearing oral mucosa
Exclusion criteria	Excluded one evidence of inflammation or autoimmune disease, current psychiatric conditions or drug abuse, or other contradictions for TMS, or starting new medication or changing medication within 4 weeks of starting the trial
Recruitment/selection of patients	Recruited through local newspaper adverts, from the oral pathology division in the MUSC dental clinic and through MUSC broadcast email
Age, gender and ethnicity	Age - Mean (SD): 63.85(9.56) years. Gender (M:F): 92.31% female. Ethnicity: Not specified
Further population details	1. Chronic orofacial pain
Extra comments	Duration of illness 63.42(65.51) years
Indirectness of population	No indirectness
Interventions	(n=14) Intervention 1: Electrical Physical Modalities - Transcranial Magnetic Stimulation (TMS). Device: MagVenture MagPro x100 stimulator with figure 8 coil. Resting motor threshold determined each for each individual. Machine set at 50% maximum output and TMS coil positioned around primary motor cortex, and moved until the area that best produced contraction of abductor pollicis brevis was identified. 10 sessions of 10Hz pulse train duration 5s, power intensity levels 110% of RMT, intertrain interval 10s for 15 minutes (total

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	of 30,000 pulses). Duration 1 week. Concurrent medication/care: Not specified. Indirectness: No indirectness (n=12) Intervention 2: Placebo/Sham. Identical treatment but the coil was shielded so that actual stimulation did not occur. Duration 1 week. Concurrent medication/care: Not specified. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCRANIAL MAGNETIC STIMULATION (TMS) versus PLACEBO/SHAM Protocol outcome 1: Pain reduction - Actual outcome: Pain (McGill pain questionnaire) at 8 weeks (follow up); Group 1: mean 1.33 (SD 0.78); n=12, Group 2: mean 2.88 (SD 1.36); n=8; SFMPQ Not specified Top=High is poor outcome; Comments: Baseline: 2.54(0.84); 3.63(1.51) Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: Lost to follow up; Group 2 Number missing: 4, Reason: Lost to follow up Protocol outcome 3: Discontinuation - Actual outcome: Discontinued intervention at 1 week; Group 1: 0/14, Group 2: 0/12 Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: Lost to follow up; Group 2 Number missing: 4, Reason: Lost to follow up	
Protocol outcomes not reported by the study	Quality of life ; Physical function ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep

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Study	Valenzuela 2017[346]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=44)
Countries and setting	Conducted in Spain; Setting: Not specified
Line of therapy	Unclear
Duration of study	Intervention time: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Burning mouth syndrome diagnosis according to international classification of headaches
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	BMS diagnosis, continuous symptoms of oral burning or pain on a daily or almost daily basis during all or part of the day for more than 6 months and absence of local or systemic factors that could produce the same symptoms
Exclusion criteria	History of head and neck malignancy radiation therapy to the head and neck area, poorly managed conditions such as diabetes, thyroid disease, Sjorgrens syndrome, rheumatological diseases, anemia, analgesics or NSAID use, pregnancy.
Recruitment/selection of patients	Consecutive patients diagnosed with idiopathic burning mouth syndrome attending the department of oral medicine (FoM and Dentistry, UoM, Spain).
Age, gender and ethnicity	Age - Mean (SD): 65.5 (10.6) years. Gender (M:F): 3:41. Ethnicity: Not specified
Further population details	1. Chronic orofacial pain
Extra comments	Duration of pain not specified
Indirectness of population	No indirectness
Interventions	(n=16) Intervention 1: Electrical Physical Modalities - Laser therapy. Low level laser. 815nm wavelength, 1W output power, 4 seconds, 4J, fluence rate 133.3Jcm-2. Applied intra-orally and continuously, perpendicularly in contact with the mucosa in areas where patient reported symptoms. Spot sizes were 0.03cm3 and ten points over each area presenting symptoms were irradiated. Duration 4 weeks. Concurrent medication/care: Not specified. Indirectness: No indirectness

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	(n=16) Intervention 2: Electrical Physical Modalities - Laser therapy. Low level laser. 815nm wavelength, 1W output power, 6 seconds, 6J, fluence rate 200Jcm-2. Applied intra-orally and continuously, perpendicularly in contact with the mucosa in areas where patient reported symptoms. Spot sizes were 0.03cm3 and ten points over each area presenting symptoms were irradiated. Duration 4 weeks. Concurrent medication/care: Not specified. Indirectness: No indirectness (n=12) Intervention 3: Placebo/Sham. Sham: same procedure but laser turned off. Duration 4 weeks. Concurrent medication/care: Not specified. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LASER THERAPY (LOW INTENSITY) versus PLACEBO/SHAM

Protocol outcome 1: Quality of life
- Actual outcome: Oral health impact profile at 4 weeks; Group 1: mean 28.5 (SD 3.1); n=16, Group 2: mean 29.25 (SD 6.1); n=12; OHIP 0-70 Top=High is poor outcome; Comments: Baseline: 29.88(3.6); 29.33(5.9)
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: NR; Group 2 Number missing: NR

Protocol outcome 2: Pain reduction
- Actual outcome: VAS at 4 weeks; Group 1: mean 6.38 (SD 1.6); n=16, Group 2: mean 7.65 (SD 1.2); n=12; VAS 0-10 Top=High is poor outcome; Comments: Baseline: 7.56(1.5); 7.83(1.3)
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: NR; Group 2 Number missing: NR

Protocol outcome 3: Psychological distress
- Actual outcome: HADS:A at 4 weeks; Group 1: mean 10.44 (SD 3.9); n=16, Group 2: mean 10.33 (SD 3.5); n=12; HADS:A 0-21 Top=High is poor outcome; Comments: Baseline: 10.44(3.9); 10.25(3.5)
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:: NR; Group 2 Number missing: NR
- Actual outcome: HADS:D at 4 weeks; Group 1: mean 7.19 (SD 4.9); n=16, Group 2: mean 7.25 (SD 4.5); n=12; HADS:D 0-21 Top=High is poor outcome; Comments: Baseline: 7.19(4.9); 7.25(4.5)
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: NR; Group 2 Number missing: NR

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LASER THERAPY (HIGH INTENSITY) versus PLACEBO/SHAM

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Protocol outcome 1: Quality of life - Actual outcome: Oral health impact profile at 4 weeks; Group 1: mean 28.25 (SD 6.1); n=16, Group 2: mean 29.25 (SD 6.3); n=12; OHIP 0-70 Top=High is poor outcome; Comments: Baseline: 29.57(5.9); 29.33(5.9) Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: NR; Group 2 Number missing: NR Protocol outcome 2: Pain reduction - Actual outcome: VAS at 4 weeks; Group 1: mean 7.06 (SD 1.8); n=16, Group 2: mean 7.65 (SD 1.2); n=12; VAS 0-10 Top=High is poor outcome; Comments: Baseline: 8.38(1.3); 7.83(1.3) Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: NR; Group 2 Number missing: NR Protocol outcome 3: Psychological distress - Actual outcome: HADS:A at 4 weeks; Group 1: mean 11.88 (SD 3.2); n=16, Group 2: mean 10.33 (SD 3.5); n=12; HADS:A 0-21 Top=High is poor outcome; Comments: Baseline: 11.75(3.4); 10.25(3.5) Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: NR; Group 2 Number missing: NR - Actual outcome: HADS:D at 4 weeks; Group 1: mean 9.88 (SD 3.3); n=16, Group 2: mean 7.25 (SD 4.5); n=12; HADS:D 0-21 Top=High is poor outcome; Comments: Baseline: 10(3.3); 7.25(4.5) Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Difference at baseline in outcome: 10(3.3); 7.25(4.5); Group 1 Number missing:: NR; Group 2 Number missing: NR	
Protocol outcomes not reported by the study	Physical function ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

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Study	Venancio 2005[354]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=30)
Countries and setting	Conducted in Brazil; Setting: Not specified
Line of therapy	Unclear
Duration of study	Intervention + follow up: 3 weeks (with 8 week follow up)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: TMD diagnosis according to criteria of the American Academy of Orofacial pain
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Pain restricted to the joint area, associated with the absence of any muscle tenderness during palpation.
Exclusion criteria	Psychiatric disorders, heart diseases, epilepsy, pregnancy, RA, degenerative joint disease, tumours, people with pacemakers
Recruitment/selection of patients	Consecutive patients that presented for diagnosis and treatment of TMD in the OTDC clinic at a dentistry school.
Age, gender and ethnicity	Age - Mean (range): 36.25(13-63) years. Gender (M:F): 5:25. Ethnicity: Not specified
Further population details	1. Chronic orofacial pain
Extra comments	Mean duration of pain 44.8 months (range 6-120 months)
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: Electrical Physical Modalities - Laser therapy. Twice a week for 3 weeks. Using Ga0Al-As laser at 780nm wavelength. Output of 30mW, 10s duration, at 6.3Jcm-2 at 3 points in each TMJ. Duration 3 weeks. Concurrent medication/care: Not reported (other than advice about resting joints, following a soft diet and conscious relaxation of masticatory muscles). Indirectness: No indirectness (n=15) Intervention 2: Placebo/Sham. Identical treatment but the laser device was not turned on. Duration 3 weeks. Concurrent medication/care: Not reported (other than advice about resting joints, following a soft diet

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	and conscious relaxation of masticatory muscles). Indirectness: No indirectness
Funding	Academic or government funding (FAPESP Sao Paulo Research Support Foundation)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LASER THERAPY versus PLACEBO/SHAM Protocol outcome 1: Pain reduction - Actual outcome: VAS at 8 weeks; Group 1: mean 1.6 (SD 2.03); n=15, Group 2: mean 3.67 (SD 2.85); n=15; VAS 0-10 Top=High is poor outcome Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life ; Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

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Study	Yagci 2014[375]
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	(n=28)
Countries and setting	Conducted in Turkey; Setting: Not specified
Line of therapy	Unclear
Duration of study	2 week intervention and 3 months follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ACR criteria for fibromyalgia
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 18-60 years, no improvement in symptoms regardless of using medical treatment for at least 3 months.
Exclusion criteria	Other diagnoses such as inflammatory rheumatic disease, current primary psychiatric disease, previous surgical treatment to the cranial area, pregnancy, or history of substance abuse
Recruitment/selection of patients	Not specified
Age, gender and ethnicity	Age - Mean (SD): 44.9(8.6) years. Gender (M:F): All female. Ethnicity: Not specified
Further population details	Chronic widespread pain
Extra comments	Mean duration of symptoms 53.5 (29.8) months
Indirectness of population	No indirectness
Interventions	(n=14) Intervention 1: Electrical Physical Modalities - Transcranial Magnetic Stimulation (TMS). 2 week interventions, with 10 sessions of low-frequency rTMS applied from Monday to Friday of each week. The stimulation area was the left primary motor cortex. Magnetic stimulation applied using a MagBenture machine, using a parabolic coil that was oriented at a tangent to the scalp. The resting motor threshold was determined before each session using single pulse stimulation over the left primary motor cortex, which was defined as the minimal intensity required to evoke MEPs of 50mV peak-to-peak amplitude in 5 out of 10 consecutive trials. The main stimulation parameters were 90% of motor threshold for 60 seconds at 1Hz and 45 second intervals between each trains. 1200 pulses were therefore administered in each session. Duration 2 weeks. Concurrent medication/care: Medications remained stable throughout the study. Indirectness: No indirectness

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	(n=14) Intervention 2: Placebo/Sham. Sham stimulation carried out with the same parabolic coil, which was placed at 90 degree angles to the motor cortex area. No further details. Duration 2 weeks. Concurrent medication/care: Medications remained stable throughout. Indirectness: No indirectness
Funding	Not reported
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCRANIAL MAGNETIC STIMULATION (TMS) versus PLACEBO/SHAM Protocol outcome 1: Quality of life - Actual outcome: FIQ at 3 months; Group 1: mean 36.95 (SD 24.27); n=13, Group 2: mean 48.13 (SD 16.79); n=12; VAS 0-10 Top=High is poor outcome; Comments: Baseline: 66.09(15.13); 65.1(12.92) Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Beck depression inventory baseline difference; Group 1 Number missing: 1, Reason: NR; Group 2 Number missing: 2, Reason: NR Protocol outcome 2: Pain reduction - Actual outcome: VAS at 3 months; Group 1: mean 4.75 (SD 2.76); n=13, Group 2: mean 5.3 (SD 2.49); n=12; VAS 0-10 Top=High is poor outcome; Comments: Baseline: 7.75(1.54); 7.61(2.14) Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Beck depression inventory baseline difference; Group 1 Number missing: 1, Reason: NR; Group 2 Number missing: 2, Reason: NR Protocol outcome 3: Psychological distress - Actual outcome: BDI at 3 months; Group 1: mean 16.75 (SD 10.6); n=13, Group 2: mean 14.15 (SD 8); n=12; Beck depression inventory 0-61 Top=High is poor outcome; Comments: Baseline: 19.58(9.33);18.53(9.7) Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Beck depression inventory baseline difference; Group 1 Number missing: 1, Reason: NR; Group 2 Number missing: 2, Reason: NR	
Protocol outcomes not reported by the study	Physical function ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

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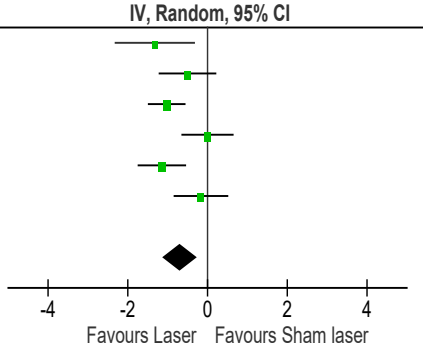
Appendix E: Forest plots

E.1 Laser therapy versus sham laser therapy

Figure 2: Quality of life at ≤3 months (Oral health impact profile, FIQ, high is poor outcome, final values)

Study or Subgroup	Laser Mean	Laser SD	Laser Total	Sham laser Mean	Sham laser SD	Sham laser Total	Weight	Std. Mean Difference IV, Random, 95% CI
Arbabi-Kalati 2015	12.8	11.4	10	28.6	11.5	10	11.1%	-1.32 [-2.31, -0.33]
Armagan 2006	58.5	10.33	16	63.63	9.59	16	15.8%	-0.50 [-1.21, 0.20]
Bardellini 2019	7.09	2.59	43	10.64	4.13	42	21.2%	-1.02 [-1.48, -0.57]
Panton 2013	55	16	20	55	12	18	17.2%	0.00 [-0.64, 0.64]
Spanemberg 2015	8.293	4.72	39	13.39	3.62	19	18.2%	-1.14 [-1.73, -0.55]
Valenzuela 2017	28.38	4.84	31	29.25	6.1	12	16.5%	-0.16 [-0.83, 0.50]
Total (95% CI)			**159**			**117**	**100.0%**	**-0.68 [-1.10, -0.25]**

Heterogeneity: Tau² = 0.17; Chi² = 13.07, df = 5 (P = 0.02); I² = 62%
Test for overall effect: Z = 3.12 (P = 0.002)



NB. Heterogeneity not explained by subgroup analysis

Figure 3: Quality of life at ≤3 months (SF-36 physical component summary score, 0-100, high is good outcome, change scores)

Study or Subgroup	Laser Mean	Laser SD	Laser Total	Sham laser Mean	Sham laser SD	Sham laser Total	Weight	Mean Difference IV, Fixed, 95% CI
Chow 2004	4	8.22	10	1.22	6.32	10	21.8%	2.78 [-3.65, 9.21]
Chow 2006	3.2	10.78	45	1.3	4.28	45	78.2%	1.90 [-1.49, 5.29]
Total (95% CI)			**55**			**55**	**100.0%**	**2.09 [-0.91, 5.09]**

Heterogeneity: Chi² = 0.06, df = 1 (P = 0.81); I² = 0%
Test for overall effect: Z = 1.37 (P = 0.17)

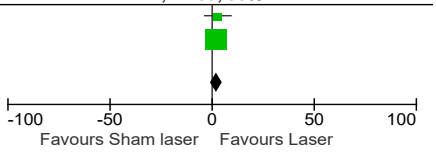
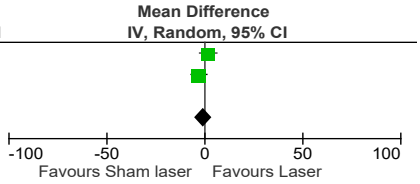


Figure 4: Quality of life at ≤3 months (SF-36 mental component summary score, 0-100, high is good outcome, change scores)

Study or Subgroup	Laser Mean	Laser SD	Laser Total	Sham laser Mean	Sham laser SD	Sham laser Total	Weight	Mean Difference IV, Random, 95% CI
Chow 2004	1.71	3.79	10	0	6.01	10	48.0%	1.71 [-2.69, 6.11]
Chow 2006	2.4	8.2	45	5.4	10.9841	45	52.0%	-3.00 [-7.00, 1.00]
Total (95% CI)			**55**			**55**	**100.0%**	**-0.74 [-5.35, 3.87]**

Heterogeneity: Tau² = 6.48; Chi² = 2.41, df = 1 (P = 0.12); I² = 58%
Test for overall effect: Z = 0.31 (P = 0.75)



NB. Heterogeneity not explained by subgroup analysis

Figure 5: Quality of life at >3 months (FIQ, 0-100, high is poor outcome, final values)

Study or Subgroup	Laser Mean	Laser SD	Laser Total	Sham laser Mean	Sham laser SD	Sham laser Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Armagan 2006	62.06	8.99	16	66.94	8.44	16	28.4%	-0.55 [-1.25, 0.16]
Bardellini 2019	7.43	3.78	43	10.43	2.99	42	71.6%	-0.87 [-1.32, -0.43]
Total (95% CI)			**59**			**58**	**100.0%**	**-0.78 [-1.16, -0.40]**

Heterogeneity: Chi² = 0.58, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 4.05 (P < 0.0001)

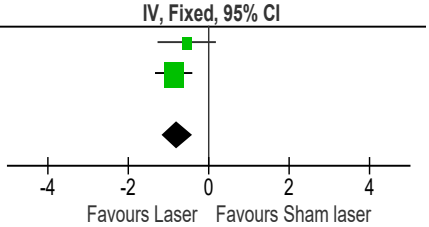


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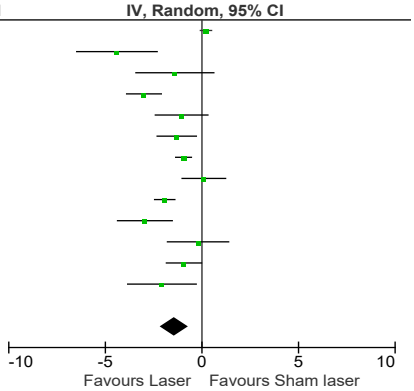
Figure 6: Pain reduction at ≤3 months (VAS, NRS, FIQ pain scale, high is poor outcome, 0-10, final values and change scores)

Study or Subgroup	Laser Mean	Laser SD	Laser Total	Sham laser Mean	Sham laser SD	Sham laser Total	Weight	Mean Difference IV, Random, 95% CI
Altan 2005	4.13	0.58	23	3.92	0.42	25	9.8%	0.21 [-0.08, 0.50]
Arbabi-Kalati 2015	3.6	3	10	8	1.5	10	5.3%	-4.40 [-6.48, -2.32]
Chow 2004	-2.1	2.84	10	-0.7	1.58	10	5.4%	-1.40 [-3.41, 0.61]
Chow 2006	-2.7	1.9971	45	0.3	2.33	45	8.6%	-3.00 [-3.90, -2.10]
da Cunha 2008	3.62	2.45	20	4.67	1.9	20	7.2%	-1.05 [-2.41, 0.31]
Del vecchio 2019	-3.517	2.2139	29	-2.214	1.6635	28	8.2%	-1.30 [-2.32, -0.29]
Gur 2002	1.24	0.72	25	2.19	0.74	25	9.7%	-0.95 [-1.35, -0.55]
Panton 2013	6.2	2.1	20	6.1	1.4	18	7.9%	0.10 [-1.02, 1.22]
Rohlig 2011	3.05	0.714	20	4.975	0.954	20	9.5%	-1.92 [-2.45, -1.40]
Spanemberg 2015	3.33	2.47	39	6.284	2.63	19	7.1%	-2.95 [-4.37, -1.54]
Sugaya 2016	2	1.89	13	2.2	1.94	10	6.6%	-0.20 [-1.78, 1.38]
Valenzuela 2017	6.72	1.74	32	7.65	1.2	12	8.5%	-0.93 [-1.84, -0.02]
Venancio 2005	1.6	2.03	15	3.67	2.85	15	6.1%	-2.07 [-3.84, -0.30]
Total (95% CI)			**301**			**257**	**100.0%**	**-1.42 [-2.12, -0.73]**

Heterogeneity: Tau² = 1.27; Chi² = 114.87, df = 12 (P < 0.00001); I² = 90%
Test for overall effect: Z = 4.00 (P < 0.0001)



NB. Heterogeneity not explained by subgroup analysis

Figure 7: Pain reduction at >3 months (VAS, high is poor outcome, 0-10, final values)

Study or Subgroup	Laser Mean	Laser SD	Laser Total	Sham laser Mean	Sham laser SD	Sham laser Total	Weight	Mean Difference IV, Fixed, 95% CI
Altan 2005	3.17	0.58	23	3.8	0.51	25	96.8%	-0.63 [-0.94, -0.32]
Sugaya 2016	2.08	2.25	13	1.8	1.89	10	3.2%	0.28 [-1.41, 1.97]
Total (95% CI)			**36**			**35**	**100.0%**	**-0.60 [-0.91, -0.30]**

Heterogeneity: Chi² = 1.07, df = 1 (P = 0.30); I² = 7%
Test for overall effect: Z = 3.86 (P = 0.0001)

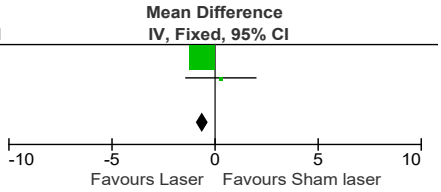


Figure 8: Psychological distress at ≤3 months (Hospital anxiety and depression rating scale, anxiety subscale, 0-21, high is poor outcome, final values)

Study or Subgroup	Laser Mean	Laser SD	Laser Total	Sham laser Mean	Sham laser SD	Sham laser Total	Weight	Mean Difference IV, Fixed, 95% CI
Valenzuela 2017	11.16	3.639	32	10.33	3.5	12	100.0%	0.83 [-1.52, 3.18]
Total (95% CI)			**32**			**12**	**100.0%**	**0.83 [-1.52, 3.18]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)

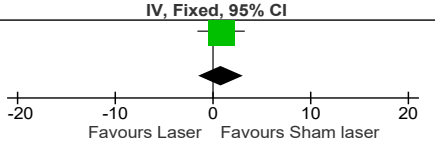


Figure 9: Psychological distress at ≤3 months (Hospital anxiety and depression rating scale, depression subscale, 0-21, high is poor outcome, final values)

Study or Subgroup	Laser Mean	Laser SD	Laser Total	Sham laser Mean	Sham laser SD	Sham laser Total	Weight	Mean Difference IV, Fixed, 95% CI
Valenzuela 2017	8.535	4.389	32	7.25	4.5	16	100.0%	1.29 [-1.39, 3.96]
Total (95% CI)			**32**			**16**	**100.0%**	**1.29 [-1.39, 3.96]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.94 (P = 0.35)

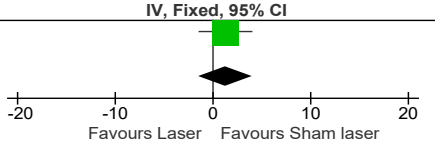
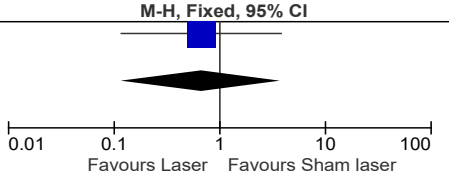


Figure 10: Discontinuation at ≤3 months

Study or Subgroup	Laser Events	Laser Total	Sham laser Events	Sham laser Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chow 2006	2	45	3	45	100.0%	0.67 [0.12, 3.80]
Total (95% CI)		**45**		**45**	**100.0%**	**0.67 [0.12, 3.80]**
Total events	2		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.46 (P = 0.65)



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E.2 TMS versus sham TMS

Figure 11: Quality of life at ≤3 months (SF-36 physical summary score, 0-100, high is good outcome, change scores)

Study or Subgroup	TMS Mean	TMS SD	TMS Total	Sham TMS Mean	Sham TMS SD	Sham TMS Total	Weight	Mean Difference IV, Fixed, 95% CI
Boyer 2014	1.4	9	16	0.4	4.8	13	100.0%	1.00 [-4.12, 6.12]
Total (95% CI)			**16**			**13**	**100.0%**	**1.00 [-4.12, 6.12]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.38 (P = 0.70)

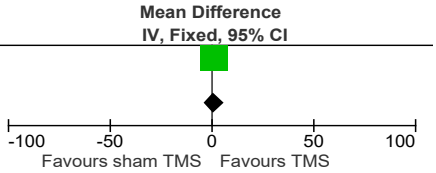

Figure 12: Quality of life at ≤3 months (SF-36 mental summary score, 0-100, high is good outcome, change scores)

Study or Subgroup	TMS Mean	TMS SD	TMS Total	Sham TMS Mean	Sham TMS SD	Sham TMS Total	Weight	Mean Difference IV, Fixed, 95% CI
Boyer 2014	5	6.9	16	-1.6	7.6	13	100.0%	6.60 [1.26, 11.94]
Total (95% CI)			**16**			**13**	**100.0%**	**6.60 [1.26, 11.94]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.42 (P = 0.02)

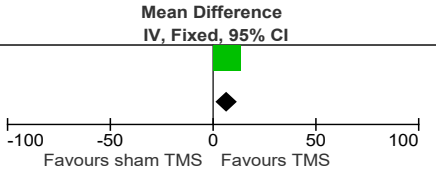

Figure 13: Quality of life at ≤3 months (WHOQOL-BREF physical domain, 4-20, high is good outcome, final values)

Study or Subgroup	TMS Mean	TMS SD	TMS Total	Sham TMS Mean	Sham TMS SD	Sham TMS Total	Weight	Mean Difference IV, Fixed, 95% CI
Tekin 2014	14.6	2.52	27	11.33	2.84	24	100.0%	3.27 [1.79, 4.75]
Total (95% CI)			**27**			**24**	**100.0%**	**3.27 [1.79, 4.75]**

Heterogeneity: Not applicable
Test for overall effect: Z = 4.33 (P < 0.0001)

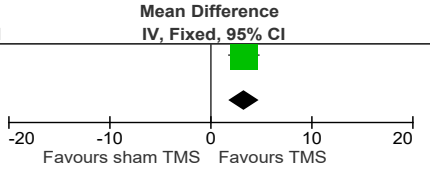

Figure 14: Quality of life at ≤3 months (WHOQOL-BREF psychological domain, 4-20, high is good outcome, final values)

Study or Subgroup	TMS Mean	TMS SD	TMS Total	Sham TMS Mean	Sham TMS SD	Sham TMS Total	Weight	Mean Difference IV, Fixed, 95% CI
Tekin 2014	13.89	2.47	27	12.71	2.49	24	100.0%	1.18 [-0.18, 2.54]
Total (95% CI)			**27**			**24**	**100.0%**	**1.18 [-0.18, 2.54]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.70 (P = 0.09)

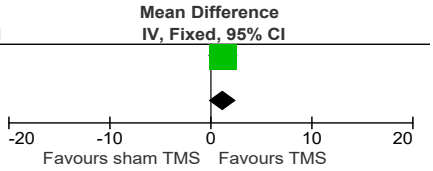

Figure 15: Quality of life at ≤3 months (FIQ, 0-100, high is poor outcome, final values)

Study or Subgroup	TMS Mean	TMS SD	TMS Total	Sham TMS Mean	Sham TMS SD	Sham TMS Total	Weight	Mean Difference IV, Fixed, 95% CI
Lee 2012	51.8	13.51	10	53.7	27.3	5	16.0%	-1.90 [-27.25, 23.45]
Short 2011	38.99	19.44	10	47.93	14.7	10	45.1%	-8.94 [-24.05, 6.17]
Yagci 2014	36.95	24.27	13	48.13	16.79	12	38.9%	-11.18 [-27.44, 5.08]
Total (95% CI)			**33**			**27**	**100.0%**	**-8.69 [-18.83, 1.46]**

Heterogeneity: Chi² = 0.37, df = 2 (P = 0.83); I² = 0%
Test for overall effect: Z = 1.68 (P = 0.09)

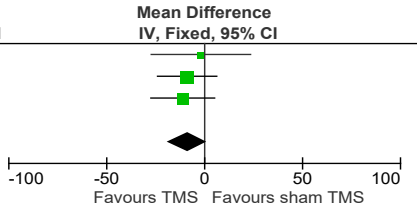

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Figure 16: Quality of life at >3 months (FIQ, 0-100, high is poor outcome, final values)

Study or Subgroup	TMS Mean	TMS SD	TMS Total	Sham TMS Mean	Sham TMS SD	Sham TMS Total	Weight	Mean Difference IV, Fixed, 95% CI
Mhalla 2011	56	17.7	15	63.3	15	15	100.0%	-7.30 [-19.04, 4.44]
Total (95% CI)			**15**			**15**	**100.0%**	**-7.30 [-19.04, 4.44]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.22 (P = 0.22)

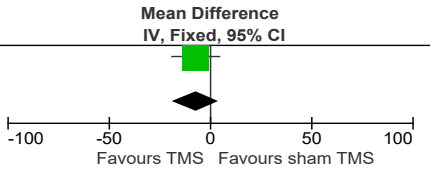
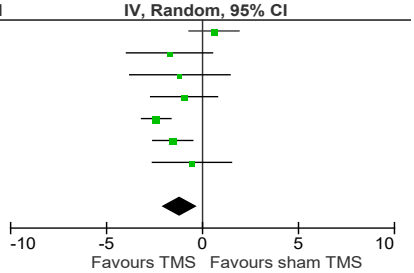


Figure 17: Pain reduction at ≤3 months (VAS, McGill Pain questionnaire, 0-10, high is poor outcome, final values)

Study or Subgroup	TMS Mean	TMS SD	TMS Total	Sham TMS Mean	Sham TMS SD	Sham TMS Total	Weight	Mean Difference IV, Random, 95% CI
Carretero 2009	8.1	1	14	7.5	2.1	12	16.7%	0.60 [-0.70, 1.90]
Dall'Agnol 2014	3.57	2.82	12	5.29	2.78	12	10.2%	-1.72 [-3.96, 0.52]
Lee 2012	6.05	2.23	10	7.23	2.53	5	8.4%	-1.18 [-3.79, 1.43]
Short 2011	4.41	1.95	10	5.37	2.02	10	13.3%	-0.96 [-2.70, 0.78]
Tekin 2014	3.796	0.983	27	6.208	1.668	24	21.2%	-2.41 [-3.18, -1.65]
Umezaki 2016	1.33	0.78	12	2.88	1.36	8	18.9%	-1.55 [-2.59, -0.51]
Yagci 2014	4.75	2.76	13	5.3	2.49	12	11.2%	-0.55 [-2.61, 1.51]
Total (95% CI)			**98**			**83**	**100.0%**	**-1.17 [-2.10, -0.24]**

Heterogeneity: Tau² = 0.91; Chi² = 16.82, df = 6 (P = 0.010); I² = 64%
Test for overall effect: Z = 2.46 (P = 0.01)



NB. Heterogeneity not explained by subgroup analysis

Figure 18: Physical function at ≤3 months (BPI functional impairment subscale, 0-10, high is poor outcome, final values)

Study or Subgroup	TMS Mean	TMS SD	TMS Total	Sham TMS Mean	Sham TMS SD	Sham TMS Total	Weight	Mean Difference IV, Fixed, 95% CI
Short 2011	3.6	2.18	10	3.79	2.69	10	100.0%	-0.19 [-2.34, 1.96]
Total (95% CI)			**10**			**10**	**100.0%**	**-0.19 [-2.34, 1.96]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.17 (P = 0.86)

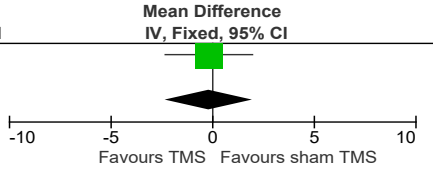


Figure 19: Psychological distress at ≤3 months (Beck depression inventory, 0-61, high is poor outcome, final values and change scores)

Study or Subgroup	TMS Mean	TMS SD	TMS Total	Sham TMS Mean	Sham TMS SD	Sham TMS Total	Weight	Mean Difference IV, Fixed, 95% CI
Boyer 2014	-1.9	2.8	16	-0.1	4.4	13	84.8%	-1.80 [-4.56, 0.96]
Lee 2012	17.85	6.553	10	18.3	5.8	5	15.2%	-0.45 [-6.96, 6.06]
Total (95% CI)			**26**			**18**	**100.0%**	**-1.59 [-4.13, 0.94]**

Heterogeneity: Chi² = 0.14, df = 1 (P = 0.71); I² = 0%
Test for overall effect: Z = 1.23 (P = 0.22)

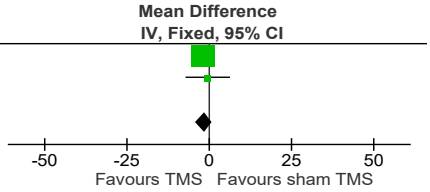


Figure 20: Psychological distress at ≤3 months (Hamilton depression rating scale, MADRS, BDI, high is poor outcome, final values)

Study or Subgroup	TMS Mean	TMS SD	TMS Total	Sham TMS Mean	Sham TMS SD	Sham TMS Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Short 2011	14.1	9.42	10	16.4	8.18	10	20.8%	-0.25 [-1.13, 0.63]
Tekin 2014	10.14	3.96	27	10.24	6	24	53.3%	-0.02 [-0.57, 0.53]
Yagci 2014	16.75	10.6	13	14.15	8	12	25.9%	0.27 [-0.52, 1.05]
Total (95% CI)			**50**			**46**	**100.0%**	**0.01 [-0.39, 0.41]**

Heterogeneity: Chi² = 0.75, df = 2 (P = 0.69); I² = 0%
Test for overall effect: Z = 0.03 (P = 0.97)

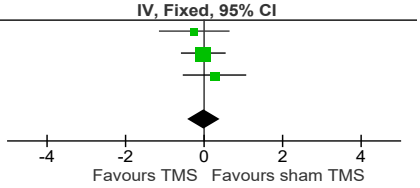


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Figure 21: Psychological distress at ≤3 months (HADS anxiety, 0-21, high is poor outcome, change scores)

Study or Subgroup	TMS Mean	TMS SD	TMS Total	Sham TMS Mean	Sham TMS SD	Sham TMS Total	Weight	Mean Difference IV, Fixed, 95% CI
Boyer 2014	0.4	1.7	16	0.5	2.3	13	100.0%	-0.10 [-1.60, 1.40]
Total (95% CI)			**16**			**13**	**100.0%**	**-0.10 [-1.60, 1.40]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.13 (P = 0.90)

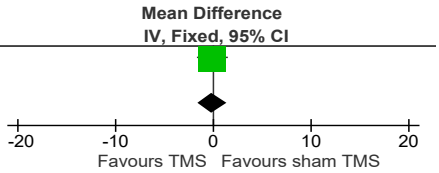


Figure 22: Psychological distress at >3 months (HADS anxiety, 0-21, high is poor outcome, change scores)

Study or Subgroup	TMS Mean	TMS SD	TMS Total	Sham TMS Mean	Sham TMS SD	Sham TMS Total	Weight	Mean Difference IV, Fixed, 95% CI
Mhalla 2011	9.2	4.9	15	9.4	5.7	15	100.0%	-0.20 [-4.00, 3.60]
Total (95% CI)			**15**			**15**	**100.0%**	**-0.20 [-4.00, 3.60]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.10 (P = 0.92)

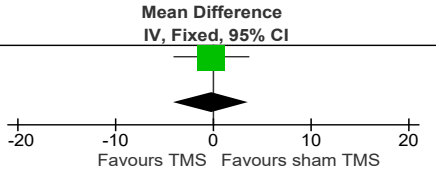


Figure 23: Psychological distress at >3 months (HADS depression, 0-21, high is poor outcome, change scores)

Study or Subgroup	TMS Mean	TMS SD	TMS Total	Sham TMS Mean	Sham TMS SD	Sham TMS Total	Weight	Mean Difference IV, Fixed, 95% CI
Mhalla 2011	8.6	4.7	15	7.4	4	15	100.0%	1.20 [-1.92, 4.32]
Total (95% CI)			**15**			**15**	**100.0%**	**1.20 [-1.92, 4.32]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.75 (P = 0.45)

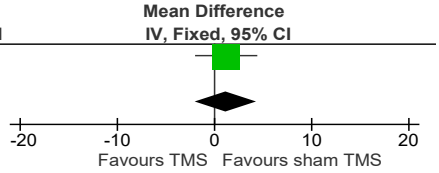


Figure 24: Pain interference at >3 months (BPI pain interference, 0-10, high is poor outcome, final values)

Study or Subgroup	TMS Mean	TMS SD	TMS Total	Sham TMS Mean	Sham TMS SD	Sham TMS Total	Weight	Mean Difference IV, Fixed, 95% CI
Mhalla 2011	4.1	1.7	15	6	1.5	15	100.0%	-1.90 [-3.05, -0.75]
Total (95% CI)			**15**			**15**	**100.0%**	**-1.90 [-3.05, -0.75]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.25 (P = 0.001)

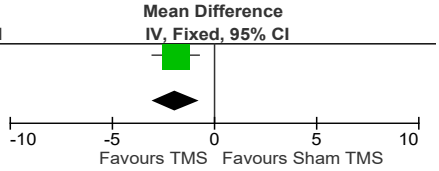
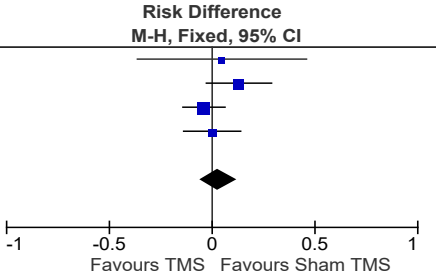


Figure 25: Discontinuation at ≤3 months

Study or Subgroup	TMS Events	TMS Total	Sham TMS Events	Sham TMS Total	Weight	Risk Difference M-H, Fixed, 95% CI
Lee 2012	5	15	2	7	13.9%	0.05 [-0.36, 0.46]
Panton 2013	3	23	0	18	29.4%	0.13 [-0.03, 0.29]
Tekin 2014	0	27	1	25	37.8%	-0.04 [-0.14, 0.06]
Umezaki 2016	0	14	0	12	18.8%	0.00 [-0.14, 0.14]
Total (95% CI)		**79**		**62**	**100.0%**	**0.03 [-0.06, 0.12]**
Total events	8		3			

Heterogeneity: Chi² = 3.53, df = 3 (P = 0.32); I² = 15%
Test for overall effect: Z = 0.65 (P = 0.51)



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E.3 TDCS versus sham TDCS

Figure 26: Quality of life at ≤3 months (SF-36 mental summary score, 0-100, high is good outcome, final values)

Study or Subgroup	TDCS Mean	TDCS SD	TDCS Total	sham TDCS Mean	sham TDCS SD	sham TDCS Total	Weight	Mean Difference IV, Fixed, 95% CI
Fagerlund 2015	48.2	15.35	24	45.4	10.85	24	100.0%	2.80 [-4.72, 10.32]
Total (95% CI)			**24**			**24**	**100.0%**	**2.80 [-4.72, 10.32]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.73 (P = 0.47)

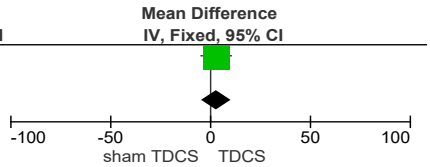

Figure 27: Quality of life at ≤3 months (SF-36 physical summary score, 0-100, high is good outcome, final values)

Study or Subgroup	TDCS Mean	TDCS SD	TDCS Total	sham TDCS Mean	sham TDCS SD	sham TDCS Total	Weight	Mean Difference IV, Fixed, 95% CI
Fagerlund 2015	34.78	9.42	24	35.92	7.34	24	100.0%	-1.14 [-5.92, 3.64]
Total (95% CI)			**24**			**24**	**100.0%**	**-1.14 [-5.92, 3.64]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.47 (P = 0.64)

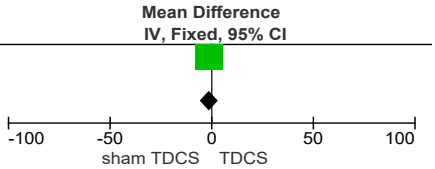

Figure 28: Quality of life at ≤3 months (SF-36 physical function subscale, 0-100, high is good outcome, final values)

Study or Subgroup	TDCS Mean	TDCS SD	TDCS Total	Sham TDCS Mean	Sham TDCS SD	Sham TDCS Total	Weight	Mean Difference IV, Fixed, 95% CI
Jales 2015	68.5	11.068	10	38	26.895	10	100.0%	30.50 [12.47, 48.53]
Total (95% CI)			**10**			**10**	**100.0%**	**30.50 [12.47, 48.53]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.32 (P = 0.0009)

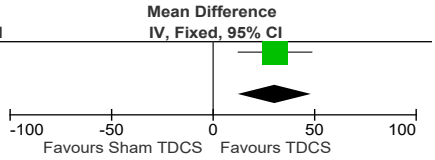

Figure 29: Quality of life at ≤3 months (SF-36 physical role subscale, 0-100, high is good outcome, final values)

Study or Subgroup	TDCS Mean	TDCS SD	TDCS Total	Sham TDCS Mean	Sham TDCS SD	Sham TDCS Total	Weight	Mean Difference IV, Fixed, 95% CI
Jales 2015	75	31.18	10	47.5	41.583	10	100.0%	27.50 [-4.71, 59.71]
Total (95% CI)			**10**			**10**	**100.0%**	**27.50 [-4.71, 59.71]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.67 (P = 0.09)

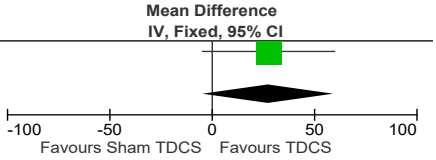

Figure 30: Quality of life at ≤3 months (SF-36 bodily pain subscale, 0-100, high is good outcome, final values)

Study or Subgroup	TDCS Mean	TDCS SD	TDCS Total	Sham TDCS Mean	Sham TDCS SD	Sham TDCS Total	Weight	Mean Difference IV, Fixed, 95% CI
Jales 2015	43	18.288	10	50	23.57	10	100.0%	-7.00 [-25.49, 11.49]
Total (95% CI)			**10**			**10**	**100.0%**	**-7.00 [-25.49, 11.49]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.74 (P = 0.46)

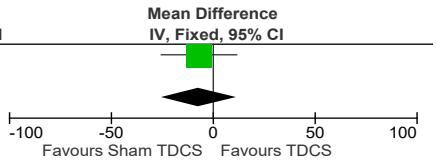

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Figure 31: Quality of life at ≤3 months (SF-36 general health subscale, 0-100, high is good outcome, final values)

Study or Subgroup	TDCS Mean	TDCS SD	TDCS Total	Sham TDCS Mean	Sham TDCS SD	Sham TDCS Total	Weight	Mean Difference IV, Fixed, 95% CI
Jales 2015	58	11.106	10	63.5	9.443	10	100.0%	-5.50 [-14.54, 3.54]
Total (95% CI)			**10**			**10**	**100.0%**	**-5.50 [-14.54, 3.54]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.19 (P = 0.23)

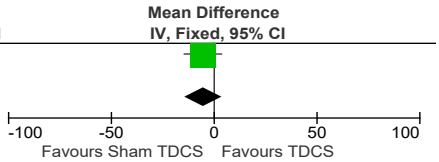

Figure 32: Quality of life at ≤3 months (SF-36 vitality subscale, 0-100, high is good outcome, final values)

Study or Subgroup	TDCS Mean	TDCS SD	TDCS Total	Sham TDCS Mean	Sham TDCS SD	Sham TDCS Total	Weight	Mean Difference IV, Fixed, 95% CI
Jales 2015	53.5	9.144	10	58	10.055	10	100.0%	-4.50 [-12.92, 3.92]
Total (95% CI)			**10**			**10**	**100.0%**	**-4.50 [-12.92, 3.92]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.05 (P = 0.30)

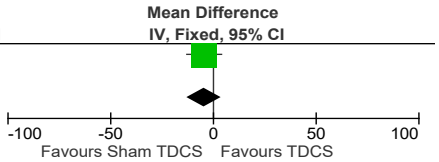

Figure 33: Quality of life at ≤3 months (SF-36 general aspects subscale, 0-100, high is good outcome, final values)

Study or Subgroup	TDCS Mean	TDCS SD	TDCS Total	Sham TDCS Mean	Sham TDCS SD	Sham TDCS Total	Weight	Mean Difference IV, Fixed, 95% CI
Jales 2015	47.5	15.366	10	50	16.667	10	100.0%	-2.50 [-16.55, 11.55]
Total (95% CI)			**10**			**10**	**100.0%**	**-2.50 [-16.55, 11.55]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.35 (P = 0.73)

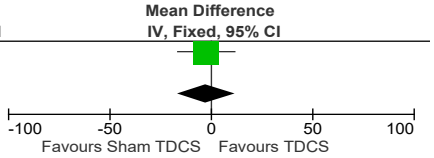

Figure 34: Quality of life at ≤3 months (SF-36 emotional role subscale, 0-100, high is good outcome, final values)

Study or Subgroup	TDCS Mean	TDCS SD	TDCS Total	Sham TDCS Mean	Sham TDCS SD	Sham TDCS Total	Weight	Mean Difference IV, Fixed, 95% CI
Jales 2015	80	35.633	10	60	43.886	10	100.0%	20.00 [-15.04, 55.04]
Total (95% CI)			**10**			**10**	**100.0%**	**20.00 [-15.04, 55.04]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.12 (P = 0.26)

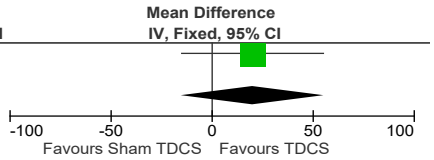

Figure 35: Quality of life at ≤3 months (SF-36 mental health subscale, 0-100, high is good outcome, final values)

Study or Subgroup	TDCS Mean	TDCS SD	TDCS Total	Sham TDCS Mean	Sham TDCS SD	Sham TDCS Total	Weight	Mean Difference IV, Fixed, 95% CI
Jales 2015	58.4	11.345	10	54	11.963	10	100.0%	4.40 [-5.82, 14.62]
Total (95% CI)			**10**			**10**	**100.0%**	**4.40 [-5.82, 14.62]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.84 (P = 0.40)

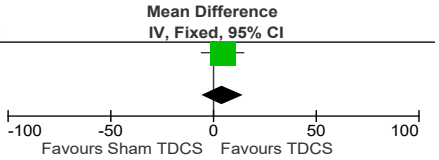

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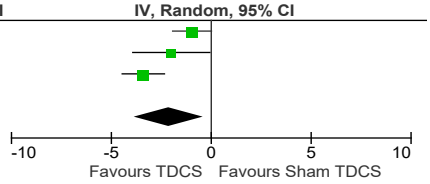
Figure 36: Pain reduction at ≤3 months (NRS, VAS, 0-10, high is poor outcome, final values)

Study or Subgroup	TDCS Mean	TDCS SD	TDCS Total	sham TDCS Mean	sham TDCS SD	sham TDCS Total	Weight	Mean Difference IV, Random, 95% CI
Fagerlund 2015	4.26	1.9	24	5.22	1.5	24	36.8%	-0.96 [-1.93, 0.01]
Jales 2015	3.6	1.838	10	5.6	2.503	10	27.2%	-2.00 [-3.92, -0.08]
Khedr 2017	3.9	2.1	18	7.3	0.9	18	36.0%	-3.40 [-4.46, -2.34]
Total (95% CI)			**52**			**52**	**100.0%**	**-2.12 [-3.82, -0.43]**

Heterogeneity: Tau² = 1.79; Chi² = 11.15, df = 2 (P = 0.004); I² = 82%
Test for overall effect: Z = 2.45 (P = 0.01)

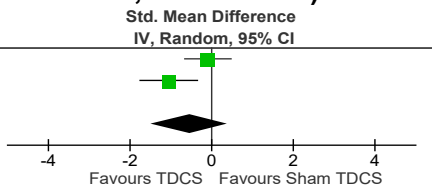


NB. Heterogeneity not explained by subgroup analysis

Figure 37: Psychological distress at ≤3 months (Hospital anxiety and depression scale, HAM-A, anxiety subscales, high is poor outcome, final values)

Study or Subgroup	TDCS Mean	TDCS SD	TDCS Total	sham TDCS Mean	sham TDCS SD	sham TDCS Total	Weight	Std. Mean Difference IV, Random, 95% CI
Fagerlund 2015	5.47	4.16	24	5.82	3.36	24	52.4%	-0.09 [-0.66, 0.48]
Khedr 2017	11.6	5.9	18	17.1	4.2	18	47.6%	-1.05 [-1.75, -0.35]
Total (95% CI)			**42**			**42**	**100.0%**	**-0.55 [-1.49, 0.39]**

Heterogeneity: Tau² = 0.35; Chi² = 4.34, df = 1 (P = 0.04); I² = 77%
Test for overall effect: Z = 1.14 (P = 0.25)

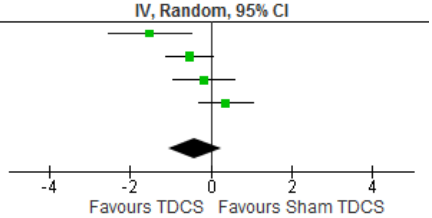


NB. Heterogeneity not explained by subgroup analysis

Figure 38: Psychological distress at ≤3 months (Hospital anxiety and depression scale, BDI, HAM-D, depression subscales, high is poor outcome, final values)

Study or Subgroup	TDCS Mean	TDCS SD	TDCS Total	sham TDCS Mean	sham TDCS SD	sham TDCS Total	Weight	Std. Mean Difference IV, Random, 95% CI
Brietzke 2019	11.8	5.63	10	21.5	6.6	10	19.7%	-1.51 [-2.54, -0.49]
Fagerlund 2015	3.76	2.77	24	5.41	3.37	24	28.6%	-0.53 [-1.10, 0.05]
Fregni 2006	16.6	7.852	22	18	7.7	10	24.9%	-0.17 [-0.92, 0.57]
Khedr 2017	19.6	6.3	18	17.6	4	18	26.8%	0.37 [-0.29, 1.03]
Total (95% CI)			**74**			**62**	**100.0%**	**-0.39 [-1.06, 0.28]**

Heterogeneity: Tau² = 0.32; Chi² = 10.10, df = 3 (P = 0.02); I² = 70%
Test for overall effect: Z = 1.15 (P = 0.25)

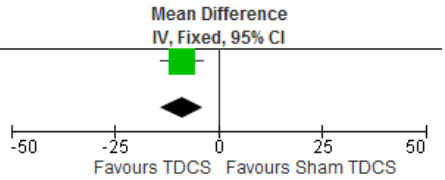


NB. Heterogeneity not explained by subgroup analysis

Figure 39: Sleep at ≤3 months (PSQI, scale range not reported, high is poor outcome, final values)

Study or Subgroup	TDCS Mean	TDCS SD	TDCS Total	sham TDCS Mean	sham TDCS SD	sham TDCS Total	Weight	Mean Difference IV, Fixed, 95% CI
Brietzke 2019	7.9	7.44	10	16.7	3.74	10	100.0%	-8.80 [-13.96, -3.64]
Total (95% CI)			**10**			**10**	**100.0%**	**-8.80 [-13.96, -3.64]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.34 (P = 0.0008)



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E.4 TENS versus sham TENS

Figure 40: Quality of life at ≤3 months (SF36 T scores, high is good outcome, change scores)

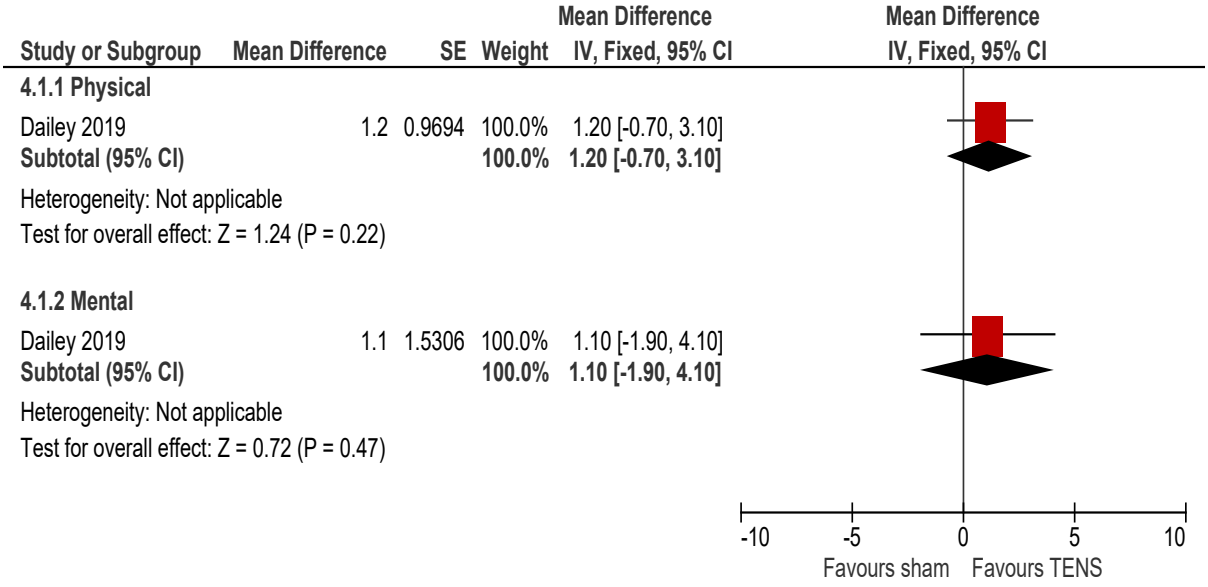
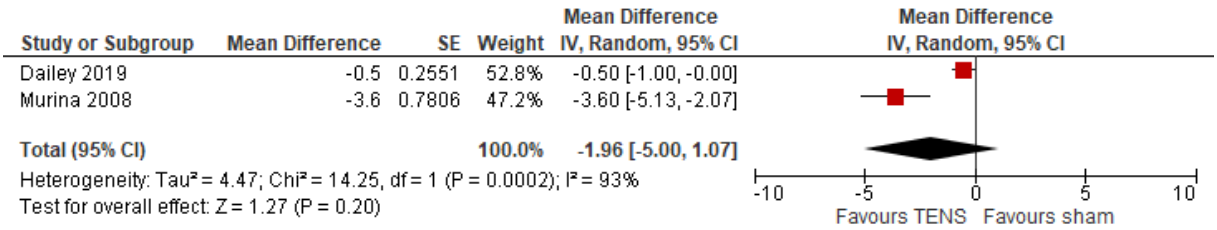


Figure 41: Pain reduction at ≤3 months (BPI, VAS, 0-10, high is poor outcome, final values and change scores)



Heterogeneity could not be explained by subgroup analysis

Figure 42: Pain reduction at >3 months (VAS, 0-10, high is poor outcome, final values)

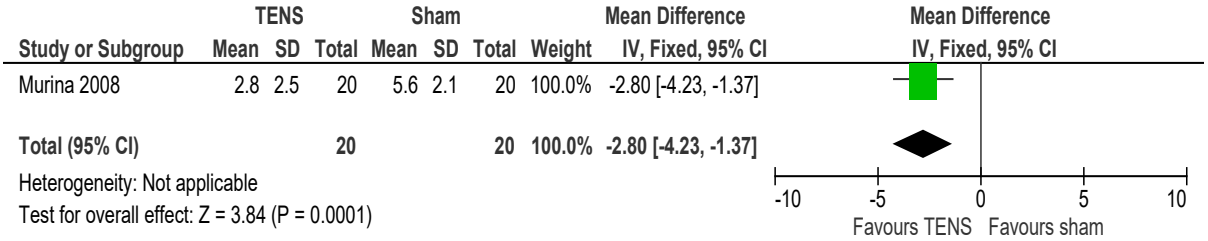


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Figure 43: Physical function at ≤3 months (6 minute walk test, high is good outcome, change scores)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
Dailey 2019	19	39.2864	100.0%	19.00 [-58.00, 96.00]
Total (95% CI)			**100.0%**	**19.00 [-58.00, 96.00]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.48 (P = 0.63)

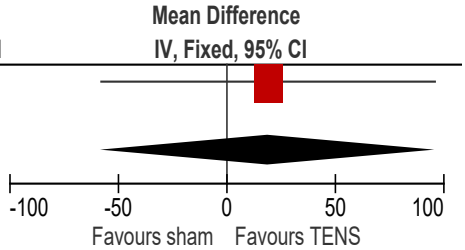

Figure 44: Psychological distress (PROMIS T scores, high is poor outcome, change scores)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
4.4.1 Depression				
Dailey 2019	-2.7	1.0204	100.0%	-2.70 [-4.70, -0.70]
Subtotal (95% CI)			**100.0%**	**-2.70 [-4.70, -0.70]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 2.65 (P = 0.008)				
4.4.2 Anxiety				
Dailey 2019	-0.5	1.1225	100.0%	-0.50 [-2.70, 1.70]
Subtotal (95% CI)			**100.0%**	**-0.50 [-2.70, 1.70]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.45 (P = 0.66)				

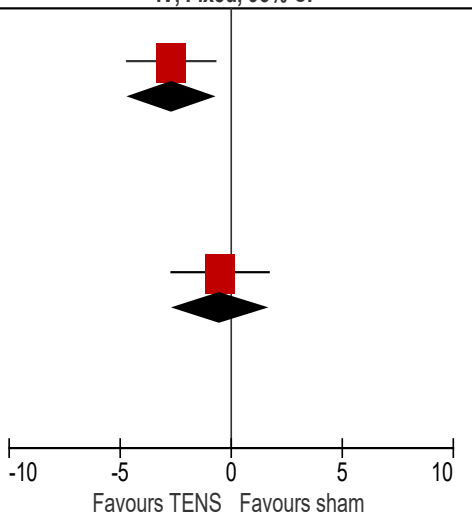

Figure 45: Pain interference at ≤3 months (BPI interference, 0-10, high is poor outcome, change scores)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
Dailey 2019	-0.7	0.3061	100.0%	-0.70 [-1.30, -0.10]
Total (95% CI)			**100.0%**	**-0.70 [-1.30, -0.10]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.29 (P = 0.02)

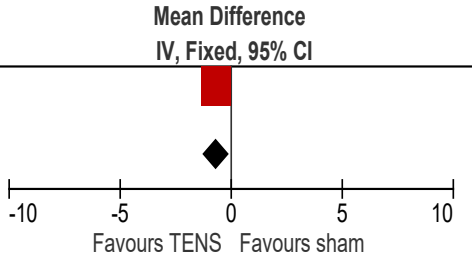

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Figure 46: Pain self-efficacy at ≤3 months (Pain self-efficacy questionnaire, 0-60, high is good outcome, change scores)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
Dailey 2019	1.6	1.7347	100.0%	1.60 [-1.80, 5.00]
Total (95% CI)			**100.0%**	**1.60 [-1.80, 5.00]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.92 (P = 0.36)

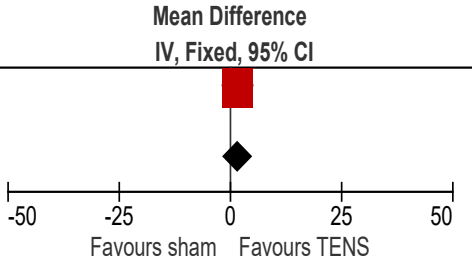
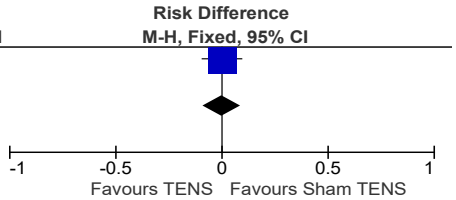


Figure 47: Discontinuation at ≤3 months

Study or Subgroup	TENS Events	TENS Total	Sham TENS Events	Sham TENS Total	Weight	Risk Difference M-H, Fixed, 95% CI
Murina 2008	0	20	0	20	100.0%	0.00 [-0.09, 0.09]
Total (95% CI)		**20**		**20**	**100.0%**	**0.00 [-0.09, 0.09]**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



E.5 TENS versus usual care

Figure 48: Quality of life at ≤3 months (SF36 T scores, high is good outcome, change scores)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
5.1.1 Physical				
Dailey 2019	1	0.9184	100.0%	1.00 [-0.80, 2.80]
Subtotal (95% CI)			**100.0%**	**1.00 [-0.80, 2.80]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.09 (P = 0.28)				
5.1.2 Mental				
Dailey 2019	2.4	1.5306	100.0%	2.40 [-0.60, 5.40]
Subtotal (95% CI)			**100.0%**	**2.40 [-0.60, 5.40]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.57 (P = 0.12)				

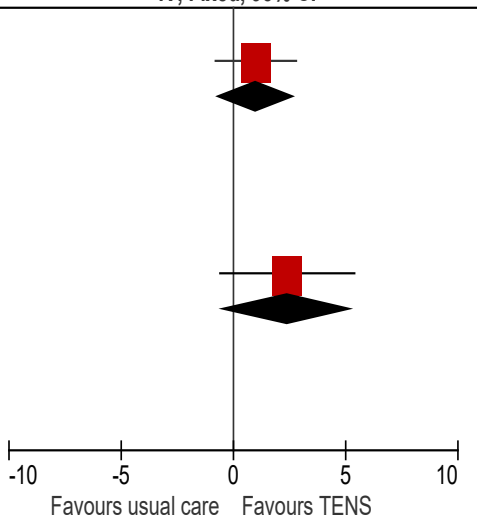


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Figure 49: Pain reduction at ≤3 months (BPI, 0-10, high is poor outcome, change scores)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
Dailey 2019	-0.9	0.2551	100.0%	-0.90 [-1.40, -0.40]
Total (95% CI)			**100.0%**	**-0.90 [-1.40, -0.40]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.53 (P = 0.0004)

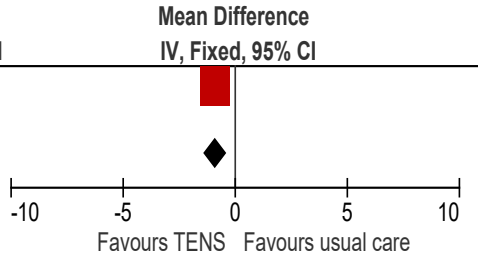

Figure 50: Physical function at ≤3 months (6 minute walk test, high is good outcome, change scores)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
Dailey 2019	42	38.7762	100.0%	42.00 [-34.00, 118.00]
Total (95% CI)			**100.0%**	**42.00 [-34.00, 118.00]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.08 (P = 0.28)

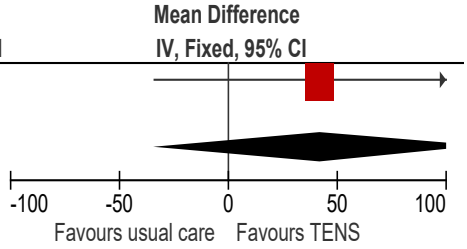

Figure 51: Psychological distress (PROMIS T scores, high is poor outcome, change scores)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
5.4.1 Depression				
Dailey 2019	-3.2	0.9694	100.0%	-3.20 [-5.10, -1.30]
Subtotal (95% CI)			**100.0%**	**-3.20 [-5.10, -1.30]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 3.30 (P = 0.0010)				
5.4.2 Anxiety				
Dailey 2019	-0.4	1.0714	100.0%	-0.40 [-2.50, 1.70]
Subtotal (95% CI)			**100.0%**	**-0.40 [-2.50, 1.70]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.37 (P = 0.71)				

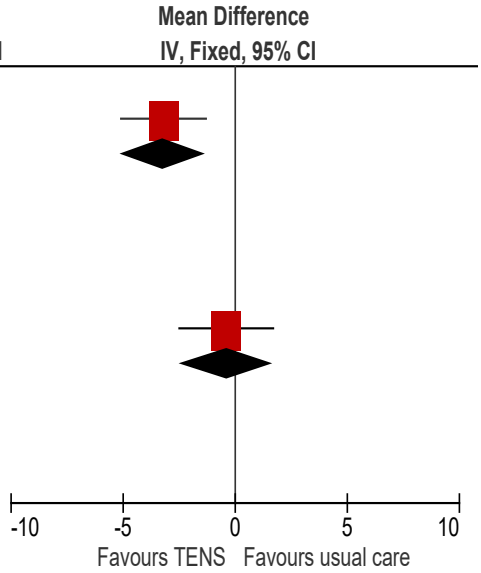

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Figure 52: Pain interference at ≤3 months (BPI interference, 0-10, high is poor outcome, change scores)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
Dailey 2019	-0.6	0.3571	100.0%	-0.60 [-1.30, 0.10]
Total (95% CI)			**100.0%**	**-0.60 [-1.30, 0.10]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.68 (P = 0.09)

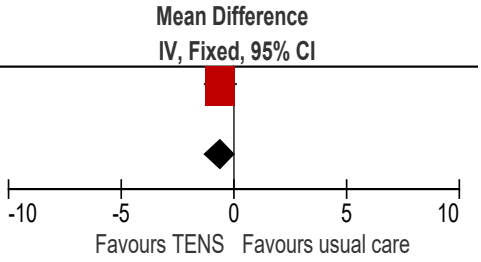
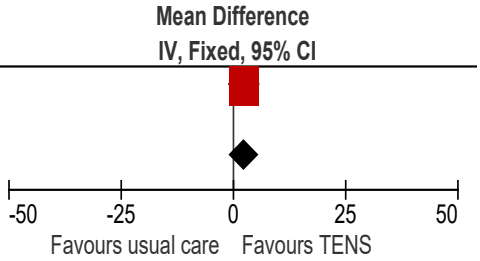


Figure 53: Pain self-efficacy at ≤3 months (Pain self-efficacy questionnaire, 0-60, high is good outcome, change scores)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
Dailey 2019	2.3	1.6837	100.0%	2.30 [-1.00, 5.60]
Total (95% CI)			**100.0%**	**2.30 [-1.00, 5.60]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.37 (P = 0.17)



E.6 PENS versus sham PENS

Figure 54: Quality of life at ≤3 months (NIH-CPSI, 0-12, high is poor outcome, final values)

Study or Subgroup	PENS Mean	PENS SD	PENS Total	Sham PENS Mean	Sham PENS SD	Sham PENS Total	Weight	Mean Difference IV, Fixed, 95% CI
Kabay 2009	2.1	0.9	45	6.7	2.1	44	100.0%	-4.60 [-5.27, -3.93]
Total (95% CI)			**45**			**44**	**100.0%**	**-4.60 [-5.27, -3.93]**

Heterogeneity: Not applicable
Test for overall effect: Z = 13.38 (P < 0.00001)

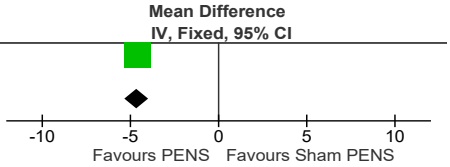
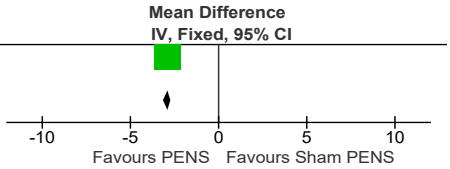


Figure 55: Pain reduction at ≤3 months (VAS, 0-10, high is poor outcome, final values)

Study or Subgroup	PENS Mean	PENS SD	PENS Total	Sham PENS Mean	Sham PENS SD	Sham PENS Total	Weight	Mean Difference IV, Fixed, 95% CI
Kabay 2009	4.3	0.6	45	7.2	0.4	44	100.0%	-2.90 [-3.11, -2.69]
Total (95% CI)			**45**			**44**	**100.0%**	**-2.90 [-3.11, -2.69]**

Heterogeneity: Not applicable
Test for overall effect: Z = 26.88 (P < 0.00001)



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E.7 PENS versus usual care

Figure 56: Quality of life at ≤3 months (SF-36 physical function subscale, 0-100, high is good outcome, final values)

Study or Subgroup	PENS Mean	PENS SD	PENS Total	Usual care Mean	Usual care SD	Usual care Total	Weight	Mean Difference IV, Fixed, 95% CI
Gokyildiz 2012	74.16	31.03	12	52.91	23.1	12	100.0%	21.25 [-0.64, 43.14]
Total (95% CI)			**12**			**12**	**100.0%**	**21.25 [-0.64, 43.14]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.90 (P = 0.06)

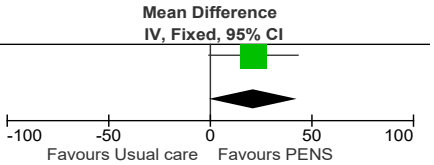

Figure 57: Quality of life at ≤3 months (SF-36 physical role subscale, 0-100, high is good outcome, final values)

Study or Subgroup	PENS Mean	PENS SD	PENS Total	Usual care Mean	Usual care SD	Usual care Total	Weight	Mean Difference IV, Fixed, 95% CI
Gokyildiz 2012	66.66	45.64	12	14.58	22.5	12	100.0%	52.08 [23.29, 80.87]
Total (95% CI)			**12**			**12**	**100.0%**	**52.08 [23.29, 80.87]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.55 (P = 0.0004)

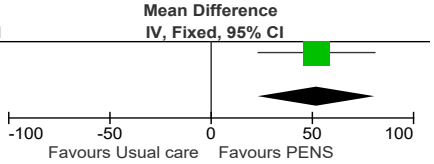

Figure 58: Quality of life at ≤3 months (SF-36 fatigue subscale, 0-100, high is good outcome, final values)

Study or Subgroup	PENS Mean	PENS SD	PENS Total	Usual care Mean	Usual care SD	Usual care Total	Weight	Mean Difference IV, Fixed, 95% CI
Gokyildiz 2012	62.91	25.97	12	45	16.23	12	100.0%	17.91 [0.58, 35.24]
Total (95% CI)			**12**			**12**	**100.0%**	**17.91 [0.58, 35.24]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.03 (P = 0.04)

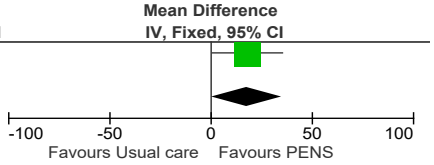

Figure 59: Quality of life at ≤3 months (SF-36 emotional role subscale, 0-100, high is good outcome, final values)

Study or Subgroup	PENS Mean	PENS SD	PENS Total	Usual care Mean	Usual care SD	Usual care Total	Weight	Mean Difference IV, Fixed, 95% CI
Gokyildiz 2012	61.11	44.57	12	13.87	26.4	12	100.0%	47.24 [17.93, 76.55]
Total (95% CI)			**12**			**12**	**100.0%**	**47.24 [17.93, 76.55]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.16 (P = 0.002)

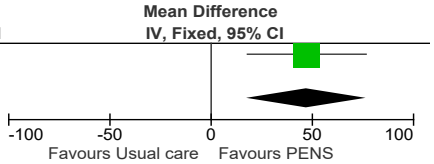

Figure 60: Quality of life at ≤3 months (SF-36 mental health subscale, 0-100, high is good outcome, final values)

Study or Subgroup	PENS Mean	PENS SD	PENS Total	Usual care Mean	Usual care SD	Usual care Total	Weight	Mean Difference IV, Fixed, 95% CI
Gokyildiz 2012	60.66	19.35	12	40.33	15.48	12	100.0%	20.33 [6.31, 34.35]
Total (95% CI)			**12**			**12**	**100.0%**	**20.33 [6.31, 34.35]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.84 (P = 0.004)

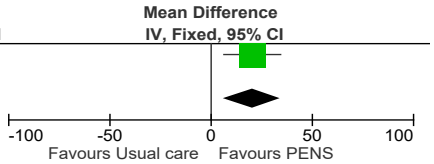

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Figure 61: Quality of life at ≤3 months (SF-36 social functioning subscale, 0-100, high is good outcome, final values)

Study or Subgroup	PENS Mean	PENS SD	PENS Total	Usual care Mean	Usual care SD	Usual care Total	Weight	Mean Difference IV, Fixed, 95% CI
Gokyildiz 2012	71.87	33.33	12	50	11.91	12	100.0%	21.87 [1.84, 41.90]
Total (95% CI)			**12**			**12**	**100.0%**	**21.87 [1.84, 41.90]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.14 (P = 0.03)

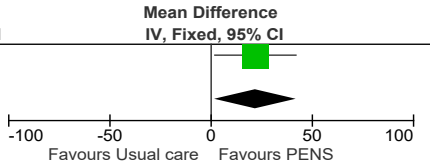


Figure 62: Quality of life at ≤3 months (SF-36 bodily pain subscale, 0-100, high is good outcome, final values)

Study or Subgroup	PENS Mean	PENS SD	PENS Total	Usual care Mean	Usual care SD	Usual care Total	Weight	Mean Difference IV, Fixed, 95% CI
Gokyildiz 2012	60	27.96	12	23.33	7.78	12	100.0%	36.67 [20.25, 53.09]
Total (95% CI)			**12**			**12**	**100.0%**	**36.67 [20.25, 53.09]**

Heterogeneity: Not applicable
Test for overall effect: Z = 4.38 (P < 0.0001)

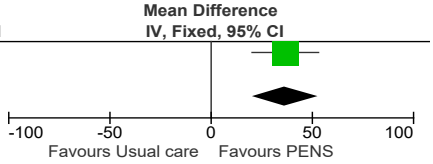
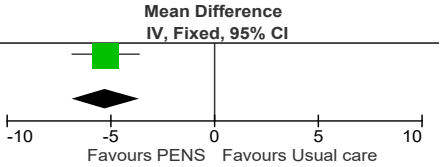


Figure 63: Pain reduction at ≤3 months (VAS, 0-10, high is poor outcome, final values)

Study or Subgroup	PENS Mean	PENS SD	PENS Total	Usual care Mean	Usual care SD	Usual care Total	Weight	Mean Difference IV, Fixed, 95% CI
Gokyildiz 2012	2.62	2.7	12	7.87	0.88	12	100.0%	-5.25 [-6.86, -3.64]
Total (95% CI)			**12**			**12**	**100.0%**	**-5.25 [-6.86, -3.64]**

Heterogeneity: Not applicable
Test for overall effect: Z = 6.40 (P < 0.00001)

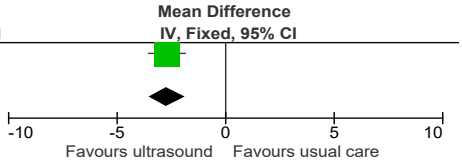


E.8 Therapeutic ultrasound versus usual care

Figure 64: Pain reduction at 3 months (VAS, 0-10, high is poor outcome, final values)

Study or Subgroup	Ultrasound Mean	Ultrasound SD	Ultrasound Total	Usual care Mean	Usual care SD	Usual care Total	Weight	Mean Difference IV, Fixed, 95% CI
Esenyel 2000	3.08	2.42	36	5.78	0.87	40	100.0%	-2.70 [-3.54, -1.86]
Total (95% CI)			**36**			**40**	**100.0%**	**-2.70 [-3.54, -1.86]**

Heterogeneity: Not applicable
Test for overall effect: Z = 6.34 (P < 0.00001)



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Appendix F: GRADE tables

Table 15: Clinical evidence profile: Laser therapy versus sham laser therapy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Laser therapy	Control	Relative (95% CI)	Absolute		
Quality of life at 2 weeks-3 months (Oral health impact profile, FIQ, high is poor outcome, final values)												
6	randomised trials	serious[3]	serious[2]	no serious indirectness	serious[1]	none	159	117	-	SMD 0.68 lower (1.1 to 0.25 lower)	⊕OOO VERY LOW	CRITICAL
Quality of life at 3 months (SF-36 physical component summary score, 0-100, high is good outcome, change scores)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	55	55	-	MD 2.09 higher (0.91 lower to 5.09 higher)	⊕⊕⊕O MODERATE	CRITICAL
Quality of life at 3 months (SF-36 mental component summary score, 0-100, high is good outcome, change scores)												
2	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[1]	none	55	55	-	MD 0.74 lower (5.35 lower to 3.87 higher)	⊕⊕OO LOW	CRITICAL
Quality of life at 24 weeks (FIQ, 0-100, high is poor outcome, final values)												
2	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	none	59	58	-	SMD 0.78 lower (1.16 to 0.4 lower)	⊕⊕OO LOW	CRITICAL
Pain reduction at 1 week to 12 weeks (VAS, NRS, FIQ pain scale, high is poor outcome, 0-10, final values and change scores)												
13	randomised trials	serious[3]	serious[2]	no serious indirectness	serious[1]	none	301	257	-	MD 1.42 lower (2.12 to 0.73 lower)	⊕OOO VERY LOW	CRITICAL
Pain reduction at 14-16 weeks (VAS, high is poor outcome, 0-10, final values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	36	35	-	MD 0.6 lower (0.91 to 0.3 lower)	⊕⊕⊕O MODERATE	CRITICAL

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Psychological distress at 4 weeks (Hospital anxiety and depression rating scale, anxiety subscale, 0-21, high is poor outcome, final values)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	none	32	12	-	MD 0.83 higher (1.52 lower to 3.18 higher)	⊕⊕OO LOW	CRITICAL
Psychological distress at 4 weeks (Hospital anxiety and depression rating scale, depression subscale, 0-21, high is poor outcome, final values)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	none	32	16	-	MD 1.29 higher (1.39 lower to 3.96 higher)	⊕⊕OO LOW	CRITICAL
Discontinuation at 3 months												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	2/45 (4.4%)	6.7%	RR 0.67 (0.12 to 3.8)	22 fewer per 1000 (from 59 fewer to 188 more)	⊕⊕OO LOW	IMPORTANT

1 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
2 Downgraded for heterogeneity, unexplained by subgroup analysis
3 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 16: Clinical evidence profile: TMS versus sham TMS

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**TMS**	**Control**	**Relative (95% CI)**	**Absolute**		
Quality of life at 10 weeks (SF-36 physical summary score, 0-100, high is good outcome, change scores)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	16	13	-	MD 1 higher (4.12 lower to 6.12 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life at 10 weeks (SF-36 mental summary score, 0-100, high is good outcome, change scores)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	16	13	-	MD 6.6 higher (1.26 to 11.94 higher)	⊕OOO VERY LOW	IMPORTANT
Quality of life at 2 weeks (WHOQOL-BREF physical domain, 4-20, high is good outcome, final values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	27	24	-	MD 3.27 higher (1.79 to 4.75 higher)	⊕⊕⊕⊕ HIGH	CRITICAL

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Quality of life at 2 weeks (WHOQOL-BREF psychological domain, 4-20, high is good outcome, final values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	27	24	-	MD 1.18 higher (0.18 lower to 2.54 higher)	⊕⊕⊕O MODERATE	CRITICAL
Quality of life at 4 weeks -3 months (FIQ, 0-100, high is poor outcome, final values)												
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	33	27	-	MD 8.69 lower (18.83 lower to 1.46 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life at 25 weeks (FIQ, 0-100, high is poor outcome, final values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	15	15	-	MD 7.3 lower (19.04 lower to 4.44 higher)	⊕OOO VERY LOW	CRITICAL
Pain reduction at 2 weeks -3 months (VAS, McGill Pain questionnaire, 0-10, high is poor outcome, final values)												
7	randomised trials	serious[1]	serious[3]	no serious indirectness	serious[2]	none	98	83	-	MD 1.17 lower (2.1 to 0.24 lower)	⊕OOO VERY LOW	CRITICAL
Physical function at 4 weeks (BPI functional impairment subscale, 0-10, high is poor outcome, final values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10	10	-	MD 0.19 lower (2.34 lower to 1.96 higher)	⊕OOO VERY LOW	CRITICAL
Psychological distress at 6-10 weeks (Beck depression inventory, 0-61, high is poor outcome, final values and change scores)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	26	18	-	MD 1.59 lower (4.13 lower to 0.94 higher)	⊕OOO VERY LOW	CRITICAL
Psychological distress at 2 weeks -3 months (Hamilton depression rating scale, MADRS, BDI, high is poor outcome, final values)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	50	46	-	SMD 0.01 higher (0.39 lower to 0.41 higher)	⊕⊕⊕O MODERATE	CRITICAL
Psychological distress at 10 weeks (HADS anxiety, 0-21, high is poor outcome, change scores)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	16	13	-	MD 0.1 lower (1.6 lower to 1.4 higher)	⊕OOO VERY LOW	CRITICAL
Psychological distress at 25 weeks (HADS anxiety, 0-21, high is poor outcome, change scores)												

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1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	15	15	-	MD 0.2 lower (4 lower to 3.6 higher)	⊕OOO VERY LOW	CRITICAL
Psychological distress at 25 weeks (HADS depression, 0-21, high is poor outcome, change scores)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	15	15	-	MD 1.2 higher (1.92 lower to 4.32 higher)	⊕OOO VERY LOW	CRITICAL
Pain interference at 25 weeks (BPI pain interference, 0-10, high is poor outcome, final values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	15	15	-	MD 1.9 lower (3.05 to 0.75 lower)	⊕OOO VERY LOW	CRITICAL
Discontinuation at 2-6 weeks (follow-up 2-6 weeks)												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	8/79 (10.1%)	2%	RD 0.03 (-0.06 to 0.12)	12 more per 1000 (from 25 fewer to 50 more)	⊕⊕OO LOW	IMPORTANT

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
3 Downgraded for heterogeneity, unexplained by subgroup analysis

Table 17: Clinical evidence profile: TDCS versus sham TDCS

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**TDCS**	**Control**	**Relative (95% CI)**	**Absolute**		
Quality of life at 4 weeks (SF-36 mental summary score, 0-100, high is good outcome, final values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	24	24	-	MD 2.8 higher (4.72 lower to 10.32 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life at 4 weeks (SF-36 physical summary score, 0-100, high is good outcome, final values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	24	24	-	MD 1.14 lower (5.92 lower to 3.64 higher)	⊕OOO VERY LOW	CRITICAL

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Quality of life at 10 weeks (SF-36 physical function subscale, 0-100, high is good outcome, final values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	10	10	-	MD 30.5 higher (12.47 to 48.53 higher)	⊕⊕⊕O MODERATE	CRITICAL
Quality of life at 10 weeks (SF-36 physical role subscale, 0-100, high is good outcome, final values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10	10	-	MD 27.5 higher (4.71 lower to 59.71 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life at 10 weeks (SF-36 bodily pain subscale, 0-100, high is good outcome, final values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10	10	-	MD 7 lower (25.49 lower to 11.49 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life at 10 weeks (SF-36 general health subscale, 0-100, high is good outcome, final values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10	10	-	MD 5.5 lower (14.54 lower to 3.54 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life at 10 weeks (SF-36 vitality subscale, 0-100, high is good outcome, final values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10	10	-	MD 4.5 lower (12.92 lower to 3.92 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life at 10 weeks (SF-36 general aspects subscale, 0-100, high is good outcome, final values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10	10	-	MD 2.5 lower (16.55 lower to 11.55 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life at 10 weeks (SF-36 emotional role subscale, 0-100, high is good outcome, final values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10	10	-	MD 20 higher (15.04 lower to 55.04 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life at 10 weeks (SF-36 mental health subscale, 0-100, high is good outcome, final values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10	10	-	MD 4.4 higher (5.82 lower to 14.62 higher)	⊕OOO VERY LOW	CRITICAL
Pain reduction at 4-10 weeks (NRS, VAS, 0-10, high is poor outcome, final values)												

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3	randomised trials	serious[1]	serious[3]	no serious indirectness	serious[2]	none	52	52	-	MD 2.12 lower (3.82 to 0.43 lower)	⊕OOO VERY LOW	CRITICAL
Psychological distress at 4-8 weeks (Hospital anxiety and depression scale, HAM-A, anxiety subscales, high is poor outcome, final values)												
2	randomised trials	serious[1]	serious[3]	no serious indirectness	serious[2]	none	42	42	-	SMD 0.55 lower (1.49 lower to 0.39 higher)	⊕OOO VERY LOW	CRITICAL
Psychological distress at 3-12 weeks (Hospital anxiety and depression scale, BDI, HAM-D, depression subscales, high is poor outcome, final values)												
4	randomised trials	serious[1]	serious[3]	no serious indirectness	serious[2]	none	74	62	-	SMD 0.39 lower (1.06 lower to 0.28 higher)	⊕OOO VERY LOW	CRITICAL
Sleep at ≤3 months (PSQI, scale range not reported, high is poor outcome, final values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	10	10	-	MD 8.8 lower (13.96 to 3.64 lower)	⊕⊕OO LOW	IMPORTANT

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
3 Downgraded for heterogeneity, unexplained by subgroup analysis

Table 18: Clinical evidence profile: TENS versus sham TENS

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TENS	Control	Relative (95% CI)	Absolute		
Quality of life at 4 weeks (SF36 physical T scores, high is good outcome, change scores)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	103	99	-	MD 1.2 higher (0.7 lower to 3.1 higher)	⊕⊕⊕O MODERATE	CRITICAL
Quality of life at 4 weeks (SF36 mental T scores, high is good outcome, change scores)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	103	99	-	MD 1.1 higher (1.9 lower to 4.1 higher)	⊕⊕⊕O MODERATE	CRITICAL
Pain reduction at 4-10 weeks (BPI, VAS, 0-10, high is poor outcome, final values and change scores)												

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2	randomised trials	serious[1]	very serious inconsistency[2]	no serious indirectness	serious[3]	none	123	119	-	MD 1.96 lower (5 lower to 1.07 higher)	⊕OOO VERY LOW	CRITICAL
Pain reduction at 22 weeks (VAS, 0-10, high is poor outcome, final values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	20	20	-	MD 2.8 lower (4.23 lower to 1.37 lower)	⊕⊕⊕O MODERATE	CRITICAL
Physical function at 4 weeks (6 minute walk test, change scores)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	103	99	-	MD 19 higher (58 lower to 96 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Psychological distress at 4 weeks (PROMIS depression T scores, high is poor outcome, change scores)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	103	99	-	MD 2.7 lower (4.7 to 0.7 lower)	⊕⊕OO LOW	CRITICAL
Psychological distress at 4 weeks (PROMIS anxiety T scores, high is poor outcome, change scores)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	103	99	-	MD 0.5 lower (2.7 lower to 1.7 higher)	⊕⊕⊕O MODERATE	CRITICAL
Pain interference (Brief pain inventory interference, 0-10, high is poor outcome, change scores)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	103	99	-	MD 0.7 lower (1.3 to 0.1 lower)	⊕⊕OO LOW	CRITICAL
Pain self-efficacy (Pain self-efficacy questionnaire, 0-60, high is good outcome, change scores)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	103	99	-	MD 1.6 higher (1.8 lower to 5 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Discontinuation at 10 weeks												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	0/20 (0%)	0%	RD 0 (-0.09 to 0.09)	0 fewer per 1000 (from 90 fewer to 90 more)	⊕⊕OO LOW	CRITICAL

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded for heterogeneity, unexplained by subgroup analysis
3 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

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Table 19: Clinical evidence profile: TENS versus usual care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TENS	Control	Relative (95% CI)	Absolute		
Quality of life at 4 weeks (SF36 physical T scores, high is good outcome, change scores)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	103	99	-	MD 1 higher (0.8 lower to 2.8 higher)	⊕⊕⊕O MODERATE	CRITICAL
Quality of life at 4 weeks (SF36 mental T scores, high is good outcome, change scores)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	103	99	-	MD 2.4 higher (0.6 lower to 5.4 higher)	⊕⊕OO LOW	CRITICAL
Pain reduction at 10 weeks (BPI, 0-10, high is poor outcome, final values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	103	99	-	MD 0.9 lower (1.4 to 0.4 lower)	⊕⊕OO LOW	CRITICAL
Physical function at 4 weeks (6 minute walk test, change scores)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	103	99	-	MD 42 higher (34 lower to 118 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Psychological distress at 4 weeks (PROMIS depression T scores, high is poor outcome, change scores)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	103	99	-	MD 3.2 lower (5.1 to 1.3 lower)	⊕⊕OO LOW	CRITICAL
Psychological distress at 4 weeks (PROMIS anxiety T scores, high is poor outcome, change scores)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	103	99	-	MD 0.4 lower (2.5 lower to 1.7 higher)	⊕⊕⊕O MODERATE	CRITICAL
Pain interference (Brief pain inventory interference, 0-10, high is poor outcome, change scores)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	103	99	-	MD 0.6 lower (1.3 lower to 0.1 higher)	⊕⊕OO LOW	CRITICAL

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Pain self-efficacy (Pain self-efficacy questionnaire, 0-60, high is good outcome, change scores)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	103	99	-	MD 2.3 higher (1 lower to 5.6 higher)	⊕⊕⊕⊕ HIGH	CRITICAL

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 20: Clinical evidence profile: PENS versus sham PENS

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**PENS**	**Control**	**Relative (95% CI)**	**Absolute**		
Quality of life at 3 months (NIH-CPSI, 0-12, high is poor outcome, final values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	45	44	-	MD 4.6 lower (5.27 to 3.93 lower)	⊕⊕OO LOW	CRITICAL
Pain reduction at 3 months (VAS, 0-10, high is poor outcome, final values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	45	44	-	MD 2.9 lower (3.11 to 2.69 lower)	⊕⊕OO LOW	CRITICAL

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 21: Clinical evidence profile: PENS versus usual care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**PENS**	**Control**	**Relative (95% CI)**	**Absolute**		
Quality of life at 3 months (SF-36 physical function, 0-100, high is good outcome, final values)												

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1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12	12	-	MD 21.25 higher (0.64 lower to 43.14 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life at 3 months (SF-36 physical role, 0-100, high is good outcome, final values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12	12	-	MD 52.08 higher (23.29 to 80.87 higher)	⊕⊕OO LOW	CRITICAL
Quality of life at 3 months (SF-36 fatigue, 0-100, high is good outcome, final values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12	12	-	MD 17.91 higher (0.58 to 35.24 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life at 3 months (SF-36 emotional role, 0-100, high is good outcome, final values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12	12	-	MD 47.24 higher (17.93 to 76.55 higher)	⊕⊕OO LOW	CRITICAL
Quality of life at 3 months (SF-36 mental health, 0-100, high is good outcome, final values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12	12	-	MD 20.33 higher (6.31 to 34.35 higher)	⊕⊕OO LOW	CRITICAL
Quality of life at 3 months (SF-36 social functioning, 0-100, high is good outcome, final values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12	12	-	MD 21.87 higher (1.84 to 41.9 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life at 3 months (SF-36 bodily pain, 0-100, high is good outcome, final values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12	12	-	MD 36.67 higher (20.25 to 53.09 higher)	⊕⊕OO LOW	CRITICAL
Pain reduction at 3 months (VAS, 0-10, high is poor outcome, final values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12	12	-	MD 5.25 lower (6.86 to 3.64 lower)	⊕⊕OO LOW	CRITICAL

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

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Table 22: Clinical evidence profile: Ultrasound versus sham ultrasound

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Therapeutic ultrasound	Control	Relative (95% CI)	Absolute		
Pain reduction at 3 months (VAS, 0-10, high is poor outcome, final values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	36	40	-	MD 2.7 lower (3.54 to 1.86 lower)	⊕⊕OO LOW	CRITICAL

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

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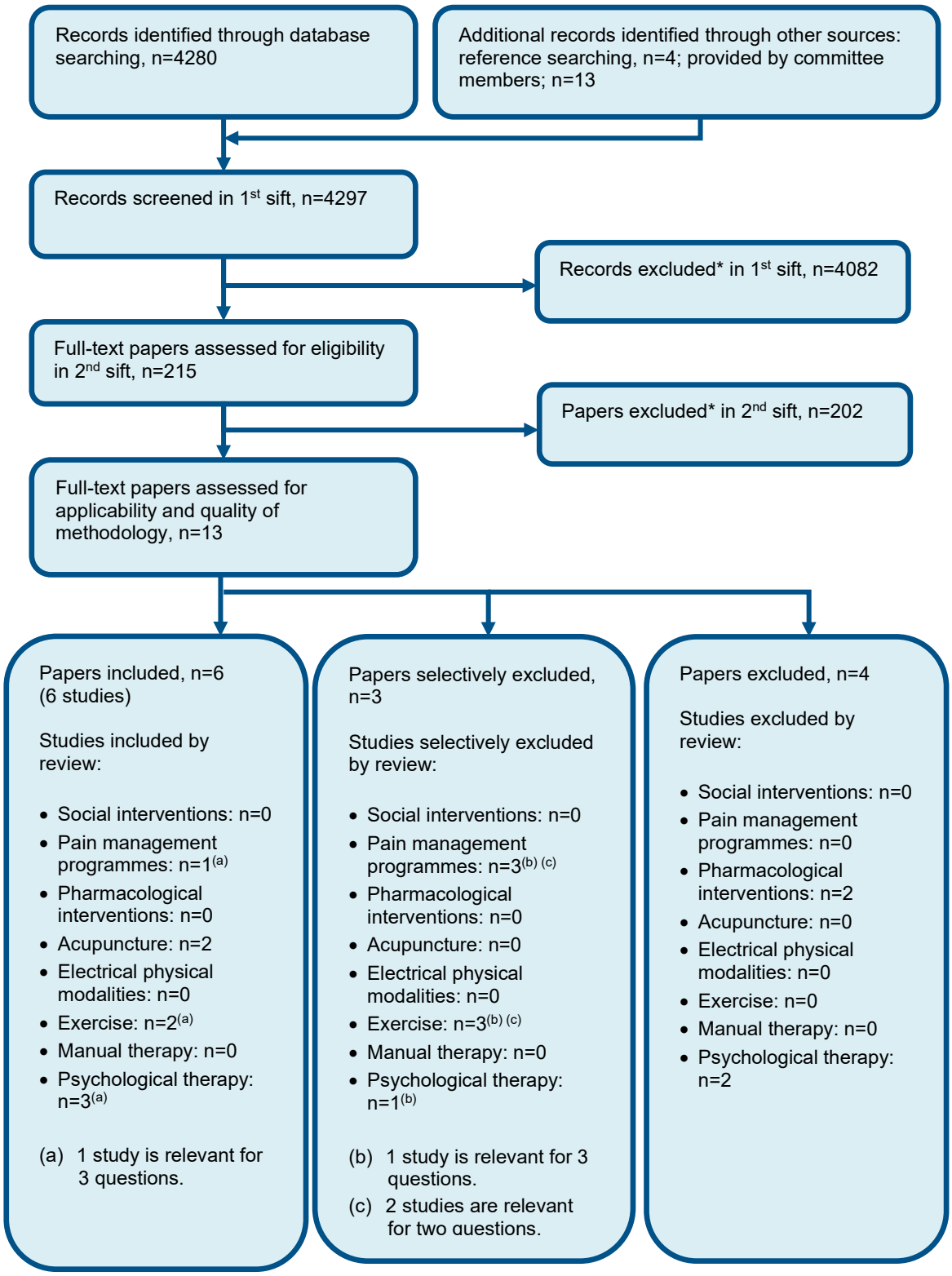
Appendix G: Health economic evidence selection



* Non-relevant population, intervention, comparison, design or setting; non-English language

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Appendix H: Health economic evidence tables

None.

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Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 23: Studies excluded from the clinical review

Study	Exclusion reason
Aarskog 2007[1]	Incorrect population
Abdulla 2013[2]	Incorrect study design
Abram 1976[3]	Not guideline condition. Incorrect population
Abtahi 2018[4]	Not guideline condition. Incorrect population
Acedo 2015[5]	Not guideline condition. Incorrect population
Adrian 2014[6]	Abstract
Ahmed 2011[7]	Not guideline condition. Incorrect population
Ahsin 2009[8]	Incorrect interventions. Incorrect population
Akturk 2013[9]	Incorrect study design
Akturk 2018[10]	Inappropriate comparison
Alayat 2016[13]	Incorrect interventions (combinations of interventions; intervention combined with exercise)
Alayat 2017[12]	Incorrect interventions (combinations of interventions; intervention combined with exercise)
Albornoz-cabello 2017[14]	Incorrect population. Not guideline condition
Allais 2003[15]	Not guideline condition. Incorrect population
Al-maweri 2017[11]	Incorrect study design
Almay 1985[16]	Incorrect population. Incorrect population
Almeida 2003[18]	Incorrect interventions. Combined treatments (ultrasound plus interferential current)
Almeida 2018[17]	Incorrect population. Inappropriate comparison
Altas 2019 [20]	Incorrect intervention (both interventions combined with exercise programme)
Amanat 2013[21]	Incorrect interventions. Combined treatments (laser plus pharmacological)
Anderssonn 1976[22]	Incorrect population
Andrade ortega 2014[23]	Incorrect interventions
Andre-obadia 2006[24]	Incorrect population.
Anon 2003[366]	Not article
Anon 2004[300]	Abstract
Anon 2017[119]	Incorrect study design
Anonymous 2016[56]	Incorrect interventions. Incorrect study design
Anonymous 2017[25]	Incorrect interventions. Combined treatments
Ansari 2013[26]	Abstract
Ansari 2014[27]	Abstract
Ardic 2002[29]	Not guideline condition. Incorrect population
Aridici 2016[30]	Incorrect interventions. Inappropriate comparison
Attal 2010[32]	Abstract
Avery 2015[33]	No useable outcomes
Ay 2011[34]	Incorrect population (not chronic)

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Study	Exclusion reason
Azatcam 2017[35]	Incorrect population (myofascial pain, unclear duration)
Barbosa 2018[36]	Incorrect comparison
Barnhoorn 2015[38]	Incorrect interventions
Barr 1987[39]	Abstract
Barr 2004[40]	Crossover study
Bates 1980[41]	Incorrect study design: not randomised
Baudic 2013[42]	Incorrect outcome
Bergeron-vezina 2018[43]	Incorrect population
Bezuur 1988[44]	Incorrect population (not chronic pain)
Biemans 2013[45]	Incorrect population. Not primary pain
Bilgili 2016[46]	Combinations of interventions. Combined with water bath and exercise
Bingol 2005[47]	Incorrect population (not chronic pain)
Bjordal 2003[48]	Incorrect study design
Boggio 2009[49]	Crossover study
Borckardt 2011[50]	Incorrect population. Healthy population
Botelho 2018 [51]	Unclear intervention duration
Boureau 1981[52]	Incorrect interventions
Busch 2013[55]	Incorrect population. Healthy population
Canadian chiropractic 2005[57]	Incorrect study design: expert opinion/guideline
Carbonario 2013[58]	Combinations of interventions. Intervention combined with exercise
Carrasco 2008[60]	Incorrect population (not chronic pain)
Carrasco 2009[59]	Incorrect population (not chronic pain)
Castro-sanchez 2011[63]	Incorrect interventions. Inappropriate comparison. Combinations of interventions
Castro-sanchez 2020 [62]	Inappropriate comparison
Ceccherelli 1989[64]	Not guideline condition. Not primary pain
Cervigni 2018[65]	Crossover study
Cetiner 2006[66]	Incorrect population (not chronic pain)
Chabal 1998[67]	Incorrect study design (survey)
Chan 2009[68]	Incorrect interventions. Acupuncture
Chee 1986[69]	Incorrect population (not chronic pain)
Chen 2008[70]	Incorrect population. Not primary pain
Cheng 1986[72]	Incorrect interventions. Acupuncture
Cheng 2019 [71]	No useable outcomes (correlational GLM model)
Choi 2014[74]	Incorrect population. Not chronic pain
Choi 2018[73]	Incorrect population. Not primary pain
Chong 2018[75]	Incorrect interventions. Electric acupuncture
Chow 2005[76]	Incorrect population (not chronic pain)
Cohen 2012[79]	Incorrect population. Incorrect interventions. Acupuncture
Conti 1997[80]	No useable outcomes
Conti 2014[81]	No useable outcomes
Cormier 2013[82]	Incorrect population.
Correa 2016[83]	Incorrect population.
Cossins 2013[84]	Systematic review is not relevant to review question or unclear PICO

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Study	Exclusion reason
Costa 2017[85]	Incorrect study design (1 day study)
Cruccu 2016[86]	Incorrect study design: expert opinion.
Cruccu 2016[87]	Incorrect study design. Systematic review is not relevant to review question or unclear PICO
Cruz 2018[88]	Incorrect population
Cummiford 2016[89]	Crossover study
Curatolo 2017[90]	No useable outcomes
Dailey 2013[93]	Crossover study
De carli 2013[97]	Incorrect population. Combinations of interventions
De giorgi 2017[98]	No useable outcomes
De souza 2018[99]	Inappropriate comparison
Defrin 2005[100]	Incorrect population. Not primary pain
Deluze 1992[102]	Incorrect interventions. Electric acupuncture
Demirkol 2015[103]	Incorrect population. Not chronic pain.
Desantana 2017[104]	Conference abstract
Di benedetto 1993[105]	Inappropriate comparison
Dibai-filho 2017[106]	Combinations of interventions
Dimitrijevic 2014[107]	Incorrect population. Not chronic pain.
Dorsher 2010[108]	Incorrect interventions. Electrical acupuncture
Dundar 2007[109]	Incorrect population. Not chronic pain.
Dundar 2014[110]	Abstract
Dundar 2015[111]	Combinations of interventions. Intervention combined with exercise
Durmus 2013[112]	Incorrect population
Eken 2018[113]	No relevant outcomes
El-Gendy 2019 [114]	Incorrect intervention. Combination of electrotherapies
Emshoff 2008[115]	Incorrect population. Not chronic pain
Escortell-mayor 2011[116]	Inappropriate comparison
Euasobhon 2018[118]	Incorrect population. Neuropathic pain
Falaki 2014[121]	Incorrect population. Not primary pain
Fernandez-rodriguez 2018[122]	Incorrect interventions. Acupuncture
Ferreira 2013[123]	Incorrect interventions. Acupuncture
Field 1992[124]	Abstract
Fikackova 2007[125]	Incorrect population. Not chronic pain
Foletti 2018[126]	Incorrect population. Not primary pain
Franco 2018[127]	Systematic review is not relevant to review question or unclear PICO
Frank 2013[128]	Incorrect population. Neuropathic pain
Fricova 2013[130]	Incorrect interventions. Not primary pain
Galhardoni 2015[131]	Systematic review is not relevant to review question or unclear PICO
Gam 1993[132]	Systematic review is not relevant to review question or unclear PICO
Gemmell 2011[133]	No relevant outcomes
Gendreau 2014[134]	Abstract
Germano maciel 2018[135]	Combinations of interventions. Intervention combined with exercise
Gibson 2017[136]	Incorrect population. Neuropathic pain

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Study	Exclusion reason
Goudra 2017[138]	Systematic review is not relevant to review question or unclear PICO
Graff-radford 1989[139]	Incorrect population (myofascial pain, unclear duration)
Graham 2013[140]	Systematic review is not relevant to review question or unclear PICO
Gray 1994[141]	Incorrect population. Not chronic pain
Gross 2000[142]	Systematic review is not relevant to review question or unclear PICO
Gross 2013[143]	Incorrect population. Systematic review is not relevant to review question or unclear PICO
Guedj 2013[144]	Conference abstract
Guirro 2015[145]	No useable outcomes
Guo 2005[146]	Incorrect interventions. Acupuncture
Gur 2002[148]	No useable outcomes (not validated scales)
Gur 2013[149]	Incorrect interventions. Inappropriate comparison
Hakguder 2003[150]	Incorrect population. Not chronic pain
Hargrove 2012[151]	No relevant outcomes
Harvey 2017[152]	Incorrect population. Over 20% of the population have chronic low back pain
He 2017[153]	Combinations of interventions
Hong 1993[154]	Crossover study
Hou 2002[155]	Incorrect population. Not chronic pain
Hou 2016[156]	Combinations of interventions. Incorrect study design
Hruby 2006[157]	Incorrect study design (cystoscopy)
Hsu 2018[158]	Incorrect study design: expert opinion
Hsueh 1997[159]	Incorrect population. Not chronic pain
Hurt 2020 [160]	Incorrect intervention. Extracorporeal shockwave therapy
Ilbuldu 2004[161]	Incorrect interventions. Acupuncture
Ilter 2014[162]	Combinations of interventions. Incorrect population. Not chronic pain
Ilter 2015[163]	Incorrect population. Not chronic pain
Istek 2014[164]	Incorrect population. Not primary pain
Ito 2002[165]	No relevant outcomes
Ivanishvili 2017[166]	Incorrect population. Neuropathic pain
Janice jimenez-torres 2017[168]	Protocol
Jeans 1979[169]	Incorrect population. Not primary pain
Jeon 2012[170]	Incorrect interventions. Combinations of interventions
Jin 2015[171]	Incorrect population. Neuropathic pain
Johansson 1980[172]	Incorrect study design
Johnson 2007[173]	Systematic review is not relevant to review question or unclear PICO
Johnson 2016[175]	Protocol
Johnson 2017[174]	Cochrane review is not relevant to review question or unclear PICO
Kadhim-saleh 2013[177]	Incorrect population. Not chronic pain
Kara 2010[178]	Incorrect population. Not primary pain
Kato 2006[179]	No useable outcomes
Katsoulis 2010[180]	Incorrect interventions. Acupuncture

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Study	Exclusion reason
Kavadar 2015[181]	Incorrect population. Not chronic pain
Kavvadias 2012[182]	Incorrect study design: expert opinion
Kemler 2001[183]	Incorrect interventions. Spinal cord stimulation
Kessler 2014[184]	Incorrect interventions. No relevant outcomes
Kim 2014[186]	Incorrect population (latent trigger points)
Kiraly 2018 [187]	Incorrect comparison
Knijnik 2016[188]	Systematic review is not relevant to review question or unclear PICO
Koca 2014[189]	Incorrect interventions. Inappropriate comparison
Kohutova 2017[190]	Incorrect interventions
Kriek 2015[191]	Crossover study
Kroeling 2005[193]	Incorrect population. Not chronic pain.
Kroeling 2013[192]	Systematic review is not relevant to review question or unclear PICO
Kruger 1998[194]	Incorrect study design
Kulekcioglu 2003[195]	Not guideline condition. Not chronic pain
La bianca 2017[196]	Conference abstract
Laakso 1997[197]	No useable outcomes
Lagueux 2018[198]	Combinations of interventions
Langley 1984[199]	Crossover study
Lara-palomo 2013[200]	Incorrect population.
Lassemi 2008[201]	Not guideline condition. Not chronic pain
Lauretti 2013[202]	All participants allocated to amitriptyline 25-50mg per day at least 3 weeks before randomisation
Leandri 1990[203]	Incorrect population
Lee 1997[204]	No useable outcomes
Lee 2013[206]	Abstract
Lev-sagie 2017[207]	Incorrect population
Lewis 2013[208]	Incorrect population. Not chronic pain
Lewis 2018[209]	Incorrect population. Neuropathic pain
Lichtbroun 2001[210]	No useable outcomes
Lima 2008[211]	Systematic review is not relevant to review question or unclear PICO
Lindholm 2015[212]	Crossover study
Lopez-martos 2018[213]	Incorrect interventions. Acupuncture
Luan 2019 [214]	Incorrect intervention. Extracorporeal shockwave therapy
Luedtke 2012[215]	Incorrect population
Lyskov 2005[216]	Crossover study
Macdonald 1995[217]	Not randomised
Macpherson 2017[218]	Incorrect interventions. Electric acupuncture
Madani 2020 [219]	No useable outcomes
Maestu 2013[220]	No useable outcomes
Magri 2017[221]	No useable outcomes
Magri 2018[222]	No useable outcomes
Maia 2012[223]	Incorrect study design. Systematic review is not relevant to review question or unclear PICO

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Study	Exclusion reason
Majithia 2016[224]	Systematic review is not relevant to review question or unclear PICO
Majlesi 2004[225]	Not chronic pain
Maloney 2014[226]	Conference abstract
Manafnezhad 2019 [227]	Incorrect interventions
Manca 2014[228]	Not chronic pain
Manfredini 2017[229]	Inappropriate comparison. No placebo
Marchand 1991[230]	Incorrect population
Marineo 2012[231]	Incorrect interventions. Inappropriate comparison
Marini 2010[232]	Incorrect population (disc displacement)
Marlow 2013[233]	Systematic review is not relevant to review question or unclear PICO
Matsutani 2007[234]	Incorrect interventions
Mazzetto 2007[235]	Not chronic pain. Incorrect population
Medeiros 2016[236]	Combinations of interventions. rTMS combined with sham DIMST (needling)
Mekhail 2018[237]	Conference abstract
Melchior 2013[238]	Not chronic pain. Incorrect population
Mendonca 2011[239]	No useable outcomes
Mendonca 2016[240]	Combinations of interventions. Intervention combined with exercise
Moisset 2016[242]	Incorrect study design: expert opinion
Molina-torres 2016[243]	Incorrect population.
Mordasini 2014[244]	Conference abstract
Moretti 2012[245]	Combinations of interventions. Inappropriate comparison
Morin 2017[246]	Incorrect population. Episodic pain
Müller 2015[247]	Incorrect interventions. Acupuncture
Munguia 2018[248]	Systematic review is not relevant to review question or unclear PICO
Muniswamy 2016[249]	Incorrect population. Neuropathic pain
Murina 2018[251]	Combinations of interventions
Mutlu 2006[253]	Unavailable
Mutlu 2013[252]	Not guideline condition. Not chronic pain
Mysliwiec 2012[254]	Incorrect population. Not primary pain
Nadershah 2020 [255]	Unclear population. Unclear duration of pain
Nardone 2018[256]	Systematic review is not relevant to review question or unclear PICO
Naterstad 2015[257]	Incorrect population.
Nct 2009[260]	Unpublished
Niddam 2007[262]	Not randomised
Noehren 2015[263]	Abstract
Nordin 1999[264]	Incorrect study design: review of guidelines
O'connell 2011[267]	Duplicate results
O'connell 2013[265]	Incorrect population.
O'connell 2018[266]	Systematic review is not relevant to review question or unclear PICO
Ofluoglu 2013[268]	Non-English language studies
Okmen 2017[269]	Incorrect population. Chronic Not primary pain

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Study	Exclusion reason
Oosterhof 2006[270]	Incorrect population
Oosterhof 2008[271]	Incorrect population (neuropathic pain, osteoarthritis)
Oosterhof 2012[272]	No useable outcomes
Oosterhof 2012[273]	Incorrect population. Not primary pain
Park 2018 [275]	Incorrect comparison (high versus low intensity)
Passard 2007[276]	No useable outcomes
Peng 1987[277]	Incorrect interventions. Electric acupuncture
Perrot 2014[278]	Systematic review is not relevant to review question or unclear PICO
Pezelj-ribaric 2013[279]	Incorrect population. Not chronic pain
Picarelli 2010[281]	Combinations of interventions. Combined with pharmacological therapy
Picarelli 2012[280]	Abstract
Plazier 2014[282]	Incorrect interventions
Powers 2018[283]	Combinations of interventions
Rayegani 2011[284]	Incorrect interventions
Reid 2001[285]	Case study
Renzenbrink 2004[286]	Incorrect population. Not primary pain
Riberto 2011[287]	Combinations of interventions. Intervention combined with exercise
Rigby 2017[288]	Incorrect population. Not chronic pain
Roizenblatt 2007[290]	No useable outcomes
Rollnik 2002[291]	Incorrect population. Not primary pain
Rowe 2005[292]	No useable outcomes
Ruiz-lopez 2017[293]	Non-English language studies
Ryan 2017[294]	Incorrect intervention (combined with a range of therapy from a physiotherapist, including but not limited to: CBT, hydrotherapy, motor imagery)
Sahin 2010[296]	No abstract/results
Sahin 2011[295]	Incorrect population (myofascial pain, duration unclear)
Sakrajai 2014[297]	Combinations of interventions. Incorrect population. Not chronic pain
Salazar 2017[298]	Combinations of interventions
Saltychev 2017[299]	Systematic review is not relevant to review question or unclear PICO
Sancakli 2015 [301]	Unclear population (no minimum duration of pain)
Santos 2018 [302]	No relevant outcomes
Sator-katzenschlager 2003[304]	Incorrect population. Incorrect interventions. Electric acupuncture.
Sator-katzenschlager 2004[303]	Incorrect interventions. Incorrect population. Electric acupuncture.
Sattayut 2012[305]	Crossover study
Sayilir 2017[307]	Incorrect population.
Sayilir 2018 [306]	Incorrect intervention (combination electrotherapy)
Schabrun 2012[308]	Incorrect population. Not chronic pain
Shafik 2006[309]	Incorrect population. Not primary pain
Shimoji 2007[310]	Incorrect population. Not primary pain
Shirani 2009[311]	Incorrect population. Not chronic pain
Shobha 2017[312]	No useable outcomes
Short 2010[313]	Abstract

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Study	Exclusion reason
Silva 2017[315]	Crossover study
Simons 2006[316]	Incorrect interventions. Inappropriate comparison
Simpson 2009[317]	Unpublished
Skorupska 2012[318]	Incorrect population. Not primary pain
Skrinjar 2020 [319]	No useable outcomes
Slattery 2002[320]	Conference abstract. Unavailable
Smania 2003[321]	Incorrect population. Not primary pain
Smania 2005[322]	No useable outcomes
Snyder-mackler 1986[323]	Incorrect population. Not primary pain
Soysal 2013[324]	Combinations of interventions
Spanemberg 2019 [326]	No useable outcomes
Srbely 2007[327]	Incorrect population. Not chronic pain
Stonnington 1976[328]	Incorrect study design. Not randomised
Sunshine 1996[330]	No useable outcomes (no variability data)
Sutton 1997[331]	Endometriosis. Incorrect population
Takla 2018 [333]	Incorrect population (not chronic primary pain)
Takla 2018 [332]	No useable outcomes
Tanwar 2016[334]	Conference abstract
Taube s 1988[335]	Incorrect outcome. No useable outcomes
Taylor 1987[337]	Incorrect population (not chronic pain)
Taylor 2004[338]	Incorrect outcome. Cost-effectiveness study
Taylor 2013[336]	Incorrect interventions
Thorsteinsson 1977[340]	Incorrect population
Tieppo francio 2017[341]	Not primary pain. Osteoarthritis
Tirlapur 2013[342]	Systematic review is not relevant to review question or unclear PICO. Incorrect study design
To 2017[343]	No useable outcomes
Uemoto 2013[344]	Incorrect study design. No useable outcomes
Valle 2009[347]	No results
Van der windt 1999[348]	Systematic review is not relevant to review question or unclear PICO
Vance 2015[349]	Incorrect study design. Not randomised
Vas 2006[350]	Incorrect interventions. Acupuncture
Vaseghi 2014[351]	Systematic review is not relevant to review question or unclear PICO
Vaseghi 2015[352]	Systematic review is not relevant to review question or unclear PICO. Systematic review: study designs inappropriate
Vayvay 2016[353]	Intervention combined with exercise. Combinations of interventions
Venezian 2010[355]	Not guideline condition. Not chronic pain
Viana 2012[356]	Not primary pain. Stroke patients
Visnjevac 2017[357]	Incorrect interventions. Systematic review is not relevant to review question or unclear PICO
Vitiello 2007[358]	Incorrect population
Vrijens 2017[359]	Systematic review is not relevant to review question or unclear PICO
Vukoja 2011[360]	Incorrect study design. Letter to editor
Walker 1987[361]	Incorrect population. Neuropathic pain

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Study	Exclusion reason
Wang 2011[363]	Non-English language studies
Wang 2014[362]	Incorrect population. Perioperative. Incorrect interventions. Acupuncture
Wang 2014[364]	Incorrect population. Not chronic pain
Waschl 2014[365]	Unavailable
Weisstanner 2014[367]	No relevant outcomes
Weisstanner 2017[368]	No relevant outcomes
Weng 2005[369]	Incorrect interventions
White 2000[372]	Crossover study
White 2007[370]	Incorrect interventions. Acupuncture
White 2012[371]	Incorrect interventions. Acupuncture
Wiffen 2005[373]	Incorrect population. Palliative care
Wilson 2014[374]	No useable outcomes
Yang 2018 [376]	Not in English
Yatci 2013[377]	Incorrect study design: expert opinion
Yesil 2017[378]	Incorrect interventions. Combinations of interventions
Yesil 2018[379]	Unavailable
Yildirim 2018 [380]	Incorrect population (pain for less than 6 weeks)
Yoshimizu 2012[381]	Crossover study
Young 1987[382]	Incorrect study design. Not randomised
Yuksel 2019 [383]	Incorrect comparison (healthy controls)
Zhu 2002[385]	Incorrect interventions. Acupuncture
Zhu 2017[384]	Systematic review is not relevant to review question or unclear PICO

I.2 Excluded health economic studies

None.

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Appendix J: Research recommendations

J.1 Laser therapy

Research question: What is the clinical and cost-effectiveness of laser therapy for managing chronic primary pain in people aged 16 years and over?

Why this is important:

Laser therapy involves the non-invasive application of a single wavelength of light to the skin over the painful area using a probe. There are various laser devices and probe configurations in clinical use. The light is absorbed in the tissues and it is hypothesised that this results in local heating and effects on local chemical activity and cellular behaviour. It is through those effects that laser therapy is purported to have an anti-inflammatory effect and promote tissue repair.

14 studies were included in this review comparing laser to sham in a range of conditions including burning mouth syndrome (4 studies), temporomandibular pain (4 studies), fibromyalgia (3 studies), neck pain (2 studies) and myofascial pain (1).

While evidence of clinical benefit was observed there remains uncertainty regarding the efficacy and effectiveness of laser therapy, though there is some promising evidence. There is therefore a need for high quality trials into the effectiveness and cost effectiveness of laser therapy for chronic primary pain.

Criteria for selecting high-priority research recommendations:

PICO question	Population: Adults (aged >16) with Chronic Primary Pain Intervention(s): Laser therapy Comparison: Sham Outcome(s): Quality of life, Pain Interference and reduction,
Importance to patients or the population	If laser therapy offers clinically important benefits over sham laser therapy when added to care, at a reasonable cost threshold then it may be an important modality to enhance clinical outcome in this patient group.
Relevance to NICE guidance	This research will reduce the existing uncertainty regarding the effectiveness and cost-effectiveness of laser therapy and enable future guidelines to clearly recommend for or against the use of laser therapy.
Relevance to the NHS	A clear recommendation for or against laser therapy will offer clinicians clearer guidance on best care for chronic primary pain.
National priorities	None
Current evidence base	The NICE chronic pain guideline found very low to moderate quality evidence for improvement with laser therapy in quality of life in the short term and one small study showing a clinically important benefit in QOL in the long term. Although there was evidence from thirteen studies demonstrating a clinically important benefit in pain reduction in the short term, this was rated as very low quality evidence. Two further studies demonstrated clinically important benefit in pain reduction in the longer term (moderate quality evidence). However no clinically important difference was noted for psychological distress or discontinuation. Conflicting evidence was found comparing laser with sham for pain and quality of life outcomes. While evidence of clinical benefit was observed in some comparisons for pain and quality of life, there were concerns with the quality and applicability of the evidence. There remains uncertainty regarding the efficacy and effectiveness of laser therapy, though there is some promising evidence. No cost-effectiveness evidence has been identified regarding use of laser for the management of chronic primary pain. However the NICE chronic pain guideline committee noted that there

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	would be resource implications, including the provision and maintenance of equipment and training therapists. There is therefore a need for a conclusive study into the clinical and cost effectiveness of laser therapy for chronic primary pain.
Equality	The recommendation is unlikely to impact on equality issues.
Study design	Randomised controlled trial with corresponding economic analysis. Post-intervention long term follow up should be included.
Feasibility	The trial is feasible and should be straightforward to carry out. There are challenges associated with the design of adequate sham controls for higher intensity laser therapy that delivers a sensation of heating that will require specific consideration when designing a trial.
Other comments	Low intensity laser therapy is easy to design sham controls for since it delivers no sensation beyond the pressure of the probe. A recommendation for laser therapy is likely to require the purchase of new equipment and staff training.
Importance	Low: the research is of interest and will fill existing evidence gaps.

J.2 Transcranial magnetic stimulation

Research question: What is the clinical and cost effectiveness of transcranial magnetic stimulation for managing chronic primary pain in people aged 16 years and over?

Why this is important:

Transcranial magnetic stimulation (TMS) has been proposed as a potential treatment option for chronic pain as stimulation of the motor cortex of the brain is known to lead to analgesia. TMS has been researched in various chronic pain conditions including those that fall within the definition of chronic primary pain. However, whether or not TMS is an effective and cost-effective treatment option for chronic primary pain remains unclear. TMS is not provided as part of current clinical practice for people with chronic primary pain and its introduction into practice would incur costs in terms of provision of the equipment and training in the use of the equipment, and therefore good quality research is required to inform this decision.

Criteria for selecting high-priority research recommendations:

PICO question	Population: Adults (aged >16) with chronic primary pain Intervention(s): TMS Comparison: Sham TMS or usual care Outcome(s): Pain reduction, health related quality of life, physical function, psychological distress, pain interference, pain self-efficacy.
Importance to patients or the population	There was a suggestion from the current evidence base that TMS may help improve pain in people with chronic primary pain. Further evidence to determine whether this benefit can be replicated in larger trials, or also has an impact on quality of life would help inform whether this should be a treatment choice for this population.
Relevance to NICE guidance	More evidence from a large RCT would help inform an update of this guideline to guide a recommendation on whether TMS should or should not be recommended for people with chronic primary pain.
Relevance to the NHS	TMS is not routinely used in current NHS practice to treat chronic primary pain, therefore good high quality evidence would be of relevance to inform whether a change in practice is warranted.
National priorities	N/A
Current evidence base	Eight studies of TMS in people with chronic primary pain were included in the guideline review. When compared to sham there was some indication of benefit in quality of life and pain interference, however this evidence was inconsistent and from relatively small sample sizes. There was more

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	evidence for a reduction in pain intensity, but in the absence of consistent benefit in other outcomes, or long term benefit, this was considered insufficient to base a recommendation on.
Equality	No specific equality issues.
Study design	An adequately powered, sham controlled, RCT with a follow-up period of greater than 3 months.
Feasibility	The design of this research is feasible, although it is noted that TMS is not widely available, which may have an impact.
Other comments	None.
Importance	Low: the research is of interest and will fill existing evidence gaps.

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Appendices

Appendix K: MIDs for continuous outcomes

Table 24: MIDs for continuous outcomes: Laser therapy versus sham laser therapy

Outcomes	MID
Quality of life at ≤3 months (Oral health impact profile, FIQ, high is poor outcome, final values)	0.5 (SMD)
Quality of life at >3 months (Oral health impact profile, FIQ, high is poor outcome, final values)	0.5 (SMD)
Pain reduction at ≤3 months (VAS, NRS, FIQ pain scale, high is poor outcome, 0-10, final values and change scores)	0.79
Pain reduction at >3 months (VAS, high is poor outcome, 0-10, final values)	0.6
Psychological distress at ≤3 months (Hospital anxiety and depression rating scale, anxiety subscale, 0-21, high is poor outcome, final values)	1.75
Psychological distress at ≤3 months (Hospital anxiety and depression rating scale, depression subscale, 0-21, high is poor outcome, final values)	2.25

Table 25: MIDs for continuous outcomes: TMS versus sham TMS

Outcomes	MID
Quality of life at ≤3 months (WHOQOL-BREF physical domain, 4-20, high is good outcome, final values)	1.42
Quality of life at ≤3 months (WHOQOL-BREF psychological domain, 4-20, high is good outcome, final values)	1.245
Quality of life at ≤3 months (FIQ, 0-100, high is poor outcome, final values)	8.395
Quality of life at >3 months (FIQ, 0-100, high is poor outcome, final values)	7.5
Pain reduction at ≤3 months (VAS, McGill Pain questionnaire, 0-10, high is poor outcome, final values)	1.05
Physical function at ≤3 months (BPI functional impairment subscale, 0-10, high is poor outcome, final values)	1.345
Psychological distress at ≤3 months (Beck depression inventory, 0-61, high is poor outcome, final values and change scores)	2.55
Psychological distress at ≤3 months (Hamilton depression rating scale, MADRS, BDI, high is poor outcome, final values)	0.5 (SMD)
Psychological distress at ≤3 months (HADS anxiety, 0-21, high is poor outcome, change scores)	1.15
Psychological distress at >3 months (HADS anxiety, 0-21, high is poor outcome, change scores)	2.85
Psychological distress at >3 months (HADS depression, 0-21, high is poor outcome, change scores)	2

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Outcomes	MID
Pain interference at >3 months (BPI pain interference, 0-10, high is poor outcome, final values)	0.75

Table 26: MIDs for continuous outcomes: TDCS versus sham TDCS

Outcomes	MID
Pain reduction at ≤3 months (NRS, VAS, 0-10, high is poor outcome, final values)	0.75
Psychological distress at ≤3 months (Hospital anxiety and depression scale, HAM-A, anxiety subscales, high is poor outcome, final values)	0.5 (SMD)
Psychological distress at ≤3 months (Hospital anxiety and depression scale, BDI, HAM-D, depression subscales, high is poor outcome, final values)	0.5 (SMD)
Sleep at ≤3 months (PSQI, scale range not reported, high is poor outcome, final values)	1.87

Table 27: MIDs for continuous outcomes: TENS versus sham TENS

Outcomes	MID
Quality of life at ≤3 months (SF36 physical T scores, high is good outcome, change scores)	3.15
Quality of life at ≤3 months (SF36 mental T scores, high is good outcome, change scores)	5.05
Pain reduction at ≤3 months (BPI intensity, VAS, 0-10, high is poor outcome, final values and change scores)	0.94
Physical function at ≤3 months (6 minute walk test, change scores)	157
Psychological distress at ≤3 months (PROMIS depression T scores, high is poor outcome, change scores)	4.15
Psychological distress at ≤3 months (PROMIS anxiety T scores, high is poor outcome, change scores)	4.18
Pain interference at ≤3 months (BPI interference, 0-10, high is poor outcome, change scores)	1.09
Pain self-efficacy at ≤3 months (PSEQ, 0-60, high is good outcome, change scores)	6.6

Table 28: MIDs for continuous outcomes: TENS versus usual care

Outcomes	MID
Quality of life at ≤3 months (SF36 physical T scores, high is good outcome, change scores)	3.25
Quality of life at ≤3 months (SF36 mental T scores, high is good outcome, change scores)	5.15
Pain reduction at ≤3 months (BPI intensity, 0-10, high is poor outcome, change scores)	0.91
Physical function at ≤3 months (6 minute walk test, change scores)	160.25

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Outcomes	MID
Psychological distress at ≤3 months (PROMIS depression T scores, high is poor outcome, change scores)	4.05
Psychological distress at ≤3 months (PROMIS anxiety T scores, high is poor outcome, change scores)	4.13
Pain interference at ≤3 months (BPI interference, 0-10, high is poor outcome, change scores)	1.27
Pain self-efficacy at ≤3 months (PSEQ, 0-60, high is good outcome, change scores)	6.63

Table 29: MIDs for continuous outcomes: PENS versus sham PENS

Outcomes	MID
Quality of life at ≤3 months (NIH-CPSI, 0-12, high is poor outcome, final values)	1.05
Pain reduction at ≤3 months (VAS, 0-10, high is poor outcome, final values)	0.2

Table 30: MIDs for continuous outcomes: PENS versus usual care

Outcomes	MID
Pain reduction at ≤3 months (VAS, 0-10, high is poor outcome, final values)	0.44

Table 31: MIDs for continuous outcomes: Therapeutic ultrasound versus usual care

Outcomes	MID
Pain reduction at ≤3 months (VAS, 0-10, high is poor outcome, final values)	0.44

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Perspectives on INTEGRATIVE MEDICINE

Perspect Integr Med 2023;2(3):155-163

Review Article

Effectiveness and Safety of Low-Level Laser Treatment for Lumbar Disc Herniation: A Systematic Review and Meta-Analysis

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Received: June 15, 2023 Revised: August 09, 2023 Accepted: August 21, 2023

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https://doi.org/10.56986/pim.2023.10.003

ABSTRACT

Background: Low-level laser treatment (LLLT) is used to treat low back pain (LBP) however, its effects on lumbar disc herniation (LDH) remain unclear. The safety and effectiveness of LLLT for LDH was determined using a systematic review of randomized clinical trials.
Methods: Studies on LLLT in adults with LDH were identified from 12 worldwide databases. A risk of bias assessment and a meta-analysis with categorization according to the type of control used (inactive, active, or add-on) was performed. The quality of evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation.
Results: The quantitative analyses included five studies. LLLT was significantly more effective at treating LDH [leg pain visual analog scale (VAS) mean difference (MD): −1.90, 95% confidence interval (CI): −2.01, −1.80, I2 80%; LBP VAS MD: −0.79, 95% CI: −0.87, −0.71, I2 80%] than inactive controls (placebo or sham). The quality of the evidence ranged from "low" to "very low." As an add-on to usual care, LLLT significantly improved pain intensity and disability compared with usual care (leg pain VAS MD: −2.52, 95% CI: −2.65, −2.40, I2 97%; LBP VAS MD: −1.47, 95% CI: −1.58, −1.36; Oswestry Disability Index MD: −4.10, 95% CI: −4.55, −3.65, I2 6%). However, the quality of the evidence ranged from "moderate" to "low."
Conclusion: LLLT significantly improved outcomes compared with the inactive controls, but was not more effective than usual care for LDH. In combination with usual care, LLLT was significantly more effective than usual care alone highlighting the potential of LLLT.

Keywords: chronic pain, disc herniation, meta-analysis, low back pain, systematic review

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Introduction

The prevalence of low back pain (LBP) and neck pain has increased substantially over the past 25 years, and in most countries, these conditions are the leading causes of years lived with disability [1]. Lumbar disc herniation (LDH), one of the most common causes of LBP and sciatica which refers to a prolapse of the nucleus pulposus, the inner core of the vertebral disc, through a tear in the outer surrounding annulus fibrosus. This results in irritation and compression of the sensory nerves, causing pain, paresthesia, tingling sensation, numbness, and muscle weakness in the distribution of the affected nerve roots [2].

Improvements in healthcare and the advancement of medical technology have contributed to the widespread trend of population aging, resulting in a continuous increase in annual healthcare expenditure [3] owing to the increasing number of patients and medical costs related to spinal conditions/diseases. A study based on the national health insurance data of Korea, determined that the number of patients treated, and the associated medical costs for LDH increased by 1.18, and 1.53 times, respectively, over 5 years from 2006-2010 [4]. Currently, surgical and conservative treatments such as medications and physical therapy are commonly used to treat LDH [2].

Low-level laser treatment (LLLT) is a type of phototherapy that uses low-power red and near-infrared light beams (600-1,100 nm in wavelength) for the application of light energy over the acupuncture or trigger points of affected areas, thereby affecting (stimulating or inhibiting) a wide range of cellular processes. This includes preventing apoptosis, augmenting tissue repair, and promoting tissue, and neuronal regeneration [5,6]. LLLT has been reported to reduce pain through the modulation of inflammatory

processes [7]. Notably, LLLT aids in the process of photobiomodulation, affecting the biochemical processes of cells and tissues, which leads to physiological changes and promotes therapeutic effects [7]. LLLT involves no pain as it is a nonthermal process with no visible heat emission and is non-invasive. Therefore, the associated adverse events (AEs) are minimal, and serious AEs have not been reported, suggesting that LLLT may be an option for primary care [8]. Therefore, studies have been undertaken to examine the clinical efficacy of LLLT [9,10]. Currently, it is frequently used to manage symptoms in patients with musculoskeletal disorders such as myofascial pain syndrome, neck pain, nonspecific chronic LBP, and chronic joint disorders [8,10-12].

Systematic reviews have reported on the effectiveness of LLLT for nonspecific chronic LBP [12,13]; however, there has been a paucity of reviews on LDH. Therefore, in this study, we examined the effectiveness and safety of LLLT for treating LDH through a systematic review based on randomized controlled trials (RCTs).

Materials and Methods

This study was based on the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [14].

1. Literature search

Three major biomedical literature databases [PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), and EMBASE] were used for the literature search. In addition, six Korean databases [KoreaMed, Korean Medical Database (KMBASE), Korean Studies Information Service System (KISS), National Digital Science Library (NDSL), https://society. kisty. re. kr from the Korea Institute of Science and Technology Information and Oriental Medicine Advanced Searching Integrated System (OASIS)], one Chinese database [Chinese National Infrastructure Structure (CNKI)], and two Japanese databases [Citation Information by NII (CiNii) and J-Stage]. The key terms used in the search included those related to symptoms of LDH (e.g., sciatica, radiculopathy), herniation of lumbar intervertebral discs (e.g., lumbar, disc), and terms related to laser treatment, including laser acupuncture (e.g., laser, LLLT, laser acupuncture), as well as a combination of these terms. The literature search was conducted on March 15, 2023. Detailed search strategies are presented in Supplementary A.

2. Selection of studies

2.1. Study types

RCTs on laser therapy, including laser acupuncture for LDH, were included in the literature review. Nonrandomized controlled trials (nRCTs), uncontrolled trials such as case series, and qualitative studies were excluded. No restrictions were imposed on the language used or publication type during the literature review.

2.2. Participants

The patient samples from this literature review included those diagnosed with LDH through radiological examination. Studies on intervertebral disc degeneration, studies in which patients with LDH were not the major participants or studies on LBP without pathoanatomical causes were excluded from the selection process.

2.3. Type of interventions

RCTs in which LLLT was performed for LDH were included, and studies without a clear description of the assessment of LLLT effectiveness were excluded. The selected studies were categorized into those comparing LLLT with inactive controls (placebo or sham controls), studies in which LLLT was applied as a single mode of intervention, and studies in which LLLT was applied as an add-on therapy.

2.4. Types of control groups

Controls and comparators in the RCTs included those with no treatment, sham LLLT, or usual care such as medication, including nonsteroidal anti-inflammatory drugs, traction, ultrasound, and exercise. In the RCTs in which other treatments were used as co-interventions in the laser treatment group, only those that received the same treatment as the co-intervention in all control or comparator groups were included in this literature review.

3. Data extraction

During the study selection process, two or more independent researchers reviewed the titles and abstracts of the studies identified from the literature search to determine eligibility based on the inclusion/exclusion criteria of study selection prior to reviewing the full text of the manuscripts. When the eligibility status could not be determined based on the analysis of titles and abstracts alone, the full text of the articles was analyzed to assess eligibility. In cases where the results of the assessments conducted by independent researchers did not align, a third party was engaged to facilitate a consensus on the assessment.

Two independent researchers analyzed the full text of the five selected studies. Data were extracted according to the established criteria of analysis for the following categories: first author, year of publication, type of study, the treatment used in the intervention group, the treatment used in the control or comparator groups, sample size, period of intervention and procedure, follow-up, outcomes measures, estimates of effectiveness, and AEs. Additionally, data on the specific methods used in the treatment, wavelength,

power, energy, laser beam size, treatment time, treatment interval, and number of treatment sessions were extracted. In instances where the data extraction conducted by each researcher was inconsistent, a consensus was reached. In cases in which an agreement was not reached, a third party intervened to reach an agreement. When discrepancies arose in the results of data extraction among researchers, resolution was achieved through discussions. When the results were not in agreement, a third party was engaged to facilitate a consensus on the final data extraction.

4. Risk of bias

Two independent researchers assessed the risk of bias (RoB) using the RoB tool of the Cochrane Collaboration. The seven domains of bias were: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment (assessor); (5) incomplete outcome data; (6) selective reporting; and (7) other bias. The assessment results were categorized into three levels of RoB: high, low, and uncertain [15]. In case of disagreement in the results of the RoB assessment by the respective researchers, a consensus was achieved based on discussions between the researchers, failing which a third party was engaged to facilitate a consensus on the final assessment.

5. Statistical analysis

A meta-analysis of the five selected articles was performed to quantitatively assess the effectiveness of LLLT. The results were expressed as means with standard deviations. Continuous variables were assessed using inverse variance analysis. The mean difference (MD) values were determined by comparing the intervention and control groups. The meta-analysis was performed using a fixed inverse variance method with Review Manager (RevMan) Version 5.4 (Cochrane Collaboration, 2020) software. Heterogeneity between the extracted studies was assessed using the chi-square test (are 2 variables independent of each other) and I^2 (unimportant, substantial, considerable heterogeneity) statistic at a significance level of $p < 0.10$.

6. Quality of evidence

The quality of evidence provided in the five studies included in the meta-analysis was assessed by reviewing each control and outcome variable according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology. The quality of evidence was determined based on the GRADE criteria: RoB, publication bias, inconsistency, indirectness, imprecision, dose-response, and large magnitude of effect. The quality of each parameter was rated as "high", "moderate", "low", or "very low"[16]. As only a limited number of studies were included in the analysis, publication bias was not assessed.

Results

1. Selection of studies

There were 1,220 records identified, including 779 from three major biomedical databases (487 from PUBMED, 184 from CENTRAL, and 108 from EMBASE), 278 from Korean databases, 73 from Chinese databases, and 90 from Japanese databases. There were 191 duplicate records excluded, and following examination of the titles and abstracts of 1,029 articles, 996 were determined to be ineligible according to the inclusion criteria. Subsequently, the full texts of the remaining 33 studies were reviewed, and 28 studies were excluded based on the selection criteria. Consequently, the full texts of five articles were analyzed (Fig. 1).

2. Characteristics of studies

2.1. Participants

From the selected five studies [17-20], 845 patients were included in this review. Of the five studies, two [17,18] were conducted in Turkey, one in Brazil [18], one in Serbia [19], and one in Pakistan [21] (Table 1 [17-21]).

According to the inclusion/exclusion criteria for study

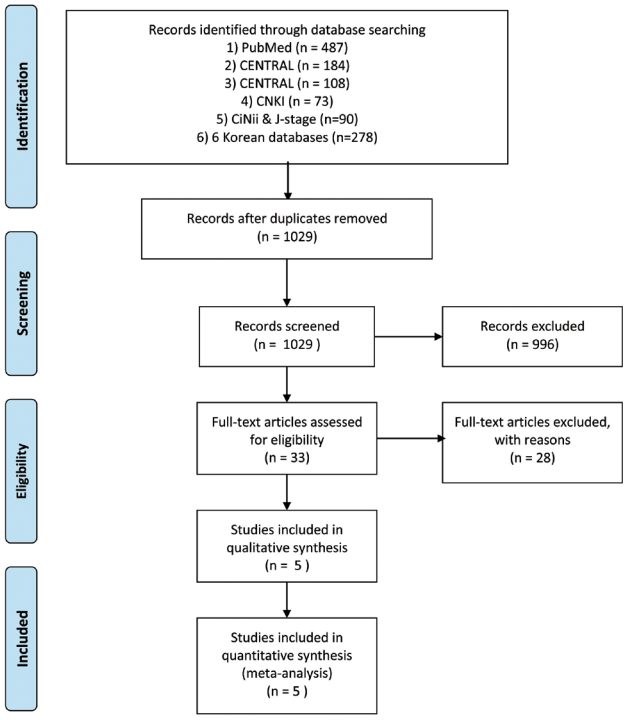

Fig. 1. Flow chart of study selection according to the diagram of Preferred Reporting Items for Literature Reviews.

Table 1. Characteristics of Included Studies.

First author (y)	Country	Condition / disease	Intervention group (*n*)	Comparison group (*n*)	Main outcomes	Adverse event	Authors conclusion
LLLT vs. placebo							
Ay (2010) [17]	Turkey	Acute & chronic LDH	LLLT (40)	Sham LLLT (40)	1) VAS (LBP) 2) Patient's global assessment 3) Physician's global assessment 4) Left lateral flexion 5) Modified Schober test 7) RMDQ 8) Modified ODI	No AEs	No difference
De Carvalho (2016) [18]	Brazil	LDH (L4-S1) with radiculopathy	LLLT (18)	Sham LLLT (13)	1) VAS (LBP) 2) VAS (leg pain) 3) AHFA 4) ODI	NR	NR
Konstantinovic (2010) [19]	Serbia	Acute LBP with radiculopathy by LDH	LLLT (182)	Sham LLLT (182)	1) VAS (leg pain) 2) VAS (LBP) 3) ODI 4) Schober test 5) PCS 6) MCS	2 patients (worsening pain)	Laser > sham
LLLT vs. usual care							
Unlu (2008) [20]	Turkey	Acute LBP with leg pain by LDH	LLLT (20)	Traction (20) Ultrasound (20)	1) lateral flexion 2) Shober test 3) Muscular tenderness 4) Positive SLR 5) VAS (LBP) 6) VAS (leg pain) 7) RMDQ 8) Modified ODI 9) Size of the herniated mass on MRI	NR	Generally, no difference
De Carvalho (2016) [18]	Brazil	LDH (L4-S1) with radiculopathy	LLLT (18)	LED (18)	1) VAS (LBP) 2) VAS (leg pain) 3) AHFA 4) ODI	NR	LED > LT
LLLT with usual care versus usual care (add-on)							
Konstantinovic (2010) [19]	Serbia	Acute LBP with radiculopathy by LDH	LLLT + nimesulide (182)	Nimesulide (182)	1) VAS (leg pain) 2) VAS (LBP) 3) ODI 4) Schober test 5) PCS 6) MCS	2 patients (worsening pain)	LLLT + nimesulide > nimesulide
Ahmed (2022) [21]	Pakistan	Acute LBP with unilateral radiculopathy by LDH	LLLT + physical therapy (55)	Physical therapy (55)	1) VAS (leg pain) 2) ODI 3) Lumbar flexion 4) Lumbar extension	NR	LLLT + physical therapy > physical therapy

LBP = lower back pain; LDH = Lumbar disc herniation; LLLT = low-level laser treatment; VAS = visual analog scale; RMDQ = Ronald Morris disability questionnaire; AHFA = affected hip flexion angle; ODI = Oswestry Disability Index; PCS = physical component summary; MCS = mental component summary; NR. = not reported; AE = adverse event; MRI = magnetic resonance imaging.

selection, only studies on patients diagnosed with LDH based on radiological and physical examinations were included, and those on patients with LBP diagnosed with degenerative intervertebral discs were excluded. Four of the five selected studies were RCTs involving patients in an acute phase (Table 1 [17-21]).

2.2. Intervention of LLLT

To assess the effectiveness of LLLT the five selected studies were categorized into three types: (1) studies comparing LLLT and sham laser treatment; (2) studies comparing LLLT with other types of usual care; and (3) studies that applied LLLT as an add-on therapy (Table 1 [17-21]). The specific treatment methods and details of the LLLT settings are summarized in Table 2 [17-21].

2.3. Controls/comparators

Three of the selected studies [17-19] compared LLLT with sham laser treatment, and two studies [18,20] compared LLLT with types of usual care; one of the two studies [18]

Table 2. LLLT Details of Included Studies.

First author (y)	Medium (model, manufacturer)	Wavelength (nm) / type	Power output (mW) / power density (mW/cm^2)	Energy density (J/cm^2) / dose/point (J/point)	Beam size / No. of treatments / treatment time	Treatment sessions & interval
Ay (2010) [17]	GaAlAs (Chattanooga group, USA)	850 / continuous	100 / NR	40 / NR	0.07 cm^2/ 2-4 points (both sides of the paraspinal tissues of the disk spaces) / 4 m/ point	15 ×, 5 × / wk, 3 wks
De Carvalho (2016) [18]	AsGa (HTM brand, São Carlos, SP, Brazil)	904 / pulse type (pulse rate 5 KHz)	38 / 238	0.23 / 4	0.16 cm^2 / 20 points (12 points: L2-S1 + 8 points: thigh in the path of L5 and S1) / 104 s/point	15 ×s, 5 × / wk, 3 wks
Konstantinovic (2010) [19]	NR (Enraf Nonius, Rotterdam, The Netherlands)	904 / pulse type (pulse rate 5,000 Hz)	100 / 20	3 / 3	1 cm^2 / 4 points (local transforaminal) / 150 s/point	15 ×, 5 × a wk
Unlu (2008) [20]	Gal-Al-As (Endolaser 476, Enraf Nonius))	830 / continuous	50 / NR	NR / 1	1 mm (diameter) / both sides of the disc spaces where herniation was detected on MRI / 4 m/point	15 ×, 5 × / wk, 3 wks
Ahmed (2022) [21]	NR	830 / NR	100/ 0.67 W/cm^2 or 300 mW/cm^2	3/3	1 cm/ 4 points/30 s/point	18 ×, 3 × / wk for 6 or 8 wks

LLLT = low-level laser treatment; NR = not reported.

compared LLLT and LED treatment, and the participants performed exercises in both groups. The other two studies [19,21] were a 3-arm RCT comparing LLLT, traction, and ultrasound; thus, the effectiveness of the three different modalities was compared. Two of the selected studies [19,21] applied LLLT as an add-on therapy: one study applied LLLT in addition to the use of oral analgesics (nimesulide), and the other applied LLLT in addition to the usual care of physical therapy (Table 1 [17-21]).

2.4. Outcomes

For the assessment of pain-related outcomes, the Visual Analog Scale (VAS) was used in all five studies, and most studies divided the type of pain into leg pain and LBP.

To assess outcomes related to functional disability, the Oswestry Disability Index (ODI) and the Modified Oswestry Disability Questionnaire were used in all five studies [17-21]. Two studies also used the Ronald Morris Disability Questionnaire in their assessment [17,20].

For mobility assessment, four studies [17,19-21] used the Schober Test and modified Schober Test to assess lumbar mobility, and the Range Of Motion was measured in four studies [17,18,20,21]. To assess the effectiveness of treatment, one study [17] used both the patient's and physician's global assessments. Health-related Quality of Life was assessed in one study [19], and the outcomes were presented using the Physical Component Summary and Mental Component Summary.

Regarding other outcome measures used in the selected studies, one study [20] presented changes in the size of the herniated mass on magnetic resonance imaging.

3. Risk of bias

In terms of the random sequence generation domain for the assessment of RoB, only one study [19] described computer-generated random numbers and thus was assessed as "low risk." The other four studies [18-21] did not have any description of random sequence generation and were assessed as "unclear risk."

In terms of the allocation concealment domain, only two studies [19,21] reported on the matter and were assessed as "low risk." In contrast, the other three studies had no description of the issue and were determined as "unclear risk."

In terms of blinding of participants and personnel, three studies using sham LLLT were assessed as "low risk," and two studies that did not describe the blinding process were assessed as "unclear risk." In the blinding of the outcome assessment domain, four studies [17,19-21] had descriptions of blinding in the outcome assessment process by separating investigators and assessors; thus, these studies were assessed as "low risk." One study [18] did not have a specific description of this aspect of blinding and was

Table 3. Meta-analysis of Outcomes and Quality of Evidence.

Variable	Overall effect	Studies (No.)	Sample size (*N*)	Quality of evidence					
	MD	95% CI	*p*	I^2	*p* (χ^2)	Statistical method			
LLLT versus placebo									
Leg pain (VAS)	-1.90	-2.01, -1.80	< 0.00001	80	0.03	Fixed Inverse Variance	2	395	Very low[abc]
LBP (VAS)	-0.79	-0.87, -0.71	< 0.00001	80	0.002	Fixed Inverse Variance	3	475	Low[ab]
Functional disability (ODI)	-1.83	-3.63, -0.02	0.05	7	0.30	Fixed Inverse Variance	2	395	Low[ac]
LLLT vs. usual care									
Leg pain (VAS)	0.61	-0.35, 1.56	0.21	0	0.87	Fixed Inverse Variance	2	96	Low[ac]
LBP (VAS)	0.51	-0.34, 1.36	0.24	0	0.99	Fixed Inverse Variance	2	96	Low[ac]
Functional disability (ODI)	-1.90	-13.59, 9.79	0.75	NA	NA	Fixed Inverse Variance	1	36	Low[ac]
LLLT with usual care versus usual care (add-on)									
Leg pain (VAS)	-2.52	-2.65, -2.40	< 0.00001	97	< 0.00001	Fixed Inverse Variance	2	474	Low[ab]
LBP (VAS)	-1.47	-1.58, -1.36	< 0.00001	NA	NA	Fixed Inverse Variance	1	364	Moderate[c]
Functional disability (ODI)	-4.10	-4.55, -3.65	< 0.00001	6	0.30	Fixed Inverse Variance	2	474	Moderate[a]

* Risk of bias.
† Inconsistency.
‡ Imprecision.
LLLT = low-level laser treatment; VAS = visual analog scale; LBP = low back pain; ODI = Oswestry Disability Index; MD = mean difference; CI = confidence interval; NA = not applicable.

assessed as an "unclear risk."

In terms of incomplete outcome data, studies with no missing values, studies where missing values did not affect the outcomes, and studies where the occurrence of missing values was similar between different intervention groups and the reasons for the occurrence of missing values were similarly assessed as "low risk."

In the selective reporting domain, two studies [17,19] that reported AEs were assessed as "low risk," and the other three did not report AEs and were assessed as "unclear risk." In the other bias domain, all five selected studies were considered to have no other bias and were assessed as "low risk."

A schematic summary of the RoB assessments of the five selected studies is presented in Fig. 2.

4. Meta-analysis

4.1. LLLT vs. sham control

The meta-analysis on the VAS for leg pain confirmed a significant difference in outcome with an MD of -1.90 [95% confidence interval (CI): -2.01, -1.80]; however, substantial heterogeneity was identified (I^2 of 80%). As a result of the meta-analysis on the VAS for LBP, a significant difference in outcome was confirmed with an MD of 0.79 (95% CI: -0.87, -0.71); however, substantial heterogeneity was identified (I^2 of 80%). In the meta-analysis on ODI, the MD was -1.83 (95% CI: -3.63, -0.02; Fig. 3).

4.2. LLLT vs. usual care

As a result of the meta-analysis on the VAS for leg pain, no significant difference in outcome was confirmed with an MD of 0.61 (95% CI: -0.35, 1.56). As a result of the meta-analysis on the VAS for LBP, no significant difference in outcome was confirmed with an MD of 0.51 (95% CI: -0.34, 1.36; Fig. 3). There was no significant difference in the outcomes compared with usual care, such as ultrasound, or physical therapies. ODI was reported in only one study with an MD of -1.90 (95% CI: -13.59, 9.79; data not shown).

4.3. LLLT with usual care vs. usual care (add-on)

As a result of the meta-analysis on the VAS for leg pain, a significant difference in the outcome of pain reduction

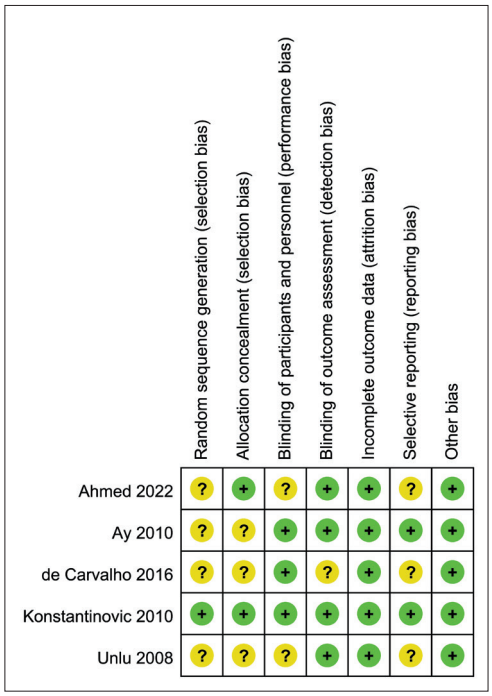

Fig. 2. Summary of risk of bias based on Cochrane risk of bias tool.

was confirmed with an MD of -2.52 (95% CI: -2.65, -2.40). However, considerable heterogeneity was identified (I^2 of 97%). As a result of the meta-analysis on the VAS for LBP, the MD was -1.47 (95% CI: -1.58, -1.36); however, only one study reported on this outcome. Meta-analysis of the ODI showed an MD of-4.10 (95% CI: -4.55, -3.65), confirming a significant difference in the outcome of improvement in functional disability (Fig. 3).

5. Safety

Only two studies reported AEs [17,19]. One study described AEs in two patients, which were cases of worsening pain. Of the two patients, one was from the LLLT group, and the other was from the nimesulide and placebo LLLT group [19]. Ay et al [17] reported no AEs.

6. Quality of evidence

The quality of evidence of the articles included in this meta-analysis was assessed according to GRADE methodology-based outcome indicators. In the comparison between LLLT and placebo (sham), leg pain (VAS) was determined to be "very low" owing to RoB, inconsistency, and imprecision, whereas LBP (VAS) and ODI of the quality of evidence were determined to be "low." In the comparison between LLLT and usual care, the quality of leg pain (VAS), LBP (VAS), and ODI were "low" owing to RoB and imprecision. In the comparison of LLLT with usual care, leg pain (VAS) quality was determined to be "low" owing to RoB

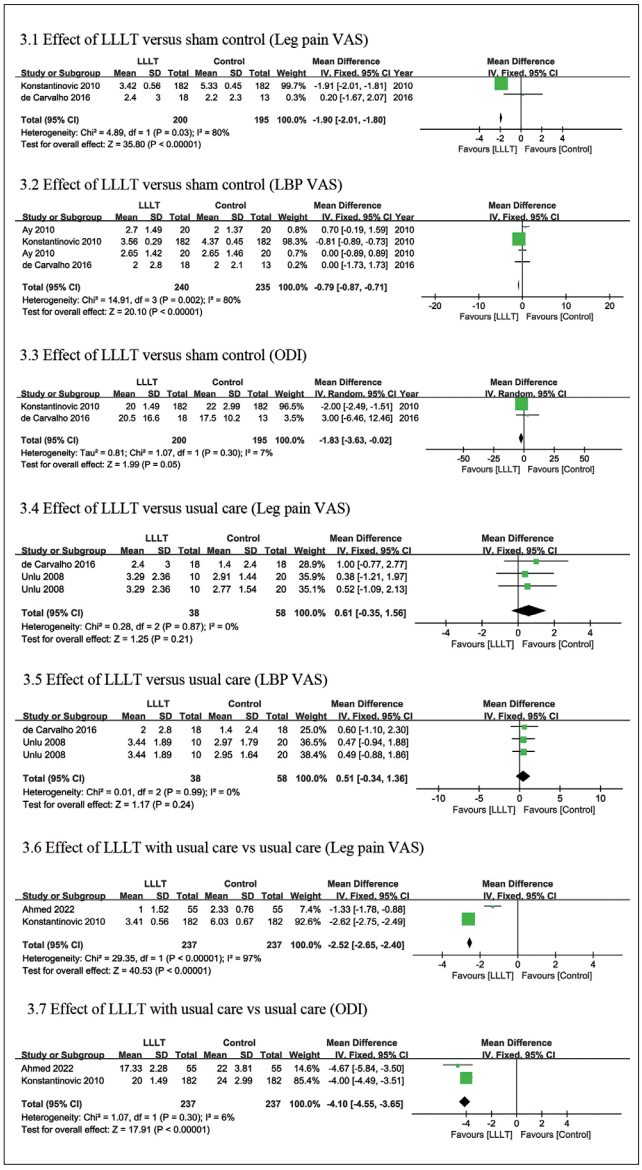

Fig. 3. Meta-analysis of LLLT.
CI = confidence interval; LLLT = low-level laser therapy.

and inconsistencies. The quality of evidence for LBP (VAS) and ODI was determined to be "moderate" owing to RoB and imprecision.

Discussion

Common treatments for LDH include surgery, injection therapy such as epidural steroid injections, and a spectrum of conservative treatments such as medications, and physical therapy [2]. In the case of surgery, as well as the nature of the irreversible treatment, there are risks of complications such as infection and failed back surgery syndrome. Epidural steroid injections are not without risk either, and are associated with a risk of infection or

neurologic complications. Therefore, an increasing number of patients choose or prefer conservative treatments with less risk involved [22-24]. Among previous systematic reviews, there have been studies on LLLT for nonspecific chronic LBP [11,25], but few on LLLT for LDH. Therefore, this review was conducted to assess the effectiveness of LLLT for LDH. Effectiveness of LLLT compared with sham treatment of radiculopathy (radiating leg pain) and LBP caused by LDH was observed (although there was substantial heterogeneity); furthermore, its effectiveness in improving functional disability was determined. Owing to the issues of substantial heterogeneity and imprecision of studies, the quality of evidence ranges from "very low" to "low." However, there was no significant difference in the outcomes compared with usual care, such as ultrasound, or physical therapy such as traction. The analysis revealed a significantly superior improvement in leg pain (although there was substantial heterogeneity) and functional disability when LLLT was applied as an add-on therapy with analgesics or physical therapy, compared with usual care alone. Thus, the findings of this study suggest the possibility of using LLLT as an add-on therapy to conventional conservative treatments.

No significant direct risks have been reported apart from the following cases: risks related to eyes, including periorbital areas, cases of active cancer cells or suspected carcinoma, and treatment for pregnant women [26]. Of the five studies in this review, two studies [17,19] reported AEs one RCT reported continued pain and one RCT reported no AEs. There were 3 RCTs that did not report on whether any AEs occurred.

The strength of the study lies in the fact that this is the first systematic review conducted to assess the efficacy and safety of LLLT for LDH in RCTs reported in published literature. However, this study had several limitations. Firstly, the number of studies included in the analysis was small, and most included studies were small-scale RCTs with small sample sizes. The studies in a meta-analysis are homogeneous (in terms of participants, interventions, and outcomes) if they share a common underlying true effect size; otherwise, they are heterogeneous. Secondly, since the laser treatment protocols differed between different RCTs and four of the five studies were aimed at patients with acute LDH, further studies are required to determine whether LLLT is effective in patients with chronic LDH.

In future studies, additional RCTs designed with more detailed considerations and rigor will be required to accurately assess whether LLLT can be applied as part of the usual care for patients with LDH.

Conclusion

In this systematic review, the effectiveness and safety of LLLT for treating radiologically diagnosed LDH was investigated. LLLT was determined to be more effective than the placebo in alleviating pain and disability in patients with LDH. The outcomes of using LLLT as monotherapy did not significantly differ from that using usual care. In contrast, when LLLT was employed as an add-on therapy with usual care, the studies reported the possibility of significant differences in outcomes. There is limited data regarding safety assessments. As there have been few published studies on the effectiveness and safety of LLLT, we also emphasize the need to establish relevant evidence through well-designed large-scale RCTs in the future.

Supplementary Material

Supplementary material is available at doi https://doi.org/10.56986/pim.2023.10.003.

Author Contributions

Conceptualization: DN. Data curation: SJL and KBP. Funding acquisition: DN. Investigation: SJL, SJN and JRK. Methodology: SJ. Project administration: YH and DN.

Supervision: KBP, YH and DN. Validation: SJ. Visualization: KBP. Writing - original draft: SJL . Writing - review & editing: YH and DN.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Funding

This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health & Welfare, Republic of Korea (grant no.: HF22C0128).

Ethical Statement

No ethical approval was needed for this study.

Data Availability

All relevant data are included in this manuscript.

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Huang et al. Arthritis Research & Therapy (2015) 17:360
DOI 10.1186/s13075-015-0882-0

Arthritis Research & Therapy

RESEARCH ARTICLE Open Access

The effectiveness of low-level laser therapy for nonspecific chronic low back pain: a systematic review and meta-analysis

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Abstract

Background: In recent decades, low-level laser therapy (LLLT) has been widely used to relieve pain caused by different musculoskeletal disorders. Though widely used, its reported therapeutic outcomes are varied and conflicting. Results similarly conflict regarding its usage in patients with nonspecific chronic low back pain (NSCLBP). This study investigated the efficacy of low-level laser therapy (LLLT) for the treatment of NSCLBP by a systematic literature search with meta-analyses on selected studies.

Method: MEDLINE, EMBASE, ISI Web of Science and Cochrane Library were systematically searched from January 2000 to November 2014. Included studies were randomized controlled trials (RCTs) written in English that compared LLLT with placebo treatment in NSCLBP patients. The efficacy effect size was estimated by the weighted mean difference (WMD). Standard random-effects meta-analysis was used, and inconsistency was evaluated by the I-squared index (I^2).

Results: Of 221 studies, seven RCTs (one triple-blind, four double-blind, one single-blind, one not mentioning blinding, totaling 394 patients) met the criteria for inclusion. Based on five studies, the WMD in visual analog scale (VAS) pain outcome score after treatment was significantly lower in the LLLT group compared with placebo (WMD = -13.57 [95 % CI = -17.42, -9.72], I^2 = 0 %). No significant treatment effect was identified for disability scores or spinal range of motion outcomes.

Conclusions: Our findings indicate that LLLT is an effective method for relieving pain in NSCLBP patients. However, there is still a lack of evidence supporting its effect on function.

Keywords: LLLT, Low-level laser therapy, Nonspecific chronic low back pain, NSCLBP, Pain relief

Background

Low back pain (LBP) is one of the most common musculoskeletal disorders [1, 2] and the leading cause of disability worldwide [3]. It affects more than two-thirds of the population during their lifetime and one in four people seek medical help for LBP in a 6-month period [4]. Musculoskeletal disorders account for 6–8 % of total disability-adjusted life years (DALYs) and of this large total, low back pain accounts for nearly half [5]. The majority of the symptoms resolve spontaneously within 1–3 months. However, 3–10 % of patients develop chronic symptoms lasting more than 6 weeks [6]. The underlying etiology of most low back pain is currently unclear. Thus, the one term, nonspecific chronic low back pain (NSCLBP), is used to refer to this condition [7]. Annually, $91 billion in medical expenses are spent for back pain with an additional $50 billion indirect costs incurred due to loss in productivity and disability benefit payments [8, 9].

The main goal of NSCLBP therapy is rarely the complete eradication of pain. Different strategies are currently utilized including surgery and drug therapy,

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exercise therapy, manipulation, acupuncture, electrical treatments, and cognitive-behavioral interventions.

In recent decades, low-level laser therapy (LLLT) has been widely used to relieve pain caused by different musculoskeletal disorders [10, 11]. Though widely used, its reported therapeutic outcomes are varied and conflicting. Results similarly conflict regarding its usage in patients with NSCLBP [12, 13]. There has been a recent increase in the number of RCTs evaluating the effectiveness of LLLT in patients with NSCLBP [12–18]. Therefore, the aim of this study was to examine the totality of evidence to evaluate the effectiveness of LLLT on symptoms and function in patients with NSCLBP through a systematic review and meta-analysis.

Methods

Search strategy and study selection

We conducted a systematic review and meta-analysis, using the approach recommended by the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) guidelines for meta-analyses of interventional studies [19]. The following bibliographic databases were searched up to 20 December 2014: Medline via PubMed from 1990, EMBASE via OVID from 1990, Web of Science from 1990 as well as the Cochrane Central Register of Controlled Trials. The search strategy was as follows: back pain OR low back pain OR backache OR lumbar adjacent pain OR chronic low back pain OR nonspecific chronic low back pain OR NSCLBP AND low-level laser therapy OR low-intensity laser therapy OR low-energy laser therapy OR LLLT OR LILT OR LELT OR infrared laser OR IR laser OR diode laser.

Two reviewers independently identified titles and abstracts relevant to LLLT for patients suffering from NSCLBP. Full texts of the published articles were analyzed and included. The reference list of the full-text articles was also reviewed. To be included in this analysis, studies had to meet the following criteria: (1) be randomized controlled trials; (2) involve patients suffering from NSCLBP; (3) compare LLLT and placebo treatment (no treatment or sham laser); (4) report pain and/or functional outcomes of patients; (5) attain a PEDro score (an 11-point scale, which is the one most often employed for physical treatments) [20] of >5 and (6) be written in English. Trials with an unbalanced additional modality between groups were excluded.

Data extraction

Study data were extracted by two reviewers and checked for accuracy by a third reviewer including the intervention description, inclusion/exclusion criteria, baseline, demographics, and values for all outcomes at baseline and after treatment. The primary outcomes of interest were the visual analog pain (VAS) pain score and disability measured by the Oswestry disability index (ODI) [21] after treatment. The secondary outcomes of interest were change in VAS pain score (defined as the mean difference between treatment arms from baseline to follow-up) and range of motion (ROM). If the data were not presented in the study as mean and standard deviation, or were presented in a form that prevented calculation of mean and standard deviation, the original authors were contacted.

Statistical analysis

All the primary and secondary outcomes were continuous data, permitting means and standard deviations to be used to calculate a weighted mean difference (WMD) and 95 % confidence interval (CI) in the meta-analysis. Data were presented as a forest plot. All results were checked for clinical and statistical heterogeneity. Heterogeneity was evaluated by a test for heterogeneity (I^2 statistic): significant heterogeneity was defined as $I^2 \leq 0.10$; substantial heterogeneity was defined as $I^2 > 50$ %. Data were pooled using a random-effects model. All analyses were conducted using Stata software, version 11.0 (Stata Inc., College Station, TX, USA).

Results

Study selection and characteristics

Figure 1 illustrates the selection process for including studies in the meta-analysis. In total, 221 potential studies were found. Based on the title and abstract content, 202 of these studies were excluded. The full texts of the remaining 19 studies were read, and a further 12 studies were excluded, resulting in seven studies [12–18] retained in the qualitative and quantitative synthesis of this review. A total of 394 patients were included: 202 patients in the LLLT group and 192 patients in the placebo group. Among the total of seven studies, three [16–18] included exercise as an additional treatment method in both study and control groups, while the other four did not. The characteristics of the included studies are listed in Table 1. Six of the seven studies achieved a high-quality PEDro score (≥7) (Table 2). Two otherwise relevant trials were excluded due to PEDro scores < =5. All outcomes with appropriately reported data were extracted and included in the meta-analysis. Outcome measures were grouped according to their construct and design (Table 3).

Meta-analysis

Pain relief

The mean VAS pain score after treatment was lower in the LLLT compared with the placebo group (WMD = -13.57 [95 % CI = -17.42, -9.72], $I^2 = 0$ %). Subgroup analysis showed that exercise as an additional treatment did not change the results (Fig. 2). Three [12, 17, 18] of the

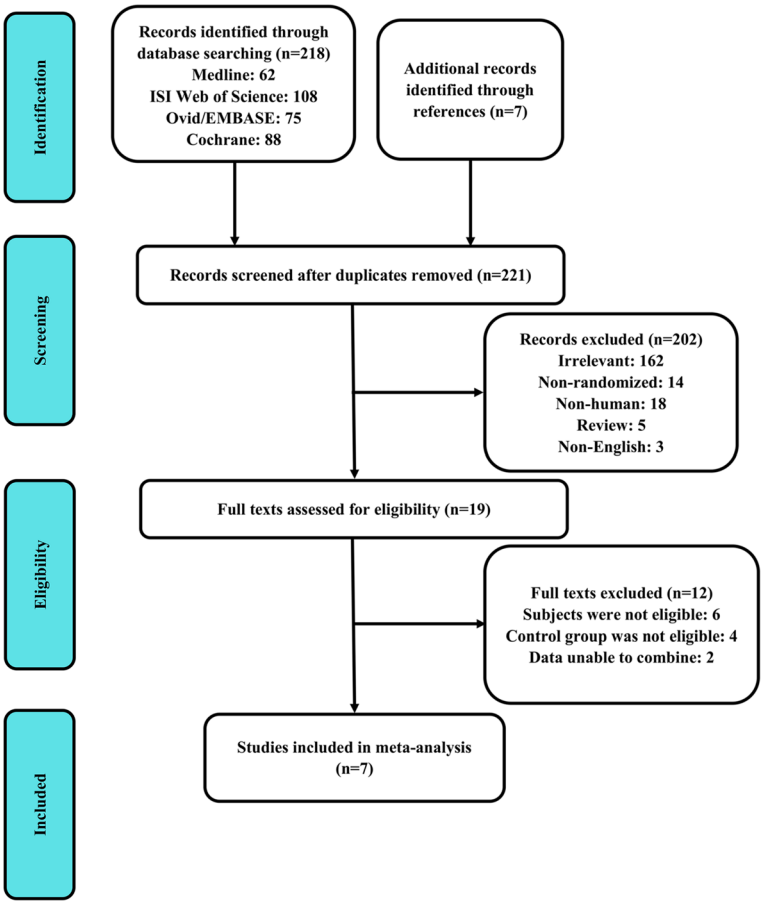

Fig. 1 CONSORT diagram showing screening process and search results for the meta-analysis of LLLT for chronic nonspecific low back pain. *LLLT* low-level laser therapy

included studies provided data on change in short-term VAS pain (follow-up minus baseline). The meta-analysis revealed significantly greater decline in VAS pain in response to LLLT compared with placebo treatment (WMD = -12.00 [95 % CI = -2.02, -21.98] I^2 = 77.6 %) (Table 4).

Disability score

Disability data measured by ODI after treatment were provided by four studies [13, 15–17]. The ODI measures intensity of pain, lifting and activities such as ability to care for oneself, ability to walk, ability to sit, sexual function, ability to stand, social life, sleep quality and ability to travel. The combined results showed no significant difference between LLLT and placebo groups (WMD = -2.89 [95 % CI = -7.88, 2.29], I^2 = 88 %) (Fig. 3).

ROM

Data on ROM after treatment were provided by three studies and included flexion (angle measured in degrees), anterior-posterior flexion (measured in centimeters) and extension (angle measured in degrees). The combined data in terms of these three parameters demonstrated no statistical difference between the treatment groups (Table 4).

Discussion

NSCLBP is defined as pain of the lumbosacral area of the spine lasting more than 12 weeks. NSCLBP is a complex and multifactorial condition that may or may not have the characteristic of limiting the patient's ROM [6]. Though various treatments options have been proposed, the management is still controversial. Most patients with NSCLBP who require medication for pain relief are likely to be middle-aged or older, and are at high risk for both adverse gastrointestinal and cardiovascular side effects [22]. Also the long-term surgical outcomes are no better than medical management [23]. Since first introduced by Mester et al. in 1968 [24], clinical application of LLLT has become more and more popular. Several experimental and clinical studies [25, 26] demonstrated its effectiveness for relief of chronic pain. Thus, many patients seek LLLT because it has no accompanying detrimental effects on systemic cardiovascular health or other adverse effects. Recently, several high-quality RCTs

Table 1 General information on low-level laser therapy (LLLT) included in the meta-analysis

Study	Type of studies	Sample size	Age (SD) years	Gender (M/F)	Dropouts (n)	VAS pain (SD)	Intervention
Klein and Eek 1990 [13]	TB-RCT	Study group ($n = 10$)	44.1 (7.9)	2/8	0	30 (12)	LLLT vs. Placebo
		Control group ($n = 10$)	41.3 (10.7)	3/8	0	33 (11)	
Soriano and Rios 1998 [14]	DB-RCT	Study group ($n = 38$)	63.2	16/22	0	79	LLLT vs. Placebo
		Control group ($n = 33$)	64.33	18/20	0	81	
Basford et al. 1999 [15]	DB-RCT	Study group ($n = 27$)	47.8 (48.0)	18/12	3	35.2 (29.0)	LLLT vs. Placebo
		Control group ($n = 29$)	48.2 (49)	13/16	0	37.4 (36.0)	
Gur et al. 2003 [16]	SB-RCT	Study group ($n = 25$)	35.2 (10.51)	7/18	0	62 (21)	LLLT + Ex vs. Placebo + Ex
		Control group ($n = 25$)	36.4 (9.83)	8/17	0	65 (16)	
Djavid et al. 2007 [17]	DB-RCT	Study group ($n = 19$)	38 (7)	12/7	0	62 (16)	LLLT + Ex vs. Placebo + Ex
		Control group ($n = 18$)	36 (10)	15/3	0	63 (20)	
Vallone et al. 2014 [18]	RCT	Study group ($n = 50$)	68 (24-89)	43/57	0	66.4 (17.7)	LLLT + Ex vs. Placebo + Ex
		Control group ($n = 50$)			0	63.6 (15.2)	
Hsieh et al. 2014 [12]	DB-RCT	Study group ($n = 33$)	60.1 (14.2)	14/19	0	78 (24)	LLLT vs. Placebo
		Control group ($n = 27$)	58.5 (10.6)	8/19	0	79 (17)	

Mean (standard deviation) are provided above for age (years) and VAS pain (*VAS* visual analog scale)
TB-RCT triple blind-randomized controlled trial, *DB-RCT* double-blind randomized controlled trial, *SB-RCT* single-bind randomized controlled trial, *M* male, *F* female, *Ex* exercise

have emerged to assess the effectiveness of LLLT in patients with NSCLBP. We performed the current analysis, including seven RCTs with 394 patients, to gain a better understanding of the overall effect of LLLT for NSCLBP based on the higher-quality studies in a field full of seemingly conflicting results. Overall the analysis suggests that: (1) LLLT can relieve NSCLBP in a manner superior to placebo treatment; (2) LLLT is not superior to placebo treatment with respect to disability or ROM outcomes.

The mechanisms for LLLT-mediated pain relief are not fully understood. Several possible mechanisms are believed to account for the effects of LLLT, such as the following: (a) increased endogenous opioid neurotransmitter production [27]; (b) raised threshold to thermal pain and enhanced local blood circulation [28]; (c) increased oxygen consumption by accelerating the redox reaction rate of the electron respiratory chain of mitochondria [29]; (d) increased adenosine triphosphate (ATP) production at the cellular level [30]; (e) increased production of anti-inflammatory cytokines [12].

Multiple variables affect the clinical therapeutic effects of laser therapy, such as wavelength, energy density, the number of treatment sessions and their duration [31, 32]. Wavelength is also considered an essential parameter for beneficial outcomes of LLLT; it determines the ability of a laser to penetrate tissue. Wavelengths in a range of 700–1000 nm are most often used to treat deep tissues because of their superior penetration [33]. The recommended LLLT wavelengths per World Association of Laser Therapy (WALT) guidelines are 780–860 nm [34] and 904 nm [35] depending upon the condition being treated. Previous studies [36, 37] have also reported better therapeutic effects of LLLT with higher energy density, number of sessions and frequency of application. All the included

Table 2 Summary of methodological quality based on PEDro classification scale

Study	Item											Total
	1	2	3	4	5	6	7	8	9	10	11	
Klein and Eek 1990 [13]	✓	✓	*x*	✓	✓	✓	✓	✓	*x*	✓	✓	9
Soriano and Rios 1998 [14]	✓	✓	*x*	✓	*x*	*x*	*x*	✓	*x*	✓	✓	6
Basford et al. 1999 [15]	✓	✓	*x*	✓	✓	✓	*x*	✓	*x*	✓	✓	8
Gur et al. 2003 [16]	✓	✓	*x*	✓	✓	*x*	*x*	✓	*x*	✓	✓	7
Djavid et al. 2007 [17]	✓	✓	*x*	✓	✓	✓	*x*	✓	*x*	✓	✓	8
Vallone et al. 2014 [18]	✓	✓	✓	✓	*x*	*x*	*x*	✓	*x*	✓	✓	7
Hsieh et al. 2014 [12]	✓	✓	✓	✓	✓	*x*	✓	✓	*x*	✓	✓	9

Items: 1-eligibility criteria specified, 2-random allocation, 3-concealed allocation, 4-groups similar at baseline, 5-subject blinding, 6-therapist blinding, 7-assessor blinding, 8-less than 15 % dropouts, 9-intention-to-treat analysis, 10-between-group statistical comparisons, 11-point measures and variability data; ✓yes, *x* no

Table 3 Technical features of laser use in the studies included for meta-analysis

Study	Laser type	Laser model (Manufacturer)	Treatment time/Number of total sessions/Number of sessions per week	Laser continuous output	Energy density (J/cm^2)	Energy per point (J/point per session)
Klein and Eek 1990 [13]	GaAs 904 nm	Omniprobe	20 m/12/3	20 W	1.3	1.3
Soriano and Rios 1998 [14]	GaAs 904 nm	NA	NA/10/5	40 mW	4	$6*10^{-6}$
Basford et al. 1999 [15]	Nd: YAG 1060 nm	NA	12 m/12/3	542 mW	239.3	48.78
Gur et al. 2003 [16]	GaAs 904 nm	Class IIIb Laser Product	30 m/20/5	4.2 mW	1	1
Djavid et al. 2007 [17]	GaAlAs 810 nm	NA	20 m/12/2	50 mW	27	5.9697
Vallone et al. 2014 [18]	GaAlAs 980 nm	LEONARDO BIO	6 m/9/3	20 W	37.5	1200
Hsieh et al. 2014 [12]	GaAlAs 890 nm	Anodyne	40 m/6/3	780 mW	10.4	NA

NA not available

studies used a wavelength within the recommended range.

It is well recognized that the effects of phototherapy are time-dependent [38]. We also observed this phenomenon as demonstrated in this meta-analysis by significant short-term but not moderate-term benefit. In contrast to pain outcomes, we did not find any significant improvement in disability or ROM due to LLLT. There might be several reasons for this. For one, the cause of NSCLBP is still unclear. Usually it is hard to determine the precise etiology of the pain. Some theories suggest that NSCLBP is linked to a reflex response of the back extensor muscles, resulting in a loss of flexion relaxation of the back muscles and a reduction of spinal flexion with secondary increased tissue strain [39]. LLLT may relieve the pain by increasing oxygen consumption and blood supply to the muscles [40]. With respect to duration, the effect is comparable to other interventions (e.g., antidepressants and traction), which are effective in the short term [41]. A primary effect on muscle may explain why we did not find any significant effect of LLLT on knee osteoarthritis (OA) pain [42], in which the sources of pain are diverse. Moreover, NSCLPB is likely a heterogeneous group of diseases, which have different etiologies but share similar symptoms. Thus, some of them might react well to LLLT while others not. Only two studies provided data on ROM. For this outcome, negative results might relate to inadequate study power that could be overcome with more high-quality investigations with ROM. Finally, like other LBP interventions, effects on pain appear to be stronger than effects on function [43].

Seven years ago, Yousefi-Nooraie et al. [44] conducted a meta-analysis of LLLT for nonspecific low back pain (NLBP); it contained seven studies of both acute and chronic NLBP [13–17, 45, 46]. The authors concluded

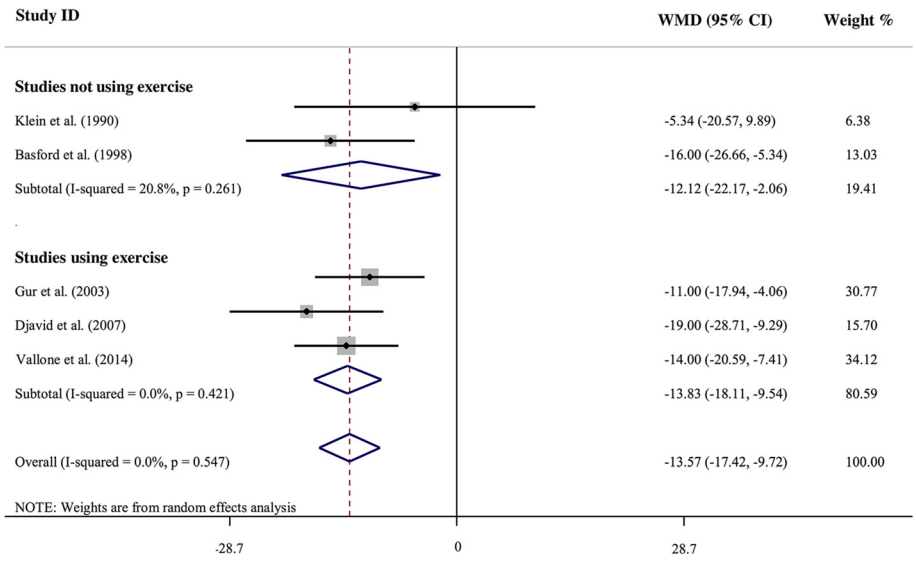

Fig. 2 Forest plot analysis of the VAS pain score after LLLT treatment. *WMD* weighted mean difference, *LLLT* low-level laser therapy, *VAS* visual analog scale; weight % stands for the portion of the total sample contributed by each study

Table 4 Meta-analyses of weighted mean differences in various continuous parameters between the LLLT and placebo groups

Outcome parameters*	Number of patients		Weighted mean difference (95 % CI)	*p* value	I^2
	LLLT group (n)	Placebo group (n)			
Change in VAS pain score after treatment (from baseline to after treatment) [12,17,18]	102	95	-12.00 [-2.02, -21.98]	0.012	77.6 %
Anterior-posterior flexion (degree)[13,17]	29	28	3.20 [-2.54, 8.93]	0.961	0 %
Anterior-posterior flexion (cm)[15,16]	35	35	-.2.84 [-5.44, 0.02]	0.480	0 %
Extension (degree)[13,17]	29	28	0.08 [-2.39, 2.54]	0.973	0 %

LLLT low-level laser therapy, *VAS* visual analog scale
*Study references provided by superscripts

that data were insufficient to confirm the clinical effectiveness of LLLT for NLBP. Our study is more specific, focusing on NCLBP, and is an update on this topic now demonstrating the likelihood of a beneficial effect of LLLT on low back pain. The difference in conclusions can likely be attributed to several strengths of our study. First, we focused on chronic LBP studies. The separation of chronic from acute NLBP is likely to decrease the heterogeneity. Second, the power of the current meta-analysis was substantially increased due to the inclusion of two additional studies corresponding to an appreciable increase in the numbers of subjects (sample size increased two times) over the prior meta-analysis. What is more, two low-quality studies were excluded due to PEDro scores <5 [44, 45]. Even if we included the results of theses two trials, the pooled results were still consistent with results of analyses of the trials of higher quality. Third, this meta-analysis was performed on the basis of the Cochrane Collaboration's principle and designed to be rigorous in its search strategy. Fourth, narrow CIs around the point estimates due to the availability of higher-quality trials resulted in more precise estimates of treatment effects.

Some limitations of the current meta-analysis warrant discussion. First and foremost, we were limited by the outcome reporting of the included studies; for instance, only two studies were available for pooling to evaluate ROM. Second, because of the relatively heterogeneous treatment protocols with respect to laser parameters and laser schedules, high heterogeneity was detected in several outcomes. To overcome this, a random-effects model was chosen. Third, three of the included studies used exercise as an additional treatment in both study and control groups, while the other four did not. This could contribute to high heterogeneity in pooled results. However, the subgroup analysis showed that the use of adjunctive exercise did not affect the results. Fourth, LLLT has been also extensively used and studied in Europe and Russia; by restricting to English language studies, we could have missed some trials. Fifth, due to our relatively small number of trials, we could not assess publication bias using funnel plots or statistical tests for small sample effects.

Conclusions

The results of our systematic review and meta-analysis have provided the best current evidence on LLLT for the treatment of NSCLBP. It suggests that LLLT is an effective method to relieve low back pain in patients who present with NSCLBP. However, there is still a lack of

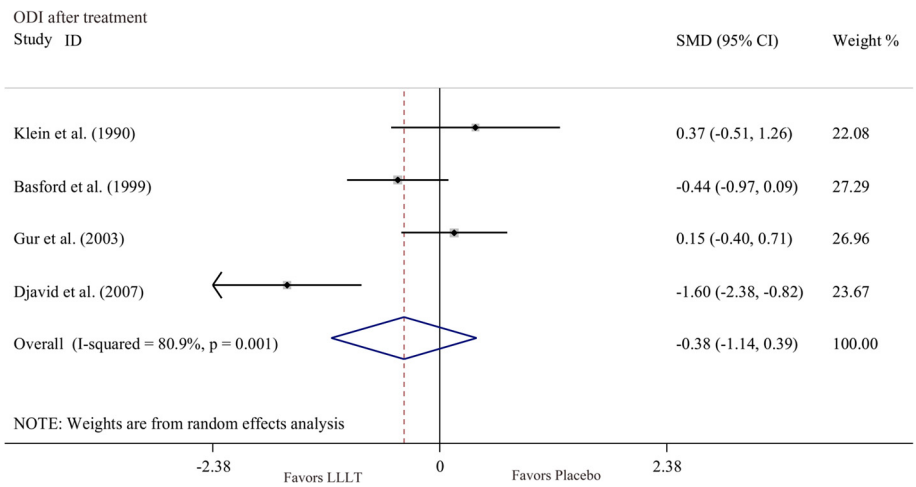

Fig. 3 Forest plot analysis of disability outcomes after LLLT treatment measured by Oswestry disability index (ODI). *LLLT* low-level laser therapy

evidence supporting its effectiveness on functional outcomes. Further research is needed to identify the optimal LLLT parameters for achieving therapeutic efficacy, particularly for functional outcomes, and for understanding its mechanisms of action.

Abbreviations

ATP: Adenosine triphosphate; CI: Confidence interval; DALYs: Disability-adjusted life years; LBP: Low back pain; LLLT: Low-level laser therapy; NLBP: Nonspecific low back pain; NSCLBP: Nonspecific chronic low back pain; OA: Osteoarthritis; ODI: Oswestry disability index; RCTs: Randomized controlled trials; ROM: range of motion; VAS: Visual analog scale; WALT: World Association of Laser Therapy; WMD: Weighted mean difference.

Competing interests

None of the authors have competing interests to disclose. No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this manuscript.

Authors' contributions

ZH, BS, FP and VBK take responsibility for the integrity of the work as a whole. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. ZH, BS, FP and VBK conceived and designed the study. ZH, JM and JC collected and assembled the data. All authors assisted with analysis and interpretation of the data. ZH and VBK drafted the manuscript. All authors assisted with manuscript revisions and read and approved the final manuscript.

Acknowledgments

We wish to acknowledge funding in support of ZH by the China Health Ministry Program (201302007). We also wish to acknowledge support of VBK by the National Institutes of Health National Institute on Aging Older American Independence Centers (NIH/NIA OAIC) P30-AG-028716. This research was funded by the China Health Ministry Program (201302007). We recognize the support of the China Scholarship Council (CSC). These organizations had no involvement in the study design, collection, analysis or interpretation of data, in the writing of the manuscript, or in the decision to submit the manuscript for publication.

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Received: 19 May 2015 Accepted: 30 November 2015
Published online: 15 December 2015

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Efficacy of low-level laser therapy on pain and disability in knee osteoarthritis: systematic review and meta-analysis of randomised placebo-controlled trials

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To cite: Stausholm MB, Naterstad IF, Joensen J, *et al*. Efficacy of low-level laser therapy on pain and disability in knee osteoarthritis: systematic review and meta-analysis of randomised placebo-controlled trials. *BMJ Open* 2019;**9**:e031142. doi:10.1136/bmjopen-2019-031142

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2019-031142).

Received 18 April 2019
Revised 11 September 2019
Accepted 17 September 2019

Check for updates

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ABSTRACT

Objectives Low-level laser therapy (LLLT) is not recommended in major knee osteoarthritis (KOA) treatment guidelines. We investigated whether a LLLT dose–response relationship exists in KOA.

Design Systematic review and meta-analysis.

Data sources Eligible articles were identified through PubMed, Embase, Cumulative Index to Nursing and Allied Health Literature, Physiotherapy Evidence Database and Cochrane Central Register of Controlled Trials on 18 February 2019, reference lists, a book, citations and experts in the field.

Eligibility criteria for selecting studies We solely included randomised placebo-controlled trials involving participants with KOA according to the American College of Rheumatology and/or Kellgren/Lawrence criteria, in which LLLT was applied to participants' knee(s). There were no language restrictions.

Data extraction and synthesis The included trials were synthesised with random effects meta-analyses and subgrouped by dose using the World Association for Laser Therapy treatment recommendations. Cochrane's risk-of-bias tool was used.

Results 22 trials (n=1063) were meta-analysed. Risk of bias was insignificant. Overall, pain was significantly reduced by LLLT compared with placebo at the end of therapy (14.23 mm Visual Analogue Scale (VAS; 95% CI 7.31 to 21.14)) and during follow-ups 1–12 weeks later (15.92 mm VAS (95% CI 6.47 to 25.37)). The subgroup analysis revealed that pain was significantly reduced by the recommended LLLT doses compared with placebo at the end of therapy (18.71 mm (95% CI 9.42 to 27.99)) and during follow-ups 2–12 weeks after the end of therapy (23.23 mm VAS (95% CI 10.60 to 35.86)). The pain reduction from the recommended LLLT doses peaked during follow-ups 2–4 weeks after the end of therapy (31.87 mm VAS significantly beyond placebo (95% CI 18.18 to 45.56)). Disability was also statistically significantly reduced by LLLT. No adverse events were reported.

Conclusion LLLT reduces pain and disability in KOA at 4–8 J with 785–860 nm wavelength and at 1–3 J with 904 nm wavelength per treatment spot.

PROSPERO registration number CRD42016035587.

Strengths and limitations of this study

- ► The review was conducted in conformance with a detailed a priori published protocol, which included, for example, laser dose subgroup criteria.
- ► No language restrictions were applied; four (18%) of the included trials were reported in non-English language.
- ► A series of meta-analyses were conducted to estimate the effect of low-level laser therapy on pain over time.
- ► Three persons each independently extracted the outcome data from the included trial articles to ensure high reproducibility of the meta-analyses.
- ► The review lacks quality-of-life analyses, a detailed disability time-effect analysis and direct comparisons between low-level laser therapy and other interventions.

INTRODUCTION

Approximately 13% of women and 10% of men in the population aged ≥60 years suffer from knee osteoarthritis (KOA) in the USA.[1] KOA is a degenerative inflammatory disease affecting the entire joint and is characterised by progressive loss of cartilage and associated with pain, disability and reduced quality of life (QoL).[1] Increased inflammatory activity is associated with higher pain intensity and more rapid KOA disease progression.[1 2]

Some of the conservative intervention options for KOA are exercise therapy, non-steroidal anti-inflammatory drugs (NSAIDs) and anti-inflammatory low-level laser therapy (LLLT). There is evidence that exercise therapy reduces pain and disability and improves QoL in persons with KOA.[3 4] NSAIDs are recommended in most KOA clinical treatment guidelines and is probably the most frequently prescribed therapy category for osteoarthritis, despite intake of these

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drugs is associated with negative side effects,[5] which is problematic, especially since the disease requires long-term treatment. Furthermore, a recently published network meta-analysis indicates that the pain relieving effect of NSAIDs in KOA beyond placebo is small to moderate (depending on drug type).[6] Likewise, in the first systematic review on this topic, the pain relieving effect of NSAIDs was estimated to be only 10.1 mm on the 0–100 mm Visual Analogue Scale (VAS) better than placebo.[7]

LLLT is a non-invasive treatment modality,[8 9] which has been reported to induce anti-inflammatory effects.[9–14] LLLT was compared with NSAID in rats with KOA by Tomazoni *et al* in a laboratory; NSAID (10 mg diclofenac/knee/session) and LLLT (830 nm wavelength, 6 J/knee/session) reduced similar levels of inflammatory cells and metalloproteinase (MP-3 and MP-13). In addition, LLLT reduced the expression of proinflammatory cytokines (interleukin-1β (IL-1β) and IL-6 and tumour necrosis factor α), myeloperoxidase and prostaglandin E_2 significantly more than NSAID did.[10 11]

LLLT has been applied to rabbits with KOA three times per week for 8 weeks in a placebo-controlled experiment by Wang *et al*.[12] At the end of treatment week 6, they found that LLLT had significantly reduced pain and synovitis and the production of IL-1β, inducible nitric oxide synthase and MP-3 and slowed down loss of metallopeptidase inhibitor 1. Two weeks later, LLLT had significantly reduced MP-1 and MP-13 and slowed down loss of collagen II, aggrecan and transforming growth factor beta, and the previous changes were sustained.[12] These findings indicate that the effects of LLLT increase over time.

Pallotta *et al*[14] conducted a study on LLLT in rats with acute knee inflammation, which demonstrated that even though LLLT (810 nm) significantly enhanced cyclooxygenase (COX-1 and COX-2) expression it significantly reduced several other inflammatory makers, that is, leucocyte infiltration, myeloperoxidase, IL-1 and IL-6 and especially prostaglandin E_2. Pallotta *et al*[14] hypothesised that the increase in COX levels by LLLT was involved in a production of inflammatory mediators related to the resolution of the inflammatory process.

LLLT is not recommended in major osteoarthritis treatment guidelines. LLLT for KOA was mentioned in the European League Against Rheumatism osteoarthritis guidelines (2018) but not recommended,[15] and in the Osteoarthritis Research Society International guidelines (2018), it was stressed that LLLT should not be considered a core intervention in the management of KOA.[16]

This may be partly due to conflicting results of two recently published systematic reviews on the current topic.[8 17] The conflicting results may arise from omission of relevant trials[8 17–23] and unresolved LLLT dose-related issues. Only Huang *et al*[17] conducted a LLLT dose–response relationship investigation in KOA, that is, by subgrouping the trials by laser dose, but they did not consider that World Association for Laser Therapy (WALT) recommends applying four times the laser dose with continuous irradiation compared to superpulsed irradiation.[22 24–26] Thus, it was unknown whether LLLT is effective in KOA, and we saw a need for a new systematic review.

The objectives of the current review were to estimate the effectiveness of LLLT in KOA regarding knee pain, disability and QoL, and we only considered placebo-controlled randomised clinical trials (RCTs) for inclusion to minimise risk of bias.

METHODS

This review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement 2009.[27]

Literature search and selection of studies

Any identified study was included if it was a placebo-controlled RCT involving participants with KOA according to the American College of Rheumatology tool and/or a radiographic inspection with the Kellgren/Lawrence (K/L) criteria, in which LLLT was applied to participants' knee(s) and self-reported pain, disability and/or QoL was reported. There were no language restrictions.

We updated a search for eligible articles indexed in PubMed, Embase, Cumulative Index to Nursing and Allied Health Literature, Physiotherapy Evidence Database and Cochrane Central Register of Controlled Trials on 18 February 2019. The database search strings contained synonyms for LLLT and KOA, and keywords were added when optional. The PubMed search string is available in the online supplementary material. The search was continued by reading reference lists of all the eligible trial and relevant review articles,[8 17 28] citations[29–33] and a laser book[34] and involving experts in the field.

Two reviewers (MBS and JMB) each independently selected the trial articles. Both reviewers scrutinised the titles/abstracts of all the publications identified in the search, and any accessible full-text article was retrieved if it was judged potential eligible by at least one reviewer. Both reviewers evaluated the full texts of all potentially eligible retrieved articles and made an independent decision to include or exclude each article, with close attention to the inclusion criteria. When selection disagreements could not be resolved by discussion, a third reviewer (IFN) made the final consensus-based decision. Any retrieved article not fulfilling the inclusion criteria was omitted and listed with reason for exclusion.

Risk-of-bias analysis

Two reviewers (MBS and JJ) each independently evaluated all included trials for risk of bias at the outcome level, using the Cochrane Collaboration's risk-of-bias tool.[35] When risk-of-bias disagreements could not be resolved by discussion, a third reviewer (IFN) made the final consensus-based decision. Likelihood of publication bias was assessed with graphical funnel plots.[35]

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Data extraction and meta-analysis

Three reviewers (MBS, JMB and KVF) each independently extracted the data for meta-analysis. Two of the reviewers (MBS and KVF) each independently collected the other trial characteristics. The data-extraction forms were subsequently compared, and data disagreements were resolved by consensus-based discussions. Summary data were extracted, unless published individual participant data were available.[21] The results from the included trials for statistical analysis were selected from outcome scales in adherence to hierarchies published by Juhl *et al*.[36]

Pain intensity was the primary outcome. As pain reported with continuous, numeric and categorical/Likert scales highly correlates with pain measured using the VAS, the scores of all pain scales were transformed to 0%–100%, corresponding to 0–100 mm VAS.[37] The pain results were combined with the mean difference (MD) method, primarily using change scores, that is, when only final scores could be obtained from a trial, change and final scores were mixed in the analysis, since the MD method allows for this without introducing bias.[35]

Self-reported disability results were synthesised with the standardised mean difference (SMD) method using change scores solely. The SMD was adjusted to Hedges' *g* and interpreted as follows: SMDs of 0.2, ~0.5 and >0.8 represent a small, moderate and large effect, respectively.[35]

Lack of QoL data prohibited an analysis of this outcome.

Random effects meta-analyses were conducted, and impact from heterogeneity (inconsistency) on the analyses was examined using I^2 statistics. An I^2 value of 0% indicates no inconsistency, and an I^2 value of 100% indicates maximal inconsistency[35]; the values were categorised as low (25%), moderate (50%) and high (75%).[38]

SDs for analysis were extracted or estimated from other variance data in a prespecified prioritised order: (1) SD, (2) SE, (3) 95% CI, (4) p value, (5) IQR, (6) median of correlations, (7) visually from graph or (8) other methods.[35]

The trials were subgrouped by adherence and non-adherence to the WALT recommendations for laser dose per treatment spot, as prespecified. WALT recommends irradiating the knee joint line/synovia with the following doses per treatment spot: ≥4 J using 5–500 mW mean power 780–860 nm wavelength laser and/or ≥1 J using 5–500 mW mean power (>1000 mW peak power) 904 nm wavelength laser.[24 25]

The main meta-analyses were conducted using two prespecified time points of assessment, that is, immediately after the end of LLLT and last time point of assessment 1–12 weeks after the end of LLLT (follow-up).

MBS performed the meta-analyses, under supervision of JMB, using the software programme Excel 2016 (Microsoft) and Review Manager Version V.5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

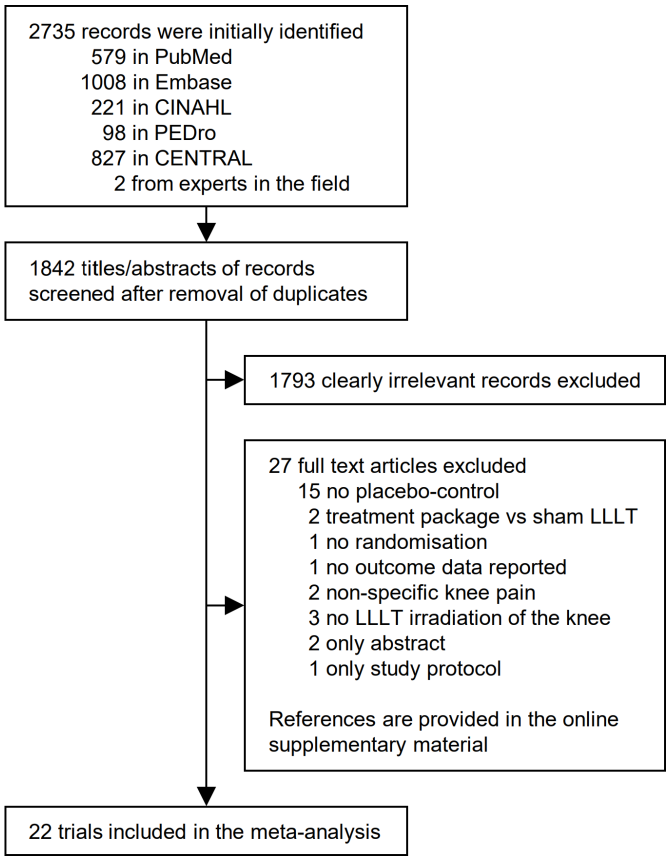

Figure 1 Flow chart illustrating the trial identification process. CENTRAL, Cochrane Central Register of Controlled Trials; CINAHL, Cumulative Index to Nursing and Allied Health Literature; LLLT, low-level laser therapy; PEDro, Physiotherapy Evidence Database.

Patient and public involvement

Patients or the public were not involved in the conceptualisation or carrying out of this research.

RESULTS

In total, 2735 records were identified in the search, of which 22 trial articles were judged eligible and included in the review (n=1089; figure 1 and tables 1–2) with data for meta-analysis (n=1063). Four included trials were not reported in the English language[19 21 23 39] and one included trial was unpublished (Gur and Oktayoglu). Excluded articles initially judged potentially eligible were listed with reasons for omission (online supplementary material).

At the group level, the mean age of the participants was 60.25 (50.11–69) years (data from 19 trials), the mean percentage of women was 69.63% (0–100%; data from 17 trials), the mean body mass index of the participants was 29.55 (25.8–38; data from 14 trials), the mean of median K/L grades was 2.37 (data from 13 trials) and the mean baseline pain was 63.61 mm VAS (35.25–92) (data from 22 trials). LLLT was used as an adjunct to exercise therapy in 11 trials. The mean duration of the treatment periods was 3.53 weeks with the recommended LLLT doses and 3.7

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Table 1 Characteristics of the included trials

First author	Intervention group at baseline	Control group at baseline	Intervention versus control programme	Outcome scales, week of reassessment
Al Rashoud 2014[31]	N: 26 Women: 62% Age: 52 years BMI: 38 VAS pain: 64 mm K/L: -	N: 23 Women: 65% Age: 56 years BMI: 37.1 VAS pain: 59 mm K/L: -	3 weeks of exercise therapy, advice and LLLT versus 3 weeks of exercise therapy, advice and sham LLLT	Pain: VAS (movement) Disability: SKFS QoL: – Week of assessment: 2, **3**, **9**, 29
Alfredo 2011/2018[29 52]	N: 24 Women: 75% Age: 61.15 years BMI: 30.16 VAS pain: 53.2 mm K/L: 3	N: 22 Women: 80% Age: 62.25 years BMI: 29.21 VAS pain: 35.4 mm K/L: 2	3 weeks of LLLT followed by 8 weeks of exercise therapy versus 3 weeks of sham LLLT followed by 8 weeks of exercise therapy	Pain: WOMAC Disability: WOMAC QoL: – Week of assessment: **3**, **11**, 24, 37
Alghadir 2014[32]	N: 20 Women: 50% Age: 55.2 years BMI: 32.34 VAS pain: 74.5 mm K/L: 2	N: 20 Women: 40% Age: 57 years BMI: 33.09 VAS pain: 75.5 mm K/L: 2	4 weeks of exercise therapy, heat packs and LLLT versus 4 weeks of exercise therapy, heat packs and sham LLLT	Pain: WOMAC Disability: WOMAC QoL: – Week of assessment: **4**
Bagheri 2011[23]	N: 18 Women: 83.13% Age: 58.32 years BMI: 28.87 VAS pain: 67 mm K/L: –	N: 18 Women: 83.13% Age: 56.14 years BMI: 27.66 VAS pain: 59 mm K/L: –	2 weeks of exercise therapy, therapeutic ultrasound, TENS and LLLT versus 2 weeks of exercise therapy, therapeutic ultrasound, TENS and sham LLLT	Pain: WOMAC (VAS) 0–100 Disability: WOMAC QoL: – Week of assessment: **2**
Bülow 1994[20]	N: 14 Women: – Age: – BMI: – VAS pain: 65.08 mm K/L: –	N: 15 Women: – Age: – BMI: – VAS pain: 56.35 mm K/L: –	3 weeks of LLLT versus 3 weeks of sham LLLT	Pain: 0–121 Likert scale (movement/rest) Disability: – QoL: – Week of assessment: **3**, **6**
Delkhosh 2018[39]	N: 15 Women: 100% Age: 55.9 years BMI: 26.5 VAS pain: 57 mm K/L: –	N: 15 Women: 100% Age: 58.3 years BMI: 27.8 VAS pain: 45 mm K/L: –	2 weeks of exercise therapy, therapeutic ultrasound, TENS and LLLT versus 2 weeks of exercise therapy, therapeutic ultrasound, TENS and sham LLLT	Pain: VAS Disability: WOMAC QoL: – Week of assessment: **2**, **8**
Fukuda 2011[30]	N: 25 Women: 80% Age: 63 years BMI: 30 VAS pain: 61 mm K/L: 2	N: 22 Women: 64% Age: 63 years BMI: 30 VAS pain: 62 mm K/L: 2	3 weeks of LLLT versus 3 weeks of sham LLLT	Pain: VNSP (movement) Disability: Lequesne QoL: – Week of assessment: **3**
Gur 2003[33] (1.5 J)	N: 30 Women: 83.3% Age: 58.64 years BMI: 31.17 VAS pain: 73.2 mm K/L: 2	N: 30 Women: 80% Age: 60.52 years BMI: 30.27 VAS pain: 67.4 mm K/L: 2	14 weeks of exercise therapy and 2 weeks of LLLT versus 14 weeks of exercise therapy and 2 weeks of sham LLLT	Pain: VAS (movement) Disability: – QoL: – Week of assessment: 6, 10, **14**
Gur 2003[33] (1 J)	N: 30 Women: 76.7% Age: 59.8 years BMI: 28.49 VAS pain: 74.4 mm K/L: 2	N: 30 Women: 80% Age: 60.52 years BMI: 30.27 VAS pain: 67.4 mm K/L: 2	14 weeks of exercise therapy and 2 weeks of LLLT versus 14 weeks of exercise therapy and 2 weeks of sham LLLT	Pain: VAS (movement) Disability: – QoL: – Week of assessment: 6, 10, **14**
Gur and Oktayoglu	N: 40 Women: 75% Age: 58.2 years BMI: 29.11 VAS pain: 88 mm K/L: 3	N: 40 Women: 72.5% Age: 58.26 years BMI: 30.11 VAS pain: 92 mm K/L: 3	14 weeks of exercise therapy and 2 weeks of LLLT versus 14 weeks of exercise therapy and 2 weeks of sham LLLT	Pain: VAS (movement) Disability: – QoL: – Week of assessment: 6, 10, **14**

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Table 1 Continued

First author	Intervention group at baseline	Control group at baseline	Intervention versus control programme	Outcome scales, week of reassessment
Gworys 2012[18]	N: 34 Women: – Age: 57.6 BMI: – VAS pain: 54 mm K/L: –	N: 31 Women: – Age: 67.7 BMI: – VAS pain: – K/L: –	2 weeks of LLLT versus 2 weeks of sham LLLT	Pain: VAS Disability: Lequesne QoL: – Week of assessment: **2**
Hegedűs 2009[53]	N: 18 Women: – Age: – BMI: – VAS pain: 57.5 mm K/L: 2	N: 17 Women: – Age: – BMI: – VAS pain: 56.2 mm K/L: 2	4 weeks of LLLT versus 4 weeks of sham LLLT	Pain: VAS Disability: – QoL: – Week of assessment: **4**, 6, **12**
Helianthi 2016[54]	N: 30 Women: 60% Age: 69 years BMI: 25.8 VAS pain: 60.2 mm K/L: 3	N: 29 Women: 82.8% Age: 68 years BMI: 26.3 VAS pain: 54.1 mm K/L: 3	5 weeks of LLLT versus 5 weeks of sham LLLT	Pain: VAS (movement) Disability: Lequesne QoL: – Week of assessment: 2, **5**, **7**
Hinman 2014[41]	N: 71 Women: 39% Age: 63.4 years BMI: 30.7 VAS pain: 41.5 mm K/L: –	N: 70 Women: 56% Age: 63.8 years BMI: 28.8 VAS pain: 43 mm K/L: –	12 weeks of LLLT versus 12 weeks of sham LLLT	Pain: WOMAC Disability: WOMAC QoL: AQoL-6D Week of assessment: **12**, 52
Jensen 1987[21]	N: 13 Women: – Age: – BMI: – VAS pain: 67 mm K/L: –	N: 16 Women: – Age: – BMI: – VAS pain: 72.6 mm K/L: –	1 week of LLLT versus 1 week of sham LLLT	Pain: 0–21 (movement) Disability: – QoL: – Week of assessment: **1**
Kheshie 2014[47]	N: 18 Women: 0% Age: 56.56 years BMI: 28.62 VAS pain: 76.8 mm K/L: 2.5	N: 15 Women: 0% Age: 55.6 years BMI: 28.51 VAS pain: 78.7 mm K/L: 2.5	6 weeks of exercise therapy and LLLT versus 6 weeks of exercise therapy and sham LLLT	Pain: WOMAC Disability: WOMAC QoL: – Week of assessment: **6**
Koutenaei 2017[55]	N: 20 Women: 85% Age: 52.3 years BMI: 28.4 VAS pain: 74 mm K/L: 3	N: 20 Women: 80% Age: 53 years BMI: 28.6 VAS pain: 65.5 mm K/L: 3	2 weeks of exercise therapy and LLLT versus 2 weeks of exercise therapy and sham LLLT	Pain: VAS (movement) Disability: – QoL: – Week of assessment: **2**, **4**
Mohammed 2018[56]	N: 20 Women: 85% Age: 55.25 years BMI:≥25 VAS pain: 70 mm K/L: 2	N: 20 Women: 85% Age: 50.11 years BMI:≥25 VAS pain: 80 mm K/L: 2	4 weeks of LLLT versus 4 weeks of sham LLLT	Pain: VAS Disability: – QoL: – Week of assessment: **4**
Nambi 2016[48]	N: 17 Women: – Age: 58 BMI: 26.9 VAS pain: 78 mm K/L: 3.1	N: 17 Women: – Age: 60 BMI: 28.3 VAS pain: 76 mm K/L: 3.2	4 weeks of exercise therapy, kinesio tape and LLLT versus 4 weeks of exercise therapy, kinesio tape and sham LLLT	Pain: VAS Disability: – QoL: – Week of assessment: **4**, **8**
Nivbrant 1992[19]	N: 15 Women: 69.2% Age: 69 years BMI: – VAS pain: 67 mm K/L: –	N: 15 Women: 84.6% Age: 66 years BMI: – VAS pain: 58 mm K/L: –	2 weeks of LLLT versus 2 weeks of sham LLLT	Pain: VAS (movement) Disability: Walking disability QoL: – Week of assessment: **2**, 3, **6**

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Table 1 Continued

First author	Intervention group at baseline	Control group at baseline	Intervention versus control programme	Outcome scales, week of reassessment
Rayegani 2012[43]	N: 12 Women: 83.3% Age: 61.7 years BMI: – VAS pain: 63 mm K/L:<4	N: 13 Women: 92.3% Age: 61.2 years BMI: – VAS pain: 52 mm K/L:<4	2 weeks of LLLT versus 2 weeks of sham LLLT	Pain: WOMAC Disability: WOMAC QoL: – Week of assessment: 6, **14**
Tascioglu 2004[40] (3 J)	N: 20 Women: 70% Age: 62.86 years BMI: 27.56 VAS pain: 68 mm K/L: 2	N: 20 Women: 65% Age: 64.27 years BMI: 29.56 VAS pain: 63.88 mm K/L: 2	2 weeks of LLLT versus 2 weeks of sham LLLT	Pain: WOMAC Disability: WOMAC QoL: – Week of assessment: **3**, 26
Tascioglu 2004[40] (1.5 J)	N: 20 Women: 75% Age: 59.92 years BMI: 28.63 VAS pain: 65.72 mm K/L: 2.5	N: 20 Women: 65% Age: 64.27 years BMI: 29.56 VAS pain: 63.88 mm K/L: 2	2 weeks of LLLT versus 2 weeks of sham LLLT	Pain: WOMAC Disability: WOMAC QoL: – Week of assessment: **3**, 26
Youssef 2016[42] (904 nm)	N: 18 Women: 66.7% Age: 67.5 BMI:<40 VAS pain: 51.67 mm K/L: 2	N: 15 Women: 66.7% Age: 66.3 years BMI:<40 VAS pain: 50 mm K/L: 2	8 weeks of exercise therapy and LLLT versus 8 weeks of exercise therapy and sham LLLT	Pain: WOMAC Disability: WOMAC QoL: – Week of assessment: **8**
Youssef 2016[42] (880 nm)	N: 18 Women: 61.1% Age: 67.3 BMI: <40 VAS pain: 52.50 mm K/L: 2	N: 15 Women: 66.7% Age: 66.3 years BMI: <40 VAS pain: 50 mm K/L: 2	8 weeks of exercise therapy and LLLT versus 8 weeks of exercise therapy and sham LLLT	Pain: WOMAC Disability: WOMAC QoL: – Week of assessment: **8**

The values for age and body mass index (BMI) are means and the values for K/L grade are medians. Baseline Visual Analogue Scale (VAS) scores have been extracted or estimated as described in the Method section. Week of assessment in bold denotes time point used for the main meta-analyses.
AQoL-6D, Assessment of Quality of Life 6 Dimensions; DIQ, Disability Index Questionnaire; K/L, Kellgren/Lawrence; LLLT, low-level laser therapy; NRS, Numeric Rating Scale; QoL, quality of life; SKFS, Saudi Knee Function Scale; TENS, Transcutaneous Electrical Nerve Stimulation; VNPS, Visual Numerical Pain Scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

weeks with the non-recommended LLLT doses (tables 1 and 2). Non-recommended LLLT doses were applied in nine of the trials. That is, Al Rashoud *et al*,[31] Bülow *et al*,[20] Tascioglu *et al*[40] and Bagheri *et al*[23] applied too few (<4) Joules per treatment spot with 830 nm wavelength, Jensen *et al*,[21] Nivbrant *et al*[19] and Hinman *et al*[41] applied too few (<1) Joules per treatment spot with 904 nm wavelength and Youssef *et al*[42] (one group) and Rayegani *et al*[43] used continuous laser with too long of a wavelength (880 nm; table 2). No adverse event was reported by any of the trial authors. None of the trial authors stated receiving funding from the laser industry (online supplementary material).

Overall, pain was significantly reduced by LLLT compared with the placebo control at the end of therapy (14.23 mm VAS (95% CI 7.31 to 21.14); I^2=93%; n=816; figure 2) and during follow-ups 1–12 weeks later (15.92 mm VAS (95% CI 6.47 to 25.37); I^2=93%; n=581; figure 3). The dose subgroup analyses demonstrated that pain was significantly reduced by the recommended LLLT doses compared with placebo at the end of therapy (18.71 mm (95% CI 9.42 to 27.99); I^2=95%; n=480; figure 2) and during follow-ups 2–12 weeks later (23.23 mm VAS (95% CI 10.60 to 35.86); I^2=95%; n=392; figure 3). The dose subgroup analyses demonstrated that pain was significantly reduced by the non-recommended LLLT doses compared with placebo at the end of therapy (6.34 mm VAS (95% CI 1.26 to 11.41); I^2=44%; n=336; figure 2), but the difference during follow-ups 1–12 weeks later was not significant (6.20 mm VAS (95% CI −0.65 to 13.05); I^2=38%; n=189; figure 3). The between-subgroup differences (recommended versus non-recommended doses) in pain results were significantly in favour of the recommended LLLT doses regarding both time points (p=0.02 and 0.02; figures 2 and 3).

Overall, disability was significantly reduced by LLLT compared with placebo at the end of therapy (SMD=0.59 (95% CI 0.33 to 0.86); I^2=57%; n=617; figure 4) and during follow-ups 1–12 weeks later (SMD=0.66 (95% CI 0.23 to 1.09); I^2=67%; n=289; figure 5). The dose subgroup analyses demonstrated that disability was significantly reduced by the recommended LLLT doses compared with placebo

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Table 2 Laser therapy characteristics of the included trials

First author	Treated area	Wavelength (nm)	Joules per treatment spot	Mean output power (mW)	Seconds per treated spot	Number of spots treated	Sessions/sessions per week
Al Rashoud 2014[31]*	Knee joint line (medial and lateral) and acupoints (SP9, SP10, ST36)	830	1.2	30	40	5	9/3
Alfredo 2011, 2018[29 52]	Knee joint line (medial and lateral)	904	3	60	50	9	9/3
Alghadir 2014[32]	Knee condyles, joint line (medial and lateral) and popliteal fossa	850	6	100	60	8	8/2
Bagheri 2011[23]*	Knee joint line	830	3	30	100	10	10/5
Bülow 1994[20]*	Painful spots in 0–10 cm radius of the knee joint line	830	1.5–4.5	25	60–180	5–15	9/3
Delkhosh 2018[39]	Knee joint	830	5	30	167	5	10/5
Fukuda 2011[30]	Front knee capsule	904	3	60	50	9	9/3
Gur 2003[33] (1.5 J)	Anterolateral and anteromedial portal of the knee	904	1.5	10	150	2	10/5
Gur 2003[33] (1 J)	Anterolateral and anteromedial portal of the knee	904	1	11.2	90	2	10/5
Gur and Oktayoglu	Anterolateral and anteromedial portal of the knee	904	1.5	10	150	2	10/5
Gworys 2012[18]	Knee joint line, patellofemoral joint and popliteal fossa	810	8	400	20	12	10/5
Hegedüs 2009[53]	Knee joint line, popliteal fossa and condyles	830	6	50	120	8	8/2
Helianthi 2016[54]	Knee joint line (lateral) and acupoints (ST36, SP9, GB34, EX-LE-4)	785	4	50	80	5	10/2
Hinman 2014[41]*	Acupoints (locations not stated)	904	0.2	10	20	6	8-12/0.67–1
Jensen 1987[21]*	Knee joint line (medial and lateral), apex and basis of patellae	904	0.054	0.3	180	4	5/5
Kheshie 2014[47]†	Front knee	830	–	160	–	–	12/2
Koutenaei 2017[55]	Front knee, popliteal fossa and femur condyles in the popliteal cavity	810	7	100	70	8	10/5
Mohammed 2018[56]	Knee joint line (lateral) and acupoints (ST36, Sp10, GB, ashi)	808	5.4	90	60	7	12/3
Nambi 2016[48]	Knee joint line, condyles and popliteal fossa	904	1.5	25	60	8	12/3
Nivbrant 1992[19]*	Knee joint line (medial and lateral) and acupoints (ST34, SP10, X32)	904	0.72	4	180	7	6/3
Rayegani 2012[43]*	Knee joint line and popliteal fossa	880	6	50	120	8	10/5
Tascioglu 2004[40] (3 J)*	Painful spots on the knee	830	3	50	60	5	10/5
Tascioglu 2004[40] (1.5 J)*	Painful spots on the knee	830	1.5	50	30	5	10/5
Youssef 2016[42] (904 nm)	Knee joint line (medial and lateral)	904	3	60	50	9	16/2
Youssef 2016[42] (880 nm)*	Knee joint line (medial and lateral), epicondyles and popliteal fossa	880	6	50	120	8	16/2

*Non-recommended low-level laser therapy dose.
†1250 Joules per session.

at the end of therapy (SMD=0.75 (95% CI 0.46 to 1.03); I^2=34%; n=339; figure 4) and during follow-ups 2–8 weeks later (SMD=1.31 (95% CI 0.92 to 1.69); I^2=0%; n=129; figure 5). The dose subgroup analyses demonstrated that disability was neither significantly reduced by the non-recommended LLLT doses compared with placebo at the end of therapy (SMD=0.36 (95% CI −0.02 to 0.73); I^2=49%; n=278; figure 4) nor during follow-ups 1–12 weeks later (SMD=0.26 (95% CI −0.06 to 0.58); I^2=0%; n=160; figure 5). The between-subgroup differences in disability results were in favour of the recommended LLLT doses over the non-recommended LLLT doses but only significantly regarding one of two time points (p=0.11 and <0.0001; figures 4–5).

No QoL meta-analysis was performed because this outcome was only assessed in a single trial, that is, by Hinman *et al* who applied a non-recommended LLLT dose and reported insignificant results.[41]

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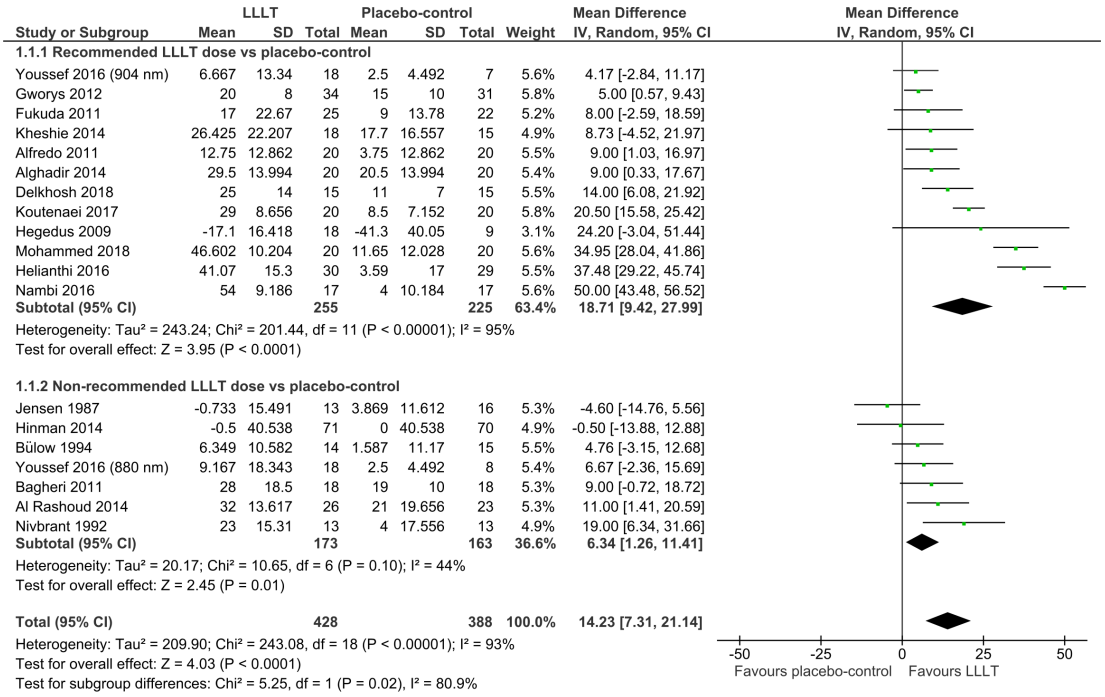

Figure 2 Pain results from immediately after the end of therapy. LLLT, low-level laser therapy.

The funnel plots indicated that there was no publication bias (online supplementary material). We additionally checked for small study bias by reducing the statistical weight of the smallest studies through a change from random to fixed effects models and this led to similar mean effect estimates, indicating that there was no small study bias (online supplementary material).[35]

Methodological quality of the included trials was judged adequate (low risk of bias), unclear (unclear risk of bias) and inadequate (high risk of bias) in 75%, 19% and 6% instances, respectively. Risk of detection bias and reporting bias appeared low in all the trials. There was a lack of information regarding random sequence generation in five trials, allocation concealment in 12 trials, blinding of therapist in four trials and incomplete outcome data in four trials. Therapist blinding was inadequate in seven trials and there was an inadequate handling of data in a single trial (figure 6). However, risk-of-bias subgroup analyses conducted post hoc revealed that there was no statistically significant interaction between the effect estimates and risk of bias, and the analyses did not display a drop in statistical heterogeneity (online supplementary material). Support for our risk of bias judgments is available (online supplementary material).

Neither did the levels of statistical heterogeneity change when we switched from the MD to the SMD method post hoc (online supplementary material).

Post hoc analyses demonstrated that LLLT was significantly superior to placebo both with exercise therapy (p=0.0009 for pain and p<0.0001 for disability) and without exercise therapy (p=0.01 for pain and p=0.008

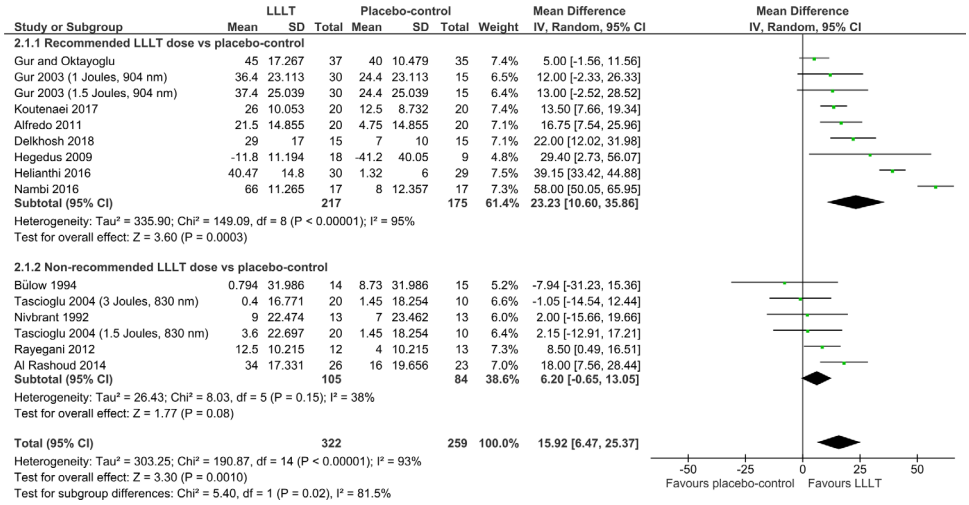

Figure 3 Pain results from follow-ups 1–12 weeks after the end of therapy. LLLT, low-level laser therapy.

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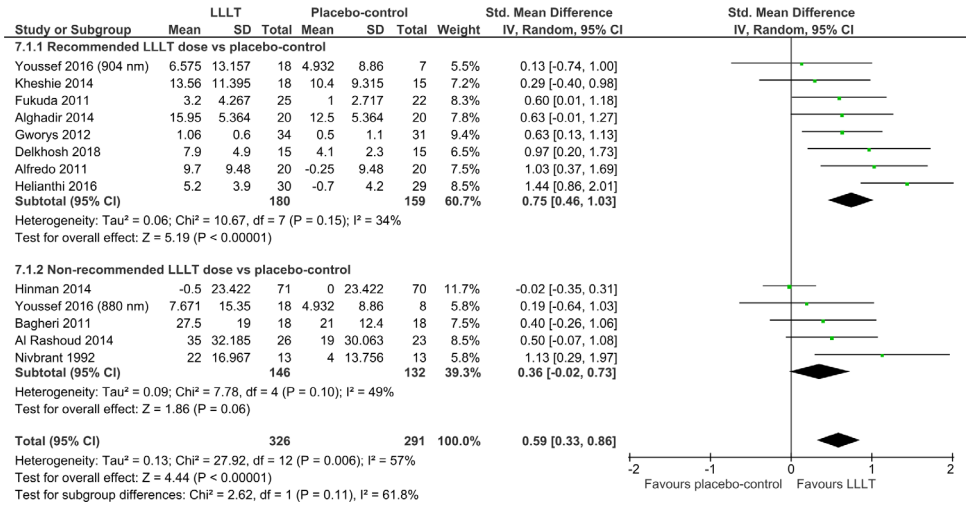

Figure 4 Disability results from immediately after the end of therapy. LLLT, low-level laser therapy.

for disability) as cointervention (online supplementary material).

Post hoc analyses were performed to more precisely estimate the pain time-effect profile for the recommended LLLT doses by imputing the results of the trials with these doses in subgroups with narrower time intervals. Pain was significantly reduced by the recommended LLLT doses compared with placebo immediately after therapy weeks 2–3 and 4–8 and at follow-ups 2–4, 6–8 and 12 weeks later; the peak point was 2–4 weeks after the end of therapy (31.87 mm VAS beyond placebo (95% CI 18.18 to 45.56); I^2=93%; n=322). The 21-week and 34-week follow-up pain results were not statistically significant (figure 7 and online supplementary material). The statistical heterogeneity in the main pain analyses of the recommended LLLT doses was high (I^2=95%; figures 2–3) but the mean statistical heterogeneity of the five subgroups covering the same time period was only moderate (I^2=58%; figure 7 and online supplementary material).

DISCUSSION

Our meta-analyses showed that pain and disability were significantly reduced by LLLT compared with placebo. We subgrouped the included trials according to the WALT recommendations (2010) for laser dose per treatment spot, and this revealed a significant dose–response relationship. Our principal finding is that the recommended LLLT doses offer clinically relevant pain relief in KOA. The non-recommended LLLT doses provided no or little positive effect.

The absolute minimally clinically important improvement (MCII) of pain in KOA has been estimated to be 19.9, 17 and 9 units on a 0–100 scale in 2005, 2012 and 2015, respectively.[44–46] It is important to note that the MCII of pain is a within-subject improvement and depends on baseline pain intensity.[44–46] The pain reduction from the recommended LLLT doses was significantly superior to placebo even at follow-ups 12 weeks after the end of therapy, and the difference was greater than 20 mm VAS from the final 4–8 weeks of therapy through follow-ups 6–8 weeks after the end of therapy. Interestingly, the pain reduction from the recommended LLLT doses peaked at follow-ups 2–4 weeks after the end of therapy (31.87 mm VAS highly significantly beyond placebo).

Disability was also significantly reduced by the recommended LLLT doses compared with placebo, that is, to

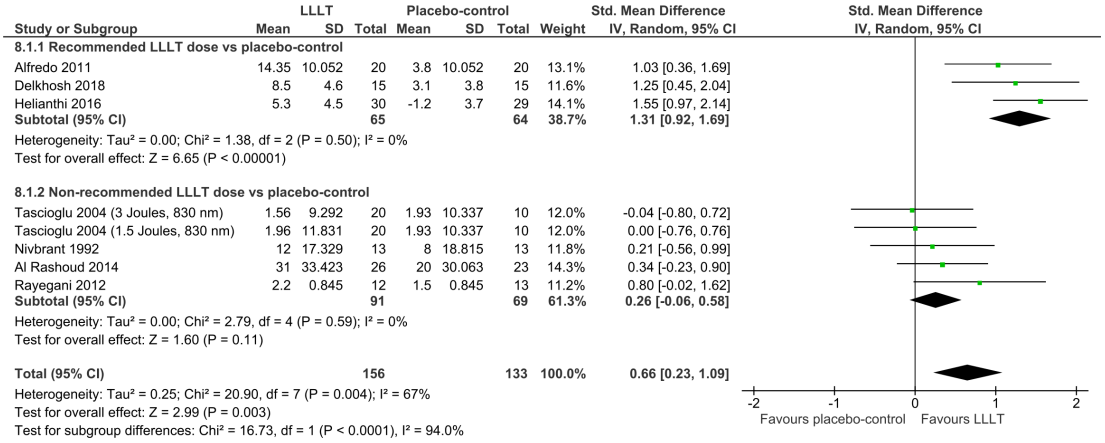

Figure 5 Disability results from follow-ups 1–12 weeks after the end of therapy. LLLT, low-level laser therapy.

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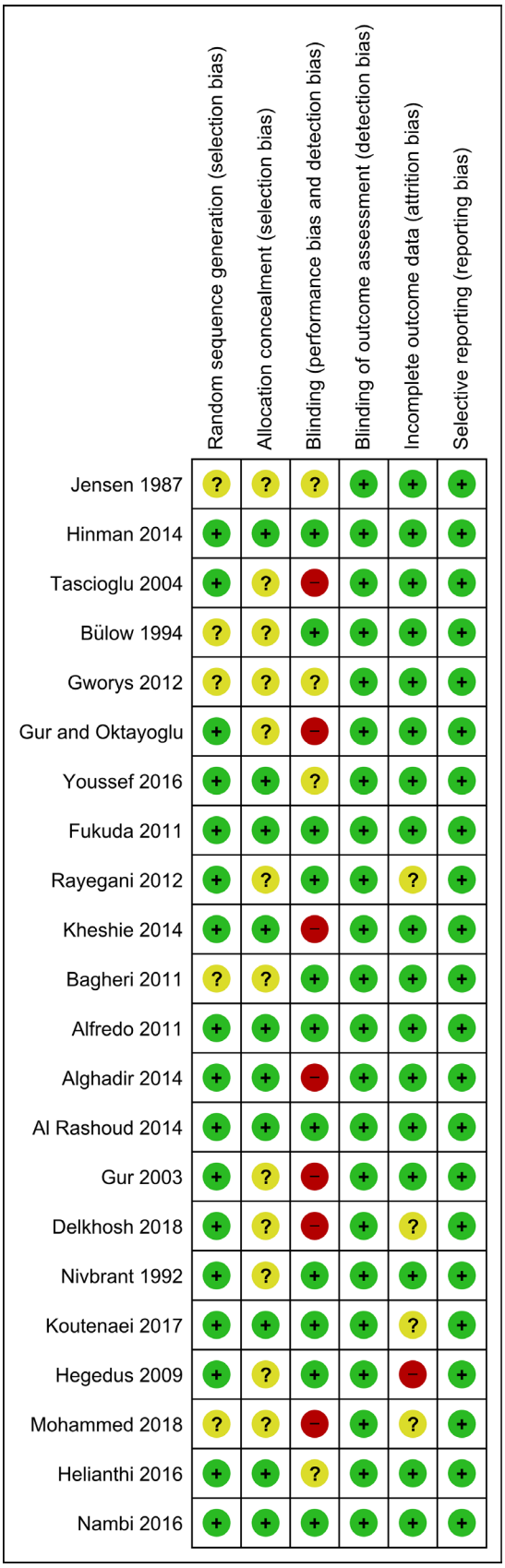

Figure 6 Risk-of-bias plot of the included trials. The trials are ranked by mean pain effect estimates, that is, more laser positive results in the bottom of the figure; the plot is based on the results from the main pain analyses (immediately after the end of therapy, primarily).

a moderate extent at the end of therapy (SMD=0.75) and to a large extent during follow-ups 2–8 weeks later (SMD=1.31). More trials with disability assessments are needed to precisely estimate the effect of LLLT on this outcome during follow-up.

Furthermore, our analyses demonstrated that LLLT is effective in KOA both with and without exercise therapy as cointervention. Strength training was seemingly only used as an adjunct to LLLT in two of the included trials,[47 48] and thus more trials with this combination of treatments are needed.

Risk of bias of the included trials appeared insignificant and could not explain the statistical heterogeneity (online supplementary material). We find it plausible that some of the statistical heterogeneity of the overall analyses is associated with the dose subgroup criteria (wavelength-specific laser doses per treatment spot) since the mean levels of statistical heterogeneity of the subgroup analyses were consistently lower than the overall levels. It is unknown to us whether other differences in the LLLT protocols impacted the results.

The statistical heterogeneity in the main pain analyses of the recommended LLLT doses was high, and some of it can be explained by the pooling of results from various time points of assessment given the pain reduction increased and subsequent decreased with time; the pain reduction time profile showed a drop in statistical heterogeneity to a moderate level.

According to WALT, the osteoarthritic knee should be laser irradiated to reduce inflammation and promote tissue repair.[24 25 49] One of the discrepancies from our review and previously published reviews of the same topic is that we omitted the RCT by Yurtkuran *et al*,[8 17 28 50] as they solely applied laser to an acupoint located distally from the knee joint (spleen 9).

In line with our findings and the WALT dose recommendations, Joensen *et al*[26] observed that the percentage of laser penetrating rat skin at 810 and 904 nm wavelength was 20% and 38%–58%, respectively. That is, to deliver the same dose beneath the skin, 2.4 times the energy on the skin surface is required with an 810 nm laser compared with a 904 nm laser device. This may be due to the different wavelengths and/or because 904 nm laser is superpulsed (pulse peak power ≥10 000 mW typically), whereas shorter wavelength laser is delivered continuously or with less intense pulsation.[26] The estimated median dose applied with the recommended LLLT was 6 and 3 J per treatment spot with 785–860 and 904 nm wavelength laser, respectively. Most of the trial authors reported LLLT parameters in detail but did not state whether the laser devices were calibrated. Therefore, in the LLLT trials with non-significant effect estimates, equipment failure cannot be ruled out.

It is important to note that no adverse events were reported by any of the trial authors and the dropout rate was minor, indicating that LLLT is harmless.

Our clinical findings that the effect of LLLT progresses over time is in line with in vivo results of Wang *et al*.[12] The

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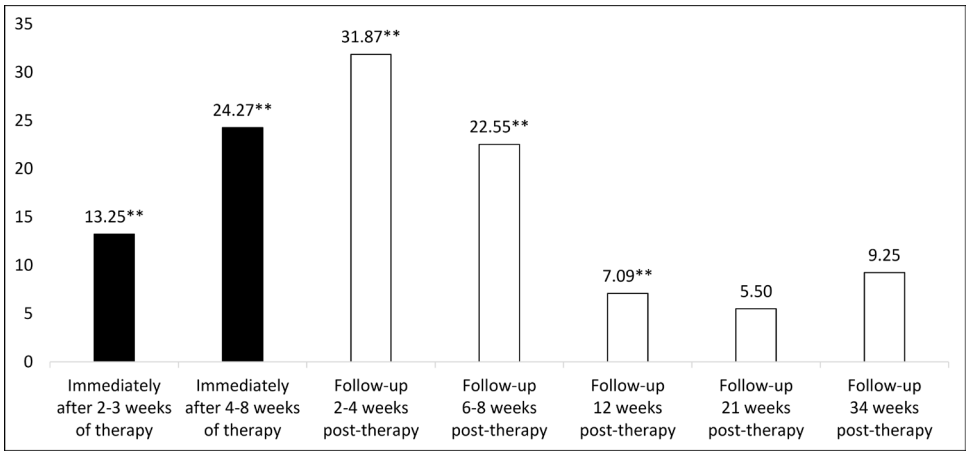

Figure 7 Pain time-effect profile (recommended low-level laser therapy (LLLT) doses versus placebo-control). Values on the y-axis are mm Visual Analogue Scale (VAS) pain results. Positive VAS score indicates that the recommended LLLT doses are superior to placebo. The related forest plot is available (online supplementary material). **The recommended LLLT doses are highly statistically significantly superior to placebo (p≤0.01).

positive effect from LLLT seems to last longer than those of widely recommended painkiller drugs.[51] The effect of using the NSAID tiaprofenic acid, for example, is probably gone within a week, unless the treatment is continued.[51] Future trials should investigate whether booster sessions of LLLT can prolong the positive effect. Comparative cost-effectiveness analyses of LLLT and NSAIDs would also be of great interest.

Strengths and limitations of this study

In contrast to previous reviews on the current topic, our review was conducted in conformance with an a priori published protocol,[8 17 28] which included a detailed plan for statistical analysis (eg, laser dose subgroup criteria). Furthermore, this is the first review on this topic without language restrictions,[8 17 28] and this expansion proved important since four (18%) of the included trials were reported in non-English language.[19 21 23 39]

We conducted a series of meta-analyses illustrating the effect of LLLT on pain over time. To ensure high reproducibility of the meta-analyses, three persons each independently extracted the outcome data from the included trial articles.

This review is not without limitations. It lacks QoL analyses, a detailed disability time-effect analysis and direct comparisons between LLLT and other interventions.

CONCLUSIONS

LLLT reduces pain and disability in KOA at 4–8 J with 785–860 nm wavelength and at 1–3 J with 904 nm wavelength per treatment spot.

Contributors MBS, JMB and HL wrote the PROSPERO protocol. MBS and JMB selected the trials, with the involvement of IFN when necessary. MBS and JJ judged the risk of bias, with the involvement of IFN when necessary. MBS and IFN did the translations. MBS, JMB and KVF extracted the data. MBS performed the analyses, under supervision of JMB. All the authors participated in interpreting of the results. MBS drafted the first version of the manuscript, and subsequently revised it, based on comments by RÁBL-M, HS and all the other authors. All the authors read and accepted the final version of the manuscript.

Funding The University of Bergen funded this research.

Competing interests JMB and RÁBL-M are post-presidents and former board members of World Association for Laser Therapy, a non-for-profit research organization from which they have never received funding, grants or fees. The other authors declared that they had no conflict of interests related to this work.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The dataset for meta-analysis is available from the corresponding author upon reasonable request. The corresponding author affirms that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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PLOS ONE

RESEARCH ARTICLE

Effects of low-level laser therapy in adults with rheumatoid arthritis: A systematic review and meta-analysis of controlled trials

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Citation: Lourinho I, Sousa T, Jardim R, Pinto AC, Iosimuta N (2023) Effects of low-level laser therapy in adults with rheumatoid arthritis: A systematic review and meta-analysis of controlled trials. PLoS ONE 18(9): e0291345. https://doi.org/10.1371/journal.pone.0291345

Editor: Michael R. Hamblin, Massachusetts General Hospital, UNITED STATES

Received: May 26, 2023

Accepted: August 27, 2023

Published: September 8, 2023

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Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: this work was supported by Coordination for the Improvement of Higher Education Personnel (CAPES), PROCAD 88887.200546/2018-00.

Competing interests: The authors have declared that no competing interests exist.

Abstract

Rheumatoid arthritis (RA) is an inflammatory, systemic and chronic disease that mainly affects the joints. It is characterized mainly by pain, edema and joint stiffness, which can lead to significant loss of functional capacity and quality of life. Several physical therapy resources are used in the treatment of AR, such as low-level laser therapy (LLLT) and its analgesic and anti-inflammatory effects. However, the efficacy of LLLT in AR is still controversial. The objective of this study is to evaluate the efficacy of low-level laser therapy in adults with RA. Methods and findings: We searched MEDLINE, EMBASE, CENTRAL, PEDro, LILACS, IBECS, CUMED, SCIELO and ClinicalTrials.gov. Two researchers independently selected studies, extracted data, evaluated the risk of bias and assessed the certainty of evidence using GRADE approach. Disagreements were resolved by a third author. Meta-analyses were performed. Currently available evidence was from 18 RCTs, with a total of 793 participants. We found low-quality evidence suggesting there may be no difference between using infrared laser and sham in terms of pain, morning stiffness, grip strength, functional capacity, inflammation, ROM, disease activity and adverse events. The evidence is very uncertain about the effects of red laser compared to sham in pain, morning stiffness. The evidence is also very uncertain about the effects of laser acupuncture compared to placebo in functional capacity, quality of life, range of motion and inflammation. Conclusions: Thus, infrared laser may not be superior to sham in RA patients. There is insufficient information to support or refute the effectiveness of red laser, laser acupuncture and reflexology for treating patients with RA.

Introduction

Rheumatoid arthritis (RA) is a disease of unknown etiology, characterized by systemic changes and inflammation of the synovial tissue of the joints, in the cartilage and bones. The prevalence

of RA between the years of 1980 and 2018 is 0.46% [1, 2]. Commonly affected joints include the peripheral synovial joints, such as metacarpal phalanges, ankles and wrists. However, there may also be involvement of the knee, shoulders, elbows and hips [3].

These impairments are accompanied by symptoms such as pain, morning stiffness and reduced range of motion, resulting in limitations in activities of daily living, self-care, work and leisure [4]. In addition, as it is a disease that has no cure, RA needs long-term pharmacological treatment for its control. However, its effects are tempered by the risk of adverse events. Non-pharmacological treatments are also needed to prevent joint deformities, which leads to high socioeconomic costs for the patient, the family and the health system [5, 6].

Therefore, physiotherapy plays an important role in the treatment of RA, as it includes several therapeutic modalities that aim at improving functional capacity and at minimizing the impact of the disease on the patients' quality of life. Among the approaches, the electrophysical agents, low-level laser therapy (LLLT), has gained increasing recognition for having physiologic effects, mainly mediated by photochemical actions at the cellular level that promote an increase in tissue microcirculation and may lead to anti-inflammatory and analgesic benefits [7–11]. However, its effects in patients with RA are controversial.

A previous systematic review suggests that LLLT can be considered to relieve pain and functional stiffness in RA [12]. However, several studies have been published since then, and this new evidence has not been summarized. Therefore, the aim of this study was to assess the efficacy of LLLT in adults with RA.

Methods

Data sources and searches

On July 6th, 2022, we searched MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, Latin American and Caribbean Health Sciences Literature (LILACS), IBECS, CUMED, Physiotherapy Evidence Database (PEDro) and Scientific Electronic Library Online (SciELO) using relevant descriptors and synonyms, adapting the search to the specifications of each database (S1 Table). To find additional studies, we also searched the Clinicaltrials.gov and searched the reference lists of included studies. We applied no language or date restrictions.

Study selection

We included randomized clinical trials evaluating the effects of continuous low-level laser therapy or pulse beam (classes III—ranging from 632.8–1000 nm) [9, 12] in patients with RA diagnosed by American College of Rheumatology (ACR) criteria [13, 14], ACR/European League Against Rheumatism (EULAR) [15] working group or using any validated classification criteria. We used Rayyan app (https://www.rayyan.ai/) to screen the titles and abstracts of search results, retrieve the full-text reports of all potentially eligible studies and select them for inclusion [16]. Studies were included if they randomized adult participants with rheumatoid arthritis to receive LLLT versus any other treatment, sham, or no treatment, and compared its effects considering the following outcomes: pain, functional capacity, adverse events, inflammation, disease activity, range of motion, morning stiffness, muscle strength or quality of life.

Data extraction and quality assessment

We performed this systematic review following the Cochrane Handbook recommendations [17] and reported it in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) recommendations (S2 Table). We registered this systematic

review protocol in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42020158163). To extract data from included studies, we used a predefined form. We collected detailed information on the populations, interventions, comparisons, outcomes, funding sources and conflicts of interest. We attempted to contact the authors of included studies to check missing details. We used the Cochrane risk-of-bias tool to assess the risk of bias inherent to each outcome of the included studies [17, 18]. We then assessed the certainty (quality) of body of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) (S3 Table) [17]. Two review authors (INLA and NCRI) independently selected studies, extracted data, assessed the risk of bias and the certainty of evidence. We resolved disagreements through discussion or when required by consulting a third author (ACPNP).

Data synthesis and analysis

After extraction, we analyzed the data using *Review Manager 5.4.1*. We analyzed dichotomous data as risks ratios (RRs), and continuous data as mean differences (MDs) or standardized mean differences (SMDs). If treatments, participants, and the underlying clinical question were similar enough for pooling to make sense, we undertook meta-analyses using a random-effects model. We used the I^2 statistics to measure heterogeneity in each analysis. We planned to carry out subgroup analyses considering age, treatment duration and LLLT parameters. We also planned to perform sensitivity analyses by exploring the influence of high risk of bias studies on treatment effects [17].

Results

Search strategy and selection of the studies

Our search strategy yielded a total of 1,339 records. After removing duplicated records, we examined 1,124 titles and abstracts. After screening titles and abstracts, 1,087 studies were excluded for not being directly related to the review question and retrieved 38 full-text reports (37 found through database and registers search and one through citation searching) for further scrutiny. Of those, 17 reports had insufficient data to include or exclude. As recommended by Cochrane Handbook [19], we did not exclude these studies, and when possible, we contacted authors for additional information. As no answers were received up to the date of submission of this paper, these studies were classified as studies awaiting classification and details on these reports are provided in S4 Table. To retrieve additional data, we also searched trial registers, such as Clinicaltrials.gov [20]. However, no additional trials were found. We excluded three reports [21–23] because they were not randomized. Finally, we included 18 studies in this review. The flow diagram can be consulted in Fig 1.

Included studies. We included 18 RCTs with a total of 793 participants. The included studies had intervention durations ranging from 4 weeks and 6 months.

The following comparisons were found:

1. Infrared laser versus sham (10 studies; 366 participants) [24–33]
2. Red laser versus sham (two studies; 89 participants) [34, 35];
3. Infrared laser versus laser acupuncture (one study; 40 participants) [36];
4. Laser acupuncture versus reflexology (one study; 30 participants) [37];
5. Laser acupuncture + teletherapy + methotrexate versus teletherapy + methotrexate (one study; 60 participants) [38];

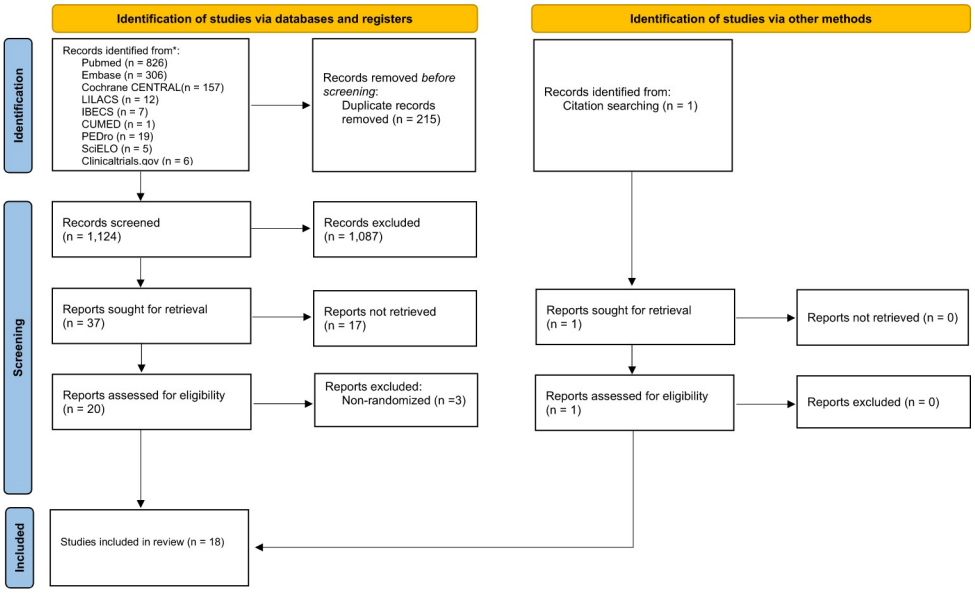

Fig 1. Flow diagram.

https://doi.org/10.1371/journal.pone.0291345.g001

6. Laser acupuncture + teletherapy versus teletherapy (one study; 60 participants) [39];
7. Infrared laser + red laser versus sham laser + naproxen (one study; 34 participants) [40];
8. Infrared laser + red laser versus naproxen (one study; 22 participants) [40];
9. Infrared laser + methotrexate + Non-steroidal anti-inflammatory drugs (NSAIDs) on demand versus methotrexate + NSAIDs on demand (one study; 114 participants) [41].

More details can be found in Table 1 and laser therapy parameters used in each study are detailed in Table 2. About the information not described in the included studies, we contacted the corresponding authors of included studies and asked whether they could provide information on those parameters, but no answer was received up to the date we submitted this article.

Risk of bias in included studies. Among the 18 included studies, 17 had an overall high risk of bias and one study [30] had "some concerns" on the overall risk of bias. The judgments for each domain of each risk of bias outcome are detailed in Fig 2. All results of the verification certainty assessment can be found in S4 Table.

Effects of interventions

Comparison: Infrared versus sham. *Pain*. Four studies [24, 25, 27, 30] used a Visual Analogue Scale (VAS) to assess pain. Pooled data from these 4 RCTs, with a total of 176 participants, suggest there may be small or no differences in pain between using laser infrared and sham after 4 to 8 weeks (MD -0.36; 95% CI -1.50 to 0.78; low certainty of evidence) (Fig 3A).

In addition to these studies, Silva et al. [33] evaluated pain with the Br-MPQ Pain Questionnaire. In this study, there was less pain in the sham group (80%) and a result of greater pain in the irradiated group (40%). Johannsen et al. [29] assessed pain using the 0–12 score range instrument and found a reduction on pain score in the infrared laser group, but when data were corrected for disease variation, the effect disappeared. Goldman et al. [26] also reported a significant difference favoring infrared laser group for pain but did not provide further

Table 1. Characteristics of randomized controlled studies included.

Study, year, location	Participants	Time since diagnosis	RA Severity	Sample size (n)	Age (Years) mean	Intervention	Time of analysis	Outcomes	Intergroup Results p-value
1.Walker et al (1987); California [35]	RA diagnoses according to ACR	ND	ND	I: 34 C: 38	I: 61,5 C:60	I: LLLT C: Sham	BL and on 10 weeks	Pain (VAS)	p = 0.07
2.Adly et al (2017); Egypt [37]	Patients fom Kasr El Ainy Medical School and National Institute of Laser Enhanced Sciences, Cairo University, Egypt. (Diagnosis criteria were not described)	ranging from 7 months to 10 years	ND	I: 15 C: 15	I: 61.83 C: 63.2	I: acupunture laser C:Reflexology	BL and on 4 weeks	Functional Capacity (HAQ) QoL (RAQoL) ROM of DFF, PFF, WF, WE and WA (goniometer) Inflammation (IL-6)	p > 0.05 p > 0.05 p < 0.05 p < 0.05
3.Miyagi et al (1989); Japan [31]	RA diagnoses according to ACR	I: 12.8 years C: 10.1 year	ND	I: 33 C: 35	I: 56.8 C: 54.5	I: LLLT C: Sham	BL and on 5 weeks	Pain (points scale) Functional Capacity (15 min of walk) Grip Strength Morning stiffness (min) Inflammation	p > 0.05 p < 0.01 p > 0.05 p > 0.05 p > 0.05
4.Hall et al (1994); England [27]	RA patients with synovitis in MCP and PIP joints (Diagnosis criteria were not described)	I:12.2 years C:9.3 years	ND	I: 20 C: 20	I: 67.1 C: 60.9	I: LLLT C: Sham	BL and on 4 weeks; follow-up of 1 and 3 months.	Pain (VAS) Functional Capacity (HAQ) Grip Strength ROM (goniometer) Inflammation	ND
5.Meireles et al (2010); Brazil [30]	RA diagnoses according to ACR	ND	ND	I: 41 C: 41	I: 52.44 C: 53.17	I: LLLT C: Sham	BL and on 8 weeks	Pain (VAS)—(RH/LH) Functional Capacity (HAQ) Morning stiffness (VAS) - (RH/LH) Grip Strength—(RH/LH) (dynamometer) ROM (goniometer) Inflammation (likert scale 1–5)	p = 0.16 / p = 0.15 p = 0.69 p = 0.27 / p = 0.06 p = 0.01 / p = 0.45 p = N.R. p = 0.01
6.Palmgren et al (1989); Denmark [32]	RA (Diagnosis criteria were not described)	ND	ND	I: 19 C: 16	I: (F: 61.1/ M: 66.0) C:(F: 57.5/ M: 8.0)	I: LLLT C: Sham	BL and on 4 weeks	Pain (VAS) Grip Strength (standardized balloon) Morning stiffness	ND
7.Silva et al (2009); Brazil [33]	Acute RA patients in MCP and PIP joints (Diagnosis criteria were not described)	ND	ND	I: 5 C: 5	I: 56,6 (19,9) C: NR	I: LLLT C: Sham	BL and on 5 weeks	Pain (MPQ)	p = 0.84
8.Ekim (2007); Turkey [24]	patients with RA and Carpal tunnel syndrome (Diagnosis criteria were not described)	I: 5.2 years C:5 years	ND	I: 10 C: 9	I: 48 (11) C: 55 (6)	I: LLLT C: Sham	BL and on 10 days, and follow-up in 3 months	Functional Capacity (Functional Status Scale) Grip Strength (dinamometer)	ND

(*Continued*)

Table 1. (Continued)

Study, year, location	Participants	Time since diagnosis	RA Severity	Sample size (n)	Age (Years) mean	Intervention	Time of analysis	Outcomes	Intergroup Results p-value
9.Johannsen et al (1994); Denmark [29]	RA patients with I and II functional level according to steinbrocker (Diagnosis criteria were not described)	ND	ND	I: 10 C: 12	I:59 C:62	I: LLLT C: Sham	BL and on 4 weeks	Pain (1–12 score range) Grip Strength (dinamometer) Morning stiffness (ordinal scale 0–2) Inflammation (CPR)	ND
10.Bliddal et al (1987); Denmark [34]	Acute RA patients in MCP joints (Diagnosis criteria were not described)	ND	ND	I: 9 C: 8	I: 57 (41–79) C: ND	I: LLLT C: Sham	BL, 3 weeks, and follow-up in 4 weeks	Pain (VAS) Morning stiffness	$p < 0.05$ (on 3 weeks) $p > 0.05$
11.Goats et al (1996); Scotland [25]	Acute RA patients from Gartnavel General Hospital (Diagnosis criteria were not described)	I:7.5 years C:9.8 years	ND	I: 25 C:10	I: 57 (14) C: 64 (8)	I: LLLT C: Sham	BL, 1st, 3rd and 6th months.	Pain (VAS) Functional Capacity (HAQ) Morning stiffness (hours) Inflammation (CRP) ROM (goniometer) Disease activity level (RAI)	ND
12.Adly et al (2021A); Egypt [36]	RA diagnosis according to ACR and EULAR	ND	ND	I: 20 C:20	I: 70.9 C: 70.3	I: LLLT C: Laser acupuncture	BL, 12 weeks	Functional Capacity (HAQ) QoL (RAQoL) Inflammation (IL-6)	$p > 0.05$ $p < 0.05$ $P > 0.05$
13.Adly et al (2021B); Egypt [42]	RA diagnosis according to ACR and EULAR	ND	ND	I: 30 C:30	E: 68.8 C:69.1	I: Laser acupuncture + teletherapy (AEV) C: teletherapy (AEV)	BL, 4 weeks	Functional Capacity (HAQ) QoL (RAQoL) Inflammation (CRP/ IL-6)	$p < 0.05$ $p < 0.05$ $p < 0.05$/ $p < 0.05$
14.Muhamed et al (2021); Iraq [40]	RA diagnosis according to ACR	ND	ND	I: 12 C1: 12 C2:10	Mean age of 49.6	I: LLLT (red +infrared) C1: sham LLLT + naproxeno C2: naproxeno	BL, 7 weeks	Pain (VAS) Morning stiffness DAS28 Inflammation (CRP)	$p = 0.01$ $p = 0.05$ $p = 0.02$ $p > 0.05$
15. Adly et al., (2022); Egypt [38]	RA diagnosis according to ACR and EULAR	ND	ND	I:30 C:30	I: 68.87 C: 69.13	I: Laser acupuncture + teletherapy + methotrexate C: teletherapy +methotrexate	BL, 4 weeks	Functional Capacity (HAQ) QoL (RAQoL) Inflammation (CRP/ IL-6)	$p > 0.05$ $p > 0.05$ $p < 0.05$/ $p < 0.05$
16. Goldman et al. (1980);U.S.A [26]	RA classified by American Rheumatism Association criteria	Ranging from 1 year to 26 years	ND	I: ND C: ND A: 30	I: ND C: ND	I: LLLT C: Sham	BL, 10 weeks, and 3 months	Erythema Pain Flexion Grip strength PIP Range of motion MCP flexion	Significant Significant Non significant Significant Non significant Non significant

(*Continued*)

Table 1. (Continued)

Study, year, location	Participants	Time since diagnosis	RA Severity	Sample size (n)	Age (Years) mean	Intervention	Time of analysis	Outcomes	Intergroup Results p-value
17. Heussler et al., (1993); Australia [28]	RA and bilateral involvement of their MCP and PIP joints (Diagnosis criteria were not described)	Ranging from 2 year to 14 years	ND	I: 25* C: 25*	I: ND C: ND	I: LLLT C: Sham	BL, 5 weeks	Pain morning stiffness Swollen ROM Grip strength Inflammation (CRP) Adverse effects	Non significant Non significant Non significant Non significant Non significant Non significant Non significant
18. Zhuravleva et al., (2021); Russian [41]	RA patients (Diagnosis criteria were not described)	ND	ND	I: 57 C: 57	I: ND C: ND	I: LLLT + methotrexate + NSAIDS C: methotrexate + NSAIDS	BL, 6 months	Pain morning stiffness N of patients needing NSAIDs	MD -0.51 (IC 95% -0.60 to -0.42)** MD -17.8 (IC 95% -19.67 to -15.93)** RR 2.1 (IC 95% 1.09 to 4.05)**

RA, rheumatoid arthritis; ACR: American College of Rheumatology; I: intervention group; C: control group; A: all; BL: baseline; HAQ: health assessment questionnaire; QoL: quality of life; RAQoL: rheumatoid arthritis quality of life; ROM: range of motion; DFF: dorsiflexion of foot; PFF: plantar flexion of foot; WF: wrist flexion; WE: wrist extension; WA: abduction wrist; VAS, visual analogue scales MCP, metacarpophalangeal joint; PIP, proximal interphalangeal joint; IL-6: interleukine 6; CRP: C-reactive protein; RAI: Ritchie Articular Index; EULAR: European Alliance of Associations for Rheumatology; DAS28: Disease activity score; LLLT = Low-level laser therapy; AEV: aerobic and virtual exercises; NSAIDS: Non-steroidal anti-inflammatory drugs; Ga-Al-Ar: gallium-aluminium-arsenate; ND: not described

*hands were randomized

**significant difference

https://doi.org/10.1371/journal.pone.0291345.t001

information for analysis. The results of the 3 studies were not pooled with the other 4 RCTs because they were reported in ways that did not allow pooling.

Morning stiffness. Four studies evaluated the duration of morning stiffness [25, 27, 30, 31]. To morning stiffness outcome, data from four RCTs were pooled to meta-analysis with a total of 209 individuals. The meta-analysis results showed that there is low certainty of evidence for small or no difference in morning stiffness between using laser infrared compared to sham after 1 to 2 months (MD = - 10.84; 95% CI –49.29 to 27.61) (Fig 3B). Heussler et al. [28] also evaluated the duration of morning stiffness and did not find a significant difference between groups, but did not provide further information for analysis.

Handgrip strength. Three studies [24, 30, 31] evaluated handgrip strength and the pooled data from these trials, with a total of 169 participants, suggest there may be small or no difference in handgrip strength between using laser infrared and sham (SMD -0.15; 95% CI -0.85 to 0.54; low certainty of evidence) (Fig 3C). Heussler et al. [28] and Johannsen et al. [29] reported they did not find a significant difference between groups. Goldman et al. [26] and Palmgren et al. [32] reported a significant difference favoring infrared laser group for grip strength. However, these studies did not provide further information for analysis. Hall et al. [27] presented data only in graphs without further information for analysis.

Table 2. Low-level laser therapy parameters of included studies.

Studies	laser type	Wavelength (nm)	Fluency J/ cm^2	Power(mW); time(s)	Irradiance (W/ cm2)	Number of points; number of sessions	Energy (J)
1.Walker et al (1987)	AlAs He-Ne	632.5; red	0.0075	1; 30	47.7	3 (radial, median and saphenous nerve on each painful joint); 3 sessions/ week	ND
2. Adly et al (2017)	GaAlAs	904; infrared	ND	100; ND	100	ND; 3 sessions/ week	4
3. Miyagi et al (1989)	GaAlAs	830; infrared	ND	20;30	ND	6 (the knee joint; 2 sessions/ week	ND
4. Hall et al (1994)	GaAlAs	820; infrared	3.600	40;90	ND	4 on each MCP and PIP joints; ND	3.6
5. Meireles et al (2010)	GaAlAs	785; infrared	3	70; ND	ND	14; 2 sessions/ week	ND
6. Palmgren et al (1989)	GaAlAs	820; infrared	3.58	15;60	ND	8; 3 sessions/ week	ND
7. Silva et al (2009)	Infrared	904: infrared	ND	8; 195	ND	ND; 2 sessions/ week	1.55
8. Ekim et al (2007)	GaAlAs	780; infrared	ND	50; 600	ND	5; 5 sessions/ week	7.5
9. Johannsen et al (1994)	GaAlAs	830; infrared	ND	21; ND	ND	4 on two MCP joints; 3 sessions/ week	2,9
10. Bliddal et al (1987)	He-Ne	633; red	6	10;300	ND	ND; 3 sessions/ week	ND
11. Goats (1996)	GaAlAs	660–950; infrared	8.1	940;240	ND	5; ND	ND
12. Adly A et al (2021)	Infrared	I:904; infrared C: 904 laser pucture; infrared	I:20.1C:4	I:500;30 C:100:40	I:650 C:100	I:3 C:7	I:ND C: 4
13. Adly B et al (2021)	Infrared	808; infrared	7.5	ND;60	100	5;ND	ND
14. Muhamed et al (2021)	GaAlAs; He-Ne	830; infrared 632,8; red	ND ND	7.3; ND 300; ND	ND ND	ND; 3 sessions/ week	ND
15. Adly A et al (2022)	Infrared	808; infrared	7.5	100;60	100	4; 6 sessions/ week	ND
16. Goldman et al. 1980	Infrared	1060; infrared	15–25	ND; 0,3	ND	MCP and PIP, ND	ND
17. Heussler et al., 1993	Infrared	820; infrared	12	50; ND	ND	MCP and PIP, ND	ND
18. Zhuravleva et al., 2021	Infrared	890; infrared	ND	5000;60–120	ND	ND;ND	ND

He-Ne: helium-neon; GaAlAs: gallium aluminum arsenide; AlAs: aluminum arsenide; ND: not described; MCP, metacarpophalangeal joint; PIP, proximal interphalangeal joint

https://doi.org/10.1371/journal.pone.0291345.t002

Functional capacity. Two studies [25, 30] evaluated functional capacity using the Health Assessment Questionnaire (HAQ) and one [24] using a Functional Scale with 8 items. Pooled data from these 3 RCTs, with a total of 136 participants, suggest there may be small or no difference in functional capacity between using laser infrared and sham (SMD -0.08; 95% CI -0.60 to 0.43; low quality of evidence) (Fig 3D). Hall et al. [27] evaluated functional capacity but presented data only in graphs without further information for analysis.

Inflammation. Two studies [25, 31] evaluated c-reactive protein (CRP) (in mg/dl) through blood collection. Pooled data from two studies, with 103 participants, suggest there may be small or no difference between using infrared laser or sham (MD = 0.18; 95% CI ((-0.51 to 0.87) (Fig 3E). Meireles et al. [30], using a Likert scale, (1—no inflammation; 2- mild inflammation; 3-moderate inflammation; 4 strong inflammation; or 5—very strong inflammation), encountered a statistically significant difference (p = 0.012) in favor of the group that received infrared laser. Johannsen et al. [29] and Meireles et al. [30] reported they did not find a

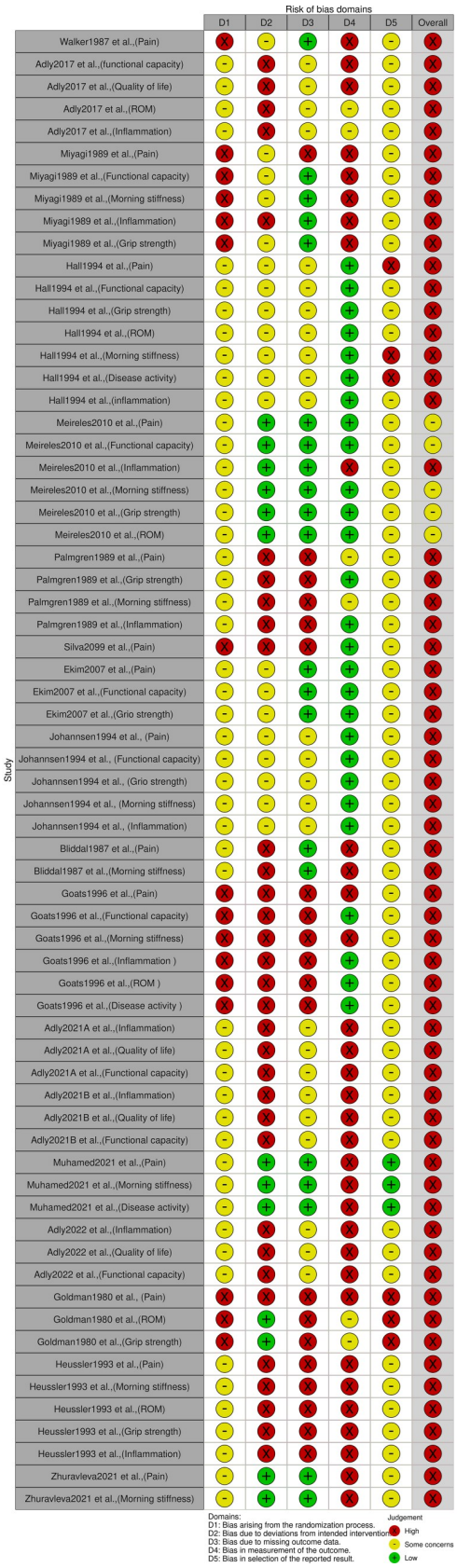

Fig 2. Risk of bias in included studies.

https://doi.org/10.1371/journal.pone.0291345.g002

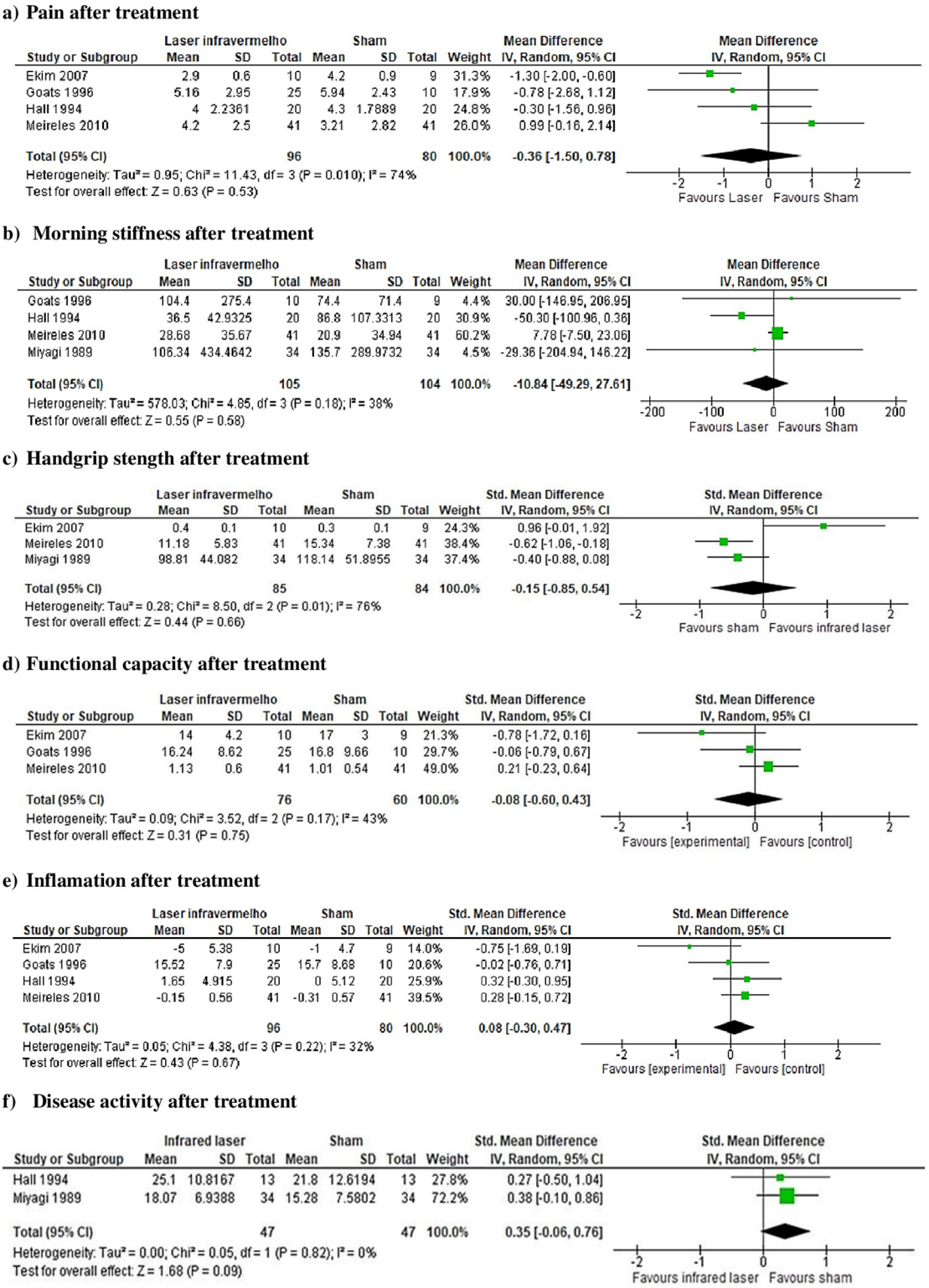

Fig 3. Meta-analysis.

https://doi.org/10.1371/journal.pone.0291345.g003

significant difference between groups and did not provide enough data for further analysis. Hall [27] presented data only in graphs without further information for analysis.

Range of motion (ROM). Meireles et al. [30] analyzed proximal interphalangeal (PIP) joints using a goniometry, results of this study with 82 participants found a small difference in ROM after 2 months (p = 0.021 favoring control group). Ekim et al. [24] found no significant difference observed between active or placebo groups in ROM at the knee. Goldman et al. [26] and Heussler [28] reported no significant difference between groups for PIP range of motion. Hall et al. [27] presented data only in graphs without further information for analysis. These results suggest there may be small or no difference between laser infrared and sham on ROM (low certainty of evidence).

Disease activity. Hall et al. [27] used the Richie index and Miyagi et al. [31] used Lansbury. Pooled data from these studies with a total of 94 participants suggested that there may be small or no difference in disease activity between using infrared laser and sham (SMD 0.35; 95% CI −0.06 to 0.76; low quality of evidence) (Fig 3F).

Adverse events. Johannsen et al. [29] reported adverse events related to interventions. In this study, two patients receiving infrared laser treatment had increased disease activity, requiring steroid treatment. These two patients were withdrawn from the study. Two other patients, one from each treatment group, complained of a burning sensation in the treated joints, but completed the study.

Ekim et al. [24] and Miyagi et al. [31] reported that no systemic or local side effects were reported during or after the treatment period. Heussler et al. [28] reported no significant difference between groups for side effects. Johannsen et al. [29] reported no side effects. Due to the few events and risk of bias in studies, the evidence is very uncertain about adverse effects of infrared laser compared to sham (very low certainty of evidence).

Comparison: Red laser versus sham. *Pain*. Two studies, Walker et al. [35] and Bliddal et al. [34], evaluated pain outcome after red laser. These studies were not sufficiently homogeneous to be pooled. Walker et al. [35] observed no difference between groups for the pain outcome. According to Bliddal et al. [34], red laser treatment is better than placebo in terms of pain relief. The quality of evidence for this outcome is very low.

Morning stiffness. Bliddal et al. [34] evaluated morning stiffness after 10 weeks of red laser. In this study, it was not possible to detect differences between red laser and sham treatment regarding relief of morning stiffness. The quality of evidence for this outcome is very low.

Adverse events. For Bliddal et al. [31], adverse effects were observed in 3 patients, who complained of a burning sensation in the irradiated joints—all in the laser-treated group. In these cases, the sensation disappeared within a few hours and none of the patients withdrew from the study. The quality of evidence for this outcome is very low.

Comparison: Infrared laser versus laser acupuncture. *Functional capacity*. The results of Adly et al. [38] with 40 participants suggest the evidence is very uncertain about the effects of infrared laser versus laser acupuncture, as assessed by the HAQ (MD 0.01; 95% CI −0.23 to 0.25; very low quality of evidence).

Quality of life. The evidence is also very uncertain about the effects of infrared laser versus laser acupuncture in the quality of life using The Rheumatoid Arthritis Quality of Life Questionnaire (RAQoL), after 4 weeks (MD 4.05; 95% CI 0.48 to 7.62; very low quality of evidence).

Inflammation. We are uncertain about the effects of infrared laser versus laser acupuncture in inflammation as assessed with interleukin 6 (MD 36.03; 95% CI -0.72 to 72.79; very low quality of evidence).

Comparison: Laser acupuncture versus reflexology. *Functional capacity*. The results of Adly [37] with 30 participants suggest the evidence is very uncertain about the effects of laser

acupuncture versus reflexology on functional capacity after 4 weeks, as assessed by the HAQ (MD 32.49; 95% CI 28.54 to 36.44; very low quality of evidence).

Quality of life. The evidence is also very uncertain about the effects of laser acupuncture versus reflexology in the quality of life using The Rheumatoid Arthritis Quality of Life Questionnaire (RAQoL), after 4 weeks (MD -4.05; 95% CI -9.18 to 1.08; very low quality of evidence).

Inflammation. We are uncertain about the effects of laser acupuncture versus reflexology in inflammation as assessed with interleukin 6 (MD 27.7; 95% CI -70.52 to 15.12; very low quality of evidence).

Range of motion. There is also very low quality of evidence on the effects of laser acupuncture versus reflexology in the range of motion, including evaluations of plantar flexion and dorsiflexion, wrist flexion and extension, and ulnar and radial deviation, although all differences were favorable to the group receiving laser acupuncture, except for ulnar deviation, where no significant difference between groups was found (Table 1).

Comparison: Laser acupuncture + teletherapy + methotrexate versus teletherapy + methotrexate. *Functional capacity*. The results of Adly et al. [38] with 60 participants suggest the evidence is very uncertain about the effects of laser acupuncture + teletherapy + methotrexate versus teletherapy + methotrexate, as assessed by the HAQ. In this study, the authors reported no significant difference between groups, without further data for analysis; very low quality of evidence.

Quality of life. We are uncertain about the effects of laser acupuncture versus reflexology in the quality of life using The Rheumatoid Arthritis Quality of Life Questionnaire (RAQoL). The authors found a significant difference between groups favoring laser acupuncture, with a mean difference of –4.533, without further data for analysis; very low quality of evidence.

Inflammation. We are uncertain about the effects of laser acupuncture versus reflexology in inflammation as assessed with interleukin 6. The authors found a significant difference between groups favoring laser acupuncture assessed using CRP and IL-6, with a mean difference of –34.68 and –41, respectively, without further data for analysis; very low quality of evidence.

Comparison: Laser acupuncture + teletherapy versus teletherapy. *Functional capacity*. The results of Adly et al. [39] with 60 participants suggest the evidence is very uncertain about the effects of laser acupuncture + teletherapy versus teletherapy on functional capacity, as assessed by the HAQ (MD 0.00–0.24 to 0.24; very low quality of evidence).

Quality of life. The evidence is also very uncertain about the effects of laser acupuncture + teletherapy versus teletherapy in the quality of life using The Rheumatoid Arthritis Quality of Life Questionnaire (RAQoL), after 4 weeks (MD –4.47; 95% CI -8.20 to –0.74; very low quality of evidence).

Inflammation. We are uncertain about the effects of laser acupuncture + teletherapy versus teletherapy in inflammation as assessed with interleukin 6 (MD –35.57; 95% CI –37.63 to –33.5, and MD –31.17; 95% CI –63.1 to 0.76; very low quality of evidence).

Comparison: Infrared laser + red laser versus sham laser + naproxen. *Pain*. The results of Al-Saraj et al. [40] with 24 participants suggest the evidence is very uncertain about the effects of infrared laser + red laser versus sham laser + naproxen on pain (MD -9.05; 95% CI -17.52 to –0.58; very low quality of evidence).

Morning stiffness. The results suggest the evidence is very uncertain about the effects of infrared laser + red laser versus sham laser + naproxen on morning stiffness (MD -7.4; 95% CI -13.4 to –1.4; very low quality of evidence).

Inflammation. We are uncertain about the effects of infrared laser + red laser versus sham laser + naproxen in inflammation as assessed with erythrocyte sedimentation rate (ESR) (MD –4.1; 95% CI -10.26 to 2.06; very low quality of evidence).

Disease activity. The evidence is also very uncertain about the effects of infrared laser + red laser versus sham laser + naproxen in the quality of life using Disease Activity Score 28 (DAS-28) (MD -0.49; 95% CI -1.00 to 0.02; very low quality of evidence).

Adverse events. The evidence is also very uncertain about the adverse effects of infrared laser + red laser versus sham laser + naproxen (RR 0.14; 95% CI 0.01 to 2.50; very low quality of evidence).

Comparison: Infrared laser + red laser versus naproxen. *Pain*. The results of Al-Saraj et al. [40] with 22 participants suggest the evidence is very uncertain about the effects of infrared laser + red laser versus sham laser + naproxen on pain (MD -7.3; 95% CI -17.33 to 2.73; very low quality of evidence).

Morning stiffness. The results of this study [40] with 22 participants suggest the evidence is very uncertain about the effects of infrared laser + red laser versus sham laser + naproxen on morning stiffness (MD -9.50; 95% CI -15.10 to –3.90; very low quality of evidence).

Inflammation. We are uncertain about the effects of infrared laser + red laser versus sham laser + naproxen in inflammation as assessed with ESR (MD –4.50; 95% CI –68.48 to 59.48; very low quality of evidence).

Disease activity. The evidence is also very uncertain about the effects of infrared laser + red laser versus sham laser + naproxen in the quality of life using Disease Activity Score 28 (DAS-28) (MD -0.22; 95% CI –0.67 to 0.23; very low quality of evidence).

Adverse events. The evidence is also very uncertain about the adverse effects of infrared laser + red laser versus naproxen (RR 0.17; 95% CI 0.01 to 3.16; very low quality of evidence).

Comparison: Infrared laser + methotrexate + non-steroidal anti-inflammatory drugs (NSAIDs) on demand versus methotrexate + NSAIDs on demand. *Pain*. Zhuravleva et al. [41] compared Infrared laser + methotrexate + NSAIDS versus methotrexate + NSAIDS using a Visual Analogue Scale (VAS). This study found a small difference between using infrared laser and control after 6 months of treatment (MD –0.51; IC 95% -0.60 to –0.42; low-certainty of evidence).

Duration of morning stiffness. The results of this study [41] suggest participants in the laser group had a shorter duration of morning stiffness compared to control (MD -17.8; IC 95% -19.67 to -15.93; low certainty of evidence).

Number of patients needing NSAID. Zhuravleva et al. [41] found that laser led to a decrease in the frequency of the need for NSAIDs compared to control (RR 2.1; IC 95% 1.09 to 4.05; low certainty of evidence).

Discussion/Conclusion

Main findings

This systematic review evaluated the current evidence on the effectiveness of LLLT in adult patients with RA. The last systematic review evaluating exclusively adults with RA was published [12] 17 years ago, showing the importance of updating the evidence through this systematic review. Our results show that there is low-quality evidence to suggest that there may be small to no differences between using infrared laser using sham in terms of pain, morning stiffness, grip strength, functional capacity, inflammation, range of motion, disease activity and adverse events. We also found that the evidence is very uncertain about the effects of red laser versus sham in pain, morning stiffness and adverse events and about the effect of laser acupuncture versus reflexology in functional capacity, quality of life and inflammation.

In this systematic review, we included 18 RCTs, of which ten showed there may be no difference between using infrared laser and using sham in any of the outcomes evaluated. Our results are different from the results of Brosseau et al. [12], where LLLT was found to reduce

pain and stiffness in a short period when compared to sham. This difference in result may be due to the fact that, in our review, we chose to separate the LLLT with red wavelength from the infrared wavelength, since the infrared LLLT penetrates more into the tissue than does the red laser [9], which Brosseau et al. [12] was unable to do as they included only a few heterogeneous studies. Furthermore, no certainty of evidence assessment was conducted in the systematic review by Brosseau et al. [12].

It is noteworthy that in Brosseau et al. [12], only studies published in French and English were included, which resulted in the inclusion of 5 studies. In this review, the authors reported that despite the positive results found, it was not possible to determine which LLLT parameters are responsible for these effects. Noting that, it is important that future reviews separate the LLLT parameters in the meta-analyses according to wavelength, treatment time, dose and laser application site when possible.

We also found that the evidence is very uncertain about the effects of red laser versus sham in pain, morning stiffness, and adverse events and about the effect of laser acupuncture versus reflexology in functional capacity, quality of life and inflammation. Some studies suggest that LLLT has promising results in controlling joint inflammation [43], reducing pain, tumor necrosis factor alpha (TNF-a) [44] and modulating the inflammatory process [45]. However, to achieve these effects, LLLT depends on specific and important parameters that determine the interaction of laser light with tissue. However, the heterogeneity of the included studies in terms of sample size, treatment time, place of LLLT application and lack of uniformity in the presentation of LLLT parameters make it difficult to interpret the results found and the effectiveness of this resource cannot be proven.

We consider as limitations of this study the inclusion of trials without adequate randomization, studies with small sample data that favor imprecision, resulting in low estimation of effects, and the heterogeneity of laser parameters found. Another limitation of this review would be the estimation of long-term effects that were observed in only two studies. We consider the strengths of this systematic review to be the use of a rigorous methodology, assessment of the risk of bias and the quality of evidence for each outcome, as well as the conduction of broad searches, without publication date or language restrictions.

In conclusion, infrared laser may not be superior to sham in RA patients. There is insufficient evidence to support or refute the effectiveness of red laser, laser acupuncture and reflexology for treating patients with RA. Further studies with more rigorous scientific methodology and larger sample size are needed to monitor the effects of LLT in patients with RA in the long term.

Supporting information

S1 Table. Search strategy for included studies.
(DOCX)

S2 Table. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).
(DOCX)

S3 Table. Studies awaiting classification.
(DOCX)

S4 Table. Grading of Recommendations Assessment, Development and Evaluation (GRADE).
(DOCX)

Author Contributions

Methodology: Ingrid Lourinho, Tamara Sousa, Roger Jardim, Ana Carolina Pinto, Natália Iosimuta.

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Comparison of Treatments for Frozen Shoulder
A Systematic Review and Meta-analysis

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Abstract

IMPORTANCE There are a myriad of available treatment options for patients with frozen shoulder, which can be overwhelming to the treating health care professional.

OBJECTIVE To assess and compare the effectiveness of available treatment options for frozen shoulder to guide musculoskeletal practitioners and inform guidelines.

DATA SOURCES Medline, EMBASE, Scopus, and CINHAL were searched in February 2020.

STUDY SELECTION Studies with a randomized design of any type that compared treatment modalities for frozen shoulder with other modalities, placebo, or no treatment were included.

DATA EXTRACTION AND SYNTHESIS Data were independently extracted by 2 individuals. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline. Random-effects models were used.

MAIN OUTCOMES AND MEASURES Pain and function were the primary outcomes, and external rotation range of movement (ER ROM) was the secondary outcome. Results of pairwise meta-analyses were presented as mean differences (MDs) for pain and ER ROM and standardized mean differences (SMDs) for function. Length of follow-up was divided into short-term (≤12 weeks), mid-term (>12 weeks to ≤12 months), and long-term (>12 months) follow-up.

RESULTS From a total of 65 eligible studies with 4097 participants that were included in the systematic review, 34 studies with 2402 participants were included in pairwise meta-analyses and 39 studies with 2736 participants in network meta-analyses. Despite several statistically significant results in pairwise meta-analyses, only the administration of intra-articular (IA) corticosteroid was associated with statistical and clinical superiority compared with other interventions in the short-term for pain (vs no treatment or placebo: MD, −1.0 visual analog scale [VAS] point; 95% CI, −1.5 to −0.5 VAS points; $P < .001$; vs physiotherapy: MD, −1.1 VAS points; 95% CI, −1.7 to −0.5 VAS points; $P < .001$) and function (vs no treatment or placebo: SMD, 0.6; 95% CI, 0.3 to 0.9; $P < .001$; vs physiotherapy: SMD 0.5; 95% CI, 0.2 to 0.7; $P < .001$). Subgroup analyses and the network meta-analysis demonstrated that the addition of a home exercise program with simple exercises and stretches and physiotherapy (electrotherapy and/or mobilizations) to IA corticosteroid may be associated with added benefits in the mid-term (eg, pain for IA coritocosteriod with home exercise vs no treatment or placebo: MD, −1.4 VAS points; 95% CI, −1.8 to −1.1 VAS points; $P < .001$).

CONCLUSIONS AND RELEVANCE The findings of this study suggest that the early use of IA corticosteroid in patients with frozen shoulder of less than 1-year duration is associated with better

(continued)

Key Points

Question Are any treatment modalities for frozen shoulder associated with better outcomes than other treatments?

Findings In this meta-analysis of 65 studies with 4097 participants, intra-articular corticosteroid was associated with increased short-term benefits compared with other nonsurgical treatments, and its superiority appeared to last for as long as 6 months. The addition of a home exercise program and/or electrotherapy or passive mobilizations may be associated with added benefits.

Meaning The results of this study suggest that intra-articular corticosteroid should be offered to patients with frozen shoulder at first contact.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

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Abstract (continued)

outcomes. This treatment should be accompanied by a home exercise program to maximize the chance of recovery.

JAMA Network Open. 2020;3(12):e2029581. doi:10.1001/jamanetworkopen.2020.29581

Introduction

Adhesive capsulitis, also known as frozen shoulder, is a common shoulder concern manifesting in progressive loss of glenohumeral movements coupled with pain.[1] It is a fibroproliferative tissue fibrosis, and although the immunobiological advances in other diseases have helped dissect the pathophysiology of this condition, overall, the molecular mechanisms underpinning it remain poorly understood.[2-5]

Frozen shoulder manifests clinically as shoulder pain with progressive restricted movement, both active and passive, along with normal radiographic scans of the glenohumeral joint.[6] It classically progresses prognostically through 3 overlapping stages of pain (stage 1, lasting 2-9 months), stiffness (stage 2, lasting 4-12 months), and recovery (stage 3, lasting 5-24 months).[7] However, this is an estimated time frame, and many patients can still experience symptoms at 6 years.[8] A primary care–based observational study estimated its incidence as 2.4 per 100 000 individuals per year,[9] with prevalence varying from less than 1% to 2% of the population.[10]

A true evidence-based model for its medical management has not been defined, with a wide spectrum of operative and nonoperative treatments available. From the international to departmental level, management strategies vary widely, reflecting the lack of good-quality evidence.[11] The British Elbow and Shoulder Society/British Orthopaedic Association (BESS/BOA) has published recommendations in a patient care pathway for frozen shoulder, with a step-up approach in terms of invasiveness advised.[12] The UK Frozen Shoulder Trial, a randomized parallel trial comparing the clinical and cost-effectiveness of early structured physiotherapy, manipulation under anesthetic (MUA), and arthroscopic capsular release (ACR) is currently under way.[13] The aim of this systematic review is to present the available evidence relevant to treatment and outcomes for frozen shoulder with the ultimate objective of guiding clinical practice, both in primary and secondary care.

Methods

The present systematic review has been conducted and authored according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.[14] Our patient, intervention, comparison, and outcome (PICO) was defined as follows: patients, patients with frozen shoulder of any etiology, duration, and severity; intervention, any treatment modality for frozen shoulder; comparison, any other treatment modality, placebo, or no treatment; and outcome, pain and function (primary outcomes) and external rotation range of movement (ER ROM) (secondary outcome) in the short term, midterm, or long term.

Eligibility

Included studies had a randomized design of any type and compared treatment modalities for frozen shoulder with other treatment modalities, placebo, or no treatment. Additionally, at least 1 of our preset outcome measures needed to be included in the study. Studies that compared different types, regimens, dosages, or durations of the same intervention were excluded (eg, different doses of corticosteroid or different exercise types). Those assessing the effectiveness of the same modality applied in different anatomical sites (eg, subacromial vs intra-articular [IA] corticosteroid) were included. Participants had to be older than 18 years with a clinical diagnosis of adhesive capsulitis. No formal diagnostic criteria were used to define frozen shoulder; however, the use of inappropriate or

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inadequate diagnostic criteria was taken into account in risk-of-bias assessments. Duration of the condition was not a criterion nor were previous treatments and follow-up. Inclusion of patients with specific conditions (eg, diabetes) was not an exclusion criterion, and it was not taken into account in analyses, provided that their proportion in the treatment groups was comparable.

Nonrandomized comparative studies, observational studies, case reports, case series, literature reviews, published conference abstracts, and studies published in languages other than English were excluded. Studies including patients with the general diagnosis of shoulder pain were also excluded even if a proportion of them had frozen shoulder. Studies assessing the effectiveness of different types of physiotherapy-led interventions, exercise, or stretching regimens were also excluded.

Search Strategy

A thorough literature search was conducted by 3 of us (D.C., M.B., and M.M.) via Medline, EMBASE, Scopus, and CINAHL in February 2020, with the following Boolean operators in all fields: (*adhesive capsulitis* OR *frozen shoulder* OR *shoulder periarthritis*) AND (*treatment* OR *management* OR *therapy*) AND *randomi**). Relevant review articles were screened to identify eligible articles that may have been missed at the initial search. Additionally, reference list screening and citation tracking in Google Scholar were performed for each eligible article.

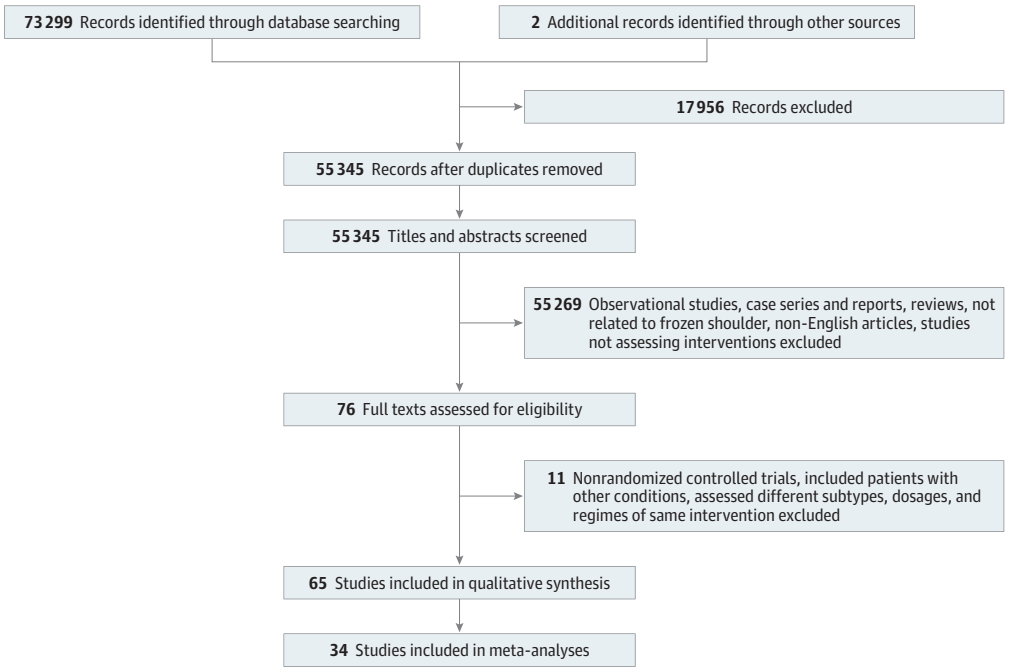
Screening

From a total of 73 299 articles that were initially identified, after exclusion of duplicate and noneligible articles, title and abstract screening, and the addition of missed studies identified subsequently, 65 studies were found to fulfil the eligibility criteria. **Figure 1** illustrates the article screening process.

Risk-of-Bias Assessment and Grading the Certainty of Evidence

The internal validity (freedom from bias) of each included study was assessed with the Cochrane Collaboration's tool for assessing risk of bias in randomized trials separately by 2 of us (D.C. and M.B.), and a third independent opinion (M.M.) was sought when disagreements existed.[15] Studies were

Figure 1. Flow Diagram Summarizing the Article Selection Process



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characterized as having low, high, or unclear overall risk of bias based on the following formula: low overall risk studies had high risk of bias in 2 or fewer domains; high overall risk studies had high risk of bias in more than 2 domains; unclear overall risk studies had unclear risk of bias in more than 2 domains, unless they also had high risk of bias in more than 2 domains, in which case they were labeled as high overall risk. Risk of bias was assessed separately for outcome measures that included patient reporting (pain, function) and those that did not (ROM); all studies with nonmasked participants were labeled as high risk in the masking of outcome measures domain for patient-reported outcomes given that the assessors were the participants themselves.

Certainty of evidence was graded with the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) tool (eTable 1 in the Supplement).[16] The scale starts with high, and depending on how many of the 5 possible limitations used in the GRADE tool were present in each comparison, the study could be downgraded to moderate, low, and very low. Grading of evidence was performed by 2 authors (D.C. and M.B.) independently and any disagreements were resolved by discussion and involvement of a third assessor (M.M.). Each outcome measure within each comparison had its own evidence grade. Our recommendations for clinical practice were based on results of either high or moderate quality evidence with both clinical and statistical significance.

Data Extraction

Two of us (D.C. and M.B.) performed data extraction. The key characteristics of each eligible article were extracted and inserted in tables in Microsoft Word version 16.43 (Microsoft Corp) to facilitate analysis and presentation. For missing data, attempts were made to contact the original investigators for included studies published less than 10 years ago.

For the presentation of results, outcomes were divided into short-term (≤12 weeks), mid-term (>2 weeks to ≤12 months), and long-term (>12 months) follow-up. When sufficient data existed, short-term follow-up was subdivided into early short-term (2-6 weeks) and late short-term (8-12 weeks). All short-term follow-up points were converted to weeks, and all mid-term follow-up points to months for consistency and easier analysis.

Comparisons of interventions reported by fewer than 3 studies were included in the supplementary results table and were not analyzed or included in the article. When 3 or more studies contributed data for outcome measures at similar follow up times (ie, 2-6 weeks, 8-12 weeks, and 4-6 months), pairwise meta-analyses were conducted. Raw mean differences (MDs) with their accompanying 95% CIs were calculated and used in the tests for each comparison of pain and ER ROM because the tools used across studies were the same. Standardized mean differences (SMDs) were used for function because different functional scores were used.

When pain results were reported in different settings (eg, at rest, at night, with activity) in studies, only pain at rest was used in results. When both active and passive ROM were used as outcome measures, passive ROM was used in our results to increase homogeneity given that most studies used passive ROM. Results for the following outcome measures were recorded in tables and combined qualitatively only based on direction of effect to yield an overall effect for each comparison: abduction ROM, flexion ROM, and quality of life. However, these were not included in the results nor was the quality of the relevant evidence graded.

Additionally, comparisons that yielded both clinically and statistically significant results (ie, greater than or equal to the minimal clinically relevant difference and $P < .05$) underwent trial sequential analysis (TSA) to rule out a type I error and further reinforce our recommendations for clinical practice. TSA is a quantitative method applying sequential monitoring boundaries to cumulative meta-analyses in a similar fashion as the application of group sequential monitoring boundaries in single trials to decide whether they could be terminated early because of a sufficiently small P value. TSA is considered an interim meta-analysis; it helps control for type I and II errors and clarifies whether additional trials are needed by considering required information size.[17] The TSA graph includes 2 horizontal lines, representing the conventional thresholds for statistical significance ($Z = 1.96$; $P < .05$); 1 vertical line, representing required information size; a curved red line,

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representing the TSA boundaries (ie, thresholds for statistical significance); and a blue line showing the cumulative amount of information as trials are added. A significant result is denoted by a crossing of the curved blue and red lines.

Finally, a network meta-analysis was conducted for treatments used by 3 or more studies for the primary outcome (pain) at late short-term (8-12 weeks) and mid-term (4-6 months) follow-up. Both direct and indirect comparisons were included in the model, and treatment rank probabilities were produced for the 2 follow-up time periods. The certainty of evidence deriving from network meta-analyses was not graded. Subgroup analyses for the effect of home exercise, different physiotherapy interventions, and chronicity of frozen shoulder were conducted when possible.

Definitions

The term *physiotherapy* was used for any supervised, physiotherapist-led, noninvasive treatment (mobilizations, application of ice and heat, diathermy, electrotherapy modalities). These were grouped and analyzed together. Exercises and stretching that were performed by the participants at home (home exercise program) or under a physiotherapist's supervision were not included in physiotherapy. Acupuncture and extracorporeal shock wave therapy (ESWT) were regarded as a separate intervention to physiotherapy. Interventions that had accompanying physiotherapy were grouped and analyzed separately from those that did not, regardless of intensity and frequency. For example, studies with a treatment group who received IA corticosteroid plus physiotherapy (eg, ice packs and diathermy) were included in the intervention category IA corticosteroid plus physiotherapy; those with a treatment group receiving only IA corticosteroid (with or without a home exercise program) were included in the IA corticosteroid category. Patients in the following groups were considered control groups and were analyzed together: no treatment, placebo, sham procedures, IA normal saline or lidocaine, simple analgesia, and home exercise alone.

The following tools and questionnaires that were found in included studies represented our function outcome measure: Shoulder Pain and Disability Index, American Shoulder and Elbow Surgeons shoulder score, Constant-Murley, and the Strengths and Difficulties Questionnaire. All patient-reported pain and function scales were uniformly converted to a scale from 0 to 10 and a scale from 0 to 100, respectively.

Statistical Analysis

The Review Manager version 5 (RevMan) software was used for pairwise meta-analyses and their accompanying forest plots and heterogeneity tests (χ^2 and I^2). TSA software version 0.9β (Copenhagen Trial Unit) was used for TSAs; random-effect models with 5% type I error and 20% power and O'Brien-Fleming α-spending function were used for all TSA analyses. The required information size was estimated by the software based on the power (20%), mean difference, variance, and heterogeneity. Stata version 16.1 (StataCorp) with the mvmeta extension (multivariate random-effects meta-regression) was used for network meta-analyses (frequentist approach).[18]

When exact mean and SD values were not reported in the included articles, approximate values (to the nearest decimal place) were derived from the graphs. When only interquartile ranges (IQRs) were reported, the SD was calculated as IQR divided by 1.35. When only the median was reported, the mean was assumed to be the same. When CIs of means were reported, SDs were calculated by dividing the length of the CI by 3.92 and then multiplying by the square root of the sample size. When SEs of mean were given, these were converted to SDs by multiplying them by the square root of the sample size. In studies in which only means and the population were given, the SD was imputed using the SDs of other similar studies using the prognostic method (ie, calculating the mean of all SDs).[19] Pooled means were calculated by adding all the means, multiplied by their sample size, and then dividing this by the sum of all sample sizes. Pooled SDs were calculated with the following formula: $SD_{pooled} = \sqrt{(SD_1^2[n_1-1]) + (SD_2^2[n_2-1]) + \ldots + (SD_k^2[n_k-1]) / (n_1 + n_2 + \ldots + n_k - k)}$, where n indicates

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sample size and k, the number of samples. The following formula was used for the sample size calculation as part of GRADE's assessment for imprecision[20]:

$$N = \frac{2(a+b)^2 SD^2}{(x_1 - x_2)}$$

In which N indicates the sample size required in each of the groups; $(x_1 - x_2)$ indicates the minimal clinically relevant difference (MCRD), defined as 1 point for VAS pain, effect size of 0.45 for functional scores, and 10° for ER ROM; SD^2 indicates the population variance, calculated using pooled SD from our treatment groups; a = 1.96, for 5% type I error; and b = 0.842, for 80% power.

The MCRD for function on functional scales would have been set at 10 points. However, because SMDs were used, which produce effect sizes, rather than MDs, the 10 points were divided by the population SD (ie, 22) that was used to calculate the optimal information size (effect sizes can be converted back to functional scores when multiplied by SD).

Potential publication bias was evaluated by Egger test for asymmetry of the funnel plot in comparisons including more than 10 studies. Expecting wide-range variability in studies' settings, a random-effects metasynthesis was employed in all comparisons.

Subgroup analyses were conducted with independent samples t tests in Graphpad version 8 (Prism) comparing pooled means and SDs. All statistical significance levels were set at $P < .05$, tests were 2-tailed, and clinical significance was defined as a MD or SMD being equal or higher than our predefined MCRD.

Results

Of the 65 eligible studies, a total of 34 studies[21-54] were included in pairwise meta-analyses with a total of 2402 participants with frozen shoulder. Duration of symptoms ranged from 1 month to 7 years and length of follow-up from 1 week to 2 years, with most follow-up occurring at 6 weeks, 12 weeks, and 6 months.

Table 1 summarizes the main characteristics of the included studies.[21-87] eTable 2 in the Supplement shows the results of the risk-of-bias assessment.

Table 2 summarizes the findings of the present review. Where feasible (ie, results at similar follow-up times in at least 3 studies), pairwise meta-analyses were conducted. The results of abduction ROM, flexion ROM, and quality of life were pooled only based on direction of effect, and their certainty of evidence was not graded. eTable 3 in the Supplement summarizes the results of comparisons reported by 1 or 2 studies only. eTable 4 in the Supplement demonstrates how the strength of evidence for each outcome measure within each comparison was derived for all follow-up time categories, per GRADE. eTable 5 in the Supplement shows the heterogeneity for each comparison (I^2 statistic) and where studies were removed to reduce heterogeneity based on sensitivity analyses.

Pairwise Meta-analysis

We conducted pairwise meta-analysis comparing the effectiveness of each intervention with other interventions (or placebo/no treatment) in the short-term (early, 2-6 weeks; late, 8-12 weeks) and mid-term (4-6 months). Data for long-term follow-up (>12 months) were inadequate for analyses. Numerical data are only presented for the statistically significant comparisons; those for nonsignificant comparisons appear in the forest plots (eFigure 1, eFigure 2, and eFigure 3 in the Supplement).

IA Corticosteroid vs No Treatment or Placebo

Short-term | IA corticosteroid appeared to be associated with superior outcomes compared with control for early short-term pain (moderate certainty; MD, −1.4 visual analog scale [VAS] points; 95%

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Table 1. Main Characteristics of Populations, Interventions, and Outcome Measures of Included Randomized Trials

Source	Participants, No. (participants who completed study, No.)	Mean age, y	Duration of symptoms	Participants per treatment group, No. (participants per treatment group who completed study, No.)	Treatment duration (follow-up)	Outcome measures
Arslan and Celiker,[21] 2001[a]	20 (20)	56	Mean, 4.1 mo	• IA corticosteroid; n = 10 (10) • Physiotherapy (hot pack, ultrasound, exercises) with NSAID; n = 10 (10) • Both groups received 12-wk home exercise program	Single IA corticosteroid injection; physiotherapy not stated for how long, likely 12 wk (0, 2, and 12 wk)	• AROM (ABD, FL, ER, and IR) • PROM (ABD, FL, ER, and IR) • Pain (VAS, 0-10), unspecified
Bal et al,[22] 2008[a]	80 individuals with 82 shoulders (64)	56.6	Range, 6 wk-6 mo	• IA corticosteroid; n = 40 (40) • Sham injection (normal saline); n = 40 (24) • Both groups received 12-wk home exercise program	Single IA corticosteroid or normal saline injection (0, 2, and 12 wk)	• PROM (ABD, FL, ER, and IR) • Night pain (VAS, 0-100) • Functional disability (SPADI) • Treatment effectiveness (UCLA end-result score)
Binder et al,[55] 1986	40 (unknown)	54.8	Mean (range), 5.5 mo (1-12 mo)	• Oral corticosteroid; n = 20 (unknown) • No treatment; n = 20 (unknown) • Both groups received home exercise program, which entailed 2-3 min of movement every hour	Oral prednisolone for 6 wk (0, 2, 4, and 6 wk then monthly to 8 mo)	• Pain (VAS, 0-10), at rest, at night, on movement • PROM (ABD, FL, and ER)
Blockey et al,[56] 1954	32 (30)	55	Mean, 5.6 mo	• Oral corticosteroid; n = 16 (14) • Oral placebo; n = 16 (16) • Both groups received home exercises for 4 wk; patients who still had restricted ROM at 4 wk underwent MUA and further 4 wk treatment with oral corticosteroid or placebo, according to initial treatment allocation	Oral corticosteroid or placebo for 4 weeks (0, 1, 4, 5, 8, and 18 wk)	• Pain (0-3) at rest and on movement" • ROM (total ABD, scapulohumeral ABD, total rotation), unclear whether active or passive
Buchbinder et al,[57] 2004	50 (46)	54.3	Mean, 23.3 wk	• Oral corticosteroid; n = 24 (24) • Oral placebo; n = 26 (22) • Both groups received home exercise program of an unknown duration	Oral corticosteroid or placebo for 3 weeks (0, 3, 6, and 12 wk)	• Pain (VAS, 0-10) at night and activity-related • Functional disability (SPADI, Croft, DASH) • Function (HAQ) • QoL (SF-36) • Patient-rated improvement • AROM (ABD, FL, ER, and IR)
Buchbinder et al,[58] 2004	46 (46)	57.3	Mean (range), 116 d (96-402 d)	• Arthrographic distension with IA corticosteroid; n = 25 (25) • Arthrography only (placebo); n = 21 (21) • Both groups received home exercise program of an unknown duration	Single injection (0, 3, 6, and 12 wk)	• Functional Disability (SPADI and PET) • Pain (SPADI and VAS, 0-10), overall (unspecified) • AROM (ABD, FL, ER, and IR)
Bulgen at al, [23] 1984[a]	45 (42)	55.8	Mean (range), 4.8 mo (1-12 mo)	• IA corticosteroid; n = 11 • Mobilizations; n = 11 • Ice with PNF; n = 12 • No treatment; n = 8 • All groups received home exercise program of unknown duration	IA corticosteroid once weekly for 6 wk; mobilizations, ice. and PNF three times weekly for 6 wk (0, 1, 2, 3, 4, 5, 6, 7, 8, and 12 wk, 4, 5, and 6 mo)	• Pain (VAS, 0-10) at rest, at night, on movement • PROM (ABD, FL, and ER)
Calis et al,[24] 2006[a]	95 shoulders (unknown)	56.9	>1 mo	• IA sodium hyaluronate; n = 27 (unknown) • IA corticosteroid; n = 26 (unknown) • Physiotherapy (hot pack, US, TENS, stretching); n = 22 (unknown) • No treatment; n = 20 (unknown) • All groups received home exercise program of unknown duration	IA sodium hyaluronate injection once weekly for 2 wk; single IA corticosteroid injection; physiotherapy for 10 d (0, 15 d, 3 mo)	• Pain (VAS, 0-10), unspecified • PROM (ABD and ER) • Function (CM)
Carette et al,[25] 2003[a]	93 (77)	55.3	Mean, 21.1 wk, everyone <1 y	• IA corticosteroid IA with physiotherapy; n = 22 (20) • IA corticosteroid; n = 25 (16) • IA placebo with physiotherapy; n = 27 (23) • IA placebo n = 23 (22) • All groups received 3-mo home exercise program; physiotherapy included TENS, mobilizations, exercises, and ice for patients with acute disease and US, mobilizations, exercise, and ice for those with chronic disease	Single injections of IA corticosteroid and placebo; supervised physiotherapy 3 sessions weekly for 4 wk (0, 6 wk, 3 mo, 6 mo, 1 y)	• Functional disability (SPADI) • Pain (SPADI, 0-100), unspecified • QoL (SF-36) • AROM and PROM (ABD, FL, and ER)

(continued)

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Table 1. Main Characteristics of Populations, Interventions, and Outcome Measures of Included Randomized Trials (continued)

Source	Participants, No. (participants who completed study, No.)	Mean age, y	Duration of symptoms	Participants per treatment group, No. (participants per treatment group who completed study, No.)	Treatment duration (follow-up)	Outcome measures
Cheing et al,[59] 2008	74 (70)	33-90, unknown mean	Mean (range), 7.2 mo (1-24 mo)	• EA; n = 25 (24) • IFE; n = 24 (23) • No treatment; n = 25 (23) • EA and IFE groups received 6-mo home exercise program	10 sessions during 4 wk for EA and IFE (0, 1 mo, 3 mo, 6 mo)	• Function (CM) • Pain (VAS, 0-10), unspecified
Chen et al,[60] 2014	40 (34)	53.4	>3 mo	• Oral corticosteroid; n = 20 (17) • ESWT; n = 20 (17) • Both groups received home exercise program of unknown duration	Oral corticosteroid for 4 wk; 3 sessions of ESWT during 4 wk (0, 2, 4, 6, and 12 wk)	• Function (CM and OSS) • AROM, from CM (ABD, FL, ER, and IR) • Pain (CM), unspecified
Cho et al,[26] 2016[a]	126 (110)	56.6	Mean, 5 mo	• IA corticosteroid; n = 42 (36) • SA corticosteroid; n = 42 (37) • IA with SA corticosteroid, n = 42 (37) • All groups received home exercise program of unknown duration	Single injections (0, 3, 6, and 12 wk)	• Function (ASES shoulder score) • Pain (VAS. 0-10) with movement • PROM (ABD, FL, ER, and IR)
Dacre et al,[27] 1989[a]	66 (62)	54.9	>4 wk	• IA corticosteroid; n = 22 (22) • Physiotherapy (mobilizations); n = 22 (20) • IA corticosteroid with physiotherapy; n = 22 (20) • No home exercise program	Supervised physiotherapy for 4-6 wk (0, 6 wk, 6 mo)	• Pain (VAS. 0-10) day, night, and with movement • PROM (ABD, ER, and IR)
Dahan et al,[61] 1999	34 (27)	52	Mean, 1 y	• Suprascapular nerve block with bupivacaine; n = 17 (15) • Placebo injection; n = 17 (12) • Both groups received home exercise program of unknown duration	3 injections over 2 weeks	• Pain (VAS, 0-10, MPQ short-form, Present Pain Index) • Function (SST) • AROM (ABD and FL) • PROM (ABD, FL and ER)
De Carli et al,[62] 2012	46 (44)	55.5	Mean, 3 mo	• MUA with ACR; n = 25 (23) • IA corticosteroid; n = 21 (21) • IA corticosteroid group received both supervised physiotherapy and home exercise program; MUA with ACR group started active strengthening 5 wk postoperation	Single MUA with ACR; IA corticosteroid once weekly for 3 wk (0, 3, 6 , and 12 wk, 6 and 12 mo)	• Function (CM, UCLA, ASES, and SST) • PROM (ABD, FL, ER, and IR) • Treatment satisfaction (VAS)
Dehghan et al,[28] 2013[a]	75 (59); patients had diabetes	54	Not stated	• NSAID (naproxen, 1g/d); n = 35 (28) • IA corticosteroid; n = 40 (29) • Both groups received home exercise program of unknown duration	Single injection of IA corticosteroid; NSAID of unknown duration (0, 2, 6, 12, and 24 wk)	• Pain (VAS, 0-10), unspecified • ROM (ABD, FL, ER, and IR), unknown if active or passive
Gallacher et al,[63] 2018	50 (39)	53.9	>3 mo	• Arthrographic distension with IA corticosteroid; n = 25 (20) • ACR with IA corticosteroid; n = 25 (19) • Both groups received home exercises and what authors described as standard physiotherapy regimen of unknown duration	Single treatment (0, 6 wk, 3 mo, 6 mo)	• Function (OSS) • QoL (EQ-5D) • PROM (ABD, FL, and ER) • Complications
Gam et al,[29] 1998[a]	22 (20)	53	Median, 5 mo	• IA corticosteroid; n = 9 (8) • IA corticosteroid with arthrographic distension; n = 13 (12) • No home exercise program	1 injection weekly for 6 wk or until no symptoms (0, 3, 6, and 12 wk)	• Pain (VAS, 0-10), at rest and with movement • PROM (FL, EXT, ABD, ELE, and ER) • Use of analgesics
Hsieh et al,[64] 2012	70 (63)	54.5	Mean, 4.5 mo	• IA sodium hyaluronate with physiotherapy (heat, electrotherapy, exercises); n = 35 (32) • Physiotherapy; n = 35 (31) • No home exercise program	Injection weekly for 3 wk; physiotherapy for 3 mo (0, 6, and 12 wk)	• AROM and PROM (FL, ABD, ER, and IR) • Pain (VAS, 0-100), unspecified • Functional disability (SPADI and SDQ) • QoL (SF-36)
Jacobs et al,[65] 2009	53 (51)	57	Median, 17.5 mo	• MUA; n = 28 (26) • IA corticosteroid with arthrographic distension; n = 25 (25) • Both groups received home exercise program of unknown duration	Single MUA; 3 IA corticosteroid injections over 18 wk (0, 2, 6, and 12 wk, 6, 9 , 12, 18, and 24 mo)	• Function (CM) • Pain (VAS, 0-100), unspecified • QoL (SF-36)

(continued)

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Table 1. Main Characteristics of Populations, Interventions, and Outcome Measures of Included Randomized Trials (continued)

Source	Participants, No. (participants who completed study, No.)	Mean age, y	Duration of symptoms	Participants per treatment group, No. (participants per treatment group who completed study, No.)	Treatment duration (follow-up)	Outcome measures
Jacobs et al,[66] 1991	47 individuals with 50 shoulders (35)	53.4	Median (range), 6 mo (1-24 mo)	• Arthrographic distension; n = 14 (unknown) • IA corticosteroid; n = 15 (unknown) • Arthrographic distension with IA corticosteroid; n = 18 (unknown) • All groups received home exercise program of unknown duration	As many as 3 injections over 12 wk (0, 6, 12, 16)	• AROM (ABD, FL, and ER) • PROM (ABD, FL, and ER) • Strength (dynamometry) • Pain with daily activities (0-5) and with movement (0-3) • Use of analgesics
Jones and Chattopadhyay,[67] 1999	30 (30)	56.5	Not stated	• Suprascapular nerve block; n = 15 (15) • IA corticosteroid; n = 15 (15) • Both groups received home exercise program of unknown duration	Single suprascapular nerve block; ≤3 IA corticosteroid injections (0, 1, 3, 7, and 12 wk)	• Pain (VAS. 0-5), unspecified • ROM (ABD, ER, and IR), unknown if active or passive
Khallaf et al,[30] 2018[a]	40 (unknown)	47.3	Mean, 1.5 mo	• IA corticosteroid; n = 20 (unknown) • SA corticosteroid; n = 20 (unknown) • Both groups received 12-wk home exercise program	Single injection (0 and 12 wk)	• Pain (VAS, 0-10), unspecified • Functional disability (SPADI) • AROM (FF, ER, IR, and EXT) • PROM (FF, ER, IR, and EXT)
Khan et al,[68] 2005	36 (35)	Unknown	Not stated	• Physiotherapy (exercises, TENS, and IRR); n = 18 (unknown) • Physiotherapy with arthrographic distension and IA corticosteroid; n = 18 (unknown)	8 wk (0, 1, 2, 3, 4, 5, 6, 7, and 8 wk)	• Pain (VAS, 0-100), unspecified • PROM (ABD, ER, and IR)
Kim et al,[69] 2017	40 (30)	55.2	Mean, 4 mo	• IA sodium hyaluronate; n = 20 (16) • IA sodium hyaluronate with IA tramadol; n = 20 (14) • Both received home exercise program of unknown duration	IA sodium hyaluronate weekly injections for 5 wk; IA tramadol for 3 wk (0, 1, 2, 3, 4, and 6 wk)	• Pain (VAS 0-10), unspecified • Functional disability (SPADI) • PROM (ABD, FL, ER, and IR)
Kivimäki and Pohjolainen,[70] 2001	30 (24)	51	Mean (range), 7 mo (3-18 mo)	• MUA with IA corticosteroid n = 15 (13) • MUA; n = 15 (11) • No home exercise program	Single treatment (0, 1 d, 4 mo)	• PROM (ABD, FL, ER, and IR)
Kivimäki et al,[71] 2007	125 (83)	53	Mean, 7.2 mo	• MUA; n = 65 (38) • No treatment; n = 60 (45) • Both groups received home exercise program of unknown duration	Single MUA (0, 6 wk, 3, 6, and 12 mo)	• PROM (ABD, FL, ER, and IR) • Pain (VAS, 0-10), unspecified • Functional disability (modified SDQ) • Function (working ability, 0-10) • Use of analgesics
Klç et al,[72] 2015	41 (41)	58.4	>1 mo	• Suprascaular nerve block with physiotherapy; n = 19 (19) • Physiotherapy; n = 22 (22) • Physiotherapy included hot packs, exercises, stretching, TENS, and US; both groups received home exercise program of unknown duration	Physiotherapy, 5 sessions a week for 3 weeks; single suprascapular nerve block (0, 3, and 7 wk)	• Pain (BPI-SF) • Function (CM)
Koh et al,[31] 2013[a]	68 (unknown)	54.4	Mean, 6 mo	• Bee venom acupuncture with physiotherapy; n = 22 (unknown) • Higher dose bee venom acupuncture with physiotherapy; n = 23 (unknown) • Sham injection (normal saline) with physiotherapy; n = 23 (unknown) • Physiotherapy included TENS, TDP, and mobilizations; all groups received 2-mohome exercise program	16 sessions during 2 mo (0, 2, 4, 8, and 12 wk)	• Disability (SPADI) • Pain (VAS, 0-10), at rest, at night, and with movement • AROM (FL, EXT, ABD, ADD, and ER) • PROM (FL, EXT, ABD, ADD, and ER)
Kraal et al,[32] 2018[a]	21 (15)	51.9	>3 mo	• IA corticosteroid with physiotherapy (mobilizations, stretching, ice and hot packs, and massage); n = 10 (unknown) • IA corticosteroid; n = 11 (unknown) • No home exercise program	Single injection but second given if no improvement at 6 wk; physiotherapy twice weekly ≤3 mo (0, 6, 12, and 26 wk)	• Functional disability (SPADI) • Pain (NPRS, 0-10), mean and at night • QoL (SF-36) • PROM (ABD and ER) • Patient satisfaction (0-5)

(continued)

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Table 1. Main Characteristics of Populations, Interventions, and Outcome Measures of Included Randomized Trials (continued)

Source	Participants, No. (participants who completed study, No.)	Mean age, y	Duration of symptoms	Participants per treatment group, No. (participants per treatment group who completed study, No.)	Treatment duration (follow-up)	Outcome measures
Lee et al,[33] 1974[a]	65 (unknown)	57.3	Between 3 mo and 5 y	• Physiotherapy (heat and exercises); n = 17 (unknown) • Analgesics; n = 15 (unknown) • IA corticosteroid with physiotherapy (heat and exercises) n = 15 (unknown) • Bicep tendon corticosteroid with physiotherapy (heat and exercises) n = 18 (unknown)	Details regarding number of injections and duration of physiotherapy and analgesics not given (0, 1, 2, 3, 4, 5, and 6 wk)	• AROM (ABD) • PROM (ABD, ER, and IR)
Lee et al,[34] 2017[a]	64 (64)	54.9	Mean, 8 mo	• IA corticosteroid; n = 32 (32) • IA corticosteroid with arthrographic distension; n = 32 (32) • Both groups received 6-wk home exercise program	Single injection (0, 3, 6, and 12 wk)	• Pain (VAS, 0-10), global • Functional disability (SPADI) • PROM (ABD, FL, EXT, ER, and IR)
Lee et al,[35] 2017[a]	30 (unknown)	58.7	Not stated	• ESWT with physiotherapy (hot packs, US, and electrotherapy); n = 15 (unknown) • Physiotherapy (hot packs, US, and electrotherapy); n = 15 (unknown) • No home exercise program	Both treatments 3 times weekly for 4 wk (0 and 4 wk)	• Pain (VAS, 0-10), unspecified • ROM (FL, ER), unknown if active or passive
Lim et al,[73] 2014	68 (62)	53.8	Mean, 7.3 mo	• IA corticosteroid; n = 34 (33) • IA sodium hyaluronate; n = 34 (29) • Both groups received home exercise program	Single injection of IA corticosteroid; 3 injections sodium hyaluronate (0, 2, and 12 wk)	• Pain (VAS, 0-10), unspecified • Function (ASES and CM) • AROM (FL, ER, and IR)
Lo et al,[36] 2020[a]	21 (unknown)	59.6	Everyone >3 mo	• Electroacupuncture with physiotherapy; n = 11 (unknown) • Sham electroacupuncture with physiotherapy; n = 10 (unknown) • Physiotherapy included hot packs, exercises, and ice packs	18 sessions during 6-9 wk (0, 1, 3, and 6 mo)	• Pain (VAS, 0-10), with movement • AROM (FL, EXT, ABD, ADD, ER, and IR) • PROM (FL, EXT, ABD, ADD, ER, and IR) • Functional disability (SPADI)
Lorbach et al,[74] 2010	40 (unknown)	51	Mean, 11 mo	• IA corticosteroid; n = 20 (unknown) • Oral corticosteroid; n = 20 (unknown) • Both groups received supervised physiotherapy (unspecified) and 8-wk home exercise program	IA corticosteroid 3 injections during 8 wk; oral corticosteroid for 25 d (0, 4, 8, and 12, 6 and 12 mo)	• Function (CM, SST, and VAS) • Pain (VAS, 0-10, reversed), unspecified • PROM (FL, ER, and IR) • Patient satisfaction (VAS)
Ma et al,[37] 2006[a]	75 (unknown)	54.8	Mean, 25.8 wk, everyone >3 mo	• Physiotherapy; n = 30 (unknown) • Acupuncture; n = 30 (unknown) • Physiotherapy with acupuncture; n = 15 (unknown) • Physiotherapy included hot pack, mobilizations, and exercises; no home exercise program	Acupuncture twice weekly for 4 wk; physiotherapy 5 times weekly for 4 wk (0, 2, and 4 wk)	• Pain (VAS, 0-10), at rest and with movement • AROM (ABD, FL, EXT, ER, and IR) • PROM (ABD, FL, EXT, ER, and IR) • QoL (SF-36)
Maryam et al,[38] 2012[a]	87 (69)	53.6	Mean, 5.8 mo, everyone <1 y	• Physiotherapy; n = 27 (8) • IA corticosteroid with physiotherapy; n = 29 (14) • IA corticosteroid; n = 31 (14) • Physiotherapy included TENS, exercises, and ice; all groups received home exercise program of unknown duration	Single injection of IA corticosteroid single injection; 10 sessions of physiotherapy (0 and 6 wk)	• Functional disability (SPADI) • Pain (SPADI, 0-100), unspecified • AROM (ABD, FL, and ER) • PROM (ABD, FL, and ER)
Mukherjee et al,[75] 2017	60 (56)	50.4	Mean, 6.3 mo	• ACR; n = 30 (28) • IA corticosteroid; n = 30 (28) • Both groups received home exercise program of unknown duration	Single treatment (0, 4, 8, 12, 16, and 20 wk)	• Pain (VAS, 0-10), unspecified • PROM (ABD, EXT, ER, and IR) • Function (CM)
Mun and Baek,[76] 2016	136 (121)	53	Mean, 6.5 mo, everyone >3 mo	• Arthrographic distension with IA corticosteroid and MUA; n = 67 (60) • IA corticosteroid; n = 69 (61) • Both groups received supervised exercises for 1 mo followed by home exercise program of unknown duration	Single injection (0, 2, 6, 12, 24, and 48 wk)	• Pain (VAS, 0-10), unspecified • Function (CM) • Satisfaction (VAS) • PROM (FL, ER, and IR)
Oh et al,[39] 2011[a]	71 (58)	57	Mean, 6.6 mo	• IA corticosteroid; n = 37 (31) • SA corticosteroid; n = 34 (27) • Both groups received home exercise program of unknown duration	Single injection (0, 3, 6, and 12 wk)	• Pain (VAS, 0-10), unspecified • Function (CM) • PROM (ABD, ER, and IR)

(continued)

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Table 1. Main Characteristics of Populations, Interventions, and Outcome Measures of Included Randomized Trials (continued)

Source	Participants, No. (participants who completed study, No.)	Mean age, y	Duration of symptoms	Participants per treatment group, No. (participants per treatment group who completed study, No.)	Treatment duration (follow-up)	Outcome measures
Park and Hwnag,[40] 2000[a]	55	56.5	Not stated	• IA corticosteroid with arthrographic distension; n = 28 (unknown) • IA corticosteroid; n = 27 (unknown) • Unclear whether home exercise program was used	Single injection (0, 1 wk, 1 mo)	• Pain (VAS, 0-10) • AROM (ABD, FL, ER, and IR) • Cyriax stages of arthritis
Park et al,[77] 2013	90 (90)	55.8	Mean (range), 5.3 mo (3-9 mo)	• Arthrographic distension with sodium hyaluronate; n = 45 (45) • IA corticosteroid n = 45 (45) • Both groups received home exercise program of unknown duration	3 injections during 4 wk (0, 2, and 6 wk)	• Functional Disability (SPADI) • Pain (VAS and SPADI) • PROM (ABD, FL, and ER) • Complications
Park et al,[78] 2014	53 (unknown)	56	Range, 3-9 mo	• Arthrographic distension with IA corticosteroid, intensive mobilization, and general physiotherapy; n = 16 (unknown) • Arthrographic distension with IA corticosteroid and general physiotherapy; n = 12 (unknown) • Intensive mobilization with general physiotherapy; n = 14 (unknown) • General physiotherapy; n = 11 (unknown) • General physiotherapy included hot packs, TENS, and US; all groups received home exercise program of unknown duration	All treatments twice weekly for 4 wk (0 and 4 wk)	• Pain (VAS, 0-10), unspecified • Functional disability (SPADI) • Function (CM) • AROM (ABD, FL, ER, and IR)
Park et al,[41] 2015	30 (unknown)	53.5	Not stated	• ESWT with physiotherapy; n = 15 (unknown) • Physiotherapy; n = 15 (unknown) • Physiotherapy included hot packs, US, and electrotherapy; no home exercise program	Twice weekly for 6 wk (0 and 4 wk)	• Pain (VAS, 0-10), unspecified • Function (patient-specific functional scales)
Prestgaard et al,[42] 2015[a]	122 (114)	54.5	Mean (range), 15 wk (1-6 mo)	• IA corticosteroid; n = 42 (39) • IA with rotator interval corticosteroid; n = 40 (39) • Sham injection (IA with rotator interval local anesthetic); n = 40 (36) • No home exercise program	Single injection (0, 3, 6, 12, and 26 wk)	• Pain (VAS, 0-10), general and at night • Shoulder disability (SPADI) • AROM (ABD, FL, and ER) • Use of analgesics • QoL (EQ-5D)
Pushpasekaran et al,[79] 2017	85 (80)	56.3	Mean (range), 15.2 mo (2.5-49 mo)	• IA corticosteroid; n = 43 (40) • 3-site injection (IA, SA, and subcoracoid); n = 42 (40) • Both groups received NSAIDs, physiotherapy (US), and 4-wk home exercise program for prior to intervention	2 treatments during 3 wk (0, 3, and 6 wk, 6 mo)	• Function (CM)
Quaraishi et al,[80] 2007	36 individuals with 38 shoulders (33)	55.2	Mean (range), 33.7 wk (12-76 wk)	• Arthrographic distension; n = 19 (18) • MUA with IA corticosteroid n = 17 (15) • Both groups received home exercise program of unknown duration	Single treatment (0, 2 mo, 6 mo)	• Pain (VAS, 0-10), unspecified • Function (CM) • PROM (ABD, FL, ER, and IR) • Satisfaction
Ranalletta et al,[43] 2015[a]	74 (69)	63.4	Mean, 12 wk, everyone >1 mo	• IA corticosteroid; n = 36 (34) • NSAID; n = 38 (35) • Both groups received supervised exercises and 12-wk home exercise program	Single IA corticosteroid injection; NSAID twice a day for unknown duration (0, 2, 4, 8, and 12)	• Pain (VAS, 0-10), overall • Function (ASES and CM) • Functional disability (qDASH) • PROM (ABD, FL, EXT, ER, and IR)
Reza et al,[44] 2013[a]	100 (100)	59.5	Mean, 115 d, everyone >3 mo	• IA corticosteroid; n = 50 (50) • Arthrographic distention with IA corticosteroid; n = 50 (50) • Both groups received home exercise program of unknown duration	Single injection (0, 2 d, 12 wk)	• Pain (VAS, 0-10), unspecified • ROM (ABD, FL, EXT, ER, and IR) unknown whether active or passive
Rizk et al,[45] 1991[a]	48 (44)	55	Mean (range), 13.2 wk (8-18 wk)	• IA corticosteroid; n = 16 (15) • Intrabursal (SA) corticosteroid; n = 16 (14) • IA LA; n = 8 (8) • Intrabursal (SA) LA; n = 8 (7) • All groups received home exercise program of unknown duration	3 injections during 2 wk (weekly 0-11 wk, 15 wk, and 6 mo)	• PROM (total ROM) • Pain (VAS, 0-5), unspecified

(continued)

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Table 1. Main Characteristics of Populations, Interventions, and Outcome Measures of Included Randomized Trials (continued)

Source	Participants, No. (participants who completed study, No.)	Mean age, y	Duration of symptoms	Participants per treatment group, No. (participants per treatment group who completed study, No.)	Treatment duration (follow-up)	Outcome measures
Roh et al,[46] 2011[a]	50 (45); patients with diabetes	54.9	Mean (range), 6.4 wk (4 wk-6 mo)	• IA corticosteroid; n = 25 (23) • No treatment; n = 25 (22) • Both groups received home exercise program of unknown duration	Single injection (0, 4, 12, and 24 wk)	• PROM (FL, ER, and IR) • Pain (VAS, 0-10), unspecified • Function (ASES)
Rouhani et al,[81] 2016	72 (64)	52.8	Not stated	• Calcitonin nasal spray with physiotherapy (details not stated); n = 36 (32) • Placebo spray with physiotherapy (details not stated); n = 36 (32) • Both groups received oral NSAIDs	Calcitonin and placebo spray for 6 weeks (0 and 6 wk)	• Pain (VAS, 0-10), overall and at night • Functional disability (DASH and SPADI) • QoL (HAQ) • PROM (ABD, FL, and ER)
Ryans et al,[47] 2005[a]	80 (78)	54.1	Mean, 10.4 wk, everyone >4 wk	• IA corticosteroid with physiotherapy; n = 20 (20) • IA corticosteroid; n = 20 (19) • IA placebo (normal saline) with physiotherapy; n = 20 (20) • IA placebo; n = 20 (19) • Physiotherapy included PNF, mobilizations, electrotherapy, and exercises; all groups received home exercise program of unknown duration	Single injection; physiotherapy of unknown duration (0, 6, and 16 wk)	• AROM (ABD, FL, ER, and IR) • PROM (ABD, FL, ER, and IR) • Pain (VAS, 0-100), at rest • Function (VAS and HAQ) • Functional disability (SDQ) • QoL (SF-36)
Schröder et al,[82] 2017	60 (60)	53.5	Mean, 15.6 mo	• Acupuncture; n = 30 (30) • Sham acupuncture; n = 30 (30) • No home exercise program	Single session (baseline and postsession)	• Function (CM) • Pain (CM, 0-15)
Schydlowsky et al,[83] 2012	18 (14)	51	Everyone >3 wk	• IA adalimumab; n = 10 (6) • IA corticosteroid; n = 8 (8) • No home exercise program	1 injection every 2 wk to 3 injections (0, 2, 4, 8, 12, and 24 wk)	• Function (CM) • Functional disability (SPADI) • AROM (ABD, FL, and ER) • PROM (ABD, FL, and ER) • Pain (SRQ)
Sharma et al,[48] 2016[a]	106 (87)	53	Median (range), 6.8 mo (2-37 mo)	• IA corticosteroid; n = 36 (34) • IA corticosteroid with arthrographic distension; n = 34 (32) • Treatment as usual (physiotherapy, analgesia, or no treatment); n = 36 (21) • No home exercise program	4 injections during 1 mo (0, 4 and 8 wk, 12 mo)	• Functional disability (SPADI) • Pain (NRS, 0-10), mean • PROM (ABD, and ER, IR)
Shin and Lee,[49] 2013[a]	191 (158)	55.7	>3 mo, mean 7.2 mo	• SA corticosteroid; n = 49 (41) • IA corticosteroid; n = 48 (42) • SA with IA corticosteroid; n = 47 (39) • NSAID; n = 49 (36) • All groups received home exercise program of >3-mo duration	Single SA and IA injection; oral NSAID for 6 wk (0, 2, 4, 8, 16, and 24 wk)	• Function (ASES) • Pain (VAS, 0-10), unspecified • Treatment satisfaction (VAS) • AROM (FL, ER, and IR)
Sun et al,[84] 2001	35 (30)	56.3	Mean, 6.5 mo	• No treatment; n = 22 (18) • Acupuncture; n = 13 (12) • Both groups received supervised exercises for 6 wk and home exercise program of unknown duration	Acupuncture twice weekly for 6 wk (0, 6, 20 wk)	• Function (CM)
Sun et al,[50] 2018[a]	97 (77)	53.9	Mean, 15.2 wk, everyone <9 mo	• IA corticosteroid; n = 30 (24) • SA corticosteroid; n = 34 (26) • Rotator interval corticosteroid; n = 33 (27) • All groups received home exercise program of unknown duration	Single injection (0, 4, 8, and 12 wk)	• Pain (VAS, 0-10), unspecified • Function (CM) • Functional disability (DASH) • PROM (ABD, FL, ER, and IR)
Tveitå et al,[51] 2008[a]	76 (69)	51.5	Mean, 7 mo, everyone 3 mo-2 y	• Arthrographic distension with IA corticosteroid; n = 39 (36) • IA corticosteroid; n = 37 (33) • No home exercise program	3 injection during 4 wk (0 and 10 wk)	• Functional disability (SPADI) • AROM (ABD, FL, ER, and IR) • PROM (ABD, FL, ER, and IR)
Vahdatpour et al,[52] 2014[a]	40 (36)	58.2	Not stated	• ESWT; n = 20 (19) • Sham ESWT; n = 20 (17) • All patients had a single IA corticosteroid injection at time of inclusion in the study and received home exercise program	Once weekly for 4 wk (0, 4 and 12 wk, 6 mo)	• Pain (SPADI 0-100), unspecified • Functional disability (SPADI) • PROM (ABD, FL, EXT, ER, and IR)

(continued)

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Table 1. Main Characteristics of Populations, Interventions, and Outcome Measures of Included Randomized Trials (continued)

Source	Participants, No. (participants who completed study, No.)	Mean age, y	Duration of symptoms	Participants per treatment group, No. (participants per treatment group who completed study, No.)	Treatment duration (follow-up)	Outcome measures
van der Windt,[53] et al 1998[a]	109 (103)	58.5	82 with <6 mo; 27 with >6 mo	• Physiotherapy (mobilizations and exercises) n = 56 (54) • IA corticosteroid; n = 53 (49) • Physiotherapy group received ice and hot packs and electrotherapy at the physiotherapist's discretion; no home exercise program	Physiotherapy for 6 wk; IA corticosteroid as many as 3 injections during 6 wk (0, 3, 7, 13,26, and 52 wk)	• Satisfaction (0-5) • Pain (VAS, 0-100), during day and at night • Functional disability (SDQ) • PROM (ABD and ER)
Widiastuti-Samekto and Sianturi,[85] 2004	28 (27)	40-69	Range, 1-6 mo	• IA corticosteroid with physiotherapy; n = 13 (13) • Oral corticosteroid with physiotherapy; n = 15 (14) • Physiotherapy was supervised and included 20 sessions of mobilizations and ice and hot packs; no home exercise program	Single IA corticosteroid injection; oral corticosteroid for 3 wk (0, 1, 2, and 3 wk)	• Treatment success (90% improvement in ABD and ER PROM) • Pain (VAS, 0-10), unspecified
Yoon et al,[54] 2016[a]	90 (86)	55	Mean, 9 mo	• IA corticosteroid; n = 30 (29) • SA corticosteroid; n = 30 (29) • Arthrographic distension with IA corticosteroid; n = 30 (28) • All groups received home exercise program of unknown duration	Single injection (0, 1, 3, and 6 mo)	• Pain (VAS, 0-10), unspecified • Function (SST and CM) • PROM (FL, ER, and IR)

Abbreviations: ABD, abduction; ACR, arthroscopic capsular release; AROM, active range of movement; ASES, American Shoulder and Elbow Surgeons questionnaire; BPI-SF, Brief Pain Inventory–Short Form; CM, Constant-Murley score; DASH, Disabilities of the Arm, Shoulder, and Hand questionnaire; EA, electroacupuncture; ELE, elevation; EQ-5D, Euro-Qol–5 Dimensions questionnaire; ER, external rotation; ESWT, extracorporeal shock wave therapy; EXT, extension; FL, flexion; HAQ, Health Assessment Questionnaire; IA, intra-articular; IFE, interferential electrotherapy; IR, internal rotation; IRR, infrared radiotherapy; LA, local anesthetic; MPQ, McGill Pain Questionnaire; MUA, manipulation under anesthesia; NPRS, numerical pain rating scale; NSAID, nonsteroidal anti-inflammatory drug; OSS, Oxford Shoulder Score; PET, problem elicitation technique; PNF, proprioceptive neuromuscular facilitations; PROM, passive range of movement; qDASH, quick DASH; QoL, quality of life; SA, subacromial; SDQ, Shoulder Disabilities Questionnaire; SF-36, 36-item short-form survey; SPADI, Shoulder Pain and Disability Index; SRQ, self-reporting questionnaire; SST, Simple Shoulder Test; TDP, transcutaneous infrared thermotherapy; TENS, transcutaneous electrical nerve stimulation; UCLA, University of California Los Angeles questionnaire; US, ultrasound; VAS, visual analog scale.

[a] Studies included in meta-analyses.

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Table 2. Results of Pairwise Comparisons of Interventions of the Included Studies

Source	Pain	Function	ROM ER	ROM ABD	ROM FL	Satisfaction or QoL
Arthrographic distension with IA corticosteroid vs IA corticosteroid only						
Jacobs et al,[41] 1991	NA	NA	No change at 4 mo	No change at 4 mo	No change at 4 mo	NA
Gam et al,[29] 1998	No change at 3, 6, or 12 wk	NA	No change at 3 and 6 wk; increase at 12 wk	No change at 3, 6, or 12 wk	Increase at 3, 6, and 12 wk	NA
Tveitå et al,[51] 2008	NA	No change at 10 wk	No change at 10 wk	No change at 10 wk	No change at 10 wk	NA
Reza et al,[44] 2013	Decrease at 12 wk	NA	Increase at 12 wk	Increase at 12 wk	Increase at 12 wk	NA
Sharma et al,[48] 2016	No change at 4 or 8 wk	No change at 4, 8, or 12 mo	No change at 4 or 8 wk	No change at 4 or 8 wk	NA	NA
Park and Hwnag,[40] 2000	No change at 1 or 4 wk	NA	No change at 1 or 4 wk	Increase at 1 wk; no change at 4 wk	Increase at 1 and 4 wk	NA
Yoon et al,[54] 2016	Increase at 4 wk; no change at 12 wk or 6 mo	Increase at 4 wk and 12 wk; no change at 6 mo	Increase at 4 wk; no change at 12 wk or 6 mo	NA	Increase at 4 wk; no change at 12 wk or 6 mo	NA
Lee et al,[34] 2017	No change at 3, 6, or 12 wk	No change at 3, 6, or 12 wk	No change at 3, 6, or 12 wk	No change at 3, 6, or 12 wk	No change at 3, 6, or 12 wk	NA
Quality of evidence	Decrease at early short-term (high)[a]; decrease at late short-term (high)[a]	No change at early short-term (moderate)[a]; no change at late short-term (high)[a]	No change at early short-term (high)[a]; no change at late short-term (high)[a]	No change at early short-term; no change at late short-term	Increase at early short-term; no change at late short-term	NA
Physiotherapy vs no treatment or placebo						
Calis et al,[24] 2006	No change at 2 or 12 wk	Decrease at 2 and 12 wk	Increase at 2 and 12 wk	Increase at 2 and 12 wk	NA	NA
Carette et al,[25] 2003	No change at 6 wk, 12 wk, 6 mo, or 12 mo	No change at 6 wk, 12 wk, 6 mo, or 12 mo	No change at 6 wk, 12 wk, 6 mo, or 12 mo	No change at 6 wk, 12 wk, 6 mo, or 12 mo	No change at 6 wk, 6 mo, or 12 mo; increase at 12 wk	No change at 6 wk, 12 wk, 6 mo, or 12 mo
Bulgen et al,[23] 1986	No change at 6 wk or 6 mo	NA	No change at 6 wk or 6 mo	No change at 6 wk or 6 mo	No change at 6 wk or 6 mo	NA
Lee et al,[33] 1974	NA	NA	Increase at 1-6 wk	Increase at 1-6 wk	NA	NA
Quality of evidence	No change at early short-term	NA	Increase at early short-term (moderate)[a,b]	No change at early short-term	NA	NA
IA corticosteroid vs IA no treatment or placebo						
Bal et al,[22] 2008	No change at 2 wk or 12 wk	Increase at 2 wk; no change at 12 wk	No change at 2 wk or 12 wk	Increase at 2 wk; no change at 12 wk	No change at 2 wk or 12 wk	NA
Calis et al,[24] 2006	No change at 2 wk; decrease at 12 wk	No change at 2 wk; increase at 12 wk	No change at 2 or 12 wk	No change at 2 wk; increase at 12 wk	NA	NA
Carette et al,[25] 2003	Decrease at 6 and 12 wk; no change at 6 or 12 mo	Increase at 6 and 12 wk; no change at 6 or 12 mo	Increase at 6 and 12 wk; no change at 6 or 12 mo	No change at 6 wk, 6 mo, or 12 mo; increase at 12 wk	No change at 6 wk, 6 mo, or 12 mo; increase at 12 wk	No change at 6 wk, 12 wk, 6 mo, or 12 mo
Bulgen et al,[23] 1986	No change at 6 wk or 6 mo	NA	Increase at 6 wk; no change at 6 mo	Increase at 6 wk; no change at 6 mo	Increase at 6 wk; no change at 6 mo	NA
Dehghan et al,[28] 2013	No change at 2, 6, 12, or 24 wk	NA	No change at 2, 6, 12, or 24 wk	No change at 2, 6, 12, or 24 wk	No change at 2, 6, 12, or 24 wk	NA
Ranalletta et al,[43] 2015	Decrease at 2, 4, and 8 wk; no change at 12 wk	Increase at 2, 4, 8, and 12 wk	Increase at 2 wk; no change at 4, 8, or 12 wk	Increase at 2, 4, 8, and 12 wk	Increase at 2, 4, 8, and 12 wk	NA
Roh et al,[46] 2011	Decrease at 4 wk; no change at 12 wk or 6 mo	Increase at 12 wk; no change at 4 wk or 6 mo	No change at 4 wk, 12 wk, or 6 mo	NA	No change at 4 wk or 6 mo; increase at 12 wk	NA
Sharma et al,[48] 2016	Decrease at 4 and 8 wk	Increase at 4 and 8 wk; no change at 12 mo	Increase at 4 and 8 wk	Increase at 4 and 8 wk	NA	NA
Shin and Lee,[49] 2013	Decrease at 2, 4, and 8 wk and 4 mo; no change at 6 mo	Increase at 2, 4, and 8 wk and 4 mo; no change at 6 mo	Increase at 2, 4, and 8 wk and 4 mo; no change at 6 mo	NA	Increase at 2, 4, and 8 wk and 4 mo; no change at 6 mo	NA
Rizk et al,[45] 1991	No change at 1-11 wk and 4 and 6 mo	NA	No change at 11 wk or 6 mo	No change at 11 wk or 6 mo	No change at 11 wk or 6 mo	NA
Ryans et al,[47] 2005	No change at 6 wk or 4 mo	No change at 6 wk or 4 mo	No change at 6 wk or 4 mo	No change at 6 wk or 4 mo	NA	NA
Prestgaard et al,[42] 2015	Decrease at 6 and 12 wk; no change at 3 wk or 6 mo	Increase at 3, 6, and 12 wk; no change at 6 mo	Increase at 6 and 12 wk; no change at 3 wk or 6 mo	No change at 3, 6, or 12 wk or 6 mo	Increase at 6 and 12 wk; no change at 3 wk or 6 mo	Increase at 6 and 12 wk; no change at 3 wk or 6 mo

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Table 2. Results of Pairwise Comparisons of Interventions of the Included Studies (continued)

Source	Pain	Function	ROM ER	ROM ABD	ROM FL	Satisfaction or QoL
Quality of evidence	Decrease at early short-term (high)[a,b]; decrease at late short-term (moderate)[a,b]; no change at mid-term (moderate)[a]	Increase at early short-term (moderate)[a,b]; increase at late short-term (moderate)[a,b]; increase at mid-term (moderate)[a]	Increase at early short-term (high)[a]; increase at late short-term (high)[a]; no change at mid-term (moderate)[a]	No change at early short-term; increase at late short-term; no change at mid-term	Increase at early short-term; increase at late short-term; no change at mid-term	No change at early short-term; no change at mid-term
IA corticosteroid with physiotherapy vs no treatment or placebo						
Ryans et al,[47] 2005	No change at 6 wk or 4 mo	Increase at 6 wk; no change at 4 mo	No change at 6 wk or 4 mo	NA	NA	NA
Carette et al,[25] 2003	Decrease at 6 and 12 wk; no change at 6 or 12 mo	Increase at 6 and 12 wk; no change at 6 or 12 mo	Increase at 6 wk, 12 wk, and 6 mo; no change at 12 mo	Increase at 6 wk, 12 wk, and 6 mo; no change at 12 mo	Increase at 6 wk, 12 wk, and 6 mo; no change at 12 mo	No change at 6 wk, 12 wk, 6 mo, or 12 mo
Lee et al,[33] 1974	NA	NA	Increase at 1-6 wk	Increase at 1-6 wk	NA	NA
Quality of evidence	NA	NA	Increase at early short-term (high)[a,b]	NA	NA	NA
IA corticosteroid vs physiotherapy						
Arslan and Celiker,[21] 2001	No change at 2 or 12 wk	NA	No change at 2 or 12 wk	No change at 2 or 12 wk	No change at 2 or 12 wk	NA
Bulgen at al,[23] 1984	No change at 6 wk or 6 mo	NA	Increase at 6 wk; no change at 6 mo	Increase at 6 wk; no change at 6 mo	Increase at 6 wk; no change at 6 mo	NA
Carette et al,[25] 2003	Decrease at 6 wk; no change at 12 wk, 6 mo, or 12 mo	Increase at 6 wk; No change at 12 wk, 6 mo, or 12 mo	No change at 6 wk, 12 wk, 6 mo, or 12 mo	No change at 6 wk, 12 wk, 6 mo, or 12 mo	No change at 6 wk, 12 wk, 6 mo, or 12 mo	No change at 6 wk, 12 wk, 6 mo, or 12 mo
Calis et al,[24] 2006	No change at 2 or 12 wk	No change at 2 or 12 wk	Decrease at 2 or 12 wk	No change at 2 or 12 wk	NA	NA
van der Windt et al,[53] 1998	Decrease at 3, 7, and 13 wk and 6 and 12 mo	Increase at 3, 7, and 13 wk and 6 and 12 mo	Increase at 3 wk, 7 wk, and 6 mo	No change at 3 wk, 7 wk, and 6 mo	NA	NA
Dacre et al,[27] 1989	No change at 6 wk or 6 mo	NA	No change at 6 wk or 6 mo	No change at 6 wk or 6 mo	NA	NA
Maryam et al,[38] 2012	No change at 6 wk or 6 mo	No change at 6 wk or 6 mo	No change at 6 wk or 6 mo	No change at 6 wk or 6 mo	No change at 6 wk or 6 mo	NA
Ryans et al,[47] 2005; with home exercise	No change at 6 wk or 4 mo	No change at 6 wk or 4 mo	No change at 6 wk or 4 mo	NA	NA	NA
Quality of evidence	No change at early short-term (moderate)[a]; decrease at late short-term (high)[a,b]; no change at mid-term (low)	Increase at early short-term (moderate)[a,b]; no change at late short-term (moderate)[a]; increase at mid-term (moderate)[a]	No change at early short-term (moderate)[a]; no change at late short-term (high)[a]; Increase at mid-term (moderate)[a]	No change at early short-term; no change at late short-term; no change at mid-term	No change at early short-term; no change at late short-term; no change at mid-term	NA
IA corticosteroid with physiotherapy vs IA corticosteroid only						
Kraal et al,[32] 2018	No change at 6 wk, 12 wk, or 6 mo	Increase at 6 wk; no change at 12 wk or 6 mo	Increase at 6 wk and 12 wk; no change at 6 mo	Increase at 6 wk and 12 wk; no change at 6 mo	Increase at 6 wk; no change at 12 wk or 6 mo	No change at 6 wk, 12 wk, or 6 mo
Dacre et al,[27] 1989	No change at 6 wk or 6 mo	NA	No change at 6 wk or 6 mo	No change at 6 wk or 6 mo	NA	NA
Maryam et al,[38] 2012	No change at 6 wk or 6 mo	No change at 6 wk or 6 mo	No change at 6 wk or 6 mo	No change at 6 wk or 6 mo	No change at 6 wk or 6 mo	NA
Carette et al,[25] 2003	No change at 6 wk, 12 wk, 6 mo, or 12 mo	No change at 6 wk, 12 wk, 6 mo, or 12 mo	No change at 6 wk, 12 wk, 6 mo, or 12 mo	No change at 6 wk, 12 wk, 6 mo, or 12 mo	Increase at 6 wk, 12 wk, and 6 mo; no change at 12 mo	No change at 6 wk, 12 wk, 6 mo, or 12 mo
Ryans et al,[47] 2005	No change at 6 wk or 4 mo	No change at 6 wk or 4 mo	No change at 6 wk or 4 mo	NA	NA	NAs
Quality of evidence	No change at early short-term (moderate)[a]; no change at mid-term (moderate)[a]	No change at early short-term (low)[a]; no change at mid-term (high)[a]	Increase at early short-term (moderate)[a,b]; no change at mid-term (high)[a]	No change at early short-term; no change at mid-term	Increase at early short-term; no change at mid-term	No change at early short-term; no change at late short-term; no change at mid-term
IA corticosteroid with physiotherapy vs physiotherapy only						
Carette et al,[25] 2003	Decrease at 6 wk; no change at 12 wk, 6 mo, or 12 mo	Increase at 6 wk; no change at 12 wk, 6 mo, or 12 mo	Increase at 6 wk, 12 wk, and 6 mo; no change at 12 mo	Increase at 6 and 12 wk; no change at 6 or 12 mo	Increase at 6 and 12 wk; no change at 6 mo or 12 mo	No change at 6 wk, 12 wk, 6 mo, or 12 mo
Dacre et al,[27] 1989	No change at 6 wk or 6 mo	NA	No change at 6 wk or 6 mo	No change at 6 wk or 6 mo	NA	NA
Maryam et al,[38] 2012	Decrease at 6 wk; no change at 6 mo	Increase at 6 wk; no change at 6 mo	No change at 6 wk or 6 mo	No change at 6 wk or 6 mo	No change at 6 wk or 6 mo	NA

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Table 2. Results of Pairwise Comparisons of Interventions of the Included Studies (continued)

Source	Pain	Function	ROM ER	ROM ABD	ROM FL	Satisfaction or QoL
Ryans et al,[47] 2005	No change at 6 wk or 4 mo	Increase at 6 wk; no change at 4 mo	No change at 6 wk or 4 mo	NA	NA	NA
Lee et al,[33] 1974	NA	NA	No change at 1, 3, 4, 5, or 6 wk; increase at 2 wk	No change at 1, 3, 4, 5, or 6 wk; increase at 2 wk	NA	NA
Quality of evidence	No change at early short-term (moderate)[a]; No change at mid-term (moderate)[a]	Increase at early short-term (low)[a,b]; no change at mid-term (low)[a]	No change at early short-term (moderate)[a]; no change at mid-term (high)[a]	No change at early short-term; no change at mid-term	No change at mid-term	NA
IA corticosteroid vs SA corticosteroid						
Sun et al,[50] 2018	Decrease at 4, 8, and 12 wk	Increase at 4, 8, and 12 wk	Increase at 4, 8, and 12 wk	Increase at 4, 8, and 12 wk	Increase at 4, 8, and 12 wk	NA
Khallaf et al,[30] 2018	No change at 12 wk	No change at 12 wk	No change at 12 wk	No change at 12 wk	No change at 12 wk	NA
Yoon et al,[54] 2016	No change at 4 wk, 12 wk, or 6 mo	No change at 4 wk, 12 wk, or 6 mo	No change at 4 wk, 12 wk, or 6 mo	NA	No change at 4 wk, 12 wk, or 6 mo	NA
Oh et al,[39] 2011	Decrease at 3 wk; no change at 6 wk or 12 wk	No change at 3 wk, 6 wk, or 12 wk	No change at 3 wk, 6 wk, or 12 wk	No change at 3 wk, 6 wk, or 12 wk	NA	NA
Shin and Lee,[49] 2013	No change at 2 wk, 4 wk, 8 wk, 4 mo, or 6 mo	No change at 2 wk, 4 wk, 8 wk, 4 mo, or 6 mo	No change at 2 wk, 4 wk, 8 wk, 4 mo, or 6 mo	NA	No change at 2 wk, 4 wk, 8 wk, 4 mo, or 6 mo	No change at 2 wk, 4 wk, 8 wk, 4 mo, or 6 mo
Cho et al,[26] 2016	Decrease at 12 wk	Increase at 12 wk	No change at 12 wk	No change at 12 wk	No change at 12 wk	NA
Rizk et al,[45] 1991	No change at 1-11 wk, 4 mo, or 6 mo	NA	No change at 11 wk or 6 mo	No change at 11 wk or 6 mo	No change at 11 wk or 6 mo	NA
Quality of evidence	Decrease at early short-term (moderate)[a]; no change at late short-term (moderate)[a]; no change at mid-term (moderate)[a]	No change at early short-term (high)[a]; increase at late short-term (high)[a]	No change at early short-term (high)[a]; no change at late short-term (high)[a]; no change at mid-term (high)[a]	Inconclusive at late short-term; no change at late short-term	No change at early short-term; no change at late short-term; No change at mid-term	NA
Acupuncture with physiotherapy vs physiotherapy only, with or without placebo acupuncture						
Lo et al,[36] 2020	No change at 4 wk, 12 wk, or 6 mo	No change at 4 wk, 12 wk, or 6 mo	No change at 4 wk, 12 wk, or 6 mo	No change at 4 wk, 12 wk, or 6 mo	No change at 4 wk, 12 wk, or 6 mo	NA
Koh et al,[31] 2013	No change at 2, 4, or 12 wk; increase at8 wk,	No change at 2 or 4 wk; increase at 8 and 12 wk	No change at 2, 4, 8, or 12 wk	No change at 2, 4, 8, or 12 wk	No change at 2, 4, 8, or 12 wk	NA
Ma et al,[37] 2006	Decrease at 4 wk	NA	No change at 4 wk	No change at 4 wk	No change at 4 wk	NA
Quality of evidence	No change at early short-term (low)[a]	NA	No change at early short-term (high)[a]	No change at early short-term; no change at late short-term	No change at early short-term; no change at late short-term	NA
ESWT with physiotherapy vs physiotherapy only with or without sham ESWT						
Vahdatpour et al,[52] 2014	Decrease at 4 wk, 12 wk, and 6 mo	Increase at 4 wk, 12 wk, and 6 mo	Increase at 4 wk, 12 wk, and 6 mo	Increase at 4 wk, 12 wk, and 6 mo	Increase at 4 wk, 12 wk, and 6 mo	NA
Lee et al,[35] 2017	Decrease at 4 wk	NA	Increase at 4 wk	NA	Increase at 4 wk	NA
Park et al,[77] 2015	Decrease at 4 wk	Increase at 4 wk	NA	NA	NA	NA
Quality of evidence	Decrease at early short-term (very low)[c]	NA	NA	NA	Increase at early short-term	NA

Abbreviations: ABD, abduction; ER, external rotation; ESWT, extracorporeal shock wave therapy; FL, flexion; IA, intra-articular; NA, not applicable; QoL, quality of life; ROM, range of movement; SA, subacromial.

[a] Meta-analysis undertaken.

[b] Results of meta-analysis clinically and statistically significant.

[c] Meta-analysis abandoned because of very high statistical inconsistency ($I^2 > 75\%$).

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CI, −1.8 to −0.9 VAS points; $P < .001$), ER ROM (high certainty; MD, 4.7°; 95% CI, 2.7° to 6.6°; $P < .001$), and function (high certainty; SMD, 0.6; 95% CI, 0.3 to 0.9; $P < .001$) and late short-term pain (moderate certainty; MD, −1.0 VAS points; −1.5 to −0.5 VAS points; $P < .001$), ER ROM (high certainty; MD, 6.8°; 95% CI, 3.4° to 10.2°; $P < .001$), and function (moderate certainty; SMD, 0.6; 95% CI, 0.3 to 0.8; $P < .001$).

Mid-term | IA corticosteroid was associated with better outcomes than control only for function (moderate certainty; SMD, 0.3; 95% CI, 0.1 to 0.5; $P = .01$). However, effects for pain and ER ROM were similar (moderate certainty for both).

Physiotherapy vs No Treatment or Placebo

Physiotherapy was found to be associated with improved outcomes compared with control in the early short-term for ER ROM (moderate certainty; MD, 11.3°; 95% CI, 8.6°-14.0°; $P < .001$). Data for other follow-up time periods were insufficient for quantitative analysis.

IA Corticosteroid Plus Physiotherapy vs No Treatment or Placebo

Combined treatment with IA corticosteroid plus physiotherapy was associated with superior outcomes vs control for early short-term ER ROM (high certainty; MD, 17.9°; 95% CI, 12.1°-23.7°; $P < .001$). Data for other follow-up periods were insufficient for quantitative analysis.

IA Corticosteroid vs Physiotherapy

Short-term | IA corticosteroid was associated with significant benefits compared with physiotherapy for early short-term function (moderate certainty; MD, 0.5; 95% CI, 0.2 to 0.7; $P < .001$) and late short-term pain (high certainty; MD, −1.1 VAS points; 95% CI, −1.7 to −0.5 VAS points; $P < .001$) only. Differences for early short-term pain (moderate certainty), late short-term function (moderate certainty), and early and late short-term ER ROM (moderate and high certainty, respectively) were insignificant.

Mid-term | IA corticosteroid was associated with better outcomes than physiotherapy for ER ROM (moderate certainty; MD, 4.6°; 95% CI, 0.7°-8.6°; $P = .02$). However, no significant differences in pain (low certainty) or function (moderate certainty) were observed.

IA Corticosteroid Plus Physiotherapy vs IA Corticosteroid Only

Short-term | Compared with IA corticosteroid alone, combined treatment with IA corticosteroid plus physiotherapy was only associated with superior outcomes for early short-term ER ROM (moderate certainty; MD, 11.6°; 95% CI, 3.7°-19.4°; $P = .004$). Pain and function in the early short-term (moderate and low certainty, respectively) and late short-term function (high certainty) were similar between groups.

Mid-term | No significant differences were found between the groups in pain, function, or ER ROM. These results had high, moderate, and high certainty, respectively.

IA Corticosteroid Plus Physiotherapy vs Physiotherapy Only

Short-term | Combined therapy with IA corticosteroid plus physiotherapy was associated with significant benefits compared with physiotherapy alone only for early short-term function (low certainty; SMD, 0.7; 95% CI, 0.3-1.0; $P < .001$). Differences for early short-term pain and ER ROM and late short-term function were not significant (moderate certainty for all).

Mid-term | No significant differences were found between the groups for pain, function, or ER ROM. These comparisons had moderate, low, and high certainty, respectively.

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IA Corticosteroid vs Subacromial Corticosteroid

Short-term | Compared with subacromial administration, administering corticosteroid intra-articularly was only associated with superior outcomes for early short-term pain (moderate certainty; MD, −0.6 VAS points; 95% CI, −1.1 to −0.1 VAS points; $P = .02$) and late short-term function (moderate certainty; SMD, 0.3; 95% CI, 0 to 0.6; $P = .03$). Improvements in late short-term pain (moderate certainty) and ER ROM (high certainty) and early short-term function (high certainty) were similar with the 2 interventions.

Mid-term | No significant differences were found between the groups for pain or ER ROM. These comparisons had moderate and high certainty, respectively.

Arthrographic Distension Plus IA Corticosteroid vs IA Corticosteroid Only

Adding arthrographic distension to IA corticosteroid appeared to be associated with greater improvements in early and late short-term pain (early: high certainty; MD, −0.9 VAS points; −1.3 to −0.4 VAS points; $P < .001$; late: high certainty; MD, −0.8 VAS points; 95% CI, −1.1 to −0.5 VAS points; $P < .001$). Early and late short-term function (moderate and high certainty, respectively) and early and late short-term ER ROM (high certainty for both) were similar with or without distension.

Acupuncture Plus Physiotherapy vs Physiotherapy Only

No differences were found with the addition of acupuncture to physiotherapy for early short-term pain and ER ROM. These comparisons had low and high certainty, respectively.

Clinically Significant Results and Trial Sequential Analysis

Despite several statistically significant differences in pairwise comparisons, most did not reach the threshold for MCRD. Only IA corticosteroid vs no treatment or placebo for early and late short-term pain and function, physiotherapy with and without IA corticosteroid vs no treatment or placebo for early short-term ER ROM, IA corticosteroid vs physiotherapy for early short-term function and late short-term pain, and combination therapy with IA corticosteroid plus physiotherapy compared with IA corticosteroid for early short-term ER ROM and with physiotherapy for early short-term function reached MCRD.

For the primary outcome measure, the clinically and statistically significant results underwent TSA, which confirmed the results ruling out a type I error in 2 comparisons (IA corticosteroid vs no treatment or placebo for early and late short-term pain) but not in the comparison of IA corticosteroid vs physiotherapy for late short-term pain. This suggests that more studies may be needed to confirm the benefit of IA corticosteroid compared with physiotherapy with more confidence.

eFigures 1 to 3 in the Supplement illustrate the results of the pairwise meta-analyses and associated forest plots for early short-term, late short-term, and mid-term follow up for pain and ER ROM. eFigure 4 in the Supplement illustrates the forest plots for function, and eFigure 5 and eFigure 6 in the Supplement illustrate the TSA graphs.

Network Meta-analysis

Figure 2 and **Figure 3** show the network maps and treatment rank probabilities for the primary outcome measure (pain) for late short-term (8-12 weeks) and mid-term (4-6 months) follow-up, respectively. eFigure 7 and eFigure 8 in the Supplement illustrates the network forests with their consistency tests.

In the late short-term, arthrographic distension plus IA corticosteroid had the highest probability (96%) of being the most effective treatment. IA corticosteroid had the highest probability (85%) of being the second most effective. Physiotherapy was the least effective treatment, followed by no treatment or placebo. No data existed in the late short-term for combined treatment with IA corticosteroid plus physiotherapy (Figure 2B).

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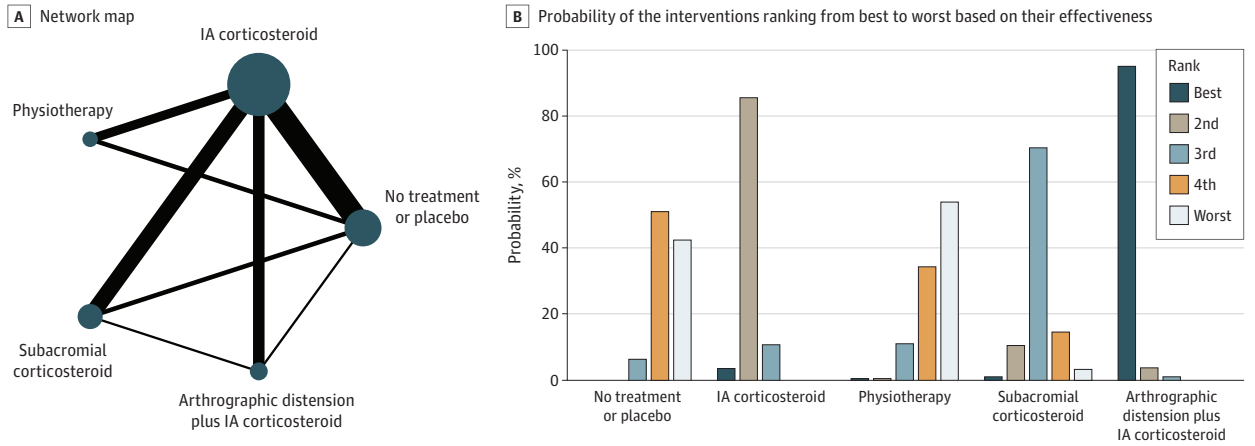
In the mid-term, combined treatment with IA corticosteroid plus physiotherapy had the highest probability (43%) of being the best treatment with physiotherapy. IA corticosteroid had the highest probability (34%) of being the second best treatment. No treatment or placebo followed by subacromial corticosteroid had the highest probability of being the worst interventions (Figure 3B).

Subgroup Analysis

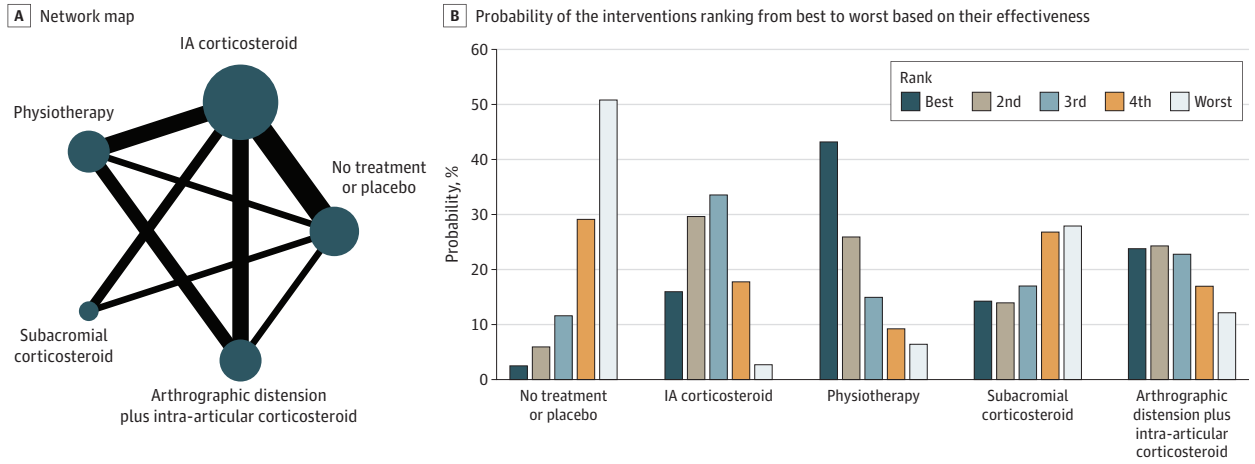
The potential benefit of home exercise was assessed by comparing the mean improvement in pain in patients who received (1) IA corticosteroid plus a home exercise program vs IA corticosteroid without home exercise, and (2) no treatment or placebo plus home exercise vs no treatment/placebo without home exercise. For the first comparison, a statistically significant (but clinically small) mean benefit of home exercise on pain improvement was identified at 8 to 12 weeks (MD, −0.5 VAS points; 95% CI, −0.9 to −0.1 VAS points; P = .01). The benefit of home exercise was much more substantial (clinically

Figure 2. Results of Network Analysis for Pain at Late Short-term (8-12 weeks) Follow-up



A, The size of the circles denotes the contribution of participants in each intervention and the thickness of the lines between circles represents the contribution of studies comparing the two interventions. B, The bar graph shows the probability of the 6 interventions ranking from best to worst based on their effectiveness. IA indicates intra-articular.

Figure 3. Results of Network Analysis for Pain at Mid-term (4-6 months) Follow-up



A, The size of the circles denotes the contribution of participants in each intervention and the thickness of the lines between circles represents the contribution of studies comparing the two interventions. B, The bar graph shows the probability of the 6 interventions ranking from best to worst based on their effectiveness. IA indicates intra-articular.

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and statistically) in those receiving no treatment or placebo (MD, −1.4 VAS points; 95% CI, −1.8 to −1.1 VAS points; $P < .001$). Both results are based on 10 studies[22,24,25,28,42,43,45,46,48,49] with low overall risk of bias.

Similarly, we assessed for an effect of IA placebo by comparing samples who received IA placebo and no treatment from the IA corticosteroid vs no treatment or placebo comparison. Both subgroups received a home exercise program. Based on 9 studies[22,24,25,28,42,43,45,46,49] with high overall risk of bias, IA placebo was associated with statistically and clinically significant effects on pain compared with no treatment (MD, −1.6 VAS points; 95% CI, −2.1 to −1.1 VAS points; $P < .001$).

There was insufficient data for a similar subgroup analysis at mid-term follow-up. Subgroup analyses for the effect of chronicity on the effectiveness of treatment modalities could not be evaluated because studies including patients with mixed stages and chronicity of frozen shoulder did not include subgroup data. Finally, subgroup analyses according to physiotherapeutic interventions were not possible because of high clinical heterogeneity (various combinations of modalities and treatment durations used). Most studies used electrotherapy modalities (transcutaneous electrical nerve stimulation, therapeutic ultrasound, diathermy) combined with mobilizations, stretching, or exercises with or without heat and ice packs.

Discussion

To our knowledge, this is the first systematic review and network meta-analysis to comprehensively analyze all nonsurgical randomized clinical trials pertaining to the treatment of frozen shoulder as well as the largest systematic review ever published in the field. Based on the available evidence, it appears that the use of an IA corticosteroid for patients with frozen shoulder of duration less than 1 year is associated with greater benefits compared with all other interventions, and its benefits may last as long as 6 months. This has important treatment ramifications for the general and specialist musculoskeletal practitioner, providing them with an accessible, cost-effective,[88] and evidence-based treatment to supplement exercise regimes, which we anticipate will inform national guidelines on frozen shoulder treatments moving forward.

In the short-term, IA corticosteroid appeared to be associated with better outcomes compared with no treatment in all outcome measures. Adding arthrographic distension to IA corticosteroid may be associated with positive effects that last at least as long as 12 weeks compared with IA corticosteroid alone; however, these benefits are probably not clinically significant. Compared with physiotherapy, IA corticosteroid seemed to be associated with better outcomes, with clinically significant differences. Combination therapy with IA corticosteroid plus physiotherapy may be associated with significant benefits compared with IA corticosteroid alone or physiotherapy alone for ER ROM and function, respectively, at 6 weeks. Compared with control, combined IA corticosteroid plus physiotherapy appeared to be associated with an early benefit in ER ROM (as long as 6 weeks), with clinical significance. Subacromial administration of corticosteroid appeared to be as efficacious as IA administration. The addition of acupuncture to physiotherapy did not seem to be associated with any added benefits. Based on the network meta-analysis, arthrographic distension with IA corticosteroid was probably the most effective intervention for pain at 12 weeks follow-up. IA corticosteroid alone ranked second, and as demonstrated by the pairwise meta-analysis, the benefit of adding distension appeared clinically nonsignificant.

Most compared interventions appeared to be associated with similar outcomes at 6-month follow up, without significant differences. The only intervention that was associated with mid-term statistically significant benefits compared with control and physiotherapy (without reaching clinical significance) was IA corticosteroid for function and ER ROM. No mid-term data exist assessing the effectiveness of adding arthrographic distension to IA corticosteroid and acupuncture to physiotherapy or comparing physiotherapy (with or without IA corticosteroid) with no treatment. Our network meta-analysis found that combined therapy with IA corticosteroid and physiotherapy, physiotherapy alone, and IA corticosteroid alone were the most effective interventions for pain at 6

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months follow-up. However, according to our pairwise meta-analyses, their clinical benefit compared with other treatments (or even no treatment) appeared very small.

A home exercise program with simple ROM exercises and stretches administered with or without IA corticosteroid appeared to be associated with short-term pain benefits. This was statistically significant but clinically nonsignificant compared with no treatment when accompanied by IA corticosteroid. It was both clinically and statistically significant on its own.

Several systematic reviews have been published assessing the effectiveness of therapeutic interventions for frozen shoulder. Sun et al[89] looked at the effectiveness if IA corticosteroid by comparing it with no treatment, and their findings were similar to ours, reporting that IA corticosteroid may be associated with benefits on pain, function, and ROM that are most pronounced in the short-term and can last as long as 6 months. The systematic review of both randomized and observational studies by Song et al[90] is also in agreement with our results, showing a possible early benefit of IA corticosteroid, which likely diminishes in the mid-term. An earlier systematic review by Maund et al,[88] which was only based on limited evidence (meta-analyses of 2 and 3 studies), was largely inconclusive, demonstrating possible benefits of IA corticosteroid (with and without physiotherapy) in conjunction with a home exercise program. A Cochrane review on arthrographic distension[91] was also in agreement with our results, showing that arthrographic distension with IA corticosteroid may be associated with short-term benefits in pain, ROM, and function. Their comparison of combined treatment vs IA corticosteroid alone yielded no significant differences; however, it was only based on 2 studies. A 2018 systematic review by Saltychev et al[92] also supports our findings, having demonstrated a small but clinically insignificant benefit of the addition of arthrographic distension to IA corticosteroid. In their systematic review, Catapano et al[93] reported that the addition of arthrographic distension to IA corticosteroid may be associated with a clinically significant benefit at 3 months; however, no quantitative analyses were conducted. Finally, a Cochrane review investigating the effects of manual therapy and exercise[94] concluded that they are probably associated with worse outcomes compared with IA corticosteroid in the short-term, which is in accordance with the findings of the present review, and another study[95] investigating the effectiveness of electrotherapy modalities was inconclusive because of lack of sufficient evidence.

In this review we aimed to assess the comparative effectiveness of all interventions for frozen shoulder, both surgical and nonsurgical; however, conclusions on the former could not be reached given that included studies did not assess the same interventions, which precluded pooling their results. The existing literature is conflicting regarding the superiority of arthroscopic capsular release (ACR) over nonoperative modalities; De Carli et al[62] reported no short-term or long-term benefits of ACR plus MUA compared with IA corticosteroid plus physiotherapy in function or ROM. Conversely, Mukherjee et al[75] found that ACR was associated with significant improvements in pain, function, and ROM compared with IA corticosteroid in the short-term and mid-term. Gallacher et al[63] demonstrated mixed results, concluding that compared with IA corticosteroid plus arthrographic distension, combined treatment with ACR and IA corticosteroid may be associated with improved function, external rotation, and flexion ROM but not quality of life and abduction ROM in the short-term and mid-term. The risk of complications, where reported, was not higher in the surgical groups.[63] The existing evidence on MUA, which is not a surgical procedure per se although it is administered under general anesthesia, is more consistent, suggesting its lack of long-term superiority compared with other commonly used nonsurgical treatments or even no treatment.[65,71,76]

Because of the paucity of robust evidence, no firm recommendations exist for clinical practice. The National Institute of Health and Care Excellence (NICE) guidelines,[96] influenced in turn by the BESS/BOA recommendations, recommend a stepped approach, starting with physiotherapy and only considering IA corticosteroid if there is no, or slow, progress.[96] With our review, we provide convincing evidence that IA corticosteroid is associated with better short-term outcomes than other treatments, with possible benefits extending in the mid-term; therefore, we recommend its early

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use with an accompanying home exercise program. This can be supplemented with physiotherapy to further increase the chances of resolution of symptoms by 6 months.

Most patients in the included studies had duration of symptoms of less than 1 year; therefore, our management recommendations are strongest for this subgroup, which includes patients most commonly encountered in clinical practice. Based on the underlying pathophysiology of the condition, usual practice is to only administer IA corticosteroid in the painful and not freezing phase (also advised by NICE guidance[95]); however, this is not backed up by evidence. In our review, studies that included patients with symptoms for more than 1 year reported equally substantial improvements in outcome measures including ROM and function; therefore, the benefits of corticosteroids may also apply to the freezing phase of frozen shoulder.[48,79]

Limitations

Despite the comprehensiveness and rigor of our methods, which include thorough risk of bias assessments and grading of evidence, we do recognize its limitations. Frozen shoulder of all chronicity was analyzed together; therefore; conclusions about specific stages and their most effective management could not be drawn. Most studies included a home exercise program, but its frequency, intensity, and duration were not taken into account in comparisons nor were separate analyses made adjusting for it. Finally, physiotherapy interventions, regardless of nature and duration, were grouped and analyzed together to minimize imprecision; in reality, some might be more effective than others. However, we only present findings that derived from thorough quantitative analyses, which were in turn substantially reinforced by the TSA, minimizing the risk for type I errors; most previous similar meta-analyses did not use TSA. Additionally, we present the first network meta-analysis including all conservative treatments for frozen shoulder. Furthermore, we based our recommendations on both statistically and clinically significant results.

Conclusions

Based on the findings of the present review, we recommend the use of IA corticosteroid for patients with frozen shoulder of duration less than 1 year because it appeared to have earlier benefits than other interventions; these benefits could last as long as 6 months. We also recommend an accompanying home exercise program with simple ROM exercises and stretches. The addition of physiotherapy in the form of an electrotherapy modality and supervised mobilizations should also be considered because it may add mid-term benefits and can be used on its own, especially when IA corticosteroid is contra-indicated. Implicated health care professionals should always emphasize to patients that frozen shoulder is a self-limiting condition that usually lasts for a few months but can sometimes take more than 1 year to resolve and its resolution may be expedited by IA corticosteroid. This should be offered at first contact, and an informed decision should be made by the patient after the risks and alternative therapies are presented to them. In the future, other interventions that have shown promising results and currently have inadequate evidence for definitive conclusions (eg, MUA, ACR, specific types of electrotherapy and mobilizations) should be assessed with large, well-designed randomized studies. Finally, future studies should include subgroup analyses assessing the effectiveness of specific interventions on frozen shoulder of different chronicity and stage.

ARTICLE INFORMATION

Accepted for Publication: October 22, 2020.

Published: December 16, 2020. doi:10.1001/jamanetworkopen.2020.29581

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Obtained funding: Millar.

Administrative, technical, or material support: Challoumas, McLean.

Supervision: Challoumas, Millar.

Conflict of Interest Disclosures: None reported.

Funding/Support: This work was funded by grant MR/R020515/1 from the Medical Research Council UK.

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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SUPPLEMENT.

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BMJ Open

Efficacy of low-level laser therapy in patients with lower extremity tendinopathy or plantar fasciitis: systematic review and meta-analysis of randomised controlled trials

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To cite: Naterstad IF, Joensen J, Bjordal JM, *et al*. Efficacy of low-level laser therapy in patients with lower extremity tendinopathy or plantar fasciitis: systematic review and meta-analysis of randomised controlled trials. *BMJ Open* 2022;**12**:e059479. doi:10.1136/bmjopen-2021-059479

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-059479).

Received 21 November 2021
Accepted 18 August 2022

Check for updates

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ABSTRACT

Objectives We investigated the effectiveness of low-level laser therapy (LLLT) in lower extremity tendinopathy and plantar fasciitis on patient-reported pain and disability.

Design Systematic review and meta-analysis.

Data sources Eligible articles in any language were identified through PubMed, Embase and Physiotherapy Evidence Database (PEDro) on the 20 August 2020, references, citations and experts.

Eligibility criteria for selection of studies Only randomised controlled trials involving participants with lower extremity tendinopathy or plantar fasciitis treated with LLLT were included.

Data extraction and synthesis Random effects meta-analyses with dose subgroups based on the World Association for Laser Therapy treatment recommendations were conducted. Risk of bias was assessed with the PEDro scale.

Results LLLT was compared with placebo (10 trials), other interventions (5 trials) and as an add-on intervention (3 trials). The study quality was moderate to high. Overall, pain was significantly reduced by LLLT at completed therapy (13.15 mm Visual Analogue Scale (VAS; 95% CI 7.82 to 18.48)) and 4–12 weeks later (12.56 mm VAS (95% CI 5.69 to 19.42)). Overall, disability was significantly reduced by LLLT at completed therapy (Standardised Mean Difference (SMD)=0.39 (95% CI 0.09 to 0.7) and 4–9 weeks later (SMD=0.32 (95% CI 0.05 to 0.59)). Compared with placebo control, the recommended doses significantly reduced pain at completed therapy (14.98 mm VAS (95% CI 3.74 to 26.22)) and 4–8 weeks later (14.00 mm VAS (95% CI 2.81 to 25.19)). The recommended doses significantly reduced pain as an add-on to exercise therapy versus exercise therapy alone at completed therapy (18.15 mm VAS (95% CI 10.55 to 25.76)) and 4–9 weeks later (15.90 mm VAS (95% CI 2.3 to 29.51)). No adverse events were reported.

Conclusion LLLT significantly reduces pain and disability in lower extremity tendinopathy and plantar fasciitis in the short and medium term. Long-term data were not available. Some uncertainty about the effect size remains due to wide CIs and lack of large trials.

PROSPERO registration number CRD42017077511.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This review was performed in conformance with a prospective published protocol, which included a plan for subgrouping the trials by laser dose.
- ⇒ There were no language restrictions; 2 (11%) of the included trials were reported in non-English language.
- ⇒ The review includes results from an unpublished trial.
- ⇒ The review features meta-analyses with direct comparisons between low-level laser therapy and placebo, other interventions and no intervention.
- ⇒ Only one reviewer extracted the data from the included trials, but the extracted data were checked for correctness by another reviewer.

INTRODUCTION

Tendinopathy and plantar fasciitis are disorders associated with substantial pain and loss of function in the lower extremity, especially prevalent in the athletic population but also common in the non-athletic population.[1–3] The aetiology of tendinopathy and plantar fasciitis is multifactorial and not fully understood. Risk factors for tendinopathy include overuse, acute trauma, ageing and genetic predisposition.[4 5] Known risk factors for plantar fasciitis are prolonged standing and jumping, reduced ankle dorsiflexion and obesity.[6–9] Disorganised and degenerating collagen fibres, increased numbers of fibroblasts, altered composition of extracellular matrix proteins, formation of new vessels and rounding of tendon cells can be found in both tendinopathy and plantar fasciitis.[10 11]

Conservative treatment for lower extremity tendinopathy and plantar fasciitis includes an array of modalities and approaches. The effect of exercise therapy in tendinopathy is well-established, and any exercise type is

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preferential to wait-and-see in the earlier stages of tendinopathy.[12] However, a superiority of exercise therapy compared with other interventions has not been demonstrated. The use of non-steroidal anti-inflammatory drugs (NSAIDs) are frequently recommended in the early stages of tendinopathy and plantar fasciitis,[13–15] even though the effectiveness of these drugs in lower extremity tendinopathies has only been investigated in a few placebo-controlled trials.[16–20] Moreover, NSAIDs have well known potentially fatal side effects, most importantly severe cardiovascular events and gastrointestinal toxicity.[21] Low-level laser therapy (LLLT), also known as photobiomodulation therapy, is a quickly administered non-invasive intervention option free from negative side effects. LLLT is an athermic photochemical modality, where red or near-infrared light is used to stimulate tissue healing and reduce pain and inflammation.[22–24] The working mechanisms of LLLT are partly established. There is evidence that LLLT increases adenosine triphosphate production,[25] modulates the reactive oxygen species, and the induction of transcription factors.[26–29] Furthermore, it has been demonstrated that LLLT inhibits the cyclooxygenase-2 gene expression and prostaglandin E_2 (PGE_2) production in tendons[30 31] and inhibits matrix metalloproteinase activity.[31 32] In addition, under application of LLLT, macrophages are more likely to act as phagocytes.[33]

There are heterogeneous results from clinical trials of LLLT on tendinopathies, and this may or may not be explained by a dose–response relationship.[34–36] Variation in LLLT parameters, such as wavelength, power density, pulse structure, application method and time-point of assessment may affect the treatment outcome. The World Association for Laser Therapy (WALT) has published treatment recommendations regarding the minimum LLLT doses required to reach a positive result.[37 38] In a systematic review by our research group regarding the effectiveness of LLLT in knee osteoarthritis, a significant dose–response relationship was discovered when the included trials were subgrouped using the WALT treatment recommendations.[39] Furthermore, in a more recent placebo-controlled trial, we found some evidence that an upper limit for the effectiveness of LLLT exists in knee osteoarthritis.[40] These clinical observations are in line with the results of several in vivo and in vitro trials.[41–44] Whether such biphasic laser dose–response relationship exists in tendon disorders is unclear. Prior systematic reviews have investigated LLLT in Achilles tendinopathy or plantar fasciitis.[12 45–49] Unfortunately, these reviews have one or more substantial limitations, such as a lack of a dose–response analysis,[12] an exclusion of relevant trials reported in non-English languages[45–48] or the mistake of synthesising the results of highly heterogenious studies using the fixed effects meta-analysis model.[49] Thus, the evidence regarding the effectiveness of LLLT on pain and disability in lower limb tendinopathy and plantar fasciitis is still somewhat unclear. Therefore, the objectives of the current review were to estimate the effectiveness of LLLT in tendinopathy and plantar fasciitis on patient-reported pain and disability using a dose–response analysis.

METHODS

This review was conducted in adherence to a prospectively registered PROSPERO protocol and is reported in accordance with the Preferred Reporting Items of Systematic reviews and Meta-Analysis statement 2009.[50]

Literature search and selection of studies

We included randomised clinical trials in which the effectiveness of LLLT in tendon disorders of the lower extremity or plantar fasciitis was compared with sham (placebo) LLLT, other interventions or no intervention, in terms of patient-reported pain and/or disability. There were no restrictions regarding publication date and language.

A search for eligible reports of trials were conducted in the databases PubMed, Embase and Physiotherapy Evidence Database (PEDro) on the 20 August 2020. Furthermore, references from relevant systematic reviews[46–49] and all the included trials were screened, and experts in the field were asked to provide additional published and unpublished trials. Abstracts were not included. The PubMed search string is included in the online supplemental material.

Two independent reviewers (IFN and MBS) read the titles/abstracts of the publications identified by the search. Any article judged potentially eligible by a reviewer was retrieved in full text. The same two reviewers evaluated the full texts of all the potentially eligible articles and made a careful decision to include or exclude each article, with close attention to the eligibility criteria. Any article not fulfilling the eligibility criteria was excluded and had its details listed with reason for exclusion (online supplemental material). Selection disagreements were resolved by discussion to consensus with the option of a third person's (JJ) final decision if necessary.

Risk of bias analysis

Two reviewers (IFN and MBS) independently assessed the risk of bias of the included trials with the 0–10 points PEDro scale.[51] This was done on outcome level, and since the outcomes of interest were patient-assessed pain and disability, the participants were considered the assessors. Therefore, the assessors can only be blinded in placebo-controlled trials. When risk-of-bias disagreements could not be resolved by discussion, a third reviewer (JJ) made the final consensus-based decision. The trials were labelled as being of 'high', 'moderate' or 'poor' methodological quality if they had a total PEDro score of ≥7, 5–6 or ≤4, respectively.[52] Risk of small study bias was assessed with a funnel plot and by comparing the difference between the point effect estimates from random and fixed effects meta-analyses.

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Data extraction and meta-analysis

Extraction of the following information was mandatory: number of participants allocated to laser and control groups, participant characteristics, type and duration of interventions, laser-specific application information (location of application, wavelength, energy density per treated spot, number of spots treated, mean power density per treated spot, treatment time per spot, treated area, laser sessions per week and total number of laser sessions), selected outcome measurement scales for data extraction, time-points of assessments, effect estimates and adverse events.

The data collection was handled in a two-person procedure by IFN and MBS. One reviewer entered all the data in Excel sheets, and the data were subsequently checked for correctness by another reviewer. If data extraction disagreements could not be resolved by discussion, a third reviewer (JMB) made the final consensus-based decision.

All the meta-analyses were conducted using random effects models, weighting the individual trial results relatively even when statistical heterogeneity is present.[53]

The pain results were synthesised using the mean difference (MD) method as this method allows for change and final scores to be combined.[54] Pain scores reported on the Visual Analogue Scale (VAS) and on the Numeric Rating Scale highly correlates[55] and were thus considered the same. Patient-reported disability results were synthesised with the Standardised Mean Difference (SMD) method using change scores solely.[54] According to Cohen, a SMD of 0.2, 0.5 and 0.8 can be considered small, moderate and large, respectively.[54]

Heterogeneity was measured using I^2-statistics (inconsistency).[56] An inconsistency level of 25%, 50% and 75% would be considered low, moderate and high, respectively.[57] Standard deviations (SDs) for meta-analysis were extracted or estimated from other variance data in the following prioritised order: SD, standard error (SE), 95% Confidence interval (CI), pvalue, interquatile range (IQR), median of correlations, visually from graph, correlation of 0.6 or mean of SDs from similar trials.

Trials were subgrouped by laser dose using the WALT treatment recommendations,[58 59] as specified in the a priori protocol. WALT recommends irradiating minimum of 2–3 points on the tendon or fascia. In Achilles and patellar tendinopathy, the recommended dose with 904 nm wavelength laser is minimum 2 J/point. When using 780–860 nm wavelength laser, the minimum dose is 4 J/point. In plantar fasciitis, the recommended minimum dose is 2 J/point with a 904 nm wavelength laser or 4 J/point with 780–860 nm wavelength laser. We subgrouped the trials as recommended laser dose or non-recommended laser dose when possible. If the trial reports lacked sufficient dose parameters to be identified as recommended or non-recommended laser dose, they were categorised as unclear laser dose.

Two time-points of assessment were selected for analysis, that is, immediately after the end of LLLT and last time-point of assessment 2–12 weeks after completed LLLT (follow-up).

IFN and MBS performed the meta-analyses using Excel 2016 (Microsoft) and Review Manager V.5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Patient and public involvement

Patients or the public were not involved in the conceptualisation or carrying out of this research.

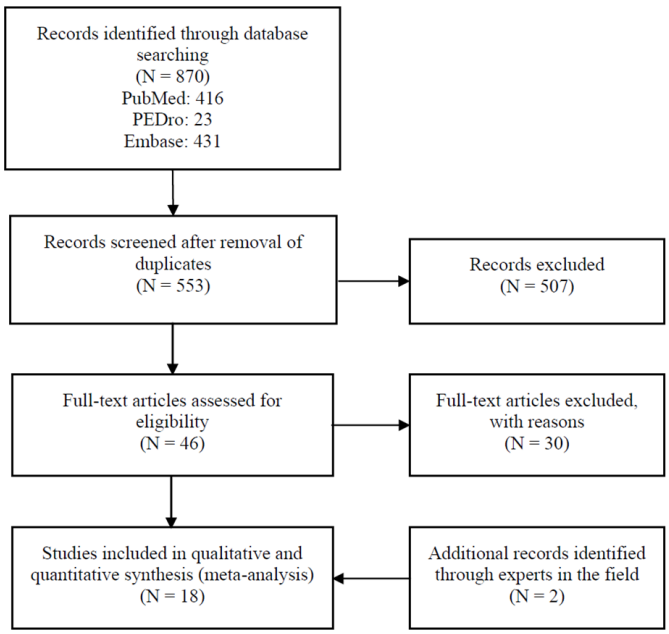

Figure 1 Flow chart illustrating the trial identification process. PEDro, physiotherapy evidence database.

RESULTS

A total of 870 records were identified in the search, of which 18 reports of trials (n=784) were included in review and meta-analysis (figure 1 and table 1). LLLT was applied to participants with patellar tendinopathy in 2 trials, Achilles tendinopathy in 5 trials and plantar fasciitis in 11 trials. LLLT was compared with placebo in 10 trials, other interventions in 5 trials and as an adjunct intervention in 3 trials. Two trials were reported in non-English language, and one trial was unpublished (Naterstad *et al.*). The excluded articles were listed with reasons for omission (online supplemental material). The mean age of the participants was 43.6 years (minimum<18, maximum 54.5, data from 14 trials), and the mean baseline pain intensity was 64.2 mm on the VAS (minimum 19.3 mm, maximum 85 mm, data from 18 trials). No adverse events were reported by any of the trial authors. None of the trial authors declared that they had received funding from the laser industry.

LLLT was compared with placebo LLLT in 10 trials,[60–68] and exercise therapy or stretching exercises was applied as a cointervention in five of these trials. LLLT was compared with exercise therapy or stretching exercises in

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Table 1 Characteristics of the included trials

First author, year	Participants at baseline (intervention)	Participants at baseline (control)	Intervention versus control	Outcome and time of reassessment after baseline (time used for analysis in bold)
Patellar tendinopathy				
Liu 2014[69], LLLT versus ET	n: 7 Age years: ≥ 18, ≤ 23 VAS pain mm: 67.9±13.2	n: 7 Age years: ≥ 18, ≤ 23 VAS pain mm: 65.7±15.4	4 weeks of LLLT versus 4 weeks of eccentric ET	Pain: VAS Disability: modified-VISA Reassessment: 4 weeks
Liu 2014[69], LLLT+ET versus ET	n: 7 Age years: ≥ 18, ≤ 23 VAS pain mm: 67.9±12.2	n: 7 Age years: ≥ 18, ≤ 23 VAS pain mm: 65.7±15.4	4 weeks of LLLT and eccentric ET versus 4 weeks of eccentric ET	Pain: VAS Disability: modified-VISA Reassessment: 4 weeks
Stergioulas 2003[60]	n: 23 Age years: 29.2±13.4 VAS pain mm: 81.7±13.4	n: 21 Age years: 29.8±13.8 VAS pain mm: 75.9±18.8	2 weeks of LLLT versus 2 weeks of sham LLLT	Pain: VAS Disability: Functional Index Questionnaire Reassessment: 2 and 6 weeks
Achilles tendinopathy				
Darre 1994[61]	n: 46 Age years: ≥ 18 VAS pain mm: 58.5±37.9	n: 43 Age years: ≥ 18 VAS pain mm: 72±34.3	2.4 weeks of LLLT versus 2.4 weeks of sham LLLT	Pain: VAS Disability: - Reassessment: 2.4 weeks
Naterstad†	n: 20 Age years: 45.4±14.7 VAS pain mm: 52.9±26.1	n: 21 Age years: 45.8±13.9 VAS pain mm: 53.8±26.7	4 weeks of LLLT and cryotherapy and 12 weeks of eccentric and concentric ET versus 4 weeks of sham LLLT and cryotherapy and 2 weeks of eccentric and concentric ET	Pain: THIP VAS most painful activity Disability: THIP VAS ADL Reassessment: 4 and 12 weeks
Stergioulas 2008[68]	n: 20 Age years: 30.1±4.8 VAS pain mm: 79.8±9.5	n: 20 Age years: 28.8±4.8 VAS pain mm: 81.8±11.6	8 weeks of LLLT and eccentric ET versus 8 weeks of sham LLLT and eccentric ET	Pain: VAS during activity Disability: - Reassessment: 4, 8 and 12 weeks
Tumilty 2008[62]	n: 10 Age years: 41.4±7.6 VAS pain mm: 47.8±25.9	n: 10 Age years: 42.5±8.5 VAS pain mm: 39±20.2	4 weeks of LLLT and 12 weeks of eccentric ET versus 4 weeks of sham LLLT and 12 weeks of eccentric ET	Pain: VAS in morning Disability: - Reassessment: 4 and 12 weeks
Tumilty 2012[63]	n: 20 Age years: 45.6±9.1 NRS pain mm: 21.1±1.2	n: 20 Age years: 46.5±6.4 NRS pain mm: 19.3±0.9	4 weeks of LLLT and 12 weeks of eccentric ET versus 4 weeks of sham LLLT and 12 weeks of eccentric ET	Pain: NRS Disability: - Reassessment: 4, 12 and 52 weeks
Plantar fasciitis				
Basford 1998[64]	n: 16 Age years: 42.5 (26–64)* VAS pain mm: 57.9 (22.2–97)*	n: 15 Age years: 42 (33–51)* VAS pain mm: 46.6 (4–86)*	4 weeks of LLLT versus 4 weeks of sham LLLT	Pain: Pain when walking in morning Disability: limping in morning Reassessment: 2, 4 and 8 weeks
Cinar 2017[70]	n: 29 Age years: 46.6±10.1 VAS pain mm: 61.3±19.4	n: 22 Age years: 44.2±9.7 VAS pain mm: 54.9±19.7	3 weeks of LLLT and stretching versus 3 weeks of stretching	Pain: VAS Disability: AOFAS-F activity limitations Reassessment: 3 and 12 weeks

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Table 1 Continued

First author, year	Participants at baseline (intervention)	Participants at baseline (control)	Intervention versus control	Outcome and time of reassessment after baseline (time used for analysis in bold)
Cinar 2018[71]	n: 24 Age years: 46.5±10.3 NRS pain mm: 6.3±1.4	n: 17 Age years: 44±8.6 NRS pain mm: 6.2±2.1	3 weeks of LLLT and 12 weeks of stretching versus 12 weeks of stretching	Pain: NRS Disability: - Reassessment: 3 and 12 weeks
Cinar 2018[71], ESWT	n: 24 Age years: 46.5±10.3 NRS pain mm: 6.3±1.4	n: 25 Age years: 45.4±9.7 NRS pain mm: 6.7±2.7	3 weeks of LLLT and 12 weeks of stretching versus 3 weeks of ESWT (2000 mJ/mm^2, session once per week) and 12 weeks of stretching	Pain: NRS Disability: - Reassessment: 3 and 12 weeks
Elsehrawy 2018[72]	n: 23 Age years: 46.4±10 VAS pain: 85±8	n:23 Age years: 46±10.2 VAS pain: 82±15	3 weeks of LLLT and stretching versus 2 weeks of ESWT (2050 shocks/min, 10 Hz, 2.5 bars once per week) and stretching	Pain: VAS Disability: FFI disability subscale Reassessment: 4 weeks
Kiritsi 2010[65]	n: 15 Age years: 41±12 VAS pain mm: 67±8.3	n: 15 Age years: 41±12 VAS pain mm: 67±9.3	6 weeks of LLLT versus 6 weeks of sham LLLT	Pain: ADL VAS Disability: - Reassessment: 6 weeks
Koteeswaran 2020[75]	n: 15 Age years: 30–60 NRS pain: 74.7±11.9	n: 15 Age years: 30–60 NRS pain: 72.7±8	2 weeks of LLLT and stretching versus 2 weeks of TUS and stretching	Pain: NRS Disability: FAAM Reassessment: 2 weeks
Lamba 2013[66]	n: 40 Age years: 40.9±10.4 VAS pain mm: 57.5±10.8	n: 40 Age years: 40.4±9.7 VAS pain mm: 62±7.6	4 weeks of LLLT and stretching versus 4 weeks of sham LLLT and stretching	Pain: VAS Disability: - Reassessment: 1,2, 3 and 4 weeks
Macias 2015[67]	n: 37 Age years: ≥ 18 VAS pain mm: 69.1±12.7	n: 32 Age years: ≥ 18 VAS pain mm: 67.6±11.8	3 weeks of LLLT versus 3 weeks of sham LLLT	Pain: VAS heel pain Disability: FFI disability subscale 8 weeks Reassessment: 1, 2, 3, 6 and 8 weeks
Sanmak 2019[73]	n: 17 Age years: 53* VAS pain mm: 70*	n: 17 Age years: 49* VAS pain mm: 80*	4 weeks of LLLT versus 3 weeks of ESWT (2 bar with 2000 shocks/min at 10 Hz once per week)	Pain: VAS Reassessment: 4 and 8 weeks
Ulusoy 2017[74], TUS	n: 20 Age years: 53.4±14.7 VAS pain mm: 68.7±12.5	n: 20 Age years: 51.0±9.6 VAS pain mm: 66.6±1.1	3 weeks of LLLT and 7 weeks of ET and stretching versus 3 weeks of TUS (1 mHz; 2 W/cm^2) and 7 weeks of ET and stretching	Pain: VAS in morning Disability: - Reassessment: 7 weeks
Ulusoy 2017[74], ESWT	n: 20 Age years: 53.4±14.7 VAS pain mm: 68.7±12.5	n: 20 Age years: 54.4±6.9 VAS pain mm: 66±11.2	3 weeks of LLLT and 7 weeks of ET and stretching versus 3 weeks of ESWT (2.5 bar with 2000 shocks/min at 10 Hz three times per week) and 7 weeks of ET and stretching	Pain: VAS in morning Disability: - Reassessment: 7 weeks

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Table 1 Continued

First author, year	Participants at baseline (intervention)	Participants at baseline (control)	Intervention versus control	Outcome and time of reassessment after baseline (time used for analysis in bold)
Yüzer 2006[76]	n: 24 Age years: 49.6±1.2 VAS pain mm: 80±12	n: 30 Age years: 51.5±11.5 VAS pain mm: 76±15	1.4 weeks of LLLT versus steroid injection	Pain: VAS Disability: - Reassessment: 5.4, 13.4 and 25.4 weeks

Numbers for age and pain are means±SD, unless otherwise indicated.
*Median with or without IQR.
†Naterstad *et al*. Efficacy of Low-level Laser Therapy as an addition to exercise and cryotherapy in chronic Achilles tendinopathy: a double-blinded randomised controlled trial.
ADL, activity of daily living; AOFAS-F, American Orthopedic Foot and Ankle Score Function; ESWT, Extracorporeal Shockwave Therapy; ET, exercise therapy; FAAM, foot and ankle ability measurement questionnaire; FFI, Foot Function Index; LLLT, Low-Level Laser Therapy; NRS, Numeric Rating Scale; THIP, Tendinopathy Health Impact Profile; TUS, therapeutic ultrasound; VAS, Visual Analogue Scale.

three trials.[69–71] A comparison between LLLT and Extracorporeal Shockwave Therapy (ESWT) in plantar fasciitis was performed in four trials.[71–74] LLLT was compared with therapeutic ultrasound in two trials[74 75] and steroid injection in one trial.[76] Recommended laser doses were applied in at least 11 trials,[60–62 65 66 68–71 74] and a non-recommended dose was used in at least 1 trial.[63] We were unable to categorise the laser doses in the remaining six trials[64 67 72 73 75 76] due to inadequately or missing descriptions of laser parameters (table 2). Two different laser doses were applied in the same session in two of the trials.[65 69]

Overall pain and disability results — LLLT versus any control

Data allowing for a meta-analysis of an immediate pain change were available from 16 trials with recommended, non-recommended or unknown laser dosing.

Overall, pain was significantly reduced by LLLT over any control immediately after completed therapy (13.15 mm VAS (95% CI 7.82 to 18.48), I^2=65%, n=784) (figure 2) and at follow-ups 4–12 weeks later (12.56 mm VAS (95% CI 5.69 to 19.42), I^2=48%, n=556) (figure 3).

Overall, the disability results immediately after completed therapy significantly favoured LLLT over any control (SMD=0.39 (95% CI 0.09 to 0.7), I^2=30%, n=260) (figure 4). A disability reduction by LLLT remained significant at follow-ups 4–9 weeks after completed therapy (SMD=0.32 (95% CI 0.05 to 0.59), I^2=4%, n=222) (figure 5).

Overall and subgroup pain results—LLLT versus placebo control

Overall, pain was significantly reduced by LLLT over placebo control immediately after completed therapy (11.48 mm VAS (95% CI 2.68 to 20.28), I^2=73%, n=507) (figure 2) and during follow-ups 4–8 weeks after completed therapy (13.62 mm VAS (95% CI 2.18 to 25.06), I^2=68%, n=277) (figure 3).

The recommended laser doses significantly reduced pain compared with placebo immediately after completed therapy (14.98 mm VAS (95% CI 3.74 to 26.22), I^2=67%, n=367) (figure 6). A non-recommended laser dose from a single trial provided no significant pain reduction compared with placebo immediately after completed therapy (−3.0 mm VAS (95% CI −11.17 to 5.17), n=40) (figure 6). Trials with unknown laser doses significantly favoured LLLT over placebo control immediately after completed therapy (10.83 mm VAS (95% CI 2.44 to 19.21), I^2=0%, n=100). The between-subgroup difference was significant (p=0.02) (figure 6).

At follow-ups 4–8 weeks after completed therapy, the recommended laser doses significantly reduced pain compared with placebo (14.00 mm VAS (95% CI 2.81 to 25.19), I^2=5%, n=136) (online supplemental figure S1). A non-recommended laser dose provided in a single trial did not significantly reduce pain compared with placebo at follow-up 8 weeks after completed therapy (0.0 mm VAS (95% CI −7.62 to 7.62), n=40) (online supplemental

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Table 2 LLLT characteristics of the included trials

First author, year	Wave-length (nm)	Mean output power (mW)	Seconds per treatment spot (s)	Joules per treatment spot (J)	Number of spots treated	Number of sessions/ Weeks	Dose recommended by WALT
Patellar tendinopathy							
Liu 2014[69]	810 810	200 200	600 300	- -	1* 2	24/4	Yes
Stergioulas 2003[60]	904	50	300	1.2	10	10/2	Yes
Achilles tendinopathy							
Darre 1994[61]	830	30	–	4	4	12/2.5	Yes
Naterstad‡	904	60	50	3	6	12/4	Yes
Stergioulas 2008[68]	820	30	–	0.9	6	12/8	Yes
Tumilty 2008[62]	810	100	30	3	6	12/4	Yes
Tumilty 2012[63]	810	7	30	0.21	6	12/4	No
Plantar fasciitis							
Basford 1998[64]	830	30	–	–	3 †	12/4	Unclear
Cinar 2017[70]	830	100	80	5.6	5	10/3	Yes
Cinar 2018[71]	830	100	80	5.6	5	10/3	Yes
Elsehrawy 2018[72]	830	–	–	–	3 †	6/3	Unclear
Kiritsi 2010[65]	904 904	60 60	– –	8.4 –	1* 2 †	18/6	Yes
Koteeswaran 2020[75]	830	–	180	–	3	9/3	Unclear
Lamba 2013[66]	820	100	80	–	3 †	12/4	Yes
Macias 2015[67]	635	17	600	–	3	6/3	Unclear
Sanmak 2019[73]	685	30	60	–	2 †	12/4	Unclear
Ulusoy 2017[74]	830	50	200	–	3 †	15/3	Yes
Yüzer 2006[76]	904	–	30	–	–	10/1.4	Unclear

*Two different dosages applied within the same session.
†Naterstad *et al*. Efficacy of Low-level Laser Therapy as an addition to exercise and cryotherapy in chronic Achilles tendinopathy: a double-blinded randomised controlled trial.
‡One or more spots/areas treated with movement of the laser probe.
LLLT, Low-Level Laser Therapy; WALT, World Association for Laser Therapy.

figure S1). At follow-ups 4–5 weeks after completed therapy, trials with unknown laser doses demonstrated a significant pain reduction by LLLT compared with placebo (23.94 mm VAS (95% CI 14.39 to 33.48), I^2=0%, n=97) (online supplemental figure S1). The between-subgroup difference was significant (p<0.001) (online supplemental figure S1).

Overall and subgroup pain results—LLLT versus other interventions

Overall, pain was significantly reduced by LLLT compared with other interventions immediately after completed therapy (13.23 mm VAS (95% CI 4.07 to 22.39), I^2=66%, n=173) (figure 2). Follow-up results of pain 4–12 weeks after completed therapy favoured LLLT over other interventions, but not significantly (9.41 mm VAS (95% CI −0.44 to 19.26), I^2=16%, n=193) (figure 3).

The recommended laser doses were compared with exercise therapy in one trial and ESWT in another trial immediately after completed therapy and the pain results favoured LLLT, but not significantly (13.91 mm VAS (95% CI −1.34 to 29.15), I^2=65%, n=63) (online supplemental figure S4).

The pain results from three trials with unknown laser doses, in which two groups received ESWT and one group received therapeutic ultrasound, favoured LLLT immediately after completed therapy, but not significantly (12.88 mm VAS (95% CI −1.29 to 27.04), I^2=77%, n=110) (online supplemental figure S4).

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Study or Subgroup	LLLT Mean	LLLT SD	LLLT Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.1.1 LLLT vs placebo								
Darre 1994, LLLT vs placebo LLLT in AT	40.5	37.91	46	52	34.37	43	5.4%	-11.50 [-26.52, 3.52]
Tumilty 2012, LLLT+ET vs placebo LLLT+ET in AT	6	17.1	20	9	7.45	20	7.8%	-3.00 [-11.17, 5.17]
Tumilty 2008, LLLT+ET vs placebo LLLT+ET in AT	22.6	29.9	10	17.2	17.75	10	3.7%	5.40 [-16.15, 26.95]
Basford 1998, LLLT vs placebo LLLT in PF	34.4	45.58	16	26.1	29.26	15	2.8%	8.30 [-18.50, 35.10]
Macias 2015, LLLT vs placebo LLLT in PF	19.8	22.49	37	8.7	14.56	32	7.6%	11.10 [2.27, 19.93]
Naterstad, LLLT+ET+CT vs placebo LLLT+ET+CT in AT	28.9	29.18	20	11.54	35.09	21	4.1%	17.36 [-2.36, 37.08]
Kiritsi 2010, LLLT vs placebo LLLT in PF	40	20.3	25	18	8.9	25	7.6%	22.00 [13.31, 30.69]
Lamba 2013, LLLT+S vs placebo LLLT+S in PF	32	53	40	8.3	53	40	3.4%	23.70 [0.47, 46.93]
Stergioulas 2008, LLLT+ET vs placebo LLLT+ET in AT	24.8	25	26	0	25	26	5.9%	24.80 [11.21, 38.39]
Stergioulas 2003, LLLT vs placebo LLLT in PT	35.5	71.04	18	6.4	12.39	17	2.0%	29.10 [-4.24, 62.44]
Subtotal (95% CI)			**258**			**249**	**50.4%**	**11.48 [2.68, 20.28]**
Heterogeneity: Tau² = 126.14; Chi² = 32.84, df = 9 (P = 0.0001); I² = 73%								
Test for overall effect: Z = 2.56 (P = 0.01)								
1.1.2 LLLT vs other intervention								
Sanmak 2019, LLLT vs ESWT in PF	10	20.16	17	10	19.23	17	6.0%	0.00 [-13.24, 13.24]
Liu 2014, LLLT vs ET in PT	52.86	12.2	7	46.43	10.69	7	6.4%	6.43 [-5.59, 18.45]
Elsehrawy 2018, LLLT+S vs ESWT+S in PF	57	15.45	23	46	15.45	23	7.5%	11.00 [2.07, 19.93]
Cinar 2018, LLLT+S+I vs ESWT+S+I in PF	38	24.9	24	16	23.1	25	5.9%	22.00 [8.54, 35.46]
Koteeswaran 2020, LLLT+S vs TU+S in PF	35.4	25.6	15	7.4	6.01	15	6.0%	28.00 [14.69, 41.31]
Subtotal (95% CI)			**86**			**87**	**31.9%**	**13.23 [4.07, 22.39]**
Heterogeneity: Tau² = 70.74; Chi² = 11.63, df = 4 (P = 0.02); I² = 66%								
Test for overall effect: Z = 2.83 (P = 0.005)								
1.1.3 LLLT vs no intervention								
Liu 2014, LLLT+ET vs ET in PT	62.86	10.4	7	46.43	10.69	7	6.8%	16.43 [5.38, 27.48]
Cinar 2018, LLLT+S+I vs S+I in PF	38	24.9	24	20	25.28	17	5.3%	18.00 [2.39, 33.61]
Cinar 2017, LLLT+S+I vs S+I in PF	38.8	28.6	27	17.7	21.92	22	5.7%	21.10 [6.95, 35.25]
Subtotal (95% CI)			**58**			**46**	**17.7%**	**18.15 [10.55, 25.76]**
Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 2 (P = 0.88); I² = 0%								
Test for overall effect: Z = 4.68 (P < 0.00001)								
Total (95% CI)			**402**			**382**	**100.0%**	**13.15 [7.82, 18.48]**
Heterogeneity: Tau² = 77.51; Chi² = 48.03, df = 17 (P < 0.0001); I² = 65%								
Test for overall effect: Z = 4.83 (P < 0.00001)								
Test for subgroup differences: Chi² = 1.40, df = 2 (P = 0.50), I² = 0%								

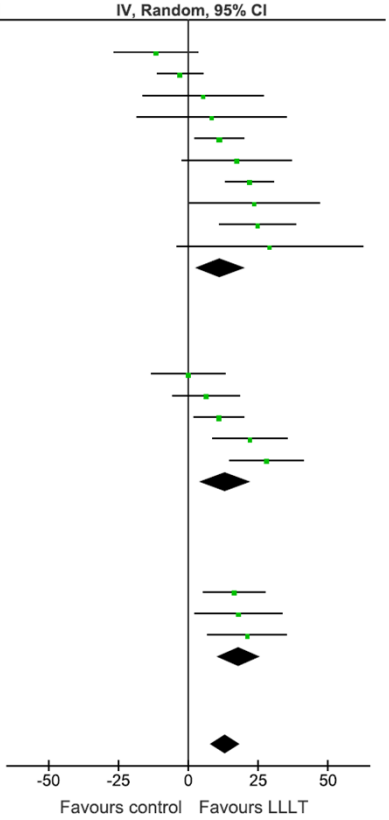

Figure 2 Overall pain results immediately after completed therapy—LLLT versus any control. AT, Achilles tendinopathy; CT, cryotherapy; ESWT, Extracorporeal Shock Wave Therapy; ET, exercise therapy; I, insoles; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy; S, stretching; TU, Therapeutic Ultrasound.

Study or Subgroup	LLLT Mean	LLLT SD	LLLT Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
2.1.1 LLLT vs placebo								
Tumilty 2012, LLLT+ET vs placebo LLLT+ET in AT	15	11.75	20	15	12.82	20	14.7%	0.00 [-7.62, 7.62]
Naterstad, LLLT+ET+CT vs placebo LLLT+ET+CT in AT	26.59	36.46	20	22.99	29.18	21	7.0%	3.60 [-16.68, 23.88]
Tumilty 2008, LLLT+ET vs placebo LLLT+ET in AT	30.9	31.73	10	20	20	10	5.9%	10.90 [-12.35, 34.15]
Stergioulas 2008, LLLT+ET vs placebo LLLT+ET in AT	17.9	26.6	20	0	26.6	20	8.8%	17.90 [1.41, 34.39]
Basford 1998, LLLT vs placebo LLLT in PF	37.4	62.57	15	19.4	61.92	13	2.0%	18.00 [-28.21, 64.21]
Macias 2015, LLLT vs placebo LLLT in PF	29.6	24.9	37	5.4	16	32	13.2%	24.20 [14.45, 33.95]
Stergioulas 2003, LLLT vs placebo LLLT in PT	60.6	88.57	18	17.3	21.87	17	2.3%	43.30 [1.08, 85.52]
Subtotal (95% CI)			**140**			**133**	**53.9%**	**13.62 [2.18, 25.06]**
Heterogeneity: Tau² = 130.26; Chi² = 18.51, df = 6 (P = 0.005); I² = 68%								
Test for overall effect: Z = 2.33 (P = 0.02)								
2.1.2 LLLT vs other intervention								
Sanmak 2019, LLLT vs ESWT in PF	20	32.64	17	30	39.76	17	5.5%	-10.00 [-34.45, 14.45]
Ulusoy 2017, LLLT+ET+S vs ESWT+ET+S in PF	39.4	40.41	8	38.6	44.4	20	3.3%	0.80 [-33.30, 34.90]
Ulusoy 2017, LLLT+ET+S vs TU+ET+S in PF	39.4	40.41	9	31	31.8	17	4.0%	8.40 [-22.02, 38.82]
Yuzer 2006, LLLT vs steroid injection in PF	48	22.91	26	38	23.32	30	11.5%	10.00 [-2.13, 22.13]
Cinar 2018, LLLT+S+I vs ESWT+S+I in PF	44	24.9	24	22	35.13	25	8.6%	22.00 [5.00, 39.00]
Subtotal (95% CI)			**84**			**109**	**32.8%**	**9.41 [-0.44, 19.26]**
Heterogeneity: Tau² = 21.59; Chi² = 4.77, df = 4 (P = 0.31); I² = 16%								
Test for overall effect: Z = 1.87 (P = 0.06)								
2.1.3 LLLT vs no intervention								
Cinar 2018, LLLT+S+I vs S+I in PF	44	26.05	24	27	29.17	17	8.4%	17.00 [-0.35, 34.35]
Cinar 2017, LLLT+S+I vs S+I in PF	44.1	61.76	27	18.2	30.15	22	4.9%	25.90 [-0.58, 52.38]
Subtotal (95% CI)			**51**			**39**	**13.3%**	**19.67 [5.16, 34.18]**
Heterogeneity: Tau² = 0.00; Chi² = 0.30, df = 1 (P = 0.58); I² = 0%								
Test for overall effect: Z = 2.66 (P = 0.008)								
Total (95% CI)			**275**			**281**	**100.0%**	**12.56 [5.69, 19.42]**
Heterogeneity: Tau² = 68.06; Chi² = 25.08, df = 13 (P = 0.02); I² = 48%								
Test for overall effect: Z = 3.59 (P = 0.0003)								
Test for subgroup differences: Chi² = 1.33, df = 2 (P = 0.51), I² = 0%								

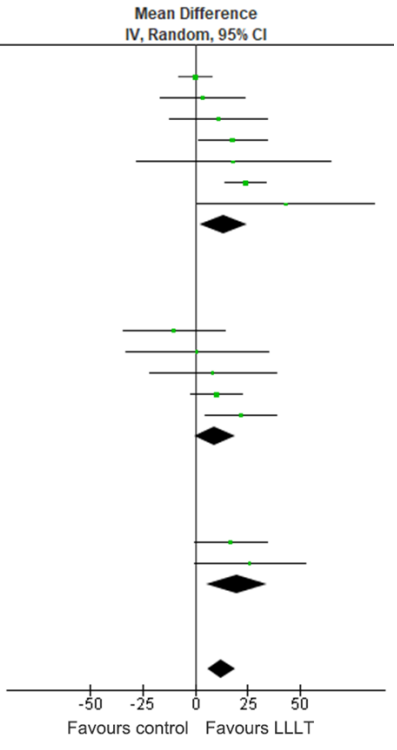

Figure 3 Overall pain results at follow-ups—LLLT versus any control. AT, Achilles tendinopathy; CT, cryotherapy; ESWT, Extracorporeal Shock Wave Therapy; ET, exercise therapy; I, insoles; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy; S, stretching; TU, therapeutic ultrasound.

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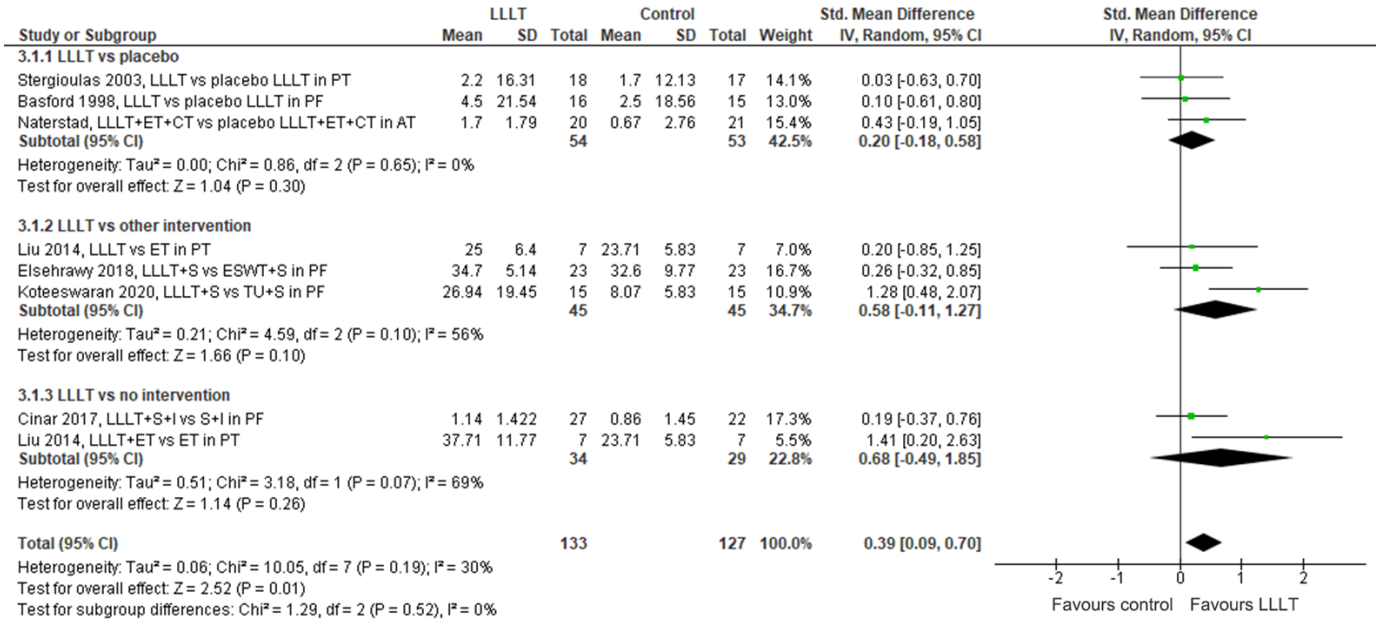

Figure 4 Overall disability results immediately after completed therapy—LLLT versus any control. AT, Achilles tendinopathy; CT, cryotherapy; ESWT, Extracorporeal Shock Wave Therapy; ET, exercise therapy; I, insoles; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy; S, stretching; TU, therapeutic ultrasound.

At follow-ups 4–12 weeks after completed therapy, pain was significantly lowered by the recommended laser doses compared with other interventions (15.90 mm VAS (95% CI 2.30 to 29.51), I^2=0%, n=103) (online supplemental figure S5). Pain was not significantly lowered by unknown laser doses compared with other interventions at follow-ups 4–12 weeks after completed therapy (2.93 mm VAS (95% CI −15.8 to 21.67), I^2=52%, n=87) (online supplemental figure S5).

Subgroup pain results—LLLT versus no intervention

Pain was significantly lowered by the recommended laser doses when used as an adjunct to exercise, stretching and insoles over exercise, stretching and insoles alone, both immediately after completed therapy (18.15 mm VAS (95% CI 10.55 to 25.76), I^2=0%, n=104) (online supplemental figure S2) and at follow-up 9 weeks after completed therapy (19.67 mm VAS (95% CI 5.16 to 34.18), I^2=0%, n=80) (online supplemental figure S3).

Overall and subgroup disability results—LLLT versus placebo control

Overall, the disability results favoured LLLT over placebo control immediately after completed therapy, but not significantly (SMD=0.24 (95% CI −0.18 to 0.58), I^2=0%, n=107) (figure 4). The same applied to the follow-up results 4–8 weeks after completed therapy (SMD=0.19 (95% CI −0.11 to 0.49), I^2=0%, n=173) (online supplemental figure S6).

The disability results immediately after completed therapy favoured the recommended laser doses over other interventions, but not significantly (SMD=0.25 (95% CI −0.21 to 0.7), I^2=0%, n=76) (online supplemental figure S7). The same applied to unknown laser doses compared with placebo

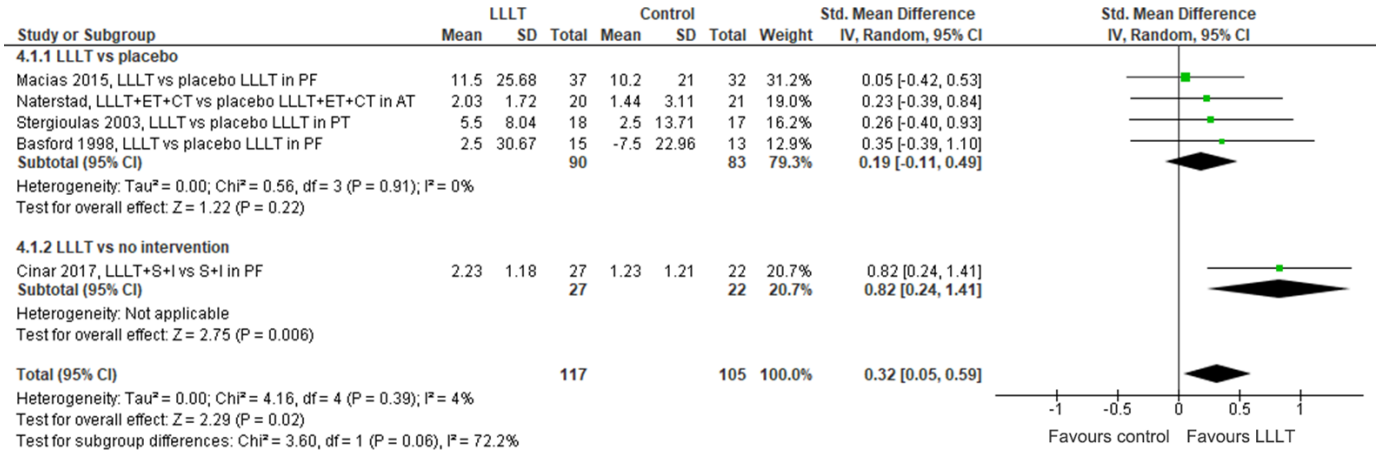

Figure 5 Overall disability results at follow-ups—LLLT versus any control. AT, Achilles tendinopathy; CT, cryotherapy; ET, exercise therapy; I, insoles; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy; S, stretching.

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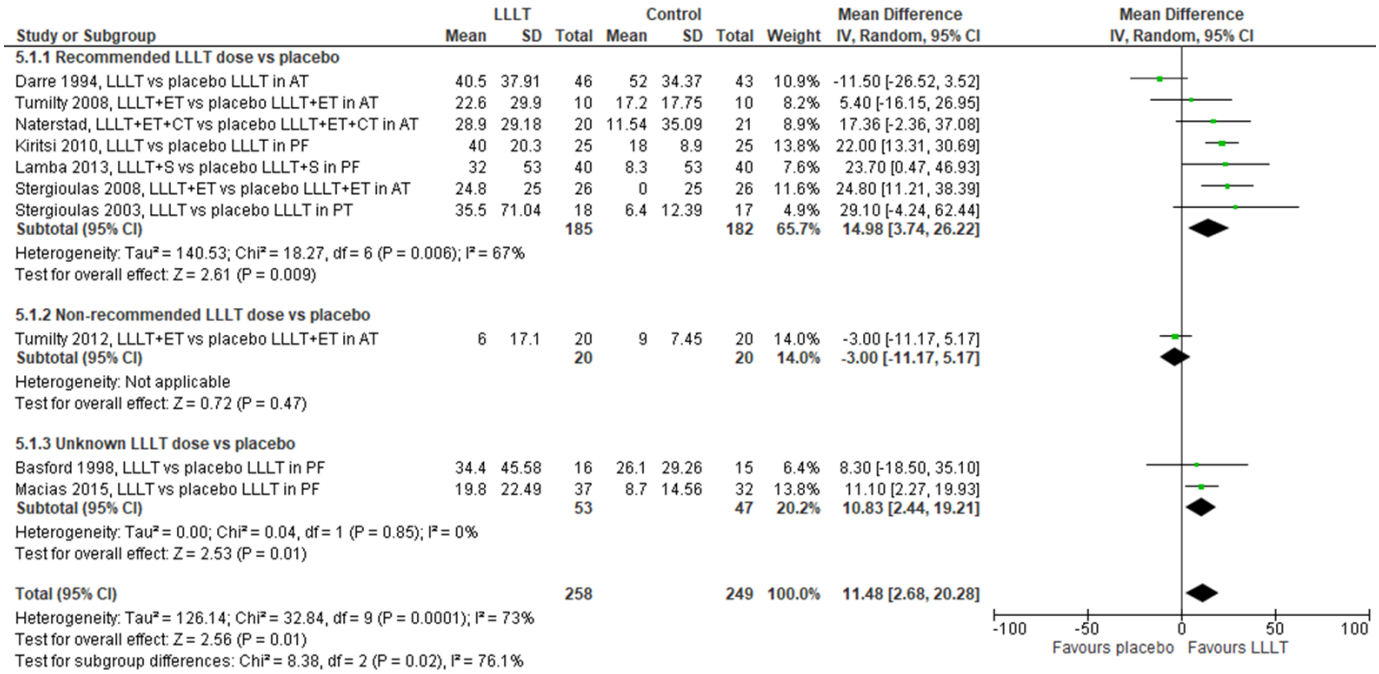

Figure 6 Subgroup pain results immediately after completed therapy—LLLT versus placebo control. AT, Achilles tendinopathy; CT, cryotherapy; ET, exercise therapy; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy; S, stretching.

control immediately after completed therapy (SMD=0.10 (95% CI −0.61 to 0.8), n=31) (online supplemental figure S7).

At follow-ups 4–8 weeks after completed therapy, the disability results favoured the recommended laser doses over other interventions, but not significantly (SMD=0.24 (95% CI −0.21 to 0.7), I^2=0%, n=76) (online supplemental figure S6). The same applied to the unknown laser doses compared with placebo-control immediately after completed therapy (SMD=0.14 (95% CI −0.26 to 0.54), I^2=0%, n=107) (online supplemental figure S6).

Overall and subgroup disability results—LLLT versus other interventions

The overall disability results immediately after completed therapy favoured LLLT, but not significantly (SMD=0.58 (95% CI −0.11 to 1.27), I^2=56%, n=90) (figure 4).

The recommended laser doses neither provided a significant disability reduction compared with other interventions immediately after completed therapy (SMD=0.20 (95% CI −0.85 to 1.25), n=14) (online supplemental figure S8). The same applied to unknown laser doses compared with other interventions immediately after completed therapy (SMD=0.73 (95% CI −0.26 to 1.72), n=76) (online supplemental figure S8).

Subgroup disability results—LLLT versus no intervention

The disability results of the recommended laser doses applied as an adjunct to exercise therapy or stretching immediately after completed therapy favoured LLLT, but not significantly (SMD=0.68 (95% CI −0.49 to 1.85), I^2=69%, n=61) (online supplemental figure S9). At follow-up 9 weeks after completed therapy, disability was significantly lowered by the recommended laser doses as an adjunct to stretching and insoles compared with exercise therapy and insoles alone (SMD=0.82 (95% CI 0.24 to 1.41), n=49) (online supplemental figure S10).

Sensitivity analysis of laser dose categorisation

The irradiation procedure by Darre *et al*[61] was judged as a recommended laser dose, based on the reported dose parameters in the paper. However, the dose description is somewhat sparse and could be misinterpreted. If the study by Darre *et al* was allocated to the unknown laser dose subgroup, the statistical heterogeneity would be eliminated in the recommended laser dose group and the estimated pain reduction would be increased to 21.12 mm VAS ((95% CI 14.94 to 27.31), I^2=0%, n=278) versus placebo immediately after completed therapy (online supplemental figure S11).

Risk of bias within studies

Ten of the included trials were found to be of high methodological quality, and the remaining eight included trials were found to be of moderate methodological quality (table 3). All the trials featured adequate randomisation. Allocation concealment was sufficient in 11 (61%) of the trials. The groups were similar at baseline in 15 (83%) of the trials. The participants were blinded in 9 (50%) of the trials. The therapists were blinded in 5 (28%) of the trials, all of which were placebo controlled. The assessors were blinded in 7 (39%) of the trials, all of which were placebo controlled. Outcome data were available from more than 85% of the participants in 14 (78%) of the trials. An intention-to-treat analysis was used in 10 (56%) of the trials. A between-group statistical comparison was

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Table 3 PEDro score

Study ID	Item number 1*	2	3	4	5	6	7	8	9	10	11	Total	Quality
Basford 1998[64]	+	+	−	+	+	−	+	+	−	+	+	7	High
Cinar 2017[70]	+	+	+	+	−	−	−	+	+	+	+	7	High
Cinar 2018[71]	+	+	+	+	−	−	−	+	+	+	+	7	High
Darre 1994[61]	+	+	+	−	+	+	−	−	−	+	−	5	Moderate
Elsehrawy 2018[72]	+	+	−	+	−	−	−	+	−	+	+	5	Moderate
Kiritsi 2010[65]	+	+	+	+	+	+	+	−	−	+	+	8	High
Koteeswaran 2020[75]	+	+	−	+	−	−	−	+	+	+	+	6	Moderate
Lamba 2013[66]	+	+	−	+	+	−	−	+	−	+	+	6	Moderate
Liu 2014[69]	+	+	−	+	−	−	−	+	+	+	+	6	Moderate
Macias 2015[67]	+	+	+	+	+	−	+	+	+	+	+	9	High
Naterstad	+	+	+	+	+	+	+	+	+	+	+	10	High
Sanmak 2019[73]	+	+	+	+	−	−	−	+	+	+	+	7	High
Stergioulas 2003[60]	+	+	−	+	+	−	+	−	−	+	+	6	Moderate
Stergioulas 2008[68]	+	+	+	+	+	−	−	−	+	+	+	8	High
Tumilty 2008[62]	+	+	+	+	+	+	+	+	+	+	+	10	High
Tumilty 2012[63]	+	+	+	+	+	+	+	+	+	+	+	10	High
Ulusoy 2017[74]	+	+	−	+	−	−	−	+	−	+	+	5	Moderate
Yüzer 2006[76]	+	+	+	+	−	−	−	−	−	+	+	5	Moderate

Naterstad et al. Efficacy of Low-level Laser Therapy as an addition to exercise and cryotherapy in chronic Achilles tendinopathy: a double-blinded randomised controlled trial.
1. Eligibility criteria specified.
2. Random allocation.
3. Concealed allocation.
4. Groups similar at baseline.
5. Subject blinding.
6. Therapist blinding.
7. Assessor blinding.
8. Less than 15% dropout.
9. Intention-to-treat analysis.
10. Between-group statistical comparisons.
11. Point measures and variability data.

*Item not included in the mean score.
PEDro, Physiotherapy Evidence Database.;

performed in all the trials. Point measures and variability outcome data were stated in 17 (94%) of the trial reports.

The lack of therapist and assessor blinding were the two most obvious methodological inadequacies. However, risk-of-bias subgroup analyses performed post-hoc revealed that there was no significant interaction between the effect estimates and the lack of blinding (online supplemental figures S12 and S13).

Risk-of-bias across studies (small study bias)

In a random effects model, small and large trials are weighted relatively even when statistical heterogeneity is present. In a fixed effects model, the heterogeneity is ignored and will not influence the weights. Smaller studies in meta-analyses tend to show more positive results than larger trials.[77] However, there was almost no difference between the pain results of the two meta-analysis models, indicating that no small study bias exists (online supplemental figures S14 and S15). Likewise, there was no obvious asymmetry in a funnel plot based on the same meta-analyses of pain, indicating that no small study bias was present (online supplemental figures S16).

DISCUSSION

We investigated the effectiveness of LLLT in tendon and aponeurosis disorders of the lower extremity. Our overall meta-analysis results demonstrated that pain and disability were statistically significantly reduced by LLLT compared with any control both immediately after completed therapy and in the follow-up period, that is, 4–12 weeks after completed therapy for pain and 4–8 weeks after completed therapy for disability.

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Like in our previous meta-analysis of LLLT in knee osteoarthritis,[39] we subgrouped the included trials in the current review using the WALT treatment recommendations.[58 59] Compared with placebo control, the recommended laser doses in the current review generally had a larger pain-relieving effect than non-recommended laser both immediately after therapy and in the follow-up period. Similarly, the recommended laser doses had a significant pain-relieving effect as an adjunct to exercise therapy, stretching and insoles both immediately after completed therapy and in the follow-up period. Compared with other treatment modalities, the recommended laser doses were significantly superior, but only at follow-up and only as a pain treatment.

The minimal clinically important improvement (MCII) for pain expressed on the VAS or NRS has not been established for tendinopathy in the lower extremity,[78] even though pain is a prominent feature of this condition. In plantar fasciitis, the MCII for VAS pain has been estimated to be 8 mm for average pain,[79] and our results are above this threshold in all comparisons.

As for disability, we found that LLLT overall had a small and significant effect both immediately after completed therapy and in the follow-up period. Compared with placebo, there were no significant effect of LLLT on disability immediately after completed therapy and at follow-ups. Only Cinar *et al*[70] provided follow-up data on disability regarding LLLT as an add-on to exercise therapy. They found a large and significant positive effect on disability 12 weeks after completed therapy; however, their results are based only on 49 participants,[70] and thus this meta-analysis result should be interpreted with caution.

We were unable to dose categorise the study by Macias *et al*,[67] since they used a laser within the visible spectrum (635 nm), which is not mentioned in the WALT treatment guidelines. Light in the red wavelengths (600–700 nm) penetrates the tissue to a lesser extent than light with a wavelength of 700–1000 nm.[80] Macias *et al* used a relatively low mean output power, but they stated that they irradiated the tissue for 600 s and achieved a significant pain reduction. The methodological quality of their trial[67] was categorised as high, with a PEDro score of 9.

Sanmak *et al*[73] also used a laser within the red spectrum, but they applied a much smaller dose. Sanmak *et al*[73] compared LLLT with ESWT in plantar fasciitis and found no difference between the groups regarding pain immediately after treatment, but an insignificant better result for ESWT 4 weeks after completed treatment. Comparing LLLT to ESWT, we would expect different effect-time profiles for pain alleviation, as the effect of ESWT might be greater at later time-points.[81] Sanmak *et al*[73] applied LLLT in a circular motion on the insertion site of the plantar fascia for 60 s and along the fascia for another 60 s. They stated that they irradiated the tissue with 2 J/cm^2, which according to our calculation (Watt*seconds) corresponds to a relatively low mean output power of 18 mW/cm^2. Moving the laser probe during irradiation will yield a smaller laser dose per treated cm^2, and larger movement will for instance reduce the energy delivered per treated cm^2. Additionally, the skin underneath the heel is thick,[82] and thus absorbs a large percentage of the laser.

We did not identify any trials focusing on trochanter tendinopathy, peroneal or tibialis posterior tendinopathy. In a double-blinded randomised trial by Lögdberg-Andersson *et al*,[83] the effect of a 904 nm wavelength laser in participants with trochanteritis or myofascial pain was investigated. They found a significant positive effect compared with placebo on pain expressed on a VAS and with algometry, both at the end of treatment and 4 weeks after.[83] This trial was not included in our review, since we were unable to isolate the participants of interest.

We were only able to identify two randomised controlled trials regarding the effect of LLLT compared with a control in patellar tendinopathy. Ashok *et al*[84] have compared the effect of LLLT to that of therapeutic ultrasound in persons with patellar tendinopathy, and they found a statistically significant effect in favour of LLLT, both on pain reduction and function. However, it should be noted that this trial is small (n=8) and only of moderate methodological quality. Another LLLT trial by Meier *et al*[85] included participants with both patellar tendinopathy (n=58) and Achilles tendinopathy (n=52). We omitted this trial, since it solely concerned the effects of an invisible (904 nm wavelength) laser versus a red (632 nm wavelength) laser. Meier *et al*[85] stated that the red laser was placebo, but the laser dose applied in the sham procedure may possibly have had a photochemical effect. Both groups achieved a positive effect on a combined index of pain and function, favouring the 904 nm wavelength laser, but the report of the trial neither includes point effect estimates, nor variability data.

The presence and role of inflammation in chronic tendinopathy have been an ongoing debate in the last few decades. There is currently increased support that inflammation has a causal role in tendinopathy, where immune cells and molecular mediators are included as inflammatory components.[86–88] PGE_2 has been suggested to sustain inflammation and pain in human tendon disease.[89] In Achilles tendinopathy, a reduction of PGE_2 and a concurrent increased pain pressure threshold after LLLT were found in a double-blinded randomised clinical trial by Bjordal *et al*,[90] where microdialysis of the tendon was performed in seven participants. The participants had aggravated the symptoms through a pain inducing activity immediately prior to the examination. Only the immediate (105 min) response to LLLT was investigated in the trial, but the findings support the notion that LLLT may have an anti-inflammatory effect in Achilles tendinopathy.

Several authors of the included trials failed to adequately describe the laser dose parameters used. A LLLT dose–response relationship has been established in systematic reviews of tendinopathy[34–36] and osteoarthritis.[39] In the current review, some of the statistical heterogeneity is plausibly due to the variation in laser doses applied. The statistical heterogeneity of the dose

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subgroup analyses was generally lower than in the overall (any dose) analyses and this indicates that the laser dose might be more important for the effect than the location of the tendinopathy. The only study that caused noteworthy statistical heterogeneity in the dose subgroup analysis with placebo control was the one by Darre *et al*.[61] Most of the pain and disability analyses comparing LLLT with other interventions were based on trials of plantar fasciitis. These analyses yielded a moderate level of statistical heterogeneity, and it may be explained by the variation in control interventions.

The included trials had a moderate to high methodological quality (mean PEDro score=7.1). Although therapist and assessor blinding lacked in many of the included studies, the lack of blinding was not significantly associated with higher effect estimates (online supplemental material).

Future trials on the topic should include larger patient samples and directly compare the effectiveness of different LLLT parameters. Additionally, systematic reviews of LLLT should include dose-response investigations.

Strengths and limitations of this study

This review was conducted in conformance with a detailed a priori published protocol, which includes, for example, a plan for subgrouping the trials by laser dose. The review includes results from two studies reported in non-English language[61 76] and an unpublished study. The review features meta-analyses with direct comparisons between LLLT and placebo LLLT, other interventions and no intervention. Although only one reviewer extracted data from the included trials, the extracted data were checked for correctness by another reviewer.

Implications for practice

The LLLT dose parameters were inadequately described in 6 (35%) of the trial articles. This prohibited a comprehensive laser dose–response relationship investigation using the WALT treatment recommendations.[37 38] Since the laser doses identified as WALT recommended doses provided significantly positive results in most instances, we suggest adhering to these recommendations until further trials increase the precision of the analysis.

CONCLUSIONS

LLLT significantly reduces pain and disability in lower extremity tendinopathy and plantar fasciitis in the short and medium terms. Long-term data were not available. Some uncertainty about the effect size remains due to wide CIs and lack of larger trials.

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Contributors IFN and MBS wrote the PROSPERO protocol. IFN and MBS selected the trials, with the involvement of JJ when necessary. IFN and MBS judged the risk of bias, with the involvement of JJ when necessary. IFN and MBS extracted the data. IFN and MBS translated the non-English articles. IFN performed the analyses, under supervision by MBS. All authors participated in interpreting of the results. IFN drafted the first version of the manuscript, and subsequently revised it, based on comments by JJ, JB, CC, RABL-M and MBS. All authors read and accepted the final version of the manuscript. IFN acts as the guarantor for this study.

Funding The Norwegian Fund for Post-Graduate Training for Physiotherapists funded this research, grant number 44 944. No other specific grant from any funding agency in the public, commercial or not-for-profit sectors was received for this work.

Disclaimer The corresponding author had full access to all data in the study and had the final responsibility for the decision to submit for publication.

Competing interests JMB and RABLM are former board members and prior presidents of the World Association for Laser Therapy, a non-profit research organisation from which they have never received funding, grants or fees. The other authors declared that they had no conflict of interests related to this work.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The dataset for meta-analysis is available from the corresponding author upon reasonable request. The corresponding author affirms that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained. The dataset for meta-analysis is available from the corresponding author upon reasonable request.

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AAOS
American Academy of Orthopaedic Surgeons

Management of Osteoarthritis of the Knee (Non-Arthroplasty)

Evidence-Based Clinical Practice Guideline

Adopted by:
The American Academy of Orthopaedic Surgeons Board of Directors
August 31, 2021

Endorsed by:

APTA American Physical Therapy Association

AAHKS American Association of Hip and Knee Surgeons

Please cite this guideline as:
American Academy of Orthopaedic Surgeons Management of Osteoarthritis of the Knee (Non-Arthroplasty) Evidence-Based Clinical Practice Guideline. https://www.aaos.org/oak3cpg Published 08/31/2021

Disclaimer

This clinical practice guideline (CPG) was developed by a physician volunteer clinical practice guideline development group based on a formal systematic review of the available scientific and clinical information and accepted approaches to treatment and/or diagnosis. This clinical practice guideline is not intended to be a fixed protocol, as some patients may require more or less treatment or different means of diagnosis. Clinical patients may not necessarily be the same as those found in a clinical trial. Patient care and treatment should always be based on a clinician's independent medical judgment, given the individual patient's specific clinical circumstances.

Disclosure Requirement
In accordance with AAOS policy, all individuals whose names appear as authors or contributors to this clinical practice guideline filed a disclosure statement as part of the submission process. All panel members provided full disclosure of potential conflicts of interest prior to voting on the recommendations contained within this clinical practice guideline.

Funding Source
This clinical practice guideline was funded exclusively by the American Academy of Orthopaedic Surgeons who received no funding from outside commercial sources to support the development of this document.

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Published 2021 by the American Academy of Orthopaedic Surgeons (AAOS)
9400 W Higgins
Rosemont, IL
First Edition
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SUMMARY OF RECOMMENDATIONS

Lateral Wedge Insoles

Lateral wedge insoles are not recommended for patients with knee osteoarthritis.

Strength of Recommendation: Strong ★★★★

Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Canes

Canes could be used to improve pain and function in patients with knee osteoarthritis.

Strength of Recommendation: Moderate ★★★☆

Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Braces

Brace treatment could be used to improve function, pain, and quality of life in patients with knee osteoarthritis

Strength of Recommendation: Moderate ★★★☆ (downgrade)

Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Oral/Dietary Supplements

The following supplements may be helpful in reducing pain and improving function for patients with mild to moderate knee osteoarthritis; however, the evidence is inconsistent/limited and additional research clarifying the efficacy of each supplement is needed.

- **Turmeric**
- **Ginger extract**
- **Glucosamine**
- **Chondroitin**
- **Vitamin D**

Strength of Recommendation: Limited ★★☆☆ (downgrade)

Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

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Topical Treatments

Topical NSAIDs should be used to improve function and quality of life for treatment of osteoarthritis of the knee, when not contraindicated.

Strength of Recommendation: Strong ★★★★

Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Supervised Exercise

Supervised exercise, unsupervised exercise, and/or aquatic exercise are recommended over no exercise to improve pain and function for treatment of knee osteoarthritis.

Strength of Recommendation: Strong ★★★★

Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Neuromuscular Training

Neuromuscular training (i.e. balance, agility, coordination) programs in combination with traditional exercise could be used to improve performance-based function and walking speed for treatment of knee osteoarthritis.

Strength of Recommendation: Moderate ★★★☆ (downgrade)

Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Self-Management

Self- management programs are recommended to improve pain and function for patients with knee osteoarthritis.

Strength of Recommendation: Strong ★★★★

Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Patient Education

Patient education programs are recommended to improve pain in patients with knee osteoarthritis.

Strength of Recommendation: Strong ★★★★

Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

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Weight Loss Intervention

Sustained weight loss is recommended to improve pain and function in overweight and obese patients with knee osteoarthritis.

Strength of Recommendation: Moderate ★★★☆ (downgrade)
Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Manual Therapy

Manual therapy in addition to an exercise program may be used to improve pain and function in patients with knee osteoarthritis.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Massage

Massage may be used in addition to usual care to improve pain and function in patients with knee osteoarthritis.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Laser Treatment

FDA-approved laser treatment may be used to improve pain and function in patients with knee osteoarthritis.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Acupuncture

Acupuncture may improve pain and function in patients with knee osteoarthritis.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

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Transcutaneous Electrical Nerve Stimulation

Modalities that may be used to improve pain and/or function in patients with knee osteoarthritis include:

a. **Transcutaneous Electrical Nerve Stimulation (pain)**

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Percutaneous Electrical Nerve Stimulation/Pulsed Electromagnetic Field Therapy

Modalities that may be used to improve pain and/or function in patients with knee osteoarthritis include:

a. **Percutaneous Electrical Nerve Stimulation (pain and function)**
b. **Pulsed Electromagnetic Field Therapy (pain)**

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Extracorporeal Shockwave Therapy

Extracorporeal shockwave therapy may be used to improve pain and function for treatment of osteoarthritis of the knee.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Oral NSAIDs

Oral NSAIDs are recommended to improve pain and function in the treatment of knee osteoarthritis when not contraindicated.

Strength of Recommendation: Strong ★★★★
Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

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Oral Acetaminophen

Oral acetaminophen is recommended to improve pain and function in the treatment of knee osteoarthritis when not contraindicated.

Strength of Recommendation: Strong ★★★★

Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Oral Narcotics

Oral narcotics, including tramadol, result in a significant increase of adverse events and are not effective at improving pain or function for treatment of osteoarthritis of the knee.

Strength of Recommendation: Strong ★★★★

Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Hyaluronic Acid

Hyaluronic acid intra-articular injection(s) is not recommended for routine use in the treatment of symptomatic osteoarthritis of the knee.

Strength of Recommendation: Moderate ★★★☆ (downgrade)

Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Intra-articular Corticosteroids

Intra-articular (IA) corticosteroids could provide short-term relief for patients with symptomatic osteoarthritis of the knee.

Strength of Recommendation: Moderate ★★★☆ (downgrade)

Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Platelet-rich Plasma

Platelet-rich plasma (PRP) may reduce pain and improve function in patients with symptomatic osteoarthritis of the knee.

Strength of Recommendation: Limited ★★☆☆ (downgrade)

Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

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Denervation Therapy

Denervation therapy may reduce pain and improve function in patients with symptomatic osteoarthritis of the knee.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Lavage/Debridement

Arthroscopy with lavage and/or debridement in patients with a primary diagnosis of knee osteoarthritis is not recommended.

Strength of Recommendation: Moderate ★★★☆
Description: Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Partial Meniscectomy

Arthroscopic partial meniscectomy can be used for the treatment of meniscal tears in patients with concomitant mild to moderate osteoarthritis who have failed physical therapy or other nonsurgical treatments.

Strength of Recommendation: Moderate ★★★☆
Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Tibial Osteotomy

High tibial osteotomy may be considered to improve pain and function in properly indicated patients with unicompartmental knee osteoarthritis.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

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Summary of Consensus Statement

There is no evidence or only conflicting supporting evidence for the following recommendations. In the absence of reliable evidence, the systematic literature review development group is making a recommendation based on their clinical opinion.

Dry Needling

In the absence of reliable evidence, it is the opinion of the workgroup that the utility/efficacy of dry needling is unclear and requires additional evidence.

Strength of Recommendation: Consensus ★☆☆☆

Description: Evidence there is no supporting evidence, or limited level evidence was downgraded due to major concerns addressed in the EtD framework. In the absence of reliable evidence, the guideline work group is making a recommendation based on their clinical opinion.

Free Floating Interpositional Devices

In the absence of reliable or new evidence, it is the opinion of the work group not to use free-floating (un-fixed) interpositional devices in patients with symptomatic medial compartment osteoarthritis of the knee.

Strength of Recommendation: Consensus ★☆☆☆

Description: Evidence there is no supporting evidence, or limited level evidence was downgraded due to major concerns addressed in the EtD framework. In the absence of reliable evidence, the guideline work group is making a recommendation based on their clinical opinion.

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INTRODUCTION

OVERVIEW

This clinical practice guideline is based on a systematic review of published studies examining the non-arthroplasty treatment of knee osteoarthritis in adults. It provides recommendations that will help practitioners to integrate the current evidence and clinical practice, and it highlights gaps in the literature in need of future research. This guideline is intended to be used by appropriately trained physicians and clinicians who manage the treatment of osteoarthritis of the knee. It also serves as an information resource for developers and applied users of clinical practice guidelines.

GOALS AND RATIONALE

The purpose of this clinical practice guideline is to evaluate the current best evidence associated with treatment. Evidence-based medicine (EBM) standards advocate for use of empirical evidence by physicians in their clinical decision making. To assist with access to the large resources of information, a systematic review of the literature in publication was conducted between March 2018 and April 28, 2020. It highlights where there is good evidence, where evidence is lacking, and what topics future research will need to target in order to help facilitate evidence-based decision making in the treatment of patients with osteoarthritis of the knee. AAOS staff methodologists assisted the physician/clinician work group in evaluating the existing literature so that they could formulate the following recommendations based on a rigorous systematic process. Musculoskeletal care is provided in many different settings and by a variety of providers. We created this guideline as an educational tool to guide qualified physicians and clinicians in making treatment decisions that improve the quality and efficacy of care. This guideline should not be construed as including all possible methods of care or excluding acceptable interventions similarly directed at obtaining favorable outcomes. The final decision to use a specific procedure must be made after assessing all concerns presented by the patient and consideration of locality-specific resources.

INTENDED USERS

This guideline is intended to be used by orthopaedic surgeons and other healthcare providers managing patients with osteoarthritis of the knee. It serves as an information resource for medical practitioners. In general, individual practicing physicians and clinicians do not have the resources required to complete a project of comparable scope and duration involving the evaluation of an extensive literature base. In April 2019, the AAOS adopted the use of the GRADE Evidence-to-Decision Framework into its clinical practice guideline development methodology. This Framework enables work group members to incorporate additional factors into the strength of each recommendation and move away from the rigidity of previous AAOS recommendation language stems. The AAOS intends for this guideline to assist treatment providers not only in making shared clinical decisions with their patients, but also in describing to patients and their loved ones why a selected intervention represents the best available course of treatment. This guideline is not intended for use as a benefits determination document. It does not cover allocation of resources, business and ethical considerations, and other factors needed to determine the material value of orthopaedic care. Users of this guideline may also want to consider the appropriate use criteria (AUC) related to the treatment of osteoarthritis of the knee.

PATIENT POPULATION

This guideline is intended for use with adults (ages 17 years and older) who have been diagnosed by a trained healthcare provider with osteoarthritis of the knee and are undergoing treatment.

SCOPE

The scope of this guideline includes non-pharmacologic and pharmacologic interventions for symptomatic osteoarthritis of the knee as well as operative procedures less invasive than knee

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replacement (arthroplasty). It does not provide recommendations for patients diagnosed with rheumatoid arthritis, osteoarthritis of other joints, or other inflammatory arthropathies.

ETIOLOGY

Osteoarthritis results from an imbalance between breakdown and repair of the tissues in the synovial joint organ and occurs as a result of multiple risk factors including trauma, overuse, and genetic predisposition.

INCIDENCE AND PREVALENCE

The incidence of knee osteoarthritis in the United States is estimated at 240 persons per 100,000 per year. Worldwide prevalence of radiographically confirmed symptomatic knee OA is estimated to be 3.8% overall, increasing with age to over 10% in the population over the age of 60.

BURDEN OF DISEASE

Osteoarthritis (of any joint) was the primary diagnosis for 23.7 million ambulatory care visits in 2013. An estimated 32.5 million adults in American, 14% of that population, suffered from symptomatic knee osteoarthritis between 2008 and 2014. Risk factors of the condition increase with age, especially in women. Although women represent 51% of the general population in the United States, they represent 78% of the patients diagnosed with osteoarthritis between 2008 and 2014. Genetics and hereditary vulnerability, elevated body mass, certain occupations, and traumatic knee injuries are other factors that increase one's risk of developing the disease.

EMOTIONAL AND PHYSICAL IMPACT

Older adults with self-reported osteoarthritis visit their physicians more frequently and experience greater functional limitations than others in the same age group. The aging of the baby boomers, rise in rates of obesity, and greater emphasis on staying active suggest that the social and physical impact of knee osteoarthritis will continue to be widespread.

POTENTIAL BENEFITS, HARM, AND CONTRAINDICATIONS

Individuals with osteoarthritis of the knee often complain of joint pain, stiffness, and difficulty with purposeful movement. The aim of treatment is to provide pain relief and improve the patient's functioning. Most interventions are associated with some potential for adverse outcomes, especially if invasive or operative. Because the clinical research does not differentiate between the sexes, it is possible future research may result in a better understanding of how a patient's sex alters treatment benefits and harms. Contraindications vary widely by procedure. Reducing risks improves treatment efficacy and is accomplished through collaboration between patient and physician.

DIFFERENCES BETWEEN THE PRESENT AND PREVIOUS GUIDELINES

This updated clinical practice guideline replaces the second edition that was completed in 2013, "Treatment of Osteoarthritis of the Knee (Non-Arthroplasty) 2nd edition." This update considered the literature that we previously examined as well as the empirical evidence published since the 2013 guideline. In April 2019, the AAOS adopted the use of the GRADE Evidence-to-Decision Framework into its clinical practice guideline development methodology. This Framework enables work group members to incorporate additional factors into the strength of each recommendation and move away from the rigidity of previous AAOS recommendation language stems. The complete listing of inclusion criteria for this guideline is detailed in the section, "Study Selection Criteria," (eAppendix 1).

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METHODS

The methods used to perform this systematic review were employed to minimize bias and enhance transparency in the selection, appraisal, and analysis of the available evidence. These processes are vital to the development of reliable, transparent, and accurate clinical recommendations. To view the full AAOS clinical practice guideline methodology please visit https://www.aaos.org/additonalresources/ .

This clinical practice guideline evaluates the management of osteoarthritis of the knee (non-arthroplasty) patient outcomes. The AAOS approach incorporates practicing physicians (clinical experts) and methodologists who are free of potential conflicts of interest relevant to the topic under study, as recommended by clinical practice guideline development experts.[1]

This clinical practice guideline was prepared by the AAOS Osteoarthritis of the Knee Guideline physician development group (clinical experts) with the assistance of the AAOS Clinical Quality and Value (CQV) Department (methodologists). To develop this clinical practice guideline, the clinical practice guideline development group held an introductory meeting on February 23, 2018 to establish the scope of the clinical practice guideline. As the physician experts, the clinical practice guideline development group defined the scope of the clinical practice guideline by creating PICO Questions (i.e. population, intervention, comparison, and outcome) that directed the literature search. The AAOS Medical Librarian created and executed the search (see Appendix III for search strategy).

LITERATURE SEARCHES

We begin the systematic review with a comprehensive search of the literature. Articles we consider were published prior to the start date of the search in a minimum of three electronic databases; PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials. The medical librarian conducts the search using key terms determined from the guideline development group's PICO questions.

A CQV methodologist will review/include only primary literature but will supplement the electronic search with a manual search of the bibliographies of secondary literature sources, such as systematic reviews, as available. The methodologist will then evaluate all recalled articles for possible inclusion based on the study selection criteria and will summarize the evidence for the guideline work group who assist with reconciling possible errors and omissions.
A study attrition diagram is provided in the appendix of each document that details the numbers of identified abstracts, recalled and selected studies, and excluded studies that were evaluated in the CPG. The search strategies used to identify the abstracts is also included in the appendix of each CPG document.

DEFINING THE STRENGTH OF RECOMMENDATION

Judging the quality of evidence is only a steppingstone towards arriving at the strength of a CPG recommendation. The strength of recommendation also takes into account the quality, quantity, and the trade-off between the benefits and harms of a treatment, the magnitude of a treatment's effect, and whether data exists on critical outcomes.

Strength of recommendation expresses the degree of confidence one can have in a recommendation. As such, the strength expresses how possible it is that a recommendation will be overturned by future evidence. It is very difficult for future evidence to overturn a recommendation that is based on many high quality randomized controlled trials that show a large effect. It is much more likely that future evidence will overturn recommendations derived from a few small retrospective comparative studies. Consequently, recommendations based on the former kind of evidence are given a "strong" strength of recommendation and recommendations based on the latter kind of evidence are given a "limited" strength.

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To develop the strength of a recommendation, AAOS staff first assigned a preliminary strength for each recommendation that took only the final quality and the quantity of evidence (see Table 1). The recommendations can be further downgraded or upgraded based on the GRADE and Evidence-to-Decision Framework criteria described above.

VOTING ON THE RECOMMENDATIONS

The recommendations and their strength were voted on by the guideline development group members during the final meeting. If disagreement between the guideline development group occurred, there was further discussion to see whether the disagreement(s) could be resolved. Recommendations were approved and adopted in instances where a simple majority (60%) of the guideline development group voted to approve; however, the guideline development group had consensus (100% approval) when voting on every recommendation for this guideline. Any recommendation strength upgrade or downgrade based on the Evidence-to-Decision Framework requires a super majority (75%) approval of the work group.

View background material via the OAK3 CPG eAppendix 1
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INTERPRETING THE STRENGTH OF EVIDENCE

Table I. LEVEL OF EVIDENCE DESCRIPTIONS

Strength	Overall Strength of Evidence	Description of Evidence Quality	Strength Visual
Strong	Strong or Moderate	Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Or Rec is upgrade from Moderate using the EtD framework	★★★★
Moderate	Strong, Moderate or Limited	Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Or Rec is upgraded or downgraded from Limited or Strong using the EtD framework.	★★★☆
Limited	Limited or Moderate	Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Or Rec is downgraded from Moderate using the EtD Framework.	★★☆☆
Consensus*	No Evidence	There is no supporting evidence, or higher quality evidence was downgraded due to major concerns addressed in the EtD framework. In the absence of reliable evidence, the guideline work group is making a recommendation based on their clinical opinion.	★☆☆☆

Table II. INTERPRETING THE STRENGTH OF A RECOMMENDATION

Strength of Recommendation	Patient Counseling (Time)	Decision Aids	Impact of Future Research
Strong	Least	Least Important, unless the evidence supports no difference between two alternative interventions	Not likely to change
Moderate	Less	Less Important	Less likely to change
Limited	More	Important	Change possible/anticipated
Consensus	Most	Most Important	Impact unknown

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REVIEW PERIOD

Following the final meeting, the CPG draft undergoes a 3-week review period for additional input from external content experts. Written comments are provided on the structured review form. All reviewers are required to disclose their conflicts of interest.

To guide who participates, the CPG work group identifies specialty societies at the introductory meeting. Organizations, not individuals, are specified.

The specialty societies are solicited for nominations of individual reviewers approximately six weeks before the final meeting. The review period is announced as it approaches, and others interested are able to volunteer to review the draft. The chairs of the guideline work group review the draft of the guideline prior to dissemination.

Some specialty societies (both orthopaedic and non-orthopaedic) ask their evidence-based practice (EBP) committee to provide review of the guideline. The organization is responsible for coordinating the distribution of our materials and consolidating their comments onto one form. The chair of the external EBP committees provides disclosure of their conflicts of interest (COI) and manages the potential conflicts of their members.

Again, the AAOS asks for comments to be assembled into a single response form by the specialty society and for the individual submitting the review to provide disclosure of potentially conflicting interests. The review stage gives external stakeholders an opportunity to provide evidence-based direction for modifications that they believe have been overlooked. Since the draft is subject to revisions until its approval by the AAOS Board of Directors as the final step in the guideline development process, confidentiality of all working drafts is essential.

The CPG is also provided to members of the AAOS Board of Directors (BOD), members of the Council on Research and Quality (CORQ), members of the Board of Councilors (BOC), and members of the Board of Specialty Societies (BOS) and members of the Committee on Evidence-Based Quality and Value (EBQV) for review and comment. The CPG is automatically forwarded to the AAOS BOD and CORQ so that they may review it and provide comment prior to being asked to approve the document. Members of the BOC and BOS are solicited for interest. If they request to see the document, it is forwarded to them for comment. Based on these bodies, over 200 commentators have the opportunity to provide input into each CPG.

The chairs of the guideline work group and the manager of the AAOS CQV unit drafts the initial responses to comments that address methodology. These responses are then reviewed by the chair and co-chair, who respond to questions concerning clinical practice and techniques. The Senior Manager of Clinical Quality and Value may provide input as well. All comments received and the initial drafts of the responses are also reviewed by all members of the guideline development group. All proposed changes to recommendation language as a result of the review period are based on the evidence. Final revisions are summarized in a report that is provided alongside the guideline document throughout the remainder of the approval processes and final publication.

The AAOS believes in the importance of demonstrating responsiveness to input received during the review process and welcomes the critiques of external specialty societies. Following final approval of the guideline, all individual responses are posted on our website http://www.aaos.org/quality with a point-by-point reply to each non-editorial comment. Reviewers who wish to remain anonymous notify the AAOS to have their names de-identified; their comments, our responses, and their COI disclosures are still posted.

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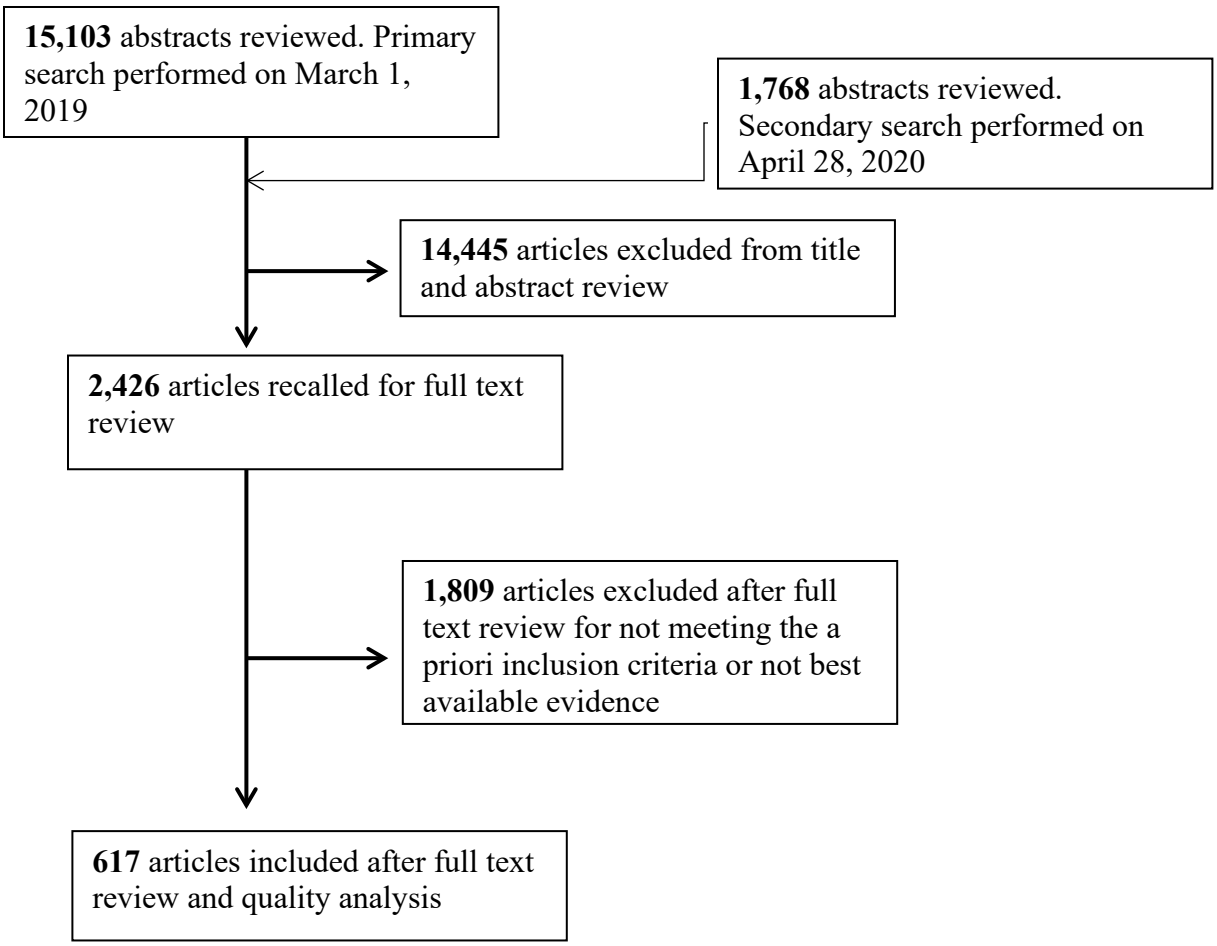
THE AAOS CPG APPROVAL PROCESS
This final clinical practice guideline draft must be approved by the AAOS Committee on Evidence Based Quality and Value Committee, and subsequently the AAOS Council on Research and Quality, and the AAOS Board of Directors. These decision-making bodies are described in the OAK CPG eAppendix. Their charge is to approve or reject its publication by majority vote.

REVISION PLANS
This clinical practice guideline represents a cross-sectional view of current treatment and may become outdated as new evidence becomes available. This clinical practice guideline will be revised in accordance with new evidence, changing practice, rapidly emerging treatment options, and new technology. This clinical practice guideline will be updated or withdrawn in five years.

CPG DISSEMINATION PLANS
The primary purpose of the present document is to provide interested readers with full documentation of the best available evidence for various procedures associated with the topic of this review. Publication of most clinical practice guidelines is announced by an Academy press release, articles authored by the clinical practice guideline development group and published in the Journal of the American Academy of Orthopaedic Surgeons, and articles published in AAOS *Now*. Most clinical practice guidelines are also distributed at the AAOS Annual Meeting in various venues such as on Academy Row and at Committee Scientific Exhibits. The final guideline recommendations and their supporting rationales will be hosted on www.OrthoGuidelines.org.

Selected clinical practice guidelines are disseminated by webinar, an Online Module for the Orthopaedic Knowledge Online website, Radio Media Tours, Media Briefings, and by distributing them at relevant Continuing Medical Education (CME) courses and at the AAOS Resource Center.

Study Attrition Flowchart



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RECOMMENDATIONS

Lateral Wedge Insoles

Lateral wedge insoles are not recommended for patients with knee osteoarthritis.

Strength of Recommendation: Strong ★★★★
Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Rationale

Although lateral heel wedges had historical support for their use in knee arthritis, contemporary studies have not shown a reliable improvement in pain relief and no contemporary studies have shown sufficient functional improvement for patients suffering from knee arthritis to recommend using lateral wedge insoles. Lateral heel wedges can be prepared as an insert for the heel alone, or included in the heel of an independent arch support (i.e. lateral heel wedge arch support of LWAS) or built into shoe itself (as was used by Hinman et al 2016). In the arthritic knee, medial compartment compression forces are commonly increased, especially in the knee with varus tibiofemoral alignment. The knee adduction moment can be calculated by gait analysis. The lateral wedge is thought to change the knee adduction moment thus relieving medial compartment pressure, hence relieving arthritic pain.

Our literature review screening culled several papers for analysis. Baker and Goggins 2007 was a high-quality study finding no important differences between insole and wedged insole. 90 patients were randomized to one treatment for 6 weeks followed by a 4-week washout period and then the opposite treatment. There were no major differences in pain during either phase of the study. More musculoskeletal symptoms and more blisters occurred with neutral insoles. No patient falls were attributed to the treatment alternatives.

Felson and Parke 2019 prescreened patients to eliminate those with patellofemoral OA and biomechanical non-responders. Lateral wedge insoles reduced knee pain, but the effect of treatment was small and was considered likely of clinical significance in only a minority of patients. 21 of 83 of patients did not show sufficient biomechanical correction. Only 28% of patients in the active phase of treatment had minimally important improvement whereas 22% of patients wearing neutral insoles reached the same level of improvement. 2 patients stopped treatment while wearing lateral wedge insoles (calf pain at night and increased knee pain) and 2 stopped while wearing neutral insoles (toe blister and increased knee pain). They also looked at volume of arthritic bone marrow lesions (BML) found by MRI and saw no significant difference in BML change between study and control groups.

In Bennell 2011, 89 patients with mild to moderate knee arthritis completed follow up with lateral insoles worn daily for 12 months. 90 patients completed follow up as the control group wearing neutral insoles. Pain relief after 12 months showed no significant difference between the groups.

In Hsieh 2016, 90 patients with Kellgren-Lawrence Grade 2 or higher radiographic changes were randomized to either a rigid insole with lateral wedge arch support (LWAS) or a soft insole with lateral wedge. Dropout rate was 20% with rigid and 15.6% with soft insoles over the 3-month long study. They concluded that patients using the soft insole LWAS had improved pain and function. However, their primary data suggests better walking time and speed going up and down stairs with rigid LWAS.

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Furthermore, pain was improved with soft LWAS only at the 3-month mark. Authors suggested longer term follow up for soft insoles.

Hinman 2016 evaluated an unloading shoe with stiff lateral midsole and 5 degree lateral wedge insole in comparison to a standard walking shoe. 164 patients were enrolled with 96% retention during the 6 months study. 83 patients received the unloading shoes and the control shoes. 14 of 83 stopped wearing the unloading shoes for various reasons and 8 of 81 stopped wearing the control shoes. 160 completed primary outcome measures at 6 months. There was no significant difference between groups with regard to pain or function, although both groups did show improvement.

20% of participants with the study shoes reported ankle and foot pain whereas 9% of control shoe participants did so. There was no difference in reason to discontinue treatment (unloading shoe 4% versus 2% control). Other reported adverse events were back pain, hip pain, knee pain, knee stiffness/swelling and shin/calf pain. 2 of 83 experimental group patients reported increase in knee pain with the unloading shoe and 2 or 81 control patients reported that the conventional shoe did not relieve knee pain.

Toda 2004 followed 84 knee female arthritis patients were followed for one month wearing either a hard rubber insole or urethane insole secured to the foot with a subtalar strap used for ankle sprains. 12 mm lateral wedge was manufactured for both. 17 of the 42 rubber insole patients had complications (foot pain in 8; popliteal pain in 6; low back pain in 3) versus 8 of the 42 using urethane insoles (popliteal pain in 4; foot pain in 3; low back pain in 1). All patients improved by the Lequesne Index with the urethane group achieving statistically significant improvement.

Niazi 2014 was a comparison of off-loading knee brace versus lateral wedge insole. 120 patients with both radiographic medial compartment arthritis and gene varum were randomized to either knee brace or lateral wedge insole. Pain improvement with the knee brace group was statistically significant compared to the lateral wedge insole, but clinically minor (VAS 3.97 in the study group compared to 4.53 in controls).

In Hatef 2013, 118 of 150 patients completed the 2-month long study (101 women and 17 men). Half were given LWAS and the control group wore neutral insoles. Patient compliance was much worse in the LWAS group. They noted statistically significant decline in knee pain and EKFS in women in the LWAS, but not men. Overall, there was improvement in the LWAS group. There was a much higher non-compliance rate in the LWAS than with the neutral insoles with 29 of 57 patients stopping use of the insoles by weeks 5 to 6 of an 8-week study.

We identified one potential study within our literature which addressed the question of special shoe versus a conventional shoe. Nigg 2006 evaluated a training shoe which purports to convert a flat hard surface into “natural uneven ground”, thus prompting increased muscle activity in the lower extremity. The control shoe was a standard walking shoe. 58 patients were enrolled in the study group and 67 in the control group. Both groups had one patient drop out (cumbersome shoes in the study group and increased knee pain with the control shoe). Pain with walking was improved at 12 weeks in both groups, without between groups difference. The study shoe showed increased pain relief at 3, 6 and 12 weeks. The control shoe showed increased pain relief at 3 and 12 weeks. They also reported improved balance from baseline in the study shoe at 12 weeks which was not statistically significant.

Benefits/Harms of Implementation

Although lower extremity pain might be increased with either neutral insole or LWAS, there is no significant harm to the patient trying either option.

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Cost Effectiveness/Resource Utilization
A standard insole or conventional walking shoe provided equivalent improvement in pain compared to lateral wedge arch support. Although the lateral wedge modifications are more expensive, the increased cost is not prohibitive and a patient attempting self-treatment could discontinue at any time with little loss of time effort or out of pocket cost.

Acceptability
Insoles are already commercially available and have long history of orthopaedic use. They can fit or be adapted to a variety of shoes, commonly already owned by the patient. Some studies reviewed (Hsieh 2016 and Hatef 2013) also described a relatively high dropout or non-compliance rate. While this does not imply frank harm to the patient, such data do suggest distinct potential for patient dissatisfaction with the treatment.

Feasibility
Although there are no immediately obvious limits to feasibility of implementing neutral insoles or LWAS for knee pain, Felson 2019 confirmed previous studies by showing 25% of their potential subjects did not correct knee adduction when using the lateral wedge.

Future Research
We did not identify any studies of sufficient size comparing a "walking shoe" versus a random or conventional shoe. The studies reviewed by the workgroup suggest that a walking shoe or a soft neutral insole might provide some degree of pain relief. Future studies addressing this treatment option could confirm some type of specialized yet commercially available shoe as beneficial to the patient with knee arthritis.

View background material via the OAK3 CPG eAppendix 1
View data summaries via the OAK3 CPG eAppendix 2

Canes

Canes could be used to improve pain and function in patients with knee osteoarthritis.

Strength of Recommendation: Moderate ★★★☆

Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Rationale

Canes have been used since antiquity for lower extremity orthopaedic disorders. With that in mind, only a small number of modern studies have formally investigated use of a cane for knee osteoarthritis. Our literature review found one high quality study (Jones 2012) showing support for use regarding moderate pain relief and another study (Van Ginckel 2019) of moderate quality showing no major improvement in pain.

Jones 2012 performed a comprehensive study of use of a cane for knee osteoarthritis. Their primary outcome was pain, but they also looked at function, general health, consumption of NSAIDs and energy expenditure. 64 patients were selected out a total of 323 patients nominated from a rheumatology clinic. The majority of possible patients (168 out of 323) refused to participate in the study. 32 patients were randomized to use of a cane for 60 days (EG, experimental group). The cane was cut to appropriate height and they received instructions on its use. The 32 control patients (CG) were instructed to maintain normal lifestyle and not to use auxiliary gait devices. At 30 and 60 days the EG patients had less pain compared to controls. The greatest improvement was in the VAS (10 cm scale): EG averaging 3.84 cm and CG 5.95 cm at 60 days). The Lequesne scale (0-24) difference was only 2.53 (CG 15.09 and EG 12.56 at 60 days). At 60 days, the study group consumed fewer NSAIDs than control.

Van Ginckel 2019 evaluated use of a cane in patients with medial compartment knee osteoarthritis and bone marrow lesions (BML) on MRI. The primary intent of their study was to identify an effect on the size of BML by using a cane. Out of 1989 potential patients (contacted by phone or online) 231 were considered eligible for radiographic screening and of those, only 79 showed arthritic changes on plain films and BML on MRI and chose to continue with the study. 40 patients were assigned to use a cane whenever walking for the next 12 weeks. 39 control patients were instructed to maintain their usual lifestyle without any gait aids. Only one patient in the control group was lost to follow up. After 3 months there was no significant improvement in BML size. Secondary information was obtained relative to clinical characteristics. There was no significant difference between the two groups with regards to knee pain (WOMAC scale) or quality of life (AQoL 6-D scale) although there was improvement in global knee pain in the group using the cane.

Benefits/Harms of Implementation

Jones 2012 addressed the increased oxygen demand for ambulation using a cane. Initially all patients had decreased ambulation distance with a cane and increased heart rate and increased oxygen consumption. After 60 days patients who had been using the cane (EG) were able to ambulate a similar distance with or without the cane suggesting an ability to adapt to the cane. Also, EG patients using the cane had more normal oxygen consumption after walking again suggesting physiologic adaptation to the cane with time.

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Outcome Importance
Our review shows moderate confirmation that canes can relieve the pain of knee arthritis and improve function in those patients.

Cost Effectiveness/Resource Utilization
Use of a cane is a common low-cost treatment which is readily available with many options and typically covered by third party payers.

Acceptability
Van Ginckel noted "patient vanity" as a common reason for non-compliance.

Feasibility
Canes have been used since antiquity although comparison studies are only being produced in the last generation. There is little downside to extended use of the cane as patients appear to adapt to the increased oxygen consumption demands.

Future Research
More studies would be beneficial to the knowledge base confirming value to patients with knee osteoarthritis.

View background material via the OAK3 CPG eAppendix 1
View data summaries via the OAK3 CPG eAppendix 2

Braces

Brace treatment could be used to improve function, pain and quality of life in patients with knee osteoarthritis.

Strength of Recommendation: Moderate ★★★☆ (downgrade)
Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Rationale

Four high, four moderate and two low quality studies were included for review, following the application of exclusion criteria by committee (Brouwer 2006b; Kirkley 1999; Callaghan 2015; Van Raaij 2010; Thoumie 2018; Hjartarson 2018; Petersen 2018; Niazi 2014; Hungerford 2013; Yu 2016). Three prospective randomized controlled trials compared bracing to control groups for treatment of symptomatic OA of the knee joint and found statistically significant and clinically meaningful improvement in patient symptoms related to symptomatic OA of the knee (Callaghan 2015; Thoumie 2018; Brouwer 2006b). Kirkley et al compared outcomes between valgus offloading brace, neoprene sleeve, and non-brace control for symptomatic OA and Varus alignment. This study reported statistically significant improvement in disease specific quality of life and function in both study groups (Kirkley 1999). The study by Brouwer et al., comparing valgus bracing to a non-braced control, and reported no significant difference in functional assessment, PRO or pain; however, clinically significant improvements were noted in walking distance (1.25km[0.15,2.35]) for the brace group. Subgroup analysis demonstrated greater positive effect of bracing in patients with varus alignment and more severe symptoms. Callaghan et al examined the effects of bracing for patella-femoral OA and found significant improvement from baseline VAS and KOOS pain scores. Finally, Hjartarson et al examined outcomes of bracing vs. placebo by removing valgus tension straps from the control group brace. In their study they reported statistically significant and clinically meaningful improvements in KOOS sub scores: symptoms, ADL, sports and recreation, and quality of life.

The Braces recommendation has been downgraded one level because of heterogeneity.

Benefits/Harms of Implementation

Braces can provide significant pain relief and improved function to patients that have unicompartmental knee osteoarthritis. Braces can provide a subjective feeling of more normal tibiofemoral kinematics, preventing excessive strain on the affected compartment while protecting against preexistent concomitant meniscal and chondral injuries. There is also a theoretical benefit of increased confidence in the knee during the different activities by providing a sense of security to the knee. There are almost no harms in trialing a brace besides some skin irritation, or the brace being uncomfortable.

Future Research

Future high-quality studies that are well powered are required to assess the real efficacy of unloader braces vs knee sleeves in a population with similar mechanical axis with a similar degree of OA.

View background material via the OAK3 CPG eAppendix 1
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Oral/Dietary Supplements

The following supplements may be helpful in reducing pain and improving function for patients with mild to moderate knee osteoarthritis; however, the evidence is inconsistent/limited and additional research clarifying the efficacy of each supplement is needed.

a) **Turmeric**
b) **Ginger extract**
c) **Glucosamine**
d) **Chondroitin**
e) **Vitamin D**

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale

The majority of 6 high quality trials (Reginster 2001, Cibere 2004, McAlindon 2004, Clegg 2006, Herrero-Beaumont 2007, Fransen 2015), the majority of 6 moderate quality trials (Noack 1994, Houpt 1999, Rindone 2000, Pavelka 2002, Giordano 2009, and Shahine 2014), and 1 low quality study that met inclusion criteria showed either improvement or no change in patient outcomes for those with osteoarthritis of the knee when taking glucosamine versus control.

The majority of 8 high quality trials (Fransen 2015, Clegg 2006, Uebelhart 2004, Reginster 2017, Morita 2018, Zegels 2013, Kahan 2009, Rondanelli 2019) and 6 moderate quality trials (Mazieres 2007, Moller 2010, Rondanelli 2019, Bourgeois 1998, Mazieres 2001, Bucsi 1998) that met inclusion criteria showed either improvement or no change in patient outcomes for those with osteoarthritis of the knee when taking chondroitin.

One high quality study (Srivastava 2016) that met inclusion criteria showed that Turmeric extract could be used over control to improve adverse events, function, and pain in patient with osteoarthritis of the knee.

One high study (Zakeri 2011) and one moderate quality study (Altman 2001) that met inclusion criteria showed that ginger extract may be used to improve pain in patients with osteoarthritis of the knee. However, there was no significant difference in function between ginger extract and control.

Three high quality studies (McAlindon 2013, Sanghi 2013, and Jin 2016) and 1 moderate quality study (Arden 2016) that met inclusion criteria showed either improvement or no significant difference in patient outcomes for those with osteoarthritis of the knee between Vitamin D and control.

The Oral/ Dietary Supplements recommendation has been downgraded two levels because of inconsistency and need for additional clarity of efficacy.

Benefits/Harms of Implementation

The United States Food and Drug Administration does not hold dietary supplements to the same standards as prescription medication. As a result, variability can exist between producers of dietary supplements.

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The patient's medications should be evaluated for potential drug-supplement interactions prior to initiating any dietary supplement.

Outcome Importance

Improvement in the predictability of the treatment effect for specific dietary supplements will either reduce an unnecessary out-of-pocket expense or provide patients with a relatively safe method for reducing pain and improving function in the treatment of mild to moderate osteoarthritis of the knee. Knowing which supplements have evidence-based support for effective treatment will reduce unnecessary out-of-pocket expenses and provide patients with a safe method for reducing pain and improving function in the treatment of mild to moderate osteoarthritis of the knee.

Cost Effectiveness/Resource Utilization

Dietary supplements are typically an out-of-pocket expense not covered by medical insurance. As a result, patients must individually consider the expense associated with utilization of dietary supplements. We did not have the analysis to comment on the cost-benefit ratio of dietary supplements compared to other over the counter or prescription medications.

Acceptability

The limited evidence supporting dietary supplements and out-of-pocket expense associated with their use will limit broader acceptance. For patients without a medication interaction, dietary supplements pose limited physical harm as it is typically difficult to consume a toxic quantity. Therefore, it is believed to be an acceptable means to potentially achieve benefit in the treatment of mild to moderate osteoarthritis of the knee.

Feasibility

Dietary supplements are widely available to patients. The associated out-of-pocket expense is the primary barrier to access.

Future Research

The most important future research will need to provide multiple investigations demonstrating reproducible results illustrating the effectiveness of dietary supplements. Additionally, future research is necessary to determine the appropriate dose, frequency, and duration of treatment with dietary supplements.

View background material via the OAK3 CPG eAppendix 1
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Topical Treatments

Topical NSAIDs should be used to improve function and quality of life for treatment of osteoarthritis of the knee, when not contraindicated.

Strength of Recommendation: Strong ★★★★
Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Rationale
Twelve high quality studies (Baer 2005, Roth 2004, Conaghan 2013, Simon 2009, Kneer 2013, Rother 2013, Bookman 2004, Wadsworth 2016, Sandelin 1997, Dehghan 2019, Dehghan 2020, Rother 2007) and two moderate quality studies (Barthel 2009, Ottillinger 2001) show that topical NSAIDs could result in improved function and quality of life over placebo gel. However, inconsistent evidence suggests no significant difference in pain and adverse events between topical NSAIDs and control.

Benefits/Harms of Implementation
Topical NSAIDs are now available over the counter for patients to buy and use. Topical NSAIDs should be used with caution in certain health conditions such as stage 4-5 chronic kidney disease, coronary artery disease, and congestive heart failure. There is a risk for skin sensitivity.

Outcome Importance
Improved function and quality of life improvement are the important outcomes from Topical NSAID use.

Cost Effectiveness/Resource Utilization
Since this will now be available over the counter, prescription coverage will be less. This could pose as a barrier to those without health savings accounts or without insurance. Also, patients might not be willing to apply a topical gel multiple times a day.

Acceptability
The use of a topical gel for osteoarthritis of the knee should be an acceptable method of treatment if cost is not prohibitive and the patient does not have any skin irritation from the gel.

Feasibility
Topical NSAIDs will be available at pharmacies over the counter. The main barrier will be cost and having to apply the gel multiple times a day.

Future Research
Future research might be directed at determining if continued topical NSAID use is required to sustain benefits or if benefits continue after usage for a defined period of time.

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Supervised Exercise

Supervised exercise, unsupervised exercise, and/or aquatic exercise are recommended over no exercise to improve pain and function for treatment of knee osteoarthritis.

Strength of Recommendation: Strong ★★★★
Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Rationale

Ten high quality studies were reviewed that compared a supervised exercise program to a non-exercise control (e.g., no treatment, heat only, education, usual primary care). (Christensen 2015,Holsgaard-Larsen 2018, Oliveira 2012, Willamson 2007, de Rooij 2017, Imoto 2012, Topp 2002, Hu 2020, Kim 2013, Chen 2014) Seven of these studies found greater improvements in pain, function, or both pain and function over the non-exercise control group (Oliveira 2012, de Rooij 2017, Imoto 2012, Topp 2002, Hu 2020, Kim 2013, Chen 2014).

One high quality study and four moderate quality studies were reviewed that compared supervised exercise to a non-supervised exercise program (e.g., home program, internet-based program, exercise brochure). (McCarthy 2004, Allen 2018, Yilmaz 2019, Tunay 2010, Bennell 2014). Patients from both groups received benefit from the interventions but there were mixed results as to whether supervised exercise was superior to the non-supervised exercise programs. It appears that both supervised or non-supervised exercise programs can result in improved pain and function in people with knee osteoarthritis.

Four high quality studies and one moderate quality study were reviewed that compared aquatic exercise to either usual primary care, education, or self-management. (Kuptniratsaikul 2019, Rewald 2020, Waller 2017, Munukka 2020, Dias 2017.) Three high quality studies reported greater improvements in pain, function, or global ratings of improvement for the aquatic groups over the control groups. (Kuptniratsaikul 2019, Rewald 2020, Dias 2017) One high quality study reported increased leisure time activity for the aquatic group compared to the control. (Waller 2017) One moderate quality study compared aquatic exercise to land-based exercise. (Silva 2008) There was no difference in WOMAC pain and function scores reported between groups for this study, but the aquatic exercise group had less pain with walking compared to the land-based group. Although there may be some benefit from aquatic exercise, inconsistent results do not allow us to recommend aquatic exercise over land-based exercise at this time.

Several studies examined clinical outcomes for different modes of exercise in patients with knee osteoarthritis. Ebnezar 2012 reported some improvement in anxiety measures when comparing yoga to non-yoga exercise. (Ebnezar 2012) Other studies compared weightbearing to non-weightbearing exercise (Bennell 2020, Jan 2009), high versus low resistance training (Jan 2008), isokinetic, isometric, and isotonic exercise (Huang 2005), and leg versus hip exercise (Lun 2015) and did not find substantial differences in the mode of exercise. It appears that exercise is beneficial, but the mode of exercise may not matter as much as engaging in any exercise program.

Benefits/Harms of Implementation

Most patients can expect an improvement in pain and function with exercise. Patients may experience a temporary increase in knee pain or muscle soreness when engaging in an exercise program.

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Cost Effectiveness/Resource Utilization

One study by Bove, et al, 2018 examined the cost-effectiveness of delivering physical therapy supervised exercise and manual therapy in booster (treatment sessions spread out periodically over 1 year) vs no-booster (treatment sessions delivered consecutively over 9 weeks) session approaches. It appeared that the booster delivery approach may be more cost-effective than the non-booster delivery approach.

Feasibility

Most exercise programs would be considered feasible. However, some patients may have difficulty with access to supervised exercise due to travel or co-pay concerns. Aquatic programs would not be feasible for patients who do not have access to a pool or walking tank.

Future Research

Identifying factors that could discriminate between people who would likely benefit from supervised programs vs independent exercise programs is an area of research that could improve clinical decision-making for prescribing exercise. More studies are also needed to examine delivery of exercise through telerehabilitation compared with in-person supervised programs. Studies should also examine differences in outcomes between varying modes of delivering telerehabilitation exercise programs. More research would also be beneficial in examining the role of booster session delivery of exercise programs.

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Neuromuscular Training

Neuromuscular training (i.e. balance, agility, coordination) programs in combination with traditional exercise could be used to improve performance-based function and walking speed for treatment of knee osteoarthritis.

Strength of Recommendation: Moderate ★★★☆ (downgrade)
Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Rationale
Three high quality studies (Fitzgerald 2011, Gomiero 2018, Apparao 2017) and two moderate quality studies (Bennell 2014 and Diracoglu 2005) comparing neuromuscular training combined with traditional strength and joint mobility exercise programs to strength and joint mobility exercise alone were reviewed. There were no differences in knee pain reported between groups in any of the studies. There were mixed results on function measures with two studies reporting greater improvements in self-reported function (Apparao 2017, Diracoglu 2005) and two studies reporting greater improvements in walking speed (Bennell 2014, Diracoglu 2005) for the neuromuscular training group.

The Neuromuscular training recommendation has been downgraded one level because of inconsistent evidence.

Benefits/Harms of Implementation
Some patients can expect an improvement in function and walking speed with neuromuscular training. Some patients may experience a temporary increase in knee pain or muscle soreness when engaging in the exercise program.

Feasibility
Neuromuscular exercise programs would be considered feasible. However, some patients may have difficulty with access to supervised exercise due to travel or co-pay concerns.

Future Research
Given the mixed results between exercise programs with and without neuromuscular exercise programs, it would be beneficial for future research to identify factors that would discriminate between patients who would have better success with a neuromuscular exercise program versus those who would have better success with a traditional strength and joint mobility exercise program.

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Self-Management

Self-management programs are recommended to improve pain and function for patients with knee osteoarthritis.

Strength of Recommendation: Strong ★★★★
Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Rationale

Self-management programs refer to formalized training and education programs that are taught by both healthcare professionals and trained layperson instructors. They typically include several sessions over several weeks. These programs train people in several elements of self-management for osteoarthritis including medication compliance, pain management and pain coping strategies, joint protection strategies during physical activity, exercise advice, problem solving approaches and stress management techniques.

Four high quality studies (Saffari 2018, Somers 2012, Hurley 2007, Omidi 2018) and one moderate quality study (Coleman 2012) compared self-management to usual care or no treatment. These studies reported greater improvements in pain, function, or both compared to the control groups. In addition, some of these studies reported greater improvements in quality of life, pain catastrophizing, and self-efficacy in the self-management groups (Saffari 2018, Somers 2012).

One high quality (Marconcin 2018) and three moderate quality studies examined the combined use of self-management and exercise to either groups that received self-management or exercise alone (Bennell 2016) or usual care (Yip 2007, Kao 2012). Yip et al. reported greater improvements in pain, time spent in leisure activities, and self-efficacy, compared to usual care. (Yip 2007) reported greater improvements in pain and function compared to the control groups. Bennell, et al, reported improvements in pain and function in all groups. There were no differences between groups on pain measures but the combined use of self-management (i.e., pain coping skills training) and exercise had greater improvements in function compared to those receiving only self-management or exercise (Bennell 2016).

An attempt was made to examine the literature on cognitive behavioral therapy (CBT) in the management of people with knee osteoarthritis. One high quality (Helminen 2015) and 4 moderate quality (Focht 2012, Focht 2017, Smith 2015, Lerman 2017) studies were reviewed. Control groups consisted of usual care (Helminen 2015), traditional exercise approaches for knee osteoarthritis, (Focht 2012, Focht 2017) or behavioral desensitization (Smith 2015, Lerman 2017). Inconsistency in outcome results across studies made it difficult to provide a recommendation for this intervention approach at this time.

Benefits/Harms of Implementation

Patients may expect improvements in pain and function, problem-solving abilities, and self-efficacy from participating in these programs. Engagement in exercise recommendations could result in some temporary increased knee pain or muscle soreness.

Outcome Importance

Pain, function, self-efficacy in managing osteoarthritis.

Feasibility

Self-management programs are feasible for patients provided they have appropriate access. Some patients may have limited access for participation, making the programs less feasible.

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Future Research

Future research should examine delivery methods designed to increase access for patients (e.g., online delivered programs). Given that some patients with severe symptoms and disability may not be able to respond to self-management programs, future research should assess whether the outcomes of self-management programs vary with disease severity. This research should determine if there is a threshold of disease or disability severity that discriminates between responders and non-responders of this treatment approach.

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Patient Education

Patient education programs are recommended to improve pain in patients with knee osteoarthritis.

Strength of Recommendation: Strong★★★★

Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Rationale

Six high-quality studies (Saffari 2018, Somers 2012, Cagnin 2019, Gilbert 2018, Baker 2019, Berman 2004) thirteen moderate quality study (Brosseau 2012, Allen 2010, O'Brien 2018, Allen 2010, Bennell 2017, Marra 2012, Rezende 2017, Sandeghi 2019, Rodriguez da Silva 2017, Rini 2015, Moseng 2020, Chen 2020, Ravaud 2009) and two limited quality studies compared patient education and control. These studies reported more significant improvements in pain compared to the control groups.

Patient education programs in studies overlap with self-management programs. Patient education programs vary from patient handout, 2+ hour DVD, one-day education to multiple sessions over a month (Saffari 2018, Cagnin 2019, Brosseau 2012, O'Brien 2018, Rezende 2017, Rodriguez da Silva 2017, Rini 2015). Many studies are challenging to evaluate the effects of education because they involve exercise classes and other proven interventions (Marra 2012, Ravaud 2009). Self-management programs train people in several elements of self-management for osteoarthritis (1148), including medication compliance, pain management, and pain coping strategies, joint protection strategies (1149) during physical activity, exercise advice, problem-solving approaches, and stress management techniques. Patient education programs may not be as labor-intensive, and further work is needed to identify the amount of education needed to improve patient-related outcome measures, like pain.

Programs that focused on education are two high quality (Saffari 2018, Cagnin 2019) and four moderate quality (Brosseau 2012, O'Brien 2018, Rodriguez da Silva 2017, Rini 2015). Saffari used seven (7) group sessions over one month and provided a CD-ROM and booklet describing preventive lifestyle procedures and the importance of treatment adherence (Saffari 2018). They found improvement in SF-12 and pain scores. Cagnin used an educational session with a physical therapist who demonstrated how recommended exercises should be performed and how patients can manage their pain. They demonstrated improvement in KOOS pain scores (Cagnin 2019). Brousseau looked at education (educational pamphlet) vs. walking and education vs. walking and behavioral intervention (Brouseau 2012). There was a non-clinically significant improvement in pain in the education-only group at 12 months compared to walking and behavioral intervention. O'Brien used weight loss education, where trained telephone interviewers provided brief advice and education about the benefits of weight loss and physical activity for knee osteoarthritis immediately after randomization [O'Brien 2018]. The intervention group provided an evidence-based public health non-disease-specific telephone-based coaching service funded by the local Australian state government to support adults in making sustained lifestyle improvements, including diet, physical activity, and achieving a healthy weight and, where appropriate, access smoking cessation services. They did not find an added benefit from the coaching service over the brief telephone education in pain nor WOMAC scores. Rini compared an internet-based app (PainCoach) [http://tri.ad/projects-2/] to usual care and found a non-clinically significant reduction in VAS pain scores (Rini 2015). Rodriguez da Silva used a single day (Saturday, from 8 a.m. to 5 p.m.), which included seven lectures of 30 min by each professional team, and 60-min workshops by the physical education, physical therapy, and occupational therapy professionals, approaching the importance of their area in knee OA treatment/management. The study did not report pain scores but did note an increase in mobility with improvements in the get-up and go test. The two high-quality and four moderate-quality studies showed

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improved pain scores from the education given during educational sessions. Most studies (15 of the 21) incorporate education with other interventions; therefore, it is impossible to isolate the effects of education in these other 15 studies.

One high quality (Gilbert 2018) and three moderate quality (Rezende 2017, Chen 202, Ravaud 2009) used the transtheoretical model (TTM) and motivational interviewing to improve osteoarthritis treatment adherence. These studies showed improvement in WOMAC pain scores. TTM has been used successfully in other conditions that benefit from lifestyle changes [PMID: 24500864].

Future Research

Further research is needed to determine the best practice of education for reducing pain and other PROM for knee OA and the delivery method. Since many studies use different components and delivery methods and multiple interventions, it is impossible to recommend one particular educational module or particular component.

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Weight Loss Intervention

Sustained weight loss is recommended to improve pain and function in overweight and obese patients with knee osteoarthritis.

Strength of Recommendation: Moderate ★★★☆ (downgrade)
Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Rationale

There were 1 high (Jenkinson et. al 2009),1 moderate (Miller 2006), and 2 low strength (Focht 2005, Rejeski 2002) studies evaluating diet and exercise as weight loss interventions to treat knee osteoarthritis. Overall pain and function improved with weight loss achieved through a combination of diet and exercise. However, when evaluating only diet vs control, 2 high (Bliddal 2011, Christensen 2015), 2 moderate (Messier 2013, Mihalko 2018) and 2 low strength (Rejeski 2002, Fochyt 2005) there was no clear clinically significant change in patient outcomes. Specifically, Christensen et al, 2015 published a high-quality study investigating the effect of weight on symptoms of knee osteoarthritis. They showed no significant difference in pain and function at 1 year. Bliddal et al, 2010 published another high quality study which investigated the effect of weight loss on symptoms of knee OA in the obese patient, showing that perceived pain (via WOMAC) was significantly lessened despite not being able to show improvement in function and quality of life at 1 year.

There were 2 moderate strength studies (Messier 2013, Mihalko 2018) which evaluated diet vs exercise, which favored exercises. To note, Messier et al 2013 published results of the IDEA trial with moderate quality study which was an attempt to determine if a 10% reduction in body weight (induced by diet, with or without exercise) would improve "clinical and mechanistic" outcomes in sedentary lifestyle patients (BMI 27 thru 41). Interestingly, in this primary study, they were unable to show an improvement in WOMAC pain but they did show improvement in the WOMAC function subscale, and also showed improvements in the 6 minute walk test.
Given the current evidence, it is at the discretion of the surgeon as to which approach is utilized to address weight loss, however a combination of diet and exercises appears to be the preferred alternative.

The Weight Loss Intervention recommendation has been downgraded one level because of inconsistent evidence.

Benefits/Harms of Implementation

There are no known or anticipated harms associated with implementing this recommendation.

Outcome Importance

Management of obesity and overweight through weight loss may have high impact on symptoms and overall health.

Cost Effectiveness/Resource Utilization

Weight loss presents a potentially high level of cost effectiveness compared to other surgical and nonsurgical approaches; however, the cost-effectiveness of different weight loss approaches is still to be determined.

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Acceptability
Currently weight loss is a commonly utilized approach in the optimization of patient who present with obesity and knee osteoarthritis, hence there should be no issues implementing this recommendation as it does not influence a major change in clinical practice. To note, patients often are reluctant or unwilling to accept referrals for weight loss as a suggestion for a path to improvement.

Feasibility
This recommendation does not interfere with other interventions or clinical practice therefore it is deemed very feasible in a subset of overweight and obese patients.

Future Research
Future research should focus on large randomized clinical trials and should focus more on function and quality of life measures since it appears obvious that pain improved through weight loss.

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Manual Therapy

Manual therapy in addition to an exercise program may be used to improve pain and function in patients with knee osteoarthritis.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale
Manual therapy consists of maneuvers applied with manual force from the treating therapist to the patient's body to improve joint mobility and/or relieve pain. The techniques may generally consist of manually applied joint mobilization techniques, manually applied joint range of motion and/or muscle stretching, and soft tissue massage. One high quality study (Fitzgerald 2016) and one moderate quality study (Deyle 2000) were reviewed that examined manual therapy combined with exercise compared to exercise alone (Fitzgerald 2016) or non-therapeutic ultrasound (placebo physical therapy) in subjects with knee osteoarthritis. (Deyle 2000) Fitzgerald, et al, reported that both groups yielded significant improvements in clinical outcomes from baseline but the manual therapy group had greater improvements in the WOMAC total score and were more likely to meet the OMERACT-OARSI Responder Criteria at the 9 week follow-up. (Fitzgerald 2016) While both groups demonstrated sustained improvements in clinical outcomes at 1 year there was no difference between groups on any measures at this timepoint. Deyle et al. reported similar findings with the manual therapy and exercise group demonstrating greater improvements at 8 weeks but no significant differences between groups at 1 year (Deyle 2000).

The Manual Therapy recommendation has been downgraded one level because of inconsistent evidence and to lack of internal consistency with recommendations of equal supporting evidence.

Benefits/Harms of Implementation
Most patients can expect an improvement in pain and function with the interventions. Patients may experience a temporary increase in knee pain or muscle soreness when engaging in a manual therapy and exercise program.

Cost Effectiveness/Resource Utilization
Bove, et al 2018 found manual therapy and exercise delivered with periodic booster sessions was more cost-effective than delivery of this same intervention without booster sessions. (Bove 2018) The cost effectiveness assessment was over a 2-year follow-up (Bove 2018).

Feasibility
The manual therapy interventions are feasible for patients who have access to in-person physical therapy. The exercise interventions are feasible both from an in-person and home program perspective.

Future Research
Future studies should examine ways to sustain the effects of manual therapy and exercise for extended follow-up periods. Research is needed to determine the effectiveness of self-applied manual therapy and telerehabilitation applications of manual therapy and exercise interventions for improving pain and function in patients with knee osteoarthritis.

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Massage

Massage may be used in addition to usual care to improve pain and function in patients with knee osteoarthritis.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale

Two high quality study (Pehlivan 2018, Sansila 2019) and one moderate quality study (Perlman 2018) were reviewed that examined massage plus usual care to a usual care control group. Pehlivan et al. applied a leg massage focusing primarily on tissues around the knee for a total of 6 sessions over 3 weeks (Pehlivan 2018). Subjects receiving massage had greater improvements in knee pain at 4 weeks follow-up compared to the usual care control group but there was no difference between groups at 8 weeks. There were also no differences in function between groups at either time point. Perlman et al. applied a 60-minute total body massage one time per week for 8 weeks, followed by bi-weekly sessions for 52 weeks (Perlman 2018). There was greater improvement in pain and function in the massage group at the 8-week follow-up, but these effects were not sustained for any of the longer-term follow-up timepoints.

The Massage recommendation has been downgraded one level because of inconsistent evidence and due to lack of internal consistency with recommendations of equal supporting evidence.

Benefits/Harms of Implementation

Patients receiving massage may experience some short-term improvements in pain and function. Massage treatments are generally safe but common side effects may include skin redness or irritation, bruising, muscle soreness, fatigue, and nausea.

Feasibility

The interventions are considered feasible and relatively accessible to the general public. Patients who have transportation issues may have difficulty with obtaining access to treatment.

Future Research

Future research may be warranted to determine how massage could be combined with other interventions for knee osteoarthritis to sustain longer term effects on pain and function.

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Laser Treatment

FDA-approved laser treatment may be used to improve pain and function in patients with knee osteoarthritis

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale
A meta-analysis was performed using pain data from two high quality studies (Gur 2003, Nazari 2018) and one moderate quality (Marquina 2012) study examining high intensity laser treatment compared to either placebo laser treatment or no treatment groups. The results of the analysis are provided in Figure 10 in appendix. The overall findings were in favor of the laser intervention over the sham or no-treatment groups. In addition, two of these studies reported greater improvements in function. (Gur 2003, Nazari 2018) Gur 2003 also compared high dose vs. low dose laser treatment on clinical outcomes and found no significant difference between the groups. (Gur 2003)

The Laser Treatment recommendation has been downgraded two levels because of feasibility, usage in practice and a lack of internal consistency with recommendations of equal supporting evidence.

Benefits/Harms of Implementation
Patients should expect to experience improvements in pain and function with the treatment. There have been no reports of serious side effects from laser treatment for pain control. Long-term exposure of the laser beam to the eyes can cause eye damage.

Feasibility
Access to the laser treatment may not be available in all clinics.

Future Research
Continued study of laser treatment for pain control, improving function and cost-effectiveness in people with knee osteoarthritis is encouraged.

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Acupuncture

Acupuncture may improve pain and function in patients with knee osteoarthritis.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale

A meta-analysis was performed using pain data from five high quality studies (Chen 2013, Suarez-Almazor 2010, Mavrommatis 2012, Berman 2004, Hinman 2014) and two moderate quality studies (Vas 2007, Berman 1999). Acupuncture treatments were either traditional (Chen 2013, Hinman 2014) or electro-acupuncture. (Suarez-Almazor 2010, Mavrommatis 2012, Vas 2007, Berman 2004, Berman 1999) Control groups consisted of either no acupuncture, (Hinman 2014) sham acupuncture, (Mavrommatis 2012, Suarez-Almazor 2010, Vas 2007, Berman 2004) sham TENS (Chen 2013), or usual care. (Berman 1999) The meta-analysis also accounted for the degree of blinding effectiveness of the studies. The results of the meta-analysis can be seen in Figure 11 in the appendix. The overall findings were in favor of acupuncture for reducing pain in subjects with knee osteoarthritis. There appeared to be no effect in two studies where blinding was effective. In studies where there was no blinding or the effects of blinding were unclear, there were greater effects favoring acupuncture. This prompted our decision to apply a limited strength of recommendation in favor of acupuncture for pain control.

A similar meta-analysis was performed using the same studies for measures of function. The results of this meta-analysis can be seen in Figure 12 in appendix. The overall findings were in favor of acupuncture for improving measures of function in subjects with knee osteoarthritis. However, the effects of blinding effectiveness on the results were similar to that described above for pain. Again, this prompted our decision to apply a limited strength of recommendation in favor of acupuncture for improving function.

Some investigators examined variations in delivery of acupuncture treatment. Ju et al. examined high intensity vs low intensity electro-acupuncture and found no difference between these approaches for pain but possibly better improvements in function favoring the high intensity group. (Ju 2015) Others found no meaningful differences between using 2-point, 4-point, or 6-point acupuncture approaches. (Qi 2016, Taechaarpornkul 2009).

The Acupuncture recommendation has been downgraded two levels because of inconsistent evidence and a lack of internal consistency with recommendations of equal supporting evidence.

Benefits/Harms of Implementation

Many patients receive benefit such as reduced pain and improved function but not all patients respond favorably to treatment. The treatment should be administered by a certified acupuncture practitioner. Common side effects can include soreness and minor bleeding or bruising where needles are inserted. Risk of infection is low if proper procedures are followed. Patients who have a bleeding disorder, pacemaker, or could be pregnant may not be safe candidates for acupuncture and should consult with their physician before having the treatment.

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Acceptability
The interventions are considered acceptable, but some individuals may not be enthusiastic about having needles inserted into their skin.

Feasibility
The intervention is feasible provided there is access to a trained practitioner. Not all clinics can provide such access.

Future Research
Continued research is encouraged, with more studies that improve blinding effectiveness in the methodology and studies that may identify patient characteristics that could discriminate between responders and non-responders of this treatment approach.

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Transcutaneous Electrical Nerve Stimulation

Modalities that may be used to improve pain and/or function in patients with knee osteoarthritis include:

a) **Transcutaneous Electrical Nerve Stimulation (pain)**

Strength of Recommendation: Limited ★★☆☆ (downgrade)

Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale

A meta-analysis was performed using pain data from two high quality studies (Palmer 2014, Inal 2016) and one moderate quality study (Atamaz 2012) in which Transcutaneous Electrical Nerve Stimulation (TENS) was compared to sham TENS in subjects with knee osteoarthritis. Blinding effectiveness was considered fair in all three studies. The results of the meta-analysis can be seen in Figure 15 in the appendix. The overall findings were in favor of receiving TENS for reducing pain in subjects with knee osteoarthritis. A similar meta-analysis was performed using the same studies for measures of function. The results of this meta-analysis can be seen in Figure 16 in the appendix. The overall findings did not favor the use of TENS to improve measures of function in subjects with knee osteoarthritis.

The Transcutaneous Electrical Nerve Stimulation recommendation has been downgraded two levels because of inconsistent evidence and a lack of internal consistency with recommendations of equal supporting evidence.

Benefits/Harms of Implementation

TENS units are small, portable, non-invasive devices that could provide pain relief and may allow some patients to reduce pain medication use. Some patients may experience skin irritations or allergic reactions to the adhesive pads used to deliver the stimulation. Use of TENS is not recommended in people with pacemakers and women who are pregnant should not apply TENS in the abdominal or pelvic regions.

Acceptability

The interventions appear to be acceptable to most patients however some patients may not like the sensation of electrical or electro-magnetic energy being applied to their bodies.

Future Research

Continued research with larger randomized trials that examine long-term effectiveness of the interventions is warranted. Studies that identify factors discriminating between responders and non-responders to the interventions would also be important.

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Percutaneous Electrical Nerve Stimulation

Modalities that may be used to improve pain and/or function in patients with knee osteoarthritis include:

a) **Percutaneous Electrical Nerve Stimulation (pain and function)**
b) **Pulsed Electromagnetic Field Therapy (pain)**

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale

One high quality study was reviewed that examined the use of Percutaneous Electrical Nerve Stimulation (PENS) combined with a Cox-2 inhibitor to sham PENS combined with a Cox-2 inhibitor in subjects with knee osteoarthritis. (He 2019) The results indicated greater improvements in pain and function measures in subjects receiving PENS compared to sham PENS.

One high quality study was reviewed that examined the use of a wearable Pulsed Electomagnetic Field (PEMF) device for pain management in subjects with knee osteoarthritis. (Bagnato 2016) Subjects were randomized to either the PEMF group or a sham PEMF group. PEMF was applied 12 hours per day for a period of 4 weeks. The results indicated greater improvement in WOMAC pain and VAS pain scores for subjects receiving PEMF over sham PEMF. There was no difference between groups on WOMAC function scores.

The Percutaneous Electrical Nerve Stimulation/Pulsed Electromagnetic Field Therapy recommendation has been downgraded one level because of feasibility issues.

Benefits/Harms of Implementation

PENS is a minimally invasive procedure. Patients may experience reduction in pain and improvement in function after receiving the intervention. Because the intervention involves the insertion of very thin needles, side effects are similar to acupuncture and include bleeding, bruising, or skin irritation at the insertion site. Infection or nerve damage are possible but very rare side effects.

PEMF devices are generally safe and can reduce pain and inflammation. The treatment often results in an increase in blood flow which, in some circumstances, could temporarily trigger an increase in pain and discomfort and oxidative stress. Some patients may report fatigue and loss of energy, sleep disturbances, dizziness, and increased urination. PEMF treatment may induce a decrease in blood pressure and heart rate so caution must be taken in patients with cardiovascular deficiencies. A fall in blood sugar levels can also result in some people with PEMF treatment so caution should be taken in patients who have difficulty regulating blood sugar. PEMF may affect blood coagulation and is not recommended in people who are taking anti-coagulant therapies.

Acceptability

The interventions appear to be acceptable to most patients however some patients may not like the sensation of electrical or electro-magnetic energy being applied to their bodies.

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Feasibility
PENS is feasible but requires a practitioner trained in the technique which could limit access for some patients. PEMF is not widely used in clinics treating patients for knee osteoarthritis and thus could limit access for some patients.

Future Research
Continued research with larger randomized trials that examine long-term effectiveness of the interventions is warranted. Studies that identify factors discriminating between responders and non-responders to the interventions would also be important.

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Extracorporeal Shockwave Therapy

Extracorporeal shockwave therapy may be used to improve pain and function for treatment of osteoarthritis of the knee.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale
A meta-analysis was performed using pain data from three high quality studies (Zhong 2019, Ediz 2018, and Uysal 2020) in which Extracorpeal Shockwave Therapy (ESWT) was compared to sham ESWT in subjects with knee osteoarthritis. The results of the meta-analysis can be seen in Figure 19 in the appendix. The overall findings were in favor of receiving ESWT for reducing pain in subjects with knee osteoarthritis. In addition, four high quality studies reported greater improvements in function scores in subjects receiving ESWT compared to the sham group at 4 to 12 weeks but not at 1-year follow-up. (Zhao 2013, Ediz 2018, Zhong 2019, Uysal 2020).

The Extracorporeal shockwave Therapy recommendation has been downgraded two levels because of inconsistent evidence and a lack of internal consistency with recommendations of equal supporting evidence.

Benefits/Harms of Implementation
Patients receiving this treatment may experience improvements in pain and function. Side effects may include redness or mild bruising, swelling, pain, numbness or tingling in the treated area, migraine headaches, and syncope.

Acceptability
Generally tolerated well but some patients may experience side-effects listed above.

Feasibility
The intervention is considered feasible but may not be widely available in clinics managing patients with knee osteoarthritis and therefore may not be accessible for all patients.

Future Research
Future studies should examine methods to sustain longer term effects of the intervention (e.g., optimal dosage, use of booster interventions), investigate the potential of ESWT as an osteoarthritis disease-modifying agent, and identify characteristics of patients that may discriminate between responders and non-responders of the intervention. The mechanisms of action of these interventions in human subjects is not well understood. Future studies investigating the mechanisms of action of these interventions in human subjects would be helpful.

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Oral NSAIDs

Oral NSAIDs are recommended to improve pain and function in the treatment of knee osteoarthritis when not contraindicated.

Strength of Recommendation: Strong ★★★★
Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Rationale

Among the 34 high-quality, 23 moderate-quality, and 1 low-quality studies that met the inclusion criteria, non-selective and selective clyclooxygenase-2 (COX-2) oral nonsteroidal anti-inflammatory drugs (NSAID) consistently improved pain and function compared to controls in the treatment of osteoarthritis of the knee (Reginster 2017; Lee 2017; Gordo 2017; Strand 2017; Essex 2014; Kongtharvonskul 2016; Altman 2015; Gibofsky 2014; Ishijima 2014; Conaghan 2013; Essex 2012; Singh 2012; Elsaman 2016; Schnitzer 2011; Kivitz 2004; Fleischmann 1997; Lee 1986; Davies 1999; Sandelin 1997; Puopolo 2007; Gibofsky 2003; Bensen 1999; Kivits 2002; Clegg 2006; Sangdee 2002; Sheldon 2005; Tannenbaum 2004; Lehmann 2005; Rother 2007; Simon 2009; Svensson 2006; Schnitzer 2010; Doherty 2011; McKenna 2001 (a); Paul 2009; Bolten 2015; Essex 2015; Ekman 2014; Ohtori 2013; Selvan 2012; Pavelka 2007; Ehrich 1999; Lee 1985; Dwicandra 2018; Asmus 2014; Smugar 2006; Bingham 2007; Altman 1998; Schnitzer 1999; Birbara 2006; Williams 2001; Miceli 2004; Mckenna 2001 (b); Pincus 2004; Lohmander 2005; Schnitzer 2005b; Williams 2000; Fleischmann 2006). Although meta-analysis of non-selective oral NSAIDs compared to controls demonstrated a meaningful reduction in pain, the results need to be interpreted with caution due to the relatively high degree of heterogeneity. The meta-analysis of non-selective oral NSAIDs compared to controls demonstrated a meaningful improvement in function with an acceptable degree of heterogeneity. In terms of selective COX-2 oral NSAIDs, the meta-analysis of celecoxib, the only available selective COX-2 oral NSAID on the United States market, demonstrated a meaningful reduction in pain and improved function with an acceptable degree of heterogeneity. The comparison of non-selective and selective COX-2 oral NSAIDs shows no significant difference in the effectiveness between the types of oral NSAIDs (Gordo 2017; Essex 2014; Essex 2016; Essex 2012; Bensen 1999; Kivits 2002; Kivitz 2004; Puopolo 2007; Hochberg 2011; Mckenna 2001 (b); Schnitzer 2005b; Malik 2017). Although NSAIDs effectively reduce pain and improve function in the treatment of osteoarthritis of the knee, providers should consider patient comorbidities, the type of NSAID administered, dose, and duration of administration. In fact, the United States Food and Drug Administration (FDA) has a black-box warning for NSAIDs citing an increased risk of serious cardiovascular thrombotic events and serious gastrointestinal events. Therefore, we recommend the lowest effective dose for the shortest duration possible for the patient. Although selective COX-2 oral NSAIDs were developed to reduce gastrointestinal adverse events compared to non-selective oral NSAIDs, meta-analysis did not reveal a significant reduction in gastrointestinal adverse events.

Benefits/Harms of Implementation

Although oral NSAIDs are widely used to treat osteoarthritis of the knee, providers must recognize the specific risks associated with each medication. Specific patient contraindications need to be assessed on an individual basis (Example: patient with cardiac conditions have an increased risk of myocardial infarction).

View background material via the OAK3 CPG eAppendix 1
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Outcome Importance
The most important consideration will be removal of oral narcotics from the medications prescribed in the treatment of osteoarthritis of the knee. This becomes particularly significant due to the rise of the opioid epidemic in the United States.

Cost Effectiveness/Resource Utilization
Evidence based decision making in selecting the optimal systemic treatment for the treatment of symptomatic knee osteoarthritis should result in improved pain and function. For a given systematic treatments as effectiveness increases without raising the risk of adverse events so will its cost effectiveness. To date, the most cost-effective systemic treatment is still to be determined.

Acceptability
Currently oral NSAIDs are commonly utilized approach in treating symptomatic knee osteoarthritis, hence there should be no issues implementing this recommendation as it does not influence a major change in clinical practice, and it provides further evidence to support and guide these practices.

Feasibility
This recommendation may be implemented immediately having a potential positive impact in clinical practice.

Future Research
Most important future research will provide high quality investigation through either prospective randomized trials or prospective cohort studies to establish efficacy within specific subgroups and populations to tailor systemic medications increasing efficacy and decreasing risk of adverse effects.

View background material via the OAK3 CPG eAppendix 1
View data summaries via the OAK3 CPG eAppendix 2

Oral Acetaminophen

Oral Acetaminophen is recommended to improve pain and function in the treatment of knee osteoarthritis when not contraindicated.

Strength of Recommendation: Strong ★★★★
Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Rationale
Among the 4 high-quality and 3 moderate quality studies that met the inclusion criteria, oral acetaminophen consistently improved pain and function compared to controls in the treatment of osteoarthritis of the knee (Herrero-Beaumont 2007; Doherty 2011; Reed 2018; Prior 2014; Micelli 2004; Pincus 2004; Altman 2007). The meta-analysis of oral acetaminophen compared to controls demonstrated a meaningful reduction in pain and improved function with no evidence of confounding heterogeneity. Overall, acetaminophen is considered a safe medication with no evidence of significantly increased adverse events among the included studies. However, the United States FDA has a black-box warning for acetaminophen secondary to concern of overdose leading to hepatoxicity or death. When oral acetaminophen was compared to NSAIDs, the use of oral NSAIDs provided a significant reduction in pain and improved function. As a result, providers may consider using oral NSAIDs instead of acetaminophen when a contraindication to oral NSAIDs does not exist in the patient.

Benefits/Harms of Implementation
Although oral acetaminophen is widely used to treat osteoarthritis of the knee, providers must recognize the specific risks associated with each medication. Specific patient contraindications to need to be assessed in an individual basis (Example: patient with renal failure).

Outcome Importance
The most important consideration will be removal of oral narcotics from the medications prescribed in the treatment of osteoarthritis of the knee. This becomes particularly significant due to the rise of the opioid epidemic in the United States.

Cost Effectiveness/Resource Utilization
Evidence based decision making in selecting the optimal systemic treatment for the treatment of symptomatic knee osteoarthritis should result in improved pain and function. For a given systematic treatments as effectiveness increases without raising the risk of adverse events so will its cost effectiveness. To date, the most cost-effective systemic treatment is still to be determined.

Acceptability
Currently acetaminophen is commonly utilized approach in treating symptomatic knee osteoarthritis, hence there should be no issues implementing this recommendation as it does not influence a major change in clinical practice, and it provides further evidence to support and guide these practices.

Feasibility
This recommendation may be implemented immediately having a potential positive impact in clinical practice.

View background material via the OAK3 CPG eAppendix 1
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Future Research

Most important future research will provide high quality investigation through either prospective randomized trials or prospective cohort studies to establish efficacy within specific subgroups and populations to tailor systemic medications increasing efficacy and decreasing risk of adverse effects.

View background material via the OAK3 CPG eAppendix 1
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Oral Narcotics

Oral narcotics, including tramadol, result in a significant increase of adverse events and are not effective at improving pain or function for treatment of osteoarthritis of the knee.

Strength of Recommendation: Strong ★★★★
Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Rationale
Among the 5 high-quality and 2 moderate quality studies that met the inclusion criteria, oral narcotic medications are not an effective treatment to reduce pain and improve function in osteoarthritis of the knee (Serrie 2017; Afilalo 2010; Mayorga 2016; Fishman 2007; Fleischmann 2001; Burch 2007; Babul 2004). In fact, the use of narcotics to treat osteoarthritis of the knee is consistently associated with a significantly high risk of adverse events. Due to the lack of efficacy and increase of adverse event, we would recommend against the use of narcotics for the treatment of osteoarthritis of the knee. Given the effective and relatively safe alternatives of oral NSAIDs and acetaminophen, oral narcotics should be avoided when the provider is considering the recommendation of an oral medication.

Benefits/Harms of Implementation
The removal of oral narcotics from the medications prescribed in the treatment of osteoarthritis of the knee will have further beneficial effects if patients fail non-surgical management and eventually progress to replacement of the knee, as they have been associated with adverse events after surgery as well.

Outcome Importance
The most important consideration will be removal of oral narcotics from the medications prescribed in the treatment of osteoarthritis of the knee. This becomes particularly significant due to the rise of the opioid epidemic in the United States.

Cost Effectiveness/Resource Utilization
Evidence based decision making in selecting the optimal systemic treatment for the treatment of symptomatic knee osteoarthritis should result in improved pain and function. For a given systematic treatments as effectiveness increases without raising the risk of adverse events so will its cost effectiveness. To date, the most cost-effective systemic treatment is still to be determined.

Acceptability
Due to the lack of efficacy and increase of adverse event, a recommendation against the use of narcotics for the treatment of osteoarthritis of the knee was made and this could present some resistance from patients who have failed oral NSAIDS and acetaminophen. Nonetheless, patients should be counseled on the risks associated with narcotics and their lack of efficacy for the purpose of treating knee osteoarthritis.

Feasibility
This recommendation may be implemented immediately having a potential positive impact in clinical practice.

View background material via the OAK3 CPG eAppendix 1
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Future Research

Most important future research will provide high quality investigation through either prospective randomized trials or prospective cohort studies to establish efficacy within specific subgroups and populations to tailor systemic medications increasing efficacy and decreasing risk of adverse effects.

View background material via the OAK3 CPG eAppendix 1
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Hyaluronic Acid

Hyaluronic acid intra-articular injection(s) is not recommended for routine use in the treatment of symptomatic osteoarthritis of the knee.

Strength of Recommendation: Moderate ★★★☆ (downgrade)
Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Rationale

Twenty-eight studies (17 high-strength (Chevalier 2010, Petterson 2018, Maheu 2019, Neustadt 2005, Baltzer 2009, Lundsgaard 2008, Altman 2004, Huang 2011, van der Weergen 2015, Altman 2009, Day 2004, Jorgensen 2010, Henrotin 2017, Henderson 1994, Hangody 2018, Saccomanno 2016, Altman 1998) and 11 moderate-strength (Jubb 2003, Navarro-Sarabia 2011, Farr 2019, Kahan 2003, Kahan 2003, Karlsson 2002, Hermans 2019, Huskisson 1999, Heybeli 2008, Petrella 2006, Takamura 2018, Wobig 1998)) assessed intraarticular hyaluronic acid (HA) injections when compared to controls. A comparison of patients from these studies and from studies validating the MCIDs were used to judge clinical significance. Results revealed that patients were demographically comparable for WOMAC and VAS pain as well as WOMAC function based on age, baseline pain scores, BMI, weight, and gender. Meta-analysis in meaningfully important difference (MID) units showed that the effect was less than 0.5 MID units, indicating a low likelihood that an appreciable number of patients achieved clinically important benefits after intraarticular HA injection (Guyatt et al.). When we differentiated high- versus low-molecular weight viscosupplementation (three high, two moderate and two low quality studies), our analyses demonstrated no significant differences among different viscosupplementation formulations. Crosslinking features of the viscosupplemtation product was assessed in two high quality studies. In patients with OA, there was no difference between cross-linked and non-cross-linked HA.

Some studies demonstrated a statistical benefit with the use of HA but could not reach the significance for a minimally clinical meaningful difference, leading to the conclusion that viscosupplementation can represent a viable option for some patients that failed other treatments when appropriately indicated. The number needed to treat to see a tangible benefit from HA was 17 patients. Furthermore, this difference was most evident at 6 weeks and 3 months. Most of the studies that exist in the literature evaluate low to moderate arthritic knees (Kellgren Lawrence of I-III) with worse results in patients with severely affected knees (KL IV).

The 2013 edition of this guideline strongly recommended against the use of viscosupplementation. In contrast to this updated version, the 2021 version found that statistically significant improvements were associated with high-molecular cross-linked hyaluronic acid but when compared to mid-range molecular weight, statistical significance was not maintained. This newer analysis did not demonstrate clinically relevant differences when compared to controls. However, as previous research reported benefits in their use, the group felt that a specific subset of patients might benefit from its use.

The Hyaluronic Acid recommendation was downgraded one level due to a lack of generalized results.

Benefits/Harms of Implementation

There are no major known or anticipated harms associated with implementing this recommendation.

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Outcome Importance
Pain and function improvement through intraarticular therapies for the treatment of knee osteoarthritis may have high impact on symptoms and overall health.

Cost Effectiveness/Resource Utilization
The cost-effectiveness of different intra-articular therapies is still to be determined, in comparison to other treatment strategies and among different intra-articular alternatives.

Acceptability
Currently intra-articular treatments are commonly utilized approach in treating symptomatic knee osteoarthritis, hence there should be no issues implementing this recommendation as it does not influence a major change in clinical practice, and it provides further evidence to support and guide these practices.

Feasibility
These recommendations do not interfere with other interventions or clinical practice therefore it is deemed very feasible in patients with symptomatic knee osteoarthritis.

Future Research
Future research in this area should embrace detailed osteoarthritis characterization including sub-group analyses and osteoarthrosis severity stratification. Furthermore, using clinically relevant outcomes and controls for bias are warranted along with cost-effectiveness analysis.

View background material via the OAK3 CPG eAppendix 1
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Intra-articular Corticosteroids

Intra-articular (IA) corticosteroids could provide short-term relief for patients with symptomatic osteoarthritis of the knee.

Strength of Recommendation: Moderate ★★★☆ (downgrade)
Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Rationale
Our search found 19 high (Campos 2017, Cai 2019, Abou-Raya 2014, Erturk 2016, de Campos 2013, Shrestha 2018, Mendes 2019, Yilmaz 2019, Chao 2010, Raynauld 2003, McAlindon 2017, Henrikson 2015, Neilsen 2018, Riis 2017, Arden 2014, Delgado-Enciso 2019, Smith 2003, Soriano-Maldonado 2016) and 6 moderate quality studies (Conaghan 2018, Langworthy 2019, Gaffney 1995, Yavuz 2012, Yilmaz 2019, Jones 1996) comparing intra-articular corticosteroids to control to treat knee osteoarthritis. Overall pain and function improved with intra-articular corticosteroids; however, it is important to note that such effect lasted only up to 3 months. When we differentiated intra-articular corticosteroids extended versus immediate release (one high, two moderate quality studies) (Bodick 2015, Conaghan 2018 and Langworthy 2019), our analyses demonstrated that, extended release IA steroids can be used over immediate release to improve patient outcomes (Moderate strength recommendation).

The Intra-Articular Corticosteroids recommendation has been downgraded one level because of potential risk in accelerating osteoarthritis from injections.

Benefits/Harms of Implementation
The AAOS Patient Safety Committee recommends avoiding musculoskeletal corticosteroid injections for two weeks before and one week after COVID vaccine administration.

Outcome Importance
Pain and function improvement through intra-articular therapies for the treatment of knee osteoarthritis may have high impact on symptoms and overall health.

Cost Effectiveness/Resource Utilization
The cost-effectiveness of different intra-articular therapies is still to be determined, in comparison to other treatment strategies and among different intra-articular alternatives.

Acceptability
Currently intra-articular treatments are commonly utilized approach in treating symptomatic knee osteoarthritis, hence there should be no issues implementing this recommendation as it does not influence a major change in clinical practice, and it provides further evidence to support and guide these practices.

Feasibility
These recommendations do not interfere with other interventions or clinical practice therefore it is deemed very feasible in patients with symptomatic knee osteoarthritis.

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Future Research

Future research in this area should embrace detailed osteoarthritis characterization including sub-group analyses and osteoarthrosis severity stratification. Furthermore, using clinically relevant outcomes and controls for bias are warranted along with cost-effectiveness analysis.

View background material via the OAK3 CPG eAppendix 1
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Platelet-rich Plasma

Platelet-rich plasma (PRP) may reduce pain and improve function in patients with symptomatic osteoarthritis of the knee.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale

There were two high (Rayegani; 2014, Gormeli; 2017) and one moderate (Akan; 2018) study with 30 people per group comparing PRP vs. control. There were mixed results in the studies for pain and function. A meta-analysis was not performed due to heterogeneity. Two studies (Akan; 2018, Gormeli; 2017) looked at PRP in severe OA with mixed results. Two studies (Rayegani; 2014, Gormeli; 2017) looked at change in all stages of OA at a six-month timeframe. The studies had mixed results. One study (Gormeli; 2017) looked at Kellgren-Lawrence 1-3 stage OA with improvement in IKDC and EQ-VAS. Therefore, due to the heterogeneity of results and the difference in early and late stage OA results, we downgraded the recommendation to Limited from Strong. We feel these recommendations may change with future research on the use of PRP in different levels of severity of OA.

The number of PRP injections had mixed results with the studies with three PRP injections (Akan; 2018, Gormeli; 2017) having positive results outcomes for pain and function. Studies with one and two PRP injections had mixed results, with the positive being less likely clinically significant changes in pain and function. Further research should be done to determine the number of PRP injections for treatment of KOA. Currently, three IA-PRP injections appear to have more favorable results.

Adverse events from PRP injections has been investigated in one high-quality study (Huang; 2018) reported adverse events for PRP vs. control. They reported hypertension and proteinuria were treatment-related side-effects. These met Common Toxicity Criteria grade ≥3. This raises questions on the safety of PRP, which needs further evaluation. Therefore, the strength of recommendation was downgraded to Limited.

When evaluating the effectiveness of PRP vs HA, there were eight high-quality studies (Sanchez; 2012, Vaquerizo; 2013, Filardo; 2015, Gormeli; 2017, Cole; 2017, Buendia-Lopez; 2018, Di Martino; 2019, Yaradilmis; 2020) and six (6) medium quality studies (Spakova; 2012, Raeissadat; 2015, Lana; 2016, Duymus; 2017, Raeissadat; 2017, Ahmad; 2018) and one low-quality studies (Sanchez; 2008) that investigated IA-PRP vs. IA-HA. Four studies were included in a meta-analysis of Total WOMAC results at the 9- OR 12-months mark. This analysis showed a clinically significant difference for IA-PRP over IA-HA. The results between IA-PRP vs IA-HA diverged after 6 months. Most studies showed similar results between IA-PRP and IA-HA at six months, except one (Yaradilimis 2020) where the LR-PRP total WOMAC was better at all time points than the IA HA. Both the patients in the IA HA and IA PRP improved in total WOMAC at six months. Patients in the IA-PRP-arms maintained improvement after 6 months at the 9- OR 12-months mark for total WOMAC vs. IA-HA which started to have a worsening score. The standard is to inject IA-HA every six months in patients with painful KOA. The preparation of the PRP (LR-PRP vs LP-PRP) was noted to be different with the LR-PRP had higher MID values than LP-PRP vs. IA-HA. The research highlights the prolonged effect of IA-PRP over IA-HA, though both appear to be equivalent at 6 months.

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Patient-related outcome measures (OARSI-OMERACT responders, percentage of subjects meeting a percentage reduction in VAS Pain OR WOMAC Pain scores) (Sanchez; 2008, Sanchez; 2012, Vaquerizo; 2013, Buendia-Lopez; 2018) more often favorited IA-PRP at both the six month and 12-month time frame. Further, research is needed using standardized PROM's to investigate the effectiveness of IA-PRP to determine if more patients will benefit from IA-PRP at six months over IA-HA.

Adverse events were higher in the PRP group than IA HA, both local soreness and injection pain (two studies (Spakova; 2012, Yaradilmis; 2020)) and one study (Huang; 2018)) systemic events (proteinuria and hypertension). One study (Vaquerizo; 2013) did not find a difference comparing any adverse event, and one study (Raeissadat; 2017) did not see a difference for minor injection-site adverse events. Therefore, there appears to be more studies finding IA-PRP to have more adverse events vs. IA-HA, more research is need to determine if the adverse events outweigh the benefit of IA-PRP over IA-HA at 9 and 12 months. This is another reason for the downgrade in evidence from Strong to Limited.

Comparisons between IA-PRP and IA-CS, there were three high (Joshi Juber; 2017, Khan; 2018, Nabi; 2018) and one moderate quality study (Huang; 2019). One study (Joshi Juber; 2017) was KL IV end-stage OA and did not find a difference. One study (Khan; 2018) was repeat injections every other month (0, 2, 4 months) with follow up at six months in KL II OAK with no difference. One study (Nabi; 2018) used patients with KL II-III given three injections one month apart showed improvement at three months (one month after the last injection) and six months (4 months after the final injection). One study (Huang; 2019) did three PRP injections every three weeks on KL I-II OAK showed improvement in pain and function at six months (4 months after last injection) and 12 months (10 months after last injection). Therefore, the IA-PRP given in three injections evaluated at 4 months post last injection is more likely to show benefit in KL II and III stages of KOA. More research is needed to evaluate long-term benefits of IA-PRP vs IA-CS over a two- or five-year period to determine if IA-PRP is cartilage sparing vs IA-CS concern for possible cartilage damage over time.

PRP is defined in LR-PRP and LP-PRP. There may be a difference in the effectiveness in knee osteoarthritis between these two preparations. Currently, there is limited data from one direct comparison (Yaradilimis; 2020) and our meta-analysis (Figure 45) of IA-PRP and IA-HA that would demonstrate that intra-articular LR-PRP vs. LP-PRP for KOA is more likely to demonstrate a benefit at 9 and 12 months. The number of studies is limited, therefore determining the better choice between LR-PRP vs. LP-PRP is still inconclusive, but at this time appears to favor LR-PRP.

The Platelet-Rich Plasma recommendation has been downgraded two levels because of inconsistent evidence.

Benefits/Harms of Implementation
Some patients may experience temporary local soreness or injection pain.

Outcome Importance
Pain and function improvement through intra-articular therapies for the treatment of knee osteoarthritis may have high impact on symptoms and overall health.

Cost Effectiveness/Resource Utilization
The cost-effectiveness of different intra-articular therapies is still to be determined, in comparison to other treatment strategies and among different intra-articular alternatives.

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Acceptability
Currently intra-articular treatments are commonly utilized approach in treating symptomatic knee osteoarthritis, hence there should be no issues implementing this recommendation as it does not influence a major change in clinical practice, and it provides further evidence to support and guide these practices.

Feasibility
These recommendations do not interfere with other interventions or clinical practice therefore it is deemed very feasible in patients with symptomatic knee osteoarthritis.

Future Research
Future research in this area should embrace detailed osteoarthritis characterization including sub-group analyses and osteoarthrosis severity stratification. Furthermore, using clinically relevant outcomes and controls for bias are warranted along with cost-effectiveness analysis. Specifically, to platelet rich plasma it will be of outmost importance to include comprehensive platelet rich plasma characterization and description of platelet rich plasma preparation protocol.

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Denervation Therapy

Denervation therapy may reduce pain and improve function in patients with symptomatic osteoarthritis of the knee.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale

For the denervation therapies, there are 2 high quality studies (Radnovic et al 2017 and Mendes et al 2019) and 2 moderate quality studies (McAlindon et al 2017 and El-Hakeim et al 2018) comparing denervation technique with placebo.

One high quality study (Radnovic et al 2017) specifically evaluated the efficacy of cryoneurolysis in comparison to placebo control in patients with knee OA. It was found that the group receiving cryoneurolysis had improved total WOMAC, WOMAC stiffness, WOMAC pain, WOMAC physical function and in VAS pain compared to placebo control group.

Another high-quality study (Mendes et al 2019) evaluated the efficacy of chemical ablation in comparison to placebo control in patients with knee OA. It was found that the group receiving chemical denervation had improved in WOMAC pain compared to placebo control group. Another moderate quality study (McAlindon et al 2017) comparing the efficacy of chemical ablation in comparison to placebo control in patients with knee OA found no major difference between the two groups.

One moderate quality study (El-Hakeim et al 2018) specifically evaluated the efficacy of thermal ablation in comparison to placebo control in patients with knee OA. It was found that the group receiving thermal ablation had improved WOMAC total, WOMAC function and VAS pain compared to placebo control group.

One high quality study (Davis et al) and one moderate evidence study (Davis et al 2018) compared IA HA to thermal ablation in patients with knee OA. The first study (Davis et al 2018) showed worse Oxford Knee Score, Global Perceived Index and Numeric Rating Scale in the HA group compared to the thermal ablation group, while the second study (Davis et al 2018) showed worse Oxford Knee Score, Change in Medication Use (mg) from Baseline, Knee pain-Numeric Rating scale and Mean Reduction in average NRS score in the HA group compared to the thermal ablation.

One high quality study (Gulec et al 2017) compared unipolar to bipolar radiofrequency ablation of the knee in patients with knee OA. In patients with OA, Bipolar intra-articular pulsed radiofrequency thermocoagulation may be used over Unipolar intra-articular pulsed radiofrequency thermocoagulation to improve patient pain.

One moderate quality study (Sari et al 2018) compared IA steroids to thermal ablation of the knee in patients with knee OA. The study showed worse WOMAC total, WOMAC function, WOMAC stiffness and worse VAS pain in the IA steroids group compared to thermal ablation group
In summary, our analysis demonstrates that denervation therapy may reduce pain and improve function in patients with symptomatic osteoarthritis of the knee.

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The Denervation Therapy recommendation has been downgraded two levels because of inconsistent evidence and bias.

Benefits/Harms of Implementation
There are no major known or anticipated harms associated with implementing this recommendation anticipated.

Outcome Importance
Pain and function improvement through denervation therapies for the treatment of knee osteoarthritis may have high impact on symptoms and overall health.

Cost Effectiveness/Resource Utilization
The cost-effectiveness of different denervation therapies is still to be determined, in comparison to other treatment strategies and among different denervation alternatives.

Acceptability
Currently denervation treatments are commonly utilized approaches in treating symptomatic knee osteoarthritis, hence there should be no issues implementing this recommendation as it does not influence a major change in clinical practice, and it provides further evidence to support and guide these practices.

Feasibility
These recommendations do not interfere with other interventions or clinical practice therefore it is deemed very feasible in patients with symptomatic knee osteoarthritis.

Future Research
Future research in this area should embrace detailed osteoarthritis characterization including sub-group analyses, osteoarthrosis severity stratification, and end stage disease in patients unable to have total knee arthroplasty (e.g. due to age or comorbities). Furthermore, using clinically relevant outcomes and controls for bias are warranted along with cost-effectiveness analysis.

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Lavage/Debridement

Arthroscopy with lavage and/or debridement in patients with a primary diagnosis of knee osteoarthritis is not recommended.

Strength of Recommendation: Moderate ★★★☆

Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Rationale

There were four studies that met the inclusion criteria for this recommendation. There was one high strength (Moseley et al 2002), two moderate strength (Kirkley et.al 2008, Kalunian et.al 2000), and one low quality (Saeed et.al 2015).

Kirkely et al 2008 compared arthroscopic surgery which, included lavage and debridement combined with physical therapy and medical treatment versus physical therapy and medical treatment alone. The outcome measures utilized were the total Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score, Short Form-36 (SF-36) Physical Component Summary score, McMaster–Toronto Arthritis Patient Preference Disability Questionnaire (MACTAR), and the Arthritis Self-Efficacy Scale (ASES) and standard-gamble utility scores. Six patients assigned to surgery elected not to have the procedure; data from these patients were analyzed, according to the intention to- treat principle, with data from the surgery group. Out of all potential outcomes, only two were statistically significant in favor of surgery. In summary, this randomized controlled trial demonstrated no benefit of arthroscopic lavage and debridement compared to physical therapy and medical treatment for osteoarthritis of the knee.

Kalunian et al. 2000 compared arthroscopic lavage (3000ml) with placebo (250ml). The study was performed at 4 different institutes and included a large number of enrolled patients from one institution with intra-articular crystals in their knee. The arthroscopes used were less than usual caliber in size ranging from 1.7mm to 2.7mm. Outcome measures were WOMAC scores at 12 months. There were not any statistically significant differences in aggregate WOMAC scores between the two treatment groups. The study concludes that irrigation may be helpful in a small subset of patients, especially those with crystals.

Mosley et al 2002 study is an RCT comparing arthroscopic debridement, arthroscopic lavage, versus placebo / sham surgery. The study provides strong evidence that knee arthroscopy with or without debridement is not better and appears to be equivalent to a placebo procedure in improving knee pain and self-reported function. However, the study raised questions regarding its limited sampling (mostly male veterans) as well as the number of potential study participants who declined randomization into a treatment group. They also used a non-validated Knee Specific Pain score. Also, patients with substantial malalignment (varus or valgus deformity) and those with advanced disease, who might have a poorer response to surgical intervention were included in the trial.

Saeed et al 2015 compared HA injections versus arthroscopic debridement in patients with OA in an RCT where only the pain component of the knee society score was utilized. In short term follow up of 6 months, arthroscopy failed to show better pain outcome than injections.

View background material via the OAK3 CPG eAppendix 1
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Most of the studies excluded patients with meniscal tear, loose body, or other mechanical derangement, with concomitant diagnosis of osteoarthritis of the knee. The present recommendation does not apply to such patients.

Benefits/Harms of Implementation

Owing to lack of strong evidence in support of clinical benefits from lavage surgery coupled with increased risks from surgery, the workgroup decided to recommend against arthroscopic debridement and/or lavage in patients with a primary diagnosis of osteoarthritis of the knee.

Future Research

Most studies included in this review had compared lavage to variety of nonoperative modalities. However, considering emergence of new modalities and technology it would be worthwhile to do high quality study with arthroscopic lavage done with a standardized size instrument comparing with nonoperative measures which could include PRP injections, nerve ablations, etc. Recent introduction of nanoscopes also warrants further studies of use of such devices in an office setting and comparing it to cost effectiveness of doing procedures in the operating room.

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Partial Meniscectomy

Arthroscopic partial meniscectomy can be used for the treatment of meniscal tears in patients with concomitant mild to moderate osteoarthritis who have failed physical therapy or other nonsurgical treatments.

Strength of Recommendation: Moderate ★★★☆

Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Rationale

The three studies discussed below compare outcomes following arthroscopic partial meniscectomy with physical therapy and demonstrate that knee arthroscopy with partial meniscectomy is as effective as physical therapy. In PICO 5, this work group recommended supervised or unsupervised exercise as opposed to no exercise to improve pain and function in patients with knee osteoarthritis. Currently, there are no studies that compare outcomes (knee pain and function) following arthroscopic partial meniscectomy versus physical therapy alone in patients who have failed to improve with an initial course of physical therapy. It is important to clearly define the appropriate indications for arthroscopic partial meniscectomy in patients with knee OA. This procedure should be considered in patients with mild-to-moderate knee OA and an MRI confirmed meniscal tear who have previously failed appropriate conservative treatment such as physical therapy, corticosteroid injections, and a course of non-steroidal anti-inflammatory medications.

Katz et al (2013) conducted a multicenter, randomized, controlled trial of symptomatic patients over the age 45 or older with a meniscal tear and evidence of mild-to-moderate knee osteoarthritis to determine efficacy of arthroscopic partial meniscectomy compared to standardized physical therapy in this patient population. Three hundred fifty-one patients were randomly assigned to surgery and postoperative physical therapy or to a standardized physical therapy regimen (with the option to cross over to surgery at the discretion of the patient and surgeon). The patients were evaluated at 6 and 12 months and the primary outcome was the difference between the groups with respect to the change in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) physical function score. The mean improvement in WOMAC score at 6 months was similar between the groups. At 6 months, 51 patients who were randomized to physical therapy alone (30%) had undergone surgery. The authors concluded that in their intention-to-treat analysis, there were no significant differences in functional improvement 6 months after randomization; however, 30% of patients in the physical therapy alone group underwent surgery. These patients were analyzed in their original group, based on the intention-to-treat analysis.

Van de Graaf et al. (2018) performed a multicenter randomized clinical trial in the Netherlands to determine whether physical therapy is inferior to arthroscopic partial meniscectomy (APM) for improving patient-reported knee function in patients with meniscal tears. Three hundred twenty-one patients were randomly assigned to APM or a predefined physical therapy protocol. Patients were excluded if they had locking of the knee, prior knee surgery, instability caused by anterior or posterior cruciate ligament rupture, severe osteoarthritis (Kellgren Lawrence score of 4), and a BMI > 35 kg/m2. Change in patient-reported knee function on the International Knee Documentation Committee Subscale Knee form (IKDC) over a 24-month period was used as the primary outcome. In the PT group, 47 patients (29%) had APM during the 24-month follow-up period. The authors noted a similar level of improvement in knee function between the APM and PT groups. They concluded that PT was noninferior to APM for improving

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patient-reported knee function over a 24-month follow-up period in patients with nonobstructive meniscal tears.

In 2007, Herrlin et al performed a prospective randomized study to compare knee function and physical activity following arthroscopic partial meniscectomy followed by supervised exercise or supervised exercise alone in patients with non-traumatic medial meniscal tear. Ninety patients were evaluated using the Knee Injury and Osteoarthritis Outcomes Score (KOOS), the Lysholm Knee Scoring Scale, and Tegner Activity Scale and a Visual Analog Scale (VAS) for pain prior to the intervention and after 8 weeks of exercise and 6 months following intervention. The authors found that after the intervention, both groups reported decreased knee pain, improved knee function, and a high satisfaction ($p<0.0001$). They, therefore, concluded that arthroscopic partial meniscectomy was not superior to supervised exercise alone in terms of reduced knee pain, improved knee function, and improved quality of life.

Benefits/Harms of Implementation

Given the risks associated with surgical intervention, only appropriately indicated patients should be considered for partial meniscectomy in the setting of mild to moderate knee osteoarthritis.

Future Research

We did not identify any studies that compare outcomes (i.e. knee pain and function) following arthroscopic partial meniscectomy versus physical therapy alone in patients who have failed to improve with an initial course of physical therapy, non-steroidal anti-inflammatory medications (NSAIDs), and a possible intra-articular steroid injection. The three studies reviewed by the work group demonstrate that knee arthroscopy with partial meniscectomy is as effective as physical therapy. Future studies should seek to compare outcomes in patients with mild to moderate knee osteoarthritis and an MRI confirmed meniscal tear who have undergone partial meniscectomy after failing to improve with a course of conservative treatment (NSAIDs, steroid injection, and physical therapy) versus those who have undergone partial meniscectomy without a dedicated course of conservative treatment.

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Tibial Osteotomy

High tibial osteotomy may be considered to improve pain and function in properly indicated patients with unicompartmental knee osteoarthritis.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale

High tibial osteotomy (HTO) has been used for pain relief of medial compartment knee osteoarthritis. Realigning the varus knee provides mechanical decompression of the medial compartment. An osteotomy line is created in the proximal tibial and either a wedge defect is created by opening the medial cortex and held open with a wedge or plate and screw hardware, or a lateral wedge is removed and secured commonly with staples or wires. In the Nerhus 2017 study, patients continued to show improvement 6 and 12 months post-operatively. Historical studies have reported pain reduction with survival rates approximately 70% at 10 years ("survival" usually interpreted with endpoint conversion to replacement) (van Outeren cites Brouwer 2014 and Niinimaki 2012).

Many studies available for review by the workgroup compared various techniques of osteotomy in randomized studies. Ogawa 2019 found osteotomy distal to the tibial tubercle to be superior to proximal osteotomy for opening wedge procedure with regard to patellofemoral pain. Arthroscopic evaluation of the knee joint at time of osteotomy and second look at time of hardware removal showed less patellar and trochlear degeneration with the distal osteotomy group.

Nerhus 2017 saw no significant functional difference between surgical patients randomized to either opening or closing wedge, with all showing improvement.

Duivenvoorden 2014 reported improved HSS scores from 71 to 81 at 6 years post-op. VAS scores improved from 6.1 baseline to a statistically significant difference at follow up of 4.0 in the opening wedge patients and 3.2 with the closing wedge (albeit no statistical difference between the groups). It should be noted that patients lost to follow up started with a VAS score 6.6, thus tempering analysis of late results.

Brouwer 2006 performed a prospective randomized trial comparing closing wedge and opening wedge techniques. Closing wedge was secured with two surgical staples and opening wedge with a Puddu plate. After one-year VAS score had improved from 6.1 to 3.6.

Van Outeren 2017 is perhaps the closest attempt to a large randomized control trial between surgery and non-operative management. However, this is still not a highest quality randomized control trial. The researchers gathered two different groups of patients at two different hospitals. The first group underwent randomization to valgus bracing versus usual care. The second group was randomized to HTO with either opening wedge or closing wedge osteotomy. The groups were matched for baseline characteristics. They found HTO more effective in pain reduction compared to non-operative methods. VAS changed from baseline 6.2 in the surgery group to 3.8 post-op. Control group improved from 6.4 to 5.0. Function was improved only in comparison of surgical patients to usual care treatment.

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The Wu 2017 study evaluated people with bilateral OA with pain around medial part of the knee. The more degenerative knee got proximal tibial osteotomy, and the other knee got usual non-operative care. The study authors included a table of individual patient data, which allowed a model that controlled for differences in baseline knee society function scores between the knees to be run. With this model, the odds ratio of achieving satisfactory knee society function scores (defined as score >= 80) with osteotomy vs. non-operative treatment was 7.51(CI 1.094, 51.6).

The Tibial Osteotomy recommendation has been downgraded one level because of inconsistent evidence.

Benefits/Harms of Implementation

As with any osteotomy surgery, bone healing and hardware complications can occur. Incomplete osteotomy can lead to unexpected fracture at the point of correction (Getgood 2011). Neurologic injury is feared but uncommon. 2 of 35 patients in both closing wedge and opening wedge groups under Nerhus et al. 2017. Duivenvoorden had only one patient with peroneal nerve injury (closing wedge group) and Brouwer only 1 of 92 (also closing wedge group). Hardware removal appeared more common with medial opening wedge techniques. Limb length discrepancy is also increased with the opening wedge technique (Kim et al. 2016). Van Outeren had non-union of the osteotomy site only in 2 opening wedge patients. Duivenvoorden found opening wedge HTO to have more complications. However, non-union of the osteotomy was more common with their closing wedge technique (Duivenvoorden 2014). Brouwer on their other hand concluded their close wedge technique to have achieved more accurate correction with less morbidity.

The increase valgus angle across the knee will change patellar tracking, as noted above by Ogawa et al. 2019. In Song et al. 2012 no patient at baseline reported anterior knee pain. Although no significant difference was seen between their closing wedge and opening wedge groups, 30% of their patients had various levels of anterior knee pain, including 9% with moderate and 6% with severe anterior knee pain (minimum follow up 3 years).
Nerhus 2017 at two years follow up reported only 1 (closing wedge group) of their total 70 patients as revision to arthroplasty. Duivenvoorden 2014 had six year follow up and reported conversion to TKA in 10 of 45 closing wedge HTO patients and 3 of 45 in the opening wedge group.

Outcome Importance

Despite the lack of a true RCT comparing HTO to non-operative management, the studies reviewed by the workgroup all agree with the premise that pain is reduced by HTO. There appear to be relatively equal outcomes whether HTO is achieved with lateral or opening wedge surgical technique. Opening wedge osteotomy distal to the tibial tubercle appears to be preferred, according to the single study examining this aspect of surgical technique (Ogawa 2019).

Cost Effectiveness/Resource Utilization

Hardware removal was relatively common, and the second surgery will add expense to the total endeavor. For reference, Brouwer reported hardware removal in 11 of 47 closing wedge cases and 27 of 45 with opening wedge HTO. Nerhus reported metal removal in 4 of 35 closing wedge cases and 8 of 35 in the opening wedge group.

Conversion to knee arthroplasty is the most expensive late effect of the procedure. As years increase post-op, conversion rates to TKA increase. No studies were identified which adequately addressed the cost-benefit of knee replacement options versus osteotomy.

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Acceptability
In select patients with isolated medial compartment arthritis, there appear to be adequate short-term results with regard to pain and function in those patients undergoing surgery.

The quality of HTO results will be dependent upon the skill and experience of the operating surgeon and the cooperation of a patient to understand he or she is entering into a post-op state with altered anatomy and a prognosis imperfectly known in comparison to other options.

Feasibility
Van Outeren rightly questions the benefits of surgical treatment versus brace treatment. Their study had only one-year follow-up and 25 of 60 patients initially in the brace group dropped. They were not optimistic for long term utility and/or compliance of brace treatment.

Future Research
Previous studies have addressed outcomes when converting UKA to TKA and likewise for converting HTO to TKA. Studies looking at functional improvement and pain relief of HTO in direct comparison to knee replacement surgery (total or partial) would be of great value to our collective knowledge base, especially if such a study could track patients from baseline into HTO versus UKA and then long term to TKA. It is unlikely such a study could be performed prospectively over such a long time, yet data from a registry might prove fruitful.

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Dry Needling

In the absence of reliable evidence, it is the opinion of the workgroup that the utility/efficacy of dry needling is unclear and requires additional evidence.

Strength of Recommendation: Consensus ★☆☆☆

Description: Evidence there is no supporting evidence, or limited level evidence was downgraded due to major concerns addressed in the EtD framework. In the absence of reliable evidence, the guideline work group is making a recommendation based on their clinical opinion.

Rationale

Two high quality studies examining the effectiveness of dry needling in combination with either exercise versus sham dry needling and exercise, (Sanchez, 2019) or dry needling combined with manual therapy and exercise versus manual therapy and exercise alone (Dunning, 2018) were reviewed. Sanchez et al. 2019 found no difference in clinical outcomes of pain or function between treatment groups. In contrast, Dunning et al. found greater improvements in measures of pain and function in the group receiving dry needling. The inconsistency in the results of these studies has prompted the workgroup not to make a recommendation for or against dry needling at this time. Additional evidence will be required before a recommendation can be made.

Future Research

Continued research with larger studies to examine the effectiveness of dry needling for reducing pain and improving function in patients with knee osteoarthritis is warranted.

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Free Floating Interpositional Devices

In the absence of reliable or new evidence, it is the opinion of the work group not to use free-floating (un-fixed) interpositional devices in patients with symptomatic medial compartment osteoarthritis of the knee.

Strength of Recommendation: Consensus ★☆☆☆

Description: Evidence there is no supporting evidence, or limited level evidence was downgraded due to major concerns addressed in the EtD framework. In the absence of reliable evidence, the guideline work group is making a recommendation based on their clinical opinion.

Rationale

One study met inclusion criteria, and no additional studies were available for review since the prior edition OAK CPG was published. The single study was a case series and retrospective review of outcomes in patients receiving the surgical intervention for isolated medial compartment OA. The study indicated high reoperation rates in the patients who were followed, with 32% of patients being revised to total knee arthroplasty during the study period. Regarding pain and functional improvement, the study reported no statistical difference in preoperative and postoperative Knee Society Scores. Given the lack of evidence to support use, the AAOS workgroup modified the grade of this recommendation to consensus, because of the high revision rates in this study, and the potential harm associated with surgical intervention (anesthesia risks, VTE, infection, and reoperation).

Cost Effectiveness/Resource Utilization

No economic analyses or resource utilization studies have been reported on this treatment option.

Future Research

Future research should be aimed at producing level one randomized control trials to define clinical efficacy and risk of complication.

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APPENDICES

Appendix I: References for Included Literature

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Appendix II: PICO Questions Used to Define Literature Search

1. In adult (>17) patients with symptomatic osteoarthritis of the knee, do assistive devices (canes, shoe inserts, etc.) improve patient outcomes?

2. In adult (>17) patients with symptomatic osteoarthritis of the knee, do braces improve patient outcomes?

3. In adult (>17) patients with symptomatic osteoarthritis of the knee, do oral/dietary supplements improve patient outcomes?

4. In adult (>17) patients with symptomatic osteoarthritis of the knee, do topical treatments improve patient outcomes?

5. In adult (>17) patients with symptomatic osteoarthritis of the knee, does exercise and activity improve patient outcomes?

6. In adult (>17) patients with symptomatic osteoarthritis of the knee, do weight loss interventions improve patient outcomes?

7. In adult (>17) patients with symptomatic osteoarthritis of the knee, is the extent of weight lost associated with improved patient outcomes?

8. In adult (>17) patients with symptomatic osteoarthritis of the knee, do manual therapies (manipulation, mobilization, massage, etc.) improve patient outcomes?

9. In adult (>17) patients with symptomatic osteoarthritis of the knee, do physical/electrotherapeutic agents (acupuncture, heat, ice, TENS, etc.) improve patient outcomes?

10. In adult (>17) patients with symptomatic osteoarthritis of the knee, what systemic treatments are most effective for improving patient outcomes?

11. In adult (>17) patients with symptomatic osteoarthritis of the knee, what locally invasive treatments are most effective for improving patient outcomes?

12. In adult (>17) patients with symptomatic osteoarthritis of the knee, does arthroscopic debridement improve patient outcomes?

13. In adult (>17) patients with symptomatic osteoarthritis of the knee, does partial meniscectomy improve patient outcomes?

14. In adult (>17) patients with symptomatic osteoarthritis of the knee, does osteotomy improve patient outcomes?

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Appendix III: Literature Search Strategy

LINE	SEARCH SYNTAX
1	((animals not humans) or cadaver).sh. or cadaver*.ti.
2	(((comment or editorial or letter or historical article) not "clinical trial") or address or news or newspaper article or case reports).pt. or case report.ti.
3	((Adolescent OR Child OR Infant) NOT Adult).sh.
4	1 or 2 or 3
5	exp "Osteoarthritis, Knee"/ or (gonitis or gonarthritis or gonarthros*).ti,ab.
6	exp "Knee Joint"/ or exp "Knee"/ or (knee or knees or femorotibial or tibial or patella or patellar).ti,ab.
7	"Osteoarthritis"/ or "Arthritis"/ or (osteoarthriti* or osteo-arthriti* or osteo-arthros* or osteoarthros*).ti,ab. or ((non-inflamm* or noninflamm* or degenerat* or hypertropic) and (arthriti* or joint* or disease*)).ti,ab.
8	5 or (6 and 7)
9	"Self-Help Devices"/ or "Orthopedic Equipment"/ or "Canes"/ or (cane or canes).ti,ab. or "Crutches"/ or (crutch or crutches).ti,ab. or exp "Orthotic Devices"/ or (orthotic or orthotics or orthoses or orthosis or braces or bracing or shoes or insole or insoles).ti,ab. or "Walkers"/ or ("assistive device" or "assistive devices" or "walking aids" or walker or walkers or splints or sleeves).ti,ab.
10	8 and 9
11	exp "Intercellular Signaling Peptides and Proteins"/ or ("growth factors" or "growth factor").ti,ab. or ((biological or biologic or cell or cell-based or cellular) ADJ2 (therapy or therapies)).ti,ab. or ("platelet rich plasma" or "platelet-rich plasma" or "PRP" or "stem cell" or "stem cells").ti,ab. or "biologics".ti,ab. or exp "Biological Therapy"/ or exp "Biological Products"/ or ("minimally manipulated" or "minimal manipulation" or "blood product" or "blood products").ti,ab. or exp "Platelet-Rich Plasma"/ or exp "Stem Cells"/ or exp "Prolotherapy"/ or (prolotherapy or prolotherapies).ti,ab. or orthobiologics.ti,ab.
12	8 and 11
13	exp "Injections, Intra-Articular"/ or exp "Viscosupplementation"/ or ((intraarticular or "intra articular") and (delivery OR administration OR injection* OR infusion or injectable)).ti,ab. or exp "Hyaluronic Acid"/ or (hyaluron* OR "hylan").ti,ab. or exp "Adrenal Cortex Hormones"/ or (corticoid* or cortical or corticostseroid* or "cortico steroid" or corticotherapy).ti,ab. or viscosupplement*.ti,ab.
14	8 and 13
15	exp "Acetaminophen"/ or ("paracetamol" or "acetaminophen" or "Tylenol").ti,ab. or exp "Anti-Inflammatory Agents, Non-Steroidal"/ or "NSAIDs".ti,ab. or exp "Cyclooxygenase 2 Inhibitors"/ or ((nonsteroidal or non-steroidal or "non steroidal") and (anti-inflammatory or "anti inflammatory" or antiinflammatory)).ti,ab. or exp "Ibuprofen"/ or ("ibuprofen" or "ibuprophen" or Advil or flurbiprofen).ti,ab. or exp "Naproxen"/ or (naproxen or Aleve).ti,ab. or exp "Celecoxib"/ OR (celecoxib or "COX-2 inhibitor" or "COX-2 inhibitors" or "COX2 inhibitor" or "COX2 inhibitors" or Celebrex).ti,ab. or exp "Diclofenac"/ or (diclofenac or misoprostol or sulindac or

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	ketoprofen or tolmetin or etodolac or fenoprofen or piroxicam or etodolac or indomethacin or meloxicam or Mobic or ketorolac or Toradol).ti,ab.
16	8 and 15
17	exp Narcotics/ or exp "Analgesics, Opioid"/ or (narcotic* or opioid* or opiate* or papaver* or oxycodone or Oxycontin or OxyER or "Oxy-ER" or "Oxy-CRF" or "OxyIR" or "Oxy-IR" or Percodan or Percocet or Endocet or Roxicet or hydrocodone or dihydrocodeinone or Vicodin or Vicoprofen or Norco or Lortrab or Lorcet or oxymorphone or Opana or morphine or Kadian or Avinza or "MS Contin" or Duramorph or Roxanol or codeine or fentanyl or Duragesic or Actiq or Sublimaze or hydromorphone or Dilaudid or meperidine or Demerol or tramadol or Ultram or buprenorphine or propoxyphene or Darvocet or Omnopon or methadone or Dolopphine or Methadose or suboxone).ti,ab.
18	8 and 17
19	exp "Weight Loss"/ or exp "Weight Reduction Programs"/ or ("weight loss" or "weight reduction" or "body weight" or "lose weight").ti,ab. or exp "Body Mass Index"/
20	8 and 19
21	"Therapeutic Irrigation"/ or ("lavage").ti,ab. or "Arthroscopy"/ or (arthroscopy or arthroscopic or arthroendoscopy).ti,ab. or exp "Meniscectomy"/ or (meniscectomy or meniscectomies or menisectomy).ti,ab. or ((meniscus or meniscal) ADJ3 (repair or resection or resections or removal or excision)).ti,ab.
22	8 and 21
23	(exp "Acupuncture Therapy"/ or (acupuncture or pharmacoacupuncture or acupotomy or auriculotherapy or "dry needling").ti,ab. or exp "Physical Therapy Modalities"/ or exp "Musculoskeletal Manipulations"/ or (physiotherap* or "physical therapy" or "physical therapies" or manipulation or manipulations or massage or "manual therapy" or "manual therapies" or mobilization).ti,ab. or exp "Electromyography"/ or exp "Electric Stimulation Therapy"/ or ("transcutaneous electric nerve stimulation" or "TENS" or "NMES" or "electrical stimulation" or electrostimulation or "electric stimulation" or "electronic stimulation" or electrotherapy or "nerve stimulation" or "muscle stimulation" or electromyograph*).ti,ab. or exp "Ultrasonic Therapy"/ or (ultrasound or laser or shockwave or "shock wave").ti,ab. or exp "Laser Therapy"/ or exp "Cryotherapy"/ or Hot Temperature/tu or (cryotherapy or cryotherapies or ice or heat or "cold therapy").ti,ab. or exp exercise/ or exp "exercise therapy"/ or ("strength training" or muscle or force or resistance or resistive or exercise or isometric* or isokinetic* or flexibility or dynamic or stretching).ti,ab.) not exp *Arthroplasty, Replacement, Knee/
24	8 and 23
25	"Osteotomy"/ or (osteotom*).ti,ab.

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26	8 and 25
27	exp "Ablation Techniques"/ or exp "Catheter ablation"/ or exp "Pulsed radiofrequency treatment"/ or Radio waves/tu or ("radiofrequency ablation" or "radiofrequency neurotomy" or "Radiofrequency denervation" or "radiofrequency thermocoagulation" or "pulsed radiofrequency" or "catheter ablation" or "thermo-ablation" or "thermal ablation" or (nerve)adj3(ablation)).ti,ab. or exp "Denervation"/ or (neurolysis or denervation or denervated or "nerve block" or "nerve blocks" or "nerve blockade" or "nerve blockades" or neurectom* or neurotom*).ti,ab.
28	8 and 27
29	exp "Glucosamine"/ or glucosamine.ti,ab. or exp "Chondroitin"/ or chondroitin.ti,ab. or exp "Dietary Supplements"/ or (supplement or supplements or nutraceutical* or neutraceutical* or nutriceutical* or neutriceutical*).ti,ab. or Ginger/ or ginger.ti,ab. or exp "Cannabinoids"/ or (cannabidiol or CBD).ti,ab. or Curcumin/ or Curcuma/ or (curcumin or curcuma or turmeric).ti,ab.
30	8 and 29
31	(10 or 12 or 14 or 16 or 18 or 20 or 22 or 24 or 26 or 28 or 30) not 4
32	31 and English.lg.
33	Limit 32 to yr="2012-Current"

Database: Embase
Interface: Elsevier (https://embase.com)
Date Searched: *April 28, 2020*

LINE	SEARCH QUERY
1	knee osteoarthritis'/exp OR gonitis:ti,ab OR gonoarthritis:ti,ab OR gonarthros*:ti,ab
2	knee'/exp OR knee:ti,ab OR knees:ti,ab OR femorotibial:ti,ab OR tibial:ti,ab OR patella:ti,ab OR patellar:ti,ab
3	osteoarthritis'/exp OR osteoarthriti*:ti,ab OR 'osteo arthriti*':ti,ab OR 'osteo arthros*':ti,ab OR osteoarthros*:ti,ab OR (('non inflamm*':ti,ab OR noninflamm*:ti,ab OR degenerat*:ti,ab OR hypertropic:ti,ab) AND (arthriti*:ti,ab OR joint*:ti,ab OR disease*:ti,ab))
4	cadaver'/de OR 'in vitro study'/exp OR 'abstract report'/de OR 'book'/de OR 'editorial'/de OR 'note'/de OR 'letter'/it OR 'case study'/de OR 'case report'/de OR 'conference abstract'/it OR 'chapter'/it OR 'conference paper'/it OR 'conference review'/it
5	(#1 OR (#2 AND #3)) NOT #4
6	self help device'/exp OR 'orthopedic equipment'/exp OR 'walking aid'/exp OR 'orthosis'/exp OR 'orthotics'/exp OR cane:ti,ab OR canes:ti,ab OR crutch:ti,ab OR crutches:ti,ab OR orthotic:ti,ab OR orthotics:ti,ab OR orthoses:ti,ab OR orthosis:ti,ab OR braces:ti,ab OR bracing:ti,ab OR shoes:ti,ab OR insole:ti,ab OR insoles:ti,ab OR 'assistive device':ti,ab OR 'assistive devices':ti,ab OR 'walking aids':ti,ab OR walker:ti,ab OR walkers:ti,ab OR splints:ti,ab OR sleeves:ti,ab

7	signal peptide'/exp OR 'biological therapy'/exp OR 'biological product'/exp OR 'biological products therapeutic use'/exp OR 'thrombocyte rich plasma'/exp OR 'stem cell'/exp or ('growth factor' or 'growth factors' or 'platelet rich plasma' or 'platelet-rich plasma' or 'PRP' or 'stem cell' or 'stem cells' or 'biologics' or 'minimally manipulated' or 'minimal manipulation' or 'blood product' or 'blood products' or prolotherapy or prolotherapies or orthobiologics):ti,ab or ((biologic or biological or cell or cell-based or cellular)NEAR/2(therapy or therapies)):ti,ab
8	intraarticular drug administration'/exp OR 'viscosupplementation'/exp OR 'viscosupplement'/exp OR 'hyaluronic acid'/exp OR 'corticosteroid'/exp OR hyaluron*:ti,ab OR hylan:ti,ab OR viscosupplement*:ti,ab OR corticoid*:ti,ab OR cortical:ti,ab OR corticosteroid*:ti,ab OR 'cortico steroid':ti,ab OR corticotherapy:ti,ab OR ((intraarticular:ti,ab OR 'intra articular':ti,ab) AND (delivery:ti,ab OR administration:ti,ab OR injection*:ti,ab OR infusion:ti,ab OR injectable:ti,ab))
9	paracetamol'/exp OR 'nonsteroid antiinflammatory agent'/exp OR 'cyclooxygenase 2 inhibitor'/exp OR 'ibuprofen'/exp OR 'naproxen'/exp OR 'celecoxib'/exp OR 'diclofenac'/exp OR acetaminophen:ti,ab OR paracetamol:ti,ab OR tylenol:ti,ab OR nsaids:ti,ab OR ibuprofen:ti,ab OR ibuprophen:ti,ab OR advil:ti,ab OR flurbiprofen:ti,ab OR naproxen:ti,ab OR aleve:ti,ab OR celecoxib:ti,ab OR 'cox-2 inhibitor':ti,ab OR 'cox-2 inhibitors':ti,ab OR 'cox2 inhibitor':ti,ab OR 'cox2 inhibitors':ti,ab OR celebrex:ti,ab OR diclofenac:ti,ab OR misprostol:ti,ab OR sulindac:ti,ab OR ketoprofen:ti,ab OR tolmetin:ti,ab OR fenorpofen:ti,ab OR piroxicam:ti,ab OR etodolac:ti,ab OR indomethacin:ti,ab OR meloxicam:ti,ab OR mobic:ti,ab OR ketorolac:ti,ab OR toradol:ti,ab OR ((nonsteroidal:ti,ab OR 'non steroidal':ti,ab) AND ('anti inflammatory':ti,ab OR antiinflammatory:ti,ab))
10	narcotic agent'/exp OR 'narcotic analgesic agent'/exp OR narcotic*:ti,ab OR opioid*:ti,ab OR opiate*:ti,ab OR papaver*:ti,ab OR oxycodone:ti,ab OR oxycontin:ti,ab OR oxyer:ti,ab OR 'oxy-er':ti,ab OR 'oxy-crf':ti,ab OR 'oxyir':ti,ab OR 'oxy-ir':ti,ab OR percodan:ti,ab OR percocet:ti,ab OR endocet:ti,ab OR roxicet:ti,ab OR hydrocodone:ti,ab OR dihydrocodeinone:ti,ab OR vicodin:ti,ab OR vicoprofen:ti,ab OR norco:ti,ab OR lortrab:ti,ab OR lorcet:ti,ab OR oxymorphone:ti,ab OR opana:ti,ab OR morphine:ti,ab OR kadian:ti,ab OR avinza:ti,ab OR 'ms contin':ti,ab OR duramorph:ti,ab OR roxanol:ti,ab OR codeine:ti,ab OR fentanyl:ti,ab OR duragesic:ti,ab OR actiq:ti,ab OR sublimaze:ti,ab OR hydromorphone:ti,ab OR dilaudid:ti,ab OR meperidine:ti,ab OR demerol:ti,ab OR tramadol:ti,ab OR ultram:ti,ab OR buprenorphine:ti,ab OR propoxyphene:ti,ab OR darvocet:ti,ab OR omnopon:ti,ab OR methadone:ti,ab OR dolopphine:ti,ab OR methadose:ti,ab OR suboxone:ti,ab
11	body weight loss'/exp OR 'weight loss program'/exp OR 'body mass'/exp OR 'weight loss':ti,ab OR 'weight reduction':ti,ab OR 'body weight':ti,ab OR 'lose weight':ti,ab

12	lavage'/de OR 'knee arthroscopy'/exp OR 'meniscectomy'/exp OR lavage:ti,ab OR arthroscopy:ti,ab OR arthroscopic:ti,ab OR arthroendoscopy:ti,ab OR meniscectomy:ti,ab OR meniscectomies:ti,ab OR menisectomy:ti,ab OR ((meniscal:ti,ab OR meniscus:ti,ab) AND near3:ti,ab AND (repair:ti,ab OR resection:ti,ab OR resections:ti,ab OR removal:ti,ab OR excision:ti,ab))
13	acupuncture'/exp OR 'physiotherapy'/exp OR 'musculoskeletal manipulation'/exp OR 'electromyography'/exp OR 'electrotherapy'/exp OR 'ultrasound therapy'/exp OR 'low level laser therapy'/exp OR 'cryotherapy'/exp OR 'kinesiotherapy'/exp OR acupuncture OR pharmacoacupuncture OR acupotomy OR auriculotherapy OR 'dry needling' OR physiotherap* OR 'physical therapy' OR 'physical therapies' OR manipulation OR manipulations OR massage OR 'manual therapy' OR 'manual therapies' OR mobilization OR 'transcutaneous electric nerve stimulation' OR 'tens' OR 'nmes' OR 'electrical stimulation' OR electrostimulation OR 'electric stimulation' OR 'electronic stimulation' OR electrotherapy OR 'nerve stimulation' OR 'muscle stimulation' OR electromyograph* OR ultrasound OR laser OR shockwave OR 'shock wave' OR cryotherapy OR cryotherapies OR ice OR heat OR 'cold therapy' OR (('strength training':ti,ab OR muscle:ti,ab OR force:ti,ab OR resistance:ti,ab OR resistive:ti,ab OR exercise:ti,ab OR isometric*:ti,ab OR isokinetic*:ti,ab OR flexibility:ti,ab OR dynamic:ti,ab OR stretching:ti,ab) NOT 'knee arthroplasty'/exp/mj)
14	osteotomy'/exp or osteotom*:ti,ab
15	pulsed radiofrequency treatment'/exp OR 'pulsed radiofrequency'/exp OR 'radiofrequency ablation'/de OR 'ablation therapy'/de OR 'catheter ablation'/exp OR 'thermal ablation'/exp OR 'thermal ablation therapy'/exp OR 'radiofrequency ablation':ti,ab OR 'radiofrequency neurotomy':ti,ab OR 'radiofrequency denervation':ti,ab OR 'radiofrequency thermocoagulation':ti,ab OR 'pulsed radiofrequency':ti,ab OR 'catheter ablation':ti,ab OR 'thermo-ablation':ti,ab OR 'thermal ablation':ti,ab OR ('nerve':ti,ab AND 'ablation':ti,ab)
16	glucosamine'/exp OR 'chondroitin'/exp OR 'dietary supplement'/exp OR 'ginger extract'/exp OR 'ginger oil'/exp OR 'ginger'/exp OR 'cannabinoid'/exp OR 'curcuma'/exp OR glucosamine:ti,ab OR chondroitin:ti,ab OR supplement:ti,ab OR supplements:ti,ab OR nutraceutical*:ti,ab OR neutraceutical*:ti,ab OR nutriceutical*:ti,ab OR neutriceutical*:ti,ab OR ginger:ti,ab OR cannabidiol:ti,ab OR 'cbd':ti,ab OR curcumin:ti,ab OR curcuma:ti,ab OR turmeric:ti,ab
17	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
18	#5 and #17
19	#5 and #17 and [english]/lim and [2012-2019]/py

Database: Cochrane Central Register of Controlled Trials (CENTRAL)
Interface: Wiley (https://www.cochranelibrary.com/central)
Date Searched: *April 28, 2020*

LINE	SEARCH QUERY
1	[mh "osteoarthritis, knee"] or gonitis:ti,ab or gonarthritis:ti,ab or gonarthros*:ti,ab
2	[mh "knee joint"] or [mh "knee"] or (knee or knees or femorotibial or tibial or patella or patellar):ti,ab

3	[mh ^osteoarthritis] or [mh ^arthritis] (osteoarthriti* or osteo-arthriti* or osteo-arthros* or osteoarthros*).ti,ab. or ((non-inflamm* or noninflamm* or degenerat* or hypertropic) and (arthriti* or joint* or disease*)):ti,ab
4	#1 or (#2 and #3)
5	[mh ^"Self-Help Devices"] or [mh ^"Orthopedic Equipment"] or [mh ^"Canes"] or (cane or canes):ti,ab or [mh ^"Crutches"] or (crutch or crutches):ti,ab or [mh "Orthotic Devices"] or (orthotic or orthotics or orthoses or orthosis or braces or bracing or shoes or insole or insoles):ti,ab or [mh "Walkers"] or ("assistive device" or "assistive devices" or "walking aids" or walker or walkers or splints or sleeves):ti,ab
6	[mh "Intercellular Signaling Peptides and Proteins"] or ("growth factors" or "growth factor"):ti,ab or ((biological or biologic or cell or cell-based or cellular) AND (therapy or therapies)):ti,ab or ("platelet rich plasma" or "platelet-rich plasma" or "PRP" or "stem cell" or "stem cells"):ti,ab or "biologics":ti,ab or [mh "Biological Therapy"] or [mh "Biological Products"] or ("minimally manipulated" or "minimal manipulation" or "blood product" or "blood products"):ti,ab or [mh "Platelet-Rich Plasma"] or [mh "Stem Cells"] or [mh "Prolotherapy"] or (prolotherapy or prolotherapies):ti,ab or orthobiologics:ti,ab
7	[mh "Injections, Intra-Articular"] or [mh "Viscosupplementation"] or ((intraarticular or "intra articular") and (delivery OR administration OR injection* OR infusion or injectable)):ti,ab or [mh "Hyaluronic Acid"] or (hyaluron* OR "hylan"):ti,ab or [mh "Adrenal Cortex Hormones"] or (corticoid* or cortical or corticostseroid* or "cortico steroid" or corticotherapy):ti,ab or viscosupplement*:ti,ab
8	[mh "Acetaminophen"] or ("paracetamol" or "acetaminophen" or "Tylenol"):ti,ab or [mh "Anti-Inflammatory Agents, Non-Steroidal"] or "NSAIDs":ti,ab or [mh "Cyclooxygenase 2 Inhibitors"] or ((nonsteroidal or non-steroidal or "non steroidal") and (anti-inflammatory or "anti inflammatory" or antiinflammatory)):ti,ab or [mh "Ibuprofen"] or ("ibuprofen" or "ibuprophen" or Advil or flurbiprofen):ti,ab or [mh "Naproxen"] or (naproxen or Aleve):ti,ab or [mh "Celecoxib"] OR (celecoxib or "COX-2 inhibitor" or "COX-2 inhibitors" or "COX2 inhibitor" or "COX2 inhibitors" or Celebrex):ti,ab or [mh "Diclofenac"] or (diclofenac or misoprostol or sulindac or ketoprofen or tolmetin or etodolac or fenoprofen or piroxicam or etodolac or indomethacin or meloxicam or Mobic or ketorolac or Toradol):ti,ab
9	[mh Narcotics] or [mh "Analgesics, Opioid"] or (narcotic* or opioid* or opiate* or papaver* or oxycodone or Oxycontin or OxyER or "Oxy-ER" or "Oxy-CRF" or "OxyIR" or "Oxy-IR" or Percodan or Percocet or Endocet or Roxicet or hydrocodone or dihydrocodeinone or Vicodin or Vicoprofen or Norco or Lortrab or Lorcet or oxymorphone or Opana or morphine or Kadian or Avinza or "MS Contin" or Duramorph or Roxanol or codeine or fentanyl or Duragesic or Actiq or Sublimaze or hydromorphone or Dilaudid or meperidine or Demerol or tramadol or Ultram or buprenorphine or propoxyphene or Darvocet or Omnopon or methadone or Dolopphine or Methadose or suboxone):ti,ab

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10	[mh "Weight Loss"] or [mh "Weight Reduction Programs"] or ("weight loss" or "weight reduction" or "body weight" or "lose weight"):ti,ab or [mh "Body Mass Index"]
11	[mh "Therapeutic Irrigation"] or ("lavage"):ti,ab or [mh ^"Arthroscopy"] or (arthroscopy or arthroscopic or arthroendoscopy):ti,ab or [mh "Meniscectomy"] or (meniscectomy or meniscectomies or menisectomy):ti,ab or ((meniscus or meniscal) near/3 (repair or resection or resections or removal or excision)):ti,ab
12	([mh "Acupuncture Therapy"] or (acupuncture or pharmacoacupuncture or acupotomy or auriculotherapy or "dry needling"):ti,ab or [mh "Physical Therapy Modalities"] or [mh "Musculoskeletal Manipulations"] or (physiotherap* or "physical therapy" or "physical therapies" or manipulation or manipulations or massage or "manual therapy" or "manual therapies" or mobilization):ti,ab or [mh "Electromyography"] or [mh "Electric Stimulation Therapy"] or ("transcutaneous electric nerve stimulation" or "TENS" or "NMES" or "electrical stimulation" or electrostimulation or "electric stimulation" or "electronic stimulation" or electrotherapy or "nerve stimulation" or "muscle stimulation" or electromyograph*):ti,ab or [mh "Ultrasonic Therapy"] or (ultrasound or laser or shockwave or "shock wave"):ti,ab or [mh "Laser Therapy"] or [mh "Cryotherapy"] or (cryotherapy or cryotherapies or ice or heat or "cold therapy"):ti,ab or [mh exercise] or [mh "exercise therapy"] or ("strength training" or muscle or force or resistance or resistive or exercise or isometric* or isokinetic* or flexibility or dynamic or stretching):ti,ab) not [mh “Arthroplasty, Replacement, Knee”[mj]]
13	[mh "Osteotomy"] or (osteotom*):ti,ab
14	[mh "Ablation Techniques"] or [mh "Catheter ablation"] or [mh "Pulsed radiofrequency treatment"] or ("radiofrequency ablation" or "radiofrequency neurotomy" or "Radiofrequency denervation" or "radiofrequency thermocoagulation" or "pulsed radiofrequency" or "catheter ablation" or "thermo-ablation" or "thermal ablation" or (nerve) near/2 (ablation)):ti,ab or [mh "Denervation"] or (neurolysis or denervation or denervated or "nerve block" or "nerve blocks" or "nerve blockade" or "nerve blockades" or neurectom* or neurotom*):ti,ab
15	[mh "Glucosamine"] or glucosamine:ti,ab or [mh "Chondroitin"] or chondroitin:ti,ab or [mh "Dietary Supplements"] or (supplement or supplements or nutraceutical* or neutraceutical* or nutriceutical* or neutriceutical*):ti,ab or [mh ^Ginger] or ginger:ti,ab or [mh "Cannabinoids"] or (cannabidiol or CBD):ti,ab or [mh ^Curcumin] or [mh ^Curcuma] or (curcumin or curcuma or turmeric):ti,ab
16	#4 and (#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15)
17	#16 not "conference abstract":pt

Appendix IV: Guideline Development Group Disclosures

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OrthAlign: Stock or stock Options Number of Shares: 1,000 N/A(Self)

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Astrazeneca,
DSI(Self)

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AAOS
American Academy of Orthopaedic Surgeons

Management of Carpal Tunnel Syndrome

Evidence-Based Clinical Practice Guideline

Adopted by:
The American Academy of Orthopaedic Surgeons Board of Directors
05/18/2024

Endorsed by:

Please cite this guideline as:
American Academy of Orthopaedic Surgeons. Management of Carpal Tunnel Syndrome Evidence-Based Clinical Practice Guideline. aaos.org/cts2cpg Published 05/18/2024.

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Disclaimer

This clinical practice guideline (CPG) was developed by a physician/clinician volunteer clinical practice guideline development group based on a formal systematic review of the available scientific and clinical information and accepted approaches to treatment and/or diagnosis. This clinical practice guideline is not intended to be a fixed protocol, as some patients may require more or less treatment or different means of diagnosis. Clinical patients may not necessarily be the same as those found in a clinical trial. Patient care and treatment should always be based on a clinician's independent medical judgment, given the individual patient's specific clinical circumstances.

Disclosure Requirement

In accordance with AAOS policy, all individuals whose names appear as authors or contributors to the clinical practice guideline filed a disclosure statement as part of the submission process. All panel members provided full disclosure of potential conflicts of interest prior to voting on the recommendations contained within this clinical practice guideline.

Funding Source

This clinical practice guideline was funded exclusively by the American Academy of Orthopaedic Surgeons who received no funding from outside commercial sources to support the development of this document.

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Published 05/18/2024 by the American Academy of Orthopaedic Surgeons
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Rosemont, IL 60018
First Edition
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SUMMARY OF RECOMMENDATIONS

Recommendations are formed when there is sufficient evidence by which to create a directional statement. This is defined as evidence from two or more high quality studies (i.e., a strong recommendation), two or more moderate quality studies (i.e., a moderate recommendation), or statements resulting in a strong or moderate strength following Evidence to Decision Framework upgrading and/or downgrading.

DIAGNOSIS: CTS-6, ULTRASONOGRAPHY, NCV/EMG

Strong evidence suggests that CTS-6 can be used to diagnose carpal tunnel syndrome, in lieu of routine use of Ultrasonography or NCV/EMG.

Quality of Evidence: High

Strength of Recommendation: Strong ★★★★

Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

DIAGNOSIS: MRI, UPPER LIMB NEURODYNAMIC TESTING

Moderate evidence suggests that MRI and Upper Limb Neurodynamic Testing should not be used to diagnose carpal tunnel syndrome.

Quality of Evidence: Moderate

Strength of Recommendation: Moderate ★★★☆

Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

CORTICOSTEROID INJECTION

Strong evidence suggests corticosteroid injection does not provide long-term improvement of carpal tunnel syndrome.

Quality of Evidence: High

Strength of Recommendation: Strong ★★★★

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Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

PLATELET-RICH PLASMA (PRP) INJECTION

Strong evidence suggests PRP Injection does not provide long-term benefits in non-operative treatment of carpal tunnel syndrome (leukocyte rich or leukocyte poor PRP).

Quality of Evidence: High

Strength of Recommendation: Strong ★★★★

Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

SURGICAL RELEASE TECHNIQUE

Strong evidence suggests that there is no difference in patient reported outcomes between a mini-open carpal tunnel release and an endoscopic carpal tunnel release.

Quality of Evidence: High

Strength of Recommendation: Strong ★★★★

Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

MODES OF ANESTHESIA

Strong evidence suggests local anesthesia alone can be used for carpal tunnel release.

Quality of Evidence: High

Strength of Recommendation: Strong ★★★★

Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

POSTOPERATIVE THERAPY

Moderate evidence suggests postoperative supervised therapy should not be routinely prescribed after carpal tunnel release.

Quality of Evidence: Moderate

Strength of Recommendation: Moderate ★★★☆

Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

POSTOPERATIVE IMMOBILIZATION

Moderate evidence suggests immobilization through sling or orthosis (e.g., splint, brace) should not be used after carpal tunnel release.

Quality of Evidence: Moderate

Strength of Recommendation: Moderate ★★★☆

Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

POSTOPERATIVE PAIN: NSAID, ACETAMINOPHEN

Strong evidence suggests that NSAIDs and/or Acetaminophen should be used after carpal tunnel release for postoperative pain management.

Quality of Evidence: High

Strength of Recommendation: Strong ★★★★

Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

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SUMMARY OF OPTIONS

Options are formed when there is little or no evidence on a topic. This is defined as low quality evidence or a single moderate quality study (i.e., a limited strength option), no evidence or only conflicting evidence (i.e., a consensus option), or statements resulting in a limited or consensus strength following Evidence to Decision Framework upgrading and/or downgrading.

RISK FACTORS: KEYBOARDING, CLERICAL WORK

In the absence of reliable evidence, it is the opinion of the workgroup that there is no association between high keyboard use and carpal tunnel syndrome.

Quality of Evidence: Very Low
Strength of Option: Consensus ★☆☆☆
There is no supporting evidence, or limited level evidence was downgraded due to major concerns addressed in the EtD framework. In the absence of reliable evidence, the guideline work group is making a recommendation based on their clinical opinion.

THERAPEUTIC ULTRASOUND

Evidence suggests therapeutic ultrasound does not provide long-term improvement of carpal tunnel syndrome.

Quality of Evidence: High
Strength of Option: Limited ★★☆☆ (Downgraded)
Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Option was downgraded based on EtD framework.

NON-OPERATIVE TREATMENTS VS. PLACEBO/CONTROL

Evidence suggests that the following non-operative treatments do not demonstrate superiority over control or placebo: acupressure, insulin injection, heat therapy, magnet therapy, nutritional supplementation, oral diuretic, oral NSAID, oral anticonvulsant, phonophoresis.

Quality of Evidence: High
Strength of Option: Limited ★★☆☆ (Downgraded)
Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Option was downgraded based on EtD framework.

NON-OPERATIVE TREATMENTS: LONG-TERM

Evidence suggests the following non-operative treatments do not improve long-term patient reported outcomes for carpal tunnel syndrome: oral corticosteroid, hyaluronic acid injection, hydro dissection, kinesiotaping, laser therapy, peloid therapy, perineural injection therapy, topical treatment, shockwave therapy, exercise, ozone injection, massage therapy, manual therapy, pulsed radiofrequency.

Quality of Evidence: High
Strength of Option: Limited ★★☆☆ (Downgraded)
Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Option was downgraded based on EtD framework.

COMPARISON OF NON-OPERATIVE TREATMENTS

Evidence suggests no significant difference in patient reported outcomes between non operative treatment techniques for carpal tunnel syndrome.

Quality of Evidence: High
Strength of Option: Limited ★★☆☆ (Downgraded)
Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Option was downgraded based on EtD framework.

SITE OF SERVICE

Limited evidence suggests carpal tunnel release may be safely conducted in the office setting.

Quality of Evidence: Low
Strength of Option: Limited ★★☆☆
Evidence from two or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

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SURGICAL DRAPING

In the absence of reliable evidence, it is the opinion of the workgroup that limited draping is an option for carpal tunnel release.

Quality of Evidence: Consensus
Strength of Option: Consensus ★☆☆☆
There is no supporting evidence, or limited level evidence was downgraded due to major concerns addressed in the EtD framework. In the absence of reliable evidence, the guideline work group is making a recommendation based on their clinical opinion.

ANTICOAGULATION

Limited evidence suggests anticoagulation medication may be safely continued for carpal tunnel release.

Quality of Evidence: Low
Strength of Option: Limited ★★☆☆
Evidence from two or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

PROPHYLACTIC PERIOPERATIVE ANTIBIOTICS

Limited evidence suggests perioperative prophylactic antibiotics are not indicated for the prevention of surgical site infection following carpal tunnel release.

Quality of Evidence: Low
Strength of Option: Limited ★★☆☆
Evidence from two or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

PREOPERATIVE TESTING

In the absence of sufficient evidence specific to carpal tunnel, it is the opinion of the workgroup that routine pre-operative testing (e.g., labs, CXR, EKG) is not indicated.

Quality of Evidence: Very Low
Strength of Option: Consensus ★☆☆☆
There is no supporting evidence, or limited level evidence was downgraded due to major concerns addressed in the EtD framework. In the absence of reliable evidence, the guideline work group is making a recommendation based on their clinical opinion.

ADJUNCTIVE TESTING

In the absence of reliable evidence, it is the opinion of the workgroup that, when multiple risk factors for amyloidosis are present, pathological analysis of tenosynovium may be performed.

Quality of Evidence: Consensus
Strength of Option: Consensus ★☆☆☆
There is no supporting evidence, or limited level evidence was downgraded due to major concerns addressed in the EtD framework. In the absence of reliable evidence, the guideline work group is making a recommendation based on their clinical opinion.

POSTOPERATIVE PAIN: TRAMADOL

In the absence of reliable evidence, it is the opinion of the workgroup that Tramadol may be considered over other opioids for postoperative pain management.

Quality of Evidence: Very Low
Strength of Option: Consensus ★☆☆☆
There is no supporting evidence, or limited level evidence was downgraded due to major concerns addressed in the EtD framework. In the absence of reliable evidence, the guideline work group is making a recommendation based on their clinical opinion.

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INTRODUCTION

OVERVIEW

This clinical practice guideline is based on a systematic review of published studies with regard to the diagnosis and treatment of carpal tunnel syndrome (CTS). It provides recommendations that will help practitioners to integrate the current evidence and clinical practice, and it highlights gaps in the literature in need of future research. This guideline is intended to be used by appropriately trained physicians and clinicians involved in the diagnosis and treatment of carpal tunnel syndrome. It also serves as an information resource for developers and applied users of clinical practice guidelines.

GOALS AND RATIONALE

The purpose of this clinical practice guideline is to evaluate the current best evidence associated with treatment. Evidence-based medicine (EBM) standards advocate for use of empirical evidence by physicians in their clinical decision making. To assist with access to the large resources of information, a systematic review of the literature in publication was conducted between March 2022 and August 2023. It highlights where there is good evidence, where evidence is lacking, and what topics future research will need to target in order to help facilitate evidence-based decision making in the diagnosis and treatment of patients with carpal tunnel syndrome. AAOS staff methodologists assisted the physician/clinician work group in evaluating the existing literature so that they could formulate the following recommendations based on a rigorous systematic process. Musculoskeletal care is provided in many different settings and by a variety of providers. We created this guideline as an educational tool to guide qualified physicians and clinicians in making treatment decisions that improve the quality and efficacy of care. This guideline should not be construed as including all possible methods of care or excluding acceptable interventions similarly directed at obtaining favorable outcomes. The final decision to use a specific procedure must be made after assessing all concerns presented by the patient and consideration of locality-specific resources.

INTENDED USERS

This guideline is intended to be used by orthopaedic surgeons and other healthcare providers managing carpal tunnel syndrome. It serves as an information resource for medical practitioners. In general, individual practicing physicians and clinicians do not have the resources required to complete a project of comparable scope and duration involving the evaluation of an extensive literature base. In April 2019, the AAOS adopted the use of the GRADE Evidence-to-Decision Framework into its clinical practice guideline development methodology. This Framework enables work group members to incorporate additional factors into the strength of each recommendation and move away from the rigidity of previous AAOS recommendation language stems. The AAOS intends for this guideline to assist treatment providers not only in making shared clinical decisions with their patients, but also in describing to patients and their loved ones why a selected intervention represents the best available course of treatment. This guideline is not intended for use as a benefits determination document. It does not cover allocation of resources, business and ethical considerations, and other factors needed to determine the material value of orthopaedic care. Users of this guideline may also want to consider the appropriate use criteria (AUC) related to the management of carpal tunnel syndrome.

View background material via the CPG eAppendix 1
View data summaries via the CPG eAppendix 2

PATIENT POPULATION

This guideline addresses the diagnosis and treatment of adult patients (≥ 18 years of age) presenting with complaints which may be attributable to carpal tunnel syndrome.

SCOPE

The scope of this guideline includes the diagnosis and treatment of carpal tunnel syndrome.

ETIOLOGY

CTS is caused by compression of the median nerve under the transverse carpal ligament. Although compression/pressure on the median nerve is the pathophysiologic basis for the observed symptoms, the etiology of elevated pressure within the carpal canal is unknown.

INCIDENCE AND PREVALENCE

CTS has an annual crude incidence of 329 cases per 100,000 person-years (Mondelli 2002). The prevalence of CTS in the general adult population ranges from 2.7-4.9%. (Atroshi 1999).

BURDEN OF DISEASE

CTS is the most common compressive neuropathy affecting the upper extremity and is an important cause of morbidity and lost productivity. In the Medicare patient population alone, the disease burden of CTS accounts for $2.7 to $4.8 billion USD annually. (Hubbard 2018) In the US, the median lost worktime from carpal tunnel syndrome is 28 days, second only to fractures. (US Bureau of Labor and Statistics 2015).

EMOTIONAL AND PHYSICAL IMPACT

The principal impact of CTS on patients relates to the sensory disturbance which may disrupt sleep and, during non-sleeping hours, impair strength and dexterity. CTS may also be associated with pain in the wrist and digits. These symptoms may have a substantial effect on an individual's ability to accomplish activities of daily living and to perform work-related duties.

POTENTIAL BENEFITS, HARM, AND CONTRAINDICATIONS

The main benefits of these guidelines include streamlining and standardizing the work up and treatment for CTS based upon the best available evidence. This may have important impact on the work up and treatment of CTS, for example by minimizing the risk of incorrect diagnosis and minimizing unnecessary care in the pre-operative (pre-operative testing), intra-operative (antibiotic use), and post-operative (immobilization) phases of surgical care. Many tests and treatments are associated with some known risks. Factors that may impact a treating clinician's recommendations include but are not limited to pre-test probability for CTS, a patient's comorbidities, etc. Further, an individual patient and their caregiver network impact treatment decisions and thus a discussion of available options as well as the risks and benefits applicable to the individual patient in the context of their values, preferences, and goals should be guided by a shared decision-making process. After a patient and/or their caregiver network have been informed of available options and have discussed each option with their clinician, an informed decision can be made.

DIFFERENCES BETWEEN THE PRESENT AND PREVIOUS GUIDELINES

This updated clinical practice guideline replaces the first edition that was completed in 2016, "Management of Carpal Tunnel Syndrome." This update considered the literature that we previously examined as well as the empirical evidence published since the 2016 guideline. In April 2019, the AAOS adopted the use of the GRADE Evidence-to-Decision Framework into its clinical practice guideline development methodology. This Framework enables work group members to incorporate additional factors into the strength of each recommendation and move away from the

rigidity of previous AAOS recommendation language stems. The complete listing of inclusion criteria for this guideline is detailed in the section, "Inclusion Criteria," (Appendix II). A notable change to this updated guideline is the focus on the long-term effect of CTS treatment options. The 2016 guideline made several recommendations regarding the short-term effects of CTS treatments which are not present in the 2024 guideline, as the CPG development work group set out to evaluate the long-term, disease-modifying benefits of various treatment options.

METHODS

The methods used to perform this systematic review were employed to minimize bias and enhance transparency in the selection, appraisal, and analysis of the available evidence. These processes are vital to the development of reliable, transparent, and accurate clinical recommendations. To view the full AAOS clinical practice guideline methodology please visit https://www.aaos.org/quality/research-resources/methodology/.

This clinical practice guideline evaluates the management of carpal tunnel syndrome. The AAOS approach incorporates practicing physicians (clinical experts) and methodologists who are free of potential conflicts of interest relevant to the topic under study, as recommended by clinical practice guideline development experts.[1]

This clinical practice guideline was prepared by the AAOS Carpal Tunnel Syndrome Guideline physician development group (clinical experts) with the assistance of the AAOS Clinical Quality and Value (CQV) Department (methodologists). To develop this clinical practice guideline, the clinical practice guideline development group held an introductory meeting on March 6th, 2022, to establish the scope of the clinical practice guideline. As the physician experts, the clinical practice guideline development group defined the scope of the clinical practice guideline by creating PICO Questions (i.e., population, intervention, comparison, and outcome) that directed the literature search. The AAOS Medical Librarian created and executed the search (see Appendix III for search strategy).

LITERATURE SEARCHES

The systematic review begins with a comprehensive search of the literature. Articles considered were published prior to the start date of the search in a minimum of three electronic databases; PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials. The medical librarian conducts the search using key terms determined from the guideline development group's PICO questions.

A CQV methodologist will review/include only primary literature but will supplement the electronic search with a manual search of the bibliographies of secondary literature sources, such as systematic reviews, as available. The methodologist will then evaluate all recalled articles for possible inclusion based on the study selection criteria and will summarize the evidence for the guideline work group who assist with reconciling possible errors and omissions.

A study attrition diagram is provided in the Methods section of each document that details the numbers of identified abstracts, recalled and selected studies, and excluded studies that were evaluated in the CPG. The search strategies used to identify the abstracts are also included in the Appendix of each CPG document.

DEFINING THE QUALITY OF EVIDENCE

The quality of evidence for a recommendation is determined by the quality and quantity of included literature for the statement. Statements with evidence from two or more "High" quality studies are considered to have "High Quality Evidence". Statements with

evidence from two or more “Moderate” quality studies, or evidence from a single “High” quality study are considered to have “Moderate Quality Evidence”. Statements with evidence from two or more “Low” quality studies or evidence from a single “Moderate” quality study are considered to have “Low Quality Evidence”. Statements with evidence from one “Low” quality study or no supporting evidence are considered to have “Very Low Quality Evidence” or “Consensus” respectively.

DEFINING THE STRENGTH OF RECOMMENDATION

Judging the quality of evidence is only a steppingstone towards arriving at the strength of a CPG recommendation. The strength of recommendation also takes into account the quality, quantity, and the trade-off between the benefits and harms of a treatment, the magnitude of a treatment’s effect, and whether data exists on critical outcomes.

Strength of recommendation expresses the degree of confidence one can have in a recommendation. As such, the strength expresses how possible it is that a recommendation will be overturned by future evidence. It is very difficult for future evidence to overturn a recommendation that is based on many high quality randomized controlled trials that show a large effect. It is much more likely that future evidence will overturn recommendations derived from a few small retrospective comparative studies. Consequently, recommendations based on the former kind of evidence are given a “strong” strength of recommendation and statement based on the latter kind of evidence are presented as options to the practicing clinician, rather than a directional recommendation, with either a “limited” strength or, in the event of no supporting or only conflicting evidence, a “consensus” strength.

VOTING ON THE RECOMMENDATIONS

The recommendations and their strength were voted on by the guideline development group members during the final meeting. If disagreement between the guideline development group occurred, there was further discussion to see whether the disagreement(s) could be resolved. Recommendations were approved and adopted in instances where a simple majority (60%) of the guideline development group voted to approve; however, the guideline development group had consensus (100% approval) when voting on every recommendation for this guideline. Any recommendation strength upgrade or downgrade based on the Evidence-to-Decision Framework requires a super majority (75%) approval of the work group.

UNDERSTANDING THE QUALITY OF EVIDENCE AND STRENGTH OF RECOMMENDATION OR OPTION Statement

Table I. Strength and Quality Descriptions

Statement Strength	Evidence Quality	Statement Description	Strength Visual
Strong	High*	Evidence from two or more "High" quality studies with consistent findings recommending for or against the intervention. Or Rec is upgraded using the EtD framework.	★★★★
Moderate	Moderate*	Evidence from two or more "Moderate" quality studies with consistent findings or evidence from a single "High" quality study recommending for or against the intervention. Or Rec is upgraded or downgraded using the EtD framework.	★★★☆
Limited	Low*	Evidence from two or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Or Rec is downgraded using the EtD framework.	★★☆☆
Consensus*	Very Low, or Consensus*	Evidence from one "Low" quality study, no supporting evidence, or Rec is downgraded using the EtD framework. In the absence of sufficient evidence, the guideline work group is making a statement based on their clinical opinion.	★☆☆☆

*Unless statement was upgraded or downgraded in strength, using the EtD Framework

Table II. Interpreting the Strength of a Recommendation or Option

Strength of Recommendation	Patient Counseling (Time)	Decision Aids	Impact of Future Research
Strong	Least	Least Important, unless the evidence supports no difference between two alternative interventions	Not likely to change
Moderate	Less	Less Important	Less likely to change
Limited	More	Important	Change possible/anticipated
Consensus	Most	Most Important	Impact unknown

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REVIEW PERIOD

Following the final meeting, the CPG draft undergoes a 3-week review period for additional input from external content experts. Written comments are provided on the structured review form. All reviewers are required to disclose their conflicts of interest.

Specialty societies relevant to the topic are solicited for nominations of individual reviewers approximately six weeks before the final meeting. The review period is announced as it approaches, and others interested are able to volunteer to review the draft. The chairs of the guideline work group review the draft of the guideline prior to dissemination.

Some specialty societies (both orthopaedic and non-orthopaedic) ask their evidence-based practice (EBP) committee to provide review of the guideline. The organization is responsible for coordinating the distribution of our materials and consolidating their comments onto one form. The chair of the external EBP committees provides disclosure of their conflicts of interest (COI) and manages the potential conflicts of their members.

Again, the AAOS asks for comments to be assembled into a single response form by the specialty society and for the individual submitting the review to provide disclosure of potentially conflicting interests. The review stage gives external stakeholders an opportunity to provide evidence-based direction for modifications that they believe have been overlooked. Since the draft is subject to revisions until its approval by the AAOS Board of Directors as the final step in the guideline development process, confidentiality of all working drafts is essential.

The CPG is also provided to members of the AAOS Board of Directors (BOD), members of the Research and Quality Council (RQC), members of the Board of Councilors (BOC), and members of the Board of Specialty Societies (BOS) and members of the Committee on Evidence-Based Quality and Value (EBQV) for review and comment. The CPG is automatically forwarded to the AAOS BOD, RQC, and EBQV so that they may review it and provide comments prior to being asked to approve the document. Based on these bodies, over 200 commentators have the opportunity to provide input into each CPG.

The chairs of the guideline work group, the manager of the AAOS CQV unit, and the Director of AAOS CQV draft the initial responses to comments that address methodology. These responses are then reviewed by the chair and co-chair, who respond to questions concerning clinical practice and techniques. All comments received and the initial drafts of the responses are also reviewed by all members of the guideline development group. All proposed changes to recommendation language as a result of the review period are based on the available evidence that met inclusion criteria. Final revisions are summarized in a report that is provided alongside the guideline document throughout the remainder of the approval processes and final publication.

The AAOS believes in the importance of demonstrating responsiveness to input received during the review process and welcomes the critiques of external specialty societies. Following final approval of the guideline, all individual responses are posted on our website http://www.aaos.org/quality with a point-by-point reply to each non-editorial comment. Reviewers who wish to remain anonymous notify the AAOS to have their names de-identified; their comments, our responses, and their COI disclosures are still posted.

THE AAOS CPG APPROVAL PROCESS

This final clinical practice guideline draft must be approved by the AAOS Committee on Evidence Based Quality and Value, and subsequently the AAOS Research and Quality Council, and the AAOS Board of Directors. These decision-making bodies are described in the CTS CPG eAppendix 1. Their charge is to approve or reject its publication by majority vote.

REVISION PLANS

This clinical practice guideline represents a cross-sectional view of current treatment and may become outdated as new evidence becomes available. This clinical practice guideline will be revised in accordance with new evidence, changing practice, rapidly emerging treatment options, and new technology. This clinical practice guideline will be updated or withdrawn in five years.

CPG DISSEMINATION PLANS

The primary purpose of the present document is to provide interested readers with full documentation of the best available evidence for various procedures associated with the topic of this review. Publication of most clinical practice guidelines is announced by an Academy press release, articles authored by the clinical practice guideline development group and published in the Journal of the American Academy of Orthopaedic Surgeons, and articles published in AAOS *Now*. Most clinical practice guidelines are also distributed at the AAOS Annual Meeting in the Resource Center. he final guideline recommendations and their supporting rationales will be hosted on www.OrthoGuidelines.org.

Selected clinical practice guidelines are disseminated by webinar, the AAOS Learning Management System (LMS), Media Briefings, and by distributing them at relevant Continuing Medical Education (CME) courses and at the AAOS Resource Center.

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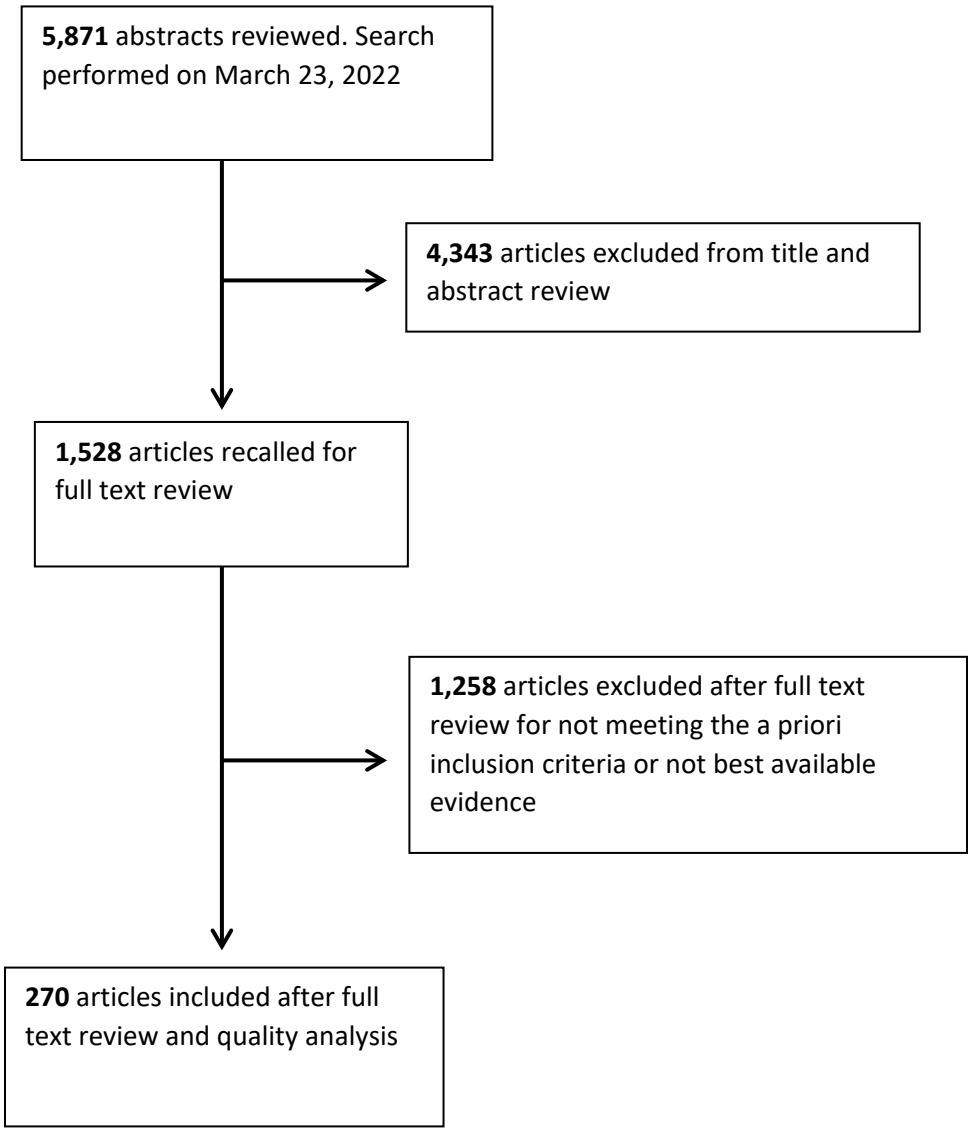
Study Attrition Flowchart



RECOMMENDATIONS

Recommendations are formed when there is sufficient evidence by which to create a directional statement. This is defined as evidence from two or more high quality studies (i.e., a strong recommendation), two or more moderate quality studies (i.e., a moderate recommendation), or statements resulting in a strong or moderate strength following Evidence to Decision Framework upgrading and/or downgrading.

DIAGNOSIS: CTS-6, ULTRASONOGRAPHY, NCV/EMG

Strong evidence suggests that CTS-6 can be used to diagnose carpal tunnel syndrome, in lieu of routine use of Ultrasonography, or NCV/EMG.

Quality of Evidence: High

Strength of Recommendation: Strong ★★★★

Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Rationale

There were ten high and five moderate quality studies supporting the use of either the CTS-6, NCV/EMG, and ultrasonography for the diagnosis of carpal tunnel syndrome (High-Quality: Wong 2004, Draghici 2020, Martikkala 2021, Falsetti 2022, Fu 2015, Moran 2009, Fowler 2014, Graham 2008, Wang 2020, Chen 2021) (Moderate-Quality: Mehrpour 2016, Mallouhi 2006, Naranjo 2007, Abdel Ghaffar 2012, Kanagasabai 2022). Although there was heterogeneity in the patient populations and comparisons for different studies there was strong and consistent evidence supporting these tools in diagnosing carpal tunnel syndrome. For example, Fowler 2014 studied ultrasonography versus NCV/EMG using CTS-6 as a reference standard (a tool that encompasses signs and symptoms used by clinicians to diagnose carpal tunnel syndrome) and found a positive predictive value of ultrasound and NCV/EMG of 94% and 89% respectively, and a negative predictive value of 82% and 80% respectively. In Fu 2015, the authors used clinical diagnosis of carpal tunnel along with NCV/EMG to test the use of ultrasonography and found a sensitivity and specificity of 91% and 93% respectively. In Graham 2008, NCV/EMG confirmation of carpal tunnel syndrome was used as the reference standard to test the correlation of the pre-test probability of having carpal tunnel syndrome using the CTS-6. The correlation of having carpal tunnel syndrome by using the CTS-6 compared to NCV/EMG diagnosis was as high as 0.9. There was no strong evidence demonstrating clinical superiority between diagnostic tools in this review, therefore we do not propose superiority of one test over the other, however, we highlight the use of CTS-6 as a diagnostic tool and/or screening tool, and the utilization of ultrasound or NCV/EMG as diagnostic tests when the positive predictive value when using the CTS-6 is low.

Benefits/Harms of Implementation

There is no specific research focused on the benefits/harms of the various modalities used to diagnose carpal tunnel syndrome that were found in this review. Roe (2022) found that from a shared decision-making perspective, patients want decision making for the testing for carpal tunnel diagnosis (ultrasound or NCV/EMG) to be equally collaborative. Harms of utilization of NCV/EMG include the unpleasant and invasive experience of the

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test, in addition to delays in treatment and costs. Similar harms related to delays and costs may be present for the utilization of ultrasound.

Outcome Importance

There was no evidence from this review that provided guidance for how the diagnostic tool used affected clinical outcomes.

Cost Effectiveness/Resource Utilization

While not the purpose of this systematic review, the guideline informs how future studies *assess* the cost effectiveness of testing for carpal tunnel syndrome.

Future Research

Future investigation can focus on differences in cost and patient outcomes based on diagnostic tools used.

DIAGNOSIS: MRI, UPPER LIMB NEURODYNAMIC TESTING

Moderate evidence suggests that MRI and Upper Limb Neurodynamic Testing should not be used to diagnose carpal tunnel syndrome.

Quality of Evidence: Moderate

Strength of Recommendation: Moderate ★★★☆

Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Rationale

The evidence shows that MRI and Upper Limb Neurodynamic testing should not be used for carpal tunnel syndrome. For the use of MRI, only one moderate quality study (Jarvik 2002) was reviewed which reported there was low specificity with moderate sensitivity using this tool to diagnosis carpal tunnel of any severity. Their findings suggest MRI was a poor tool in the diagnostic algorithm for Carpal Tunnel syndrome. Similarly, the use of Neurodynamic testing is as a tool for the diagnosis of Carpal Tunnel Syndrome was evaluated in a randomized controlled trial (Beddaa 2022) with high quality evidence demonstrating poor specificity (47%) and moderate sensitivity (76%) compared to the reference standard of Electrodiagnostic testing. Overall, the recommendation above is based on moderate evidence with limited to moderate strength that MRI and Upper Limb Neurodynamic Testing should not be used in the standard work up for the diagnosis of carpal tunnel syndrome.

Benefits/Harms of Implementation

Based on available evidence with low Specificity and moderate Sensitivity for both MRI and Neurodynamic testing, outcomes show that neither test provides benefit in the diagnosis of carpal tunnel syndrome compared to other more appropriate tools (CTS-6, Ultrasound, electrodiganostics). These tests have associated costs to patients and health systems and appear to provide no improved accuracy in the diagnosis of this condition.

Outcome Importance

Given the availability of alternative methods of diagnosis, and the importance of appropriate diagnostic clarity for patients, the use of these tools for diagnosis is not recommended.

Cost Effectiveness/Resource Utilization

Considering the associated costs of MRI and Neurodynamic testing they provide poor cost effectiveness in the standard work up for a patient presenting with Carpal Tunnel syndrome. This is important given the relative cost and availability differences between these tools and clinical exam testing (CTS-6) and the low-cost availability of alternatives.

Acceptability

Overall, the acceptability of this recommendation is expected to be high as obtaining MRI and Neurodynamic testing is not common practice. In addition, the associated costs and the potential for poor diagnostic clarity given the limited specificity of these tests make the value attached to use poor.

Feasibility

Because of the alternative diagnostic options for carpal tunnel syndrome, including exam alone (CTS-6), it is feasible to not utilize MRI or neurodynamic testing in the evaluation of a patient for carpal tunnel syndrome.

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Future Research

Additional high-quality studies should compare MRI and Neurodynamic testing against other standards of diagnosis outside of CTS-6, ultrasound, or electrodiagnostic testing if there were a hypothesis on a diagnostic advantage (e.g., improved specificity/sensitivity compared to alternate tests).

CORTICOSTEROID INJECTION

Strong evidence suggests corticosteroid injection does not provide long-term improvement of carpal tunnel syndrome.

Quality of Evidence: High

Strength of Recommendation: Strong ★★★★

Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Rationale

While many high-quality studies addressed efficacy of corticosteroid steroid injections (CSI), either as a primary intervention or comparison group, fewer included long term follow up. Three high quality studies with follow up ranging from 6 months to 5 years demonstrated no benefits (Hofer 2021, Salman 2018, Atroshi 2013). A study comparing CSI to nighttime immobilization found no significant differences at 1-2 years (Burton 2022) and an additional study comparing CSI to prolotherapy also showed no difference at 1 year (Aghaei 2021). Taken together, there is strong evidence that, while there may be short-term improvement in symptoms with CSI, there is no long-term benefit.

Benefits/Harms of Implementation

CSI may provide short term improvement in symptoms. A therapeutic injection may cause localized pain and swelling, rare allergic reactions, and a small possibility of nerve damage.

Outcome Importance

CSI are very common and popular interventions with high utilization in clinical practice, thus this recommendation informs standard treatment for many surgeons.

Cost Effectiveness/Resource Utilization

CSI are, individually, inexpensive interventions relative to many other treatments. Limited data address cost-effectiveness.

Acceptability

We expect this recommendation to be generally accepted, however, CSI for short term relief of symptoms may continue.

Feasibility

Minimizing use of CSI for any long-term benefit is readily available and feasible.

Future Research

Future investigation can focus on assessing the short-term benefits to patients, in relation to the cost, to evaluate the cost-effectiveness and value of CSI, given the lack of long-term effectiveness.

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View data summaries via the CPG eAppendix 2

PLATELET-RICH PLASMA (PRP) INJECTION

Strong evidence suggests PRP Injection does not provide long-term benefits in non-operative treatment of carpal tunnel syndrome (leukocyte rich or leukocyte poor PRP).

Quality of Evidence: High

Strength of Recommendation: Strong ★★★★

Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Rationale

A randomized controlled trial with 12-month follow-up of PRP vs saline control showed similar improvement in symptom severity scale and functional status at all time points without clinically meaningful differences, though cross-sectional area and electrodiagnostic parameters showed some beneficial effect from PRP (Chen, 2021). While other high-level studies failed to follow patients long-term, short-term effects of PRP have shown mixed results. Raeissadat (2018) conducted a randomized controlled trial that compared the effects of wrist splitting alone versus wrist splinting combined with a single local PRP injection. They found that over the 10-week treatment period in comparison to control, a single PRP injection did not significantly enhance the effects of conservative treatment in terms of pain, symptom severity, functional status, and electrophysiological parameters. In contrast, Malhias (2018) performed an RCT which found PRP lead to increased success rates defined by a 25% difference in Q-DASH scores in comparison to placebo at 12 weeks.

Benefits/Harms of Implementation

PRP is an endogenously sourced blood product. Harvesting requires venipuncture and risks of injection are low. Benefits are unclear.

Cost Effectiveness/Resource Utilization

PRP is relatively expensive due to the cost of purification and separation equipment necessary to isolate and extract the platelet-rich fraction from whole blood. With no clear benefit to patient outcomes, its utilization may be wasteful.

Acceptability

PRP is performed by many practitioners despite limited evidence of effectiveness. It is not considered a standard treatment for carpal tunnel syndrome.

Feasibility

Implementation of this recommendation is feasible as it recommends against the use of PRP for the treatment of carpal tunnel syndrome.

Future Research

There are few placebo-controlled trials of PRP with long-term follow up. More high-level research with longer follow up is critical to evaluating any significant differences between PRP and placebo.

SURGICAL RELEASE TECHNIQUE

Strong evidence suggests that there is no difference in patient reported outcomes between a mini-open carpal tunnel release and an endoscopic carpal tunnel release.

Quality of Evidence: High

Strength of Recommendation: Strong ★★★★

Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Rationale

There are multiple high and moderate quality studies that were identified to evaluate the difference in outcomes between a mini-open carpal tunnel release and an endoscopic carpal tunnel release. These studies consistently demonstrated no difference in long-term outcomes (e.g., patient reported outcome measures, range of motion, grip strength) between the two techniques (Oh 2017, Kang 2013, Larsen 2013, Aslani 2012, Wang 2022, Capa-Grasa 2014). We used mini-open carpal tunnel release as a term to describe a small incision in the palm that does not cross the wrist crease, which is smaller in size than more traditional open approaches.

Benefits/Harms of Implementation

There is no consistently demonstrated benefit of utilizing a mini-open carpal tunnel release or an endoscopic carpal tunnel release. Endoscopic carpal tunnel release may afford a shorter return to work however this may depend upon post operative protocols, patient occupation, and other factors. Endoscopic carpal tunnel release can be associated with greater costs, which may affect patient preference for this option. Although not included in this review, complication rates for endoscopic carpal tunnel release may be higher than previously described and should be considered (Carrol 2023).

Cost Effectiveness/Resource Utilization

Cost data regarding endoscopic and mini open carpal tunnel release vary and are based upon several factors including surgical location (e.g., office, operating room) and stakeholder perspective (e.g., societal, payer) (Barnes 2021, Zhang 2016). Prior studies evaluating the cost effectiveness of these approaches have favored mini-open carpal tunnel release when completed in the office setting, however, advances in endoscopic release in the office may need to be considered. Recent literature on higher complication rates with endoscopic release may affect future CAEs on this topic.

Acceptability

Mini-open and endoscopic release are both accepted surgical techniques for carpal tunnel release.

Feasibility

Both techniques are feasible, however each technique should be performed only by those who are trained in each technique.

Future Research

Future investigations can focus on the development of tools to help guide patients in understanding the benefits, risks, and costs associated with each technique to support a shared decision-making approach that aligns with patient preferences.

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MODES OF ANESTHESIA

Strong evidence suggests local anesthesia alone can be used for carpal tunnel release.

Quality of Evidence: High

Strength of Recommendation: Strong ★★★★

Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Rationale

There are three high quality and six low quality studies that suggest local anesthesia alone can be used for carpal tunnel release. Three randomized controlled trials evaluated local anesthesia as compared to intravenous regional anesthesia (Nabhan 2011, Okamura 2021, Sorensen 2013). One study demonstrated decreased tourniquet time and OR time in the local anesthesia cohort with no differences in patient reported outcomes (Nabhan 2011). Another study demonstrated lower intraoperative and postoperative pain and analgesic use in the local anesthesia cohort (Okamura 2021). Sorensen et al, demonstrated that patients in the local anesthesia cohort reported less postoperative pain and analgesic use. Lower quality studies have demonstrated adequate and/or improved pain control in the local anesthetic cohort (Kang 2019), low or no increased risks of complications (Rellan 2021, Wellington 2021), and similar patient reported outcomes as compared to other anesthetic modalities (Tulipan 2017, Tulipan 2018).

Benefits/Harms of Implementation

There are potential benefits and harms associated with local anesthetic and intravenous regional anesthesia that should be discussed with patients. For example, local anesthetic may allow for flexibility in procedure location (e.g., office-based surgery) and ability to drive oneself home, however it may be anxiety provoking for some patients. A shared decision-making approach on the use of local only for surgery may be beneficial.

Cost Effectiveness/Resource Utilization

Cost effectiveness and resource utilization were not primary outcomes of this review, and costs and resource utilization vary based upon context, however in general, carpal tunnel release with local anesthetic results in lower costs and resource utilization compared to other forms of anesthesia (e.g., monitored anesthesia care) (Carr 2019, Kamal 2019).

Acceptability

Based on descriptions in the literature, local anesthesia has been adopted by surgeons and patients in multiple countries as an acceptable approach for carpal tunnel release.

Feasibility

Local anesthesia is readily available and feasible as it does not require any additional medications or changes to the surgical approach.

Future Research

Future investigation can focus on the development of tools to help understand patient preference and guide patients in understanding the benefits, risks, and costs associated with available anesthetic techniques. The financial advantages of local only anesthesia may be further explored in future cost effectiveness analyses.

POSTOPERATIVE THERAPY

Moderate evidence suggests postoperative supervised therapy should not be routinely prescribed after carpal tunnel release.

Quality of Evidence: Moderate

Strength of Recommendation: Moderate ★★★☆

Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Rationale

This recommendation is based on one high-quality, two moderate-quality, and one low-quality study evaluating the use of physical therapy after carpal tunnel release (Provinciali 2000, Pomerance 2007, Schroeder 2022, Gil 2020). These studies consistently demonstrate that there are no functional or outcome benefits of using therapy after carpal tunnel release. There was one high-quality study that demonstrated short term benefits (of improved motor dexterity at one month and shorter return-to-work) (Provinciali 2000).

Benefits/Harms of Implementation

The benefit of the use of therapy after carpal tunnel release has not been demonstrated. Its use may result in unnecessary costs (direct, indirect, intangible). There may be scenarios or patients in whom post-operative therapy may be beneficial, however, studies are required to identify this potential patient population. While formal physical therapy is not substantiated across the majority of patients, it may benefit some patients on a case-by-case basis.

Future Research

Future research is needed to determine which patients may benefit from physical therapy after carpal tunnel release. Research evaluating the cost-effectiveness of physical therapy post-operatively, particularly in specific patient populations, may be beneficial to promote high-quality low-cost care.

View background material via the CPG eAppendix 1
View data summaries via the CPG eAppendix 2

POSTOPERATIVE IMMOBILIZATION

Moderate evidence suggests immobilization through sling or orthosis (e.g., splint, brace) should not be used after carpal tunnel release.

Quality of Evidence: Moderate

Strength of Recommendation: Moderate ★★★☆

Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Rationale

This recommendation is based on one high-quality, five moderate-quality, and one low-quality study evaluating the use of postoperative splinting in comparison to no splinting. These studies demonstrate that there are no functional or outcome benefits of utilizing splinting after carpal tunnel release.

One high-quality article (Logli 2018) demonstrated no difference in patient reported or clinical outcomes at any follow up period to 12 months after mini-open CTS surgery in patients who utilized a non-removable orthotic (plaster, Webril cotton wrap) or patients who used a soft dressing (gauze wrap) when compared to a removable orthotic (V-Strap wrist brace).

One moderate-quality article (Cebesoy 2007) showed that patients who had been treated with a surgical intervention for CTS had a significantly better BCTQ-SSS score when treated with a post-op Bulky Bandage than patients who were treated with a splint.

One moderate-quality article (Ritting 2012) showed that patients treated with early mobilization after surgical intervention for CTS had better grip strength and tip pinch strength than patients treated with medicated gauze, cotton gauze, cast padding, and elastic roller bandage.

One moderate-quality article (Cook 1995) showed that patients who began range of motion exercises after CTS surgery post-op day one had significantly better outcomes in return to daily living, light duty work, and full duty work than patients who were splinted for two weeks following surgery. Grip strength, key-pinch strength, and VAS pain were also improved in the unrestricted movement group, however these effects only lasted until the one-month follow-up.

Two moderate-quality articles (Finsen 1999 and Huemer 2007) and one low-quality article (Kroeze 2020) showed no significant differences in observed outcomes between their restricted and unrestricted movement groups.

Benefits/Harms of Implementation

There are no harms associated with implantation of this recommendation.

Future Research

Future investigation should focus on determining benefits of early post operative mobilization, return to unrestricted activities of daily living and work activities.

POSTOPERATIVE PAIN: NSAID, ACETAMINOPHEN

Strong evidence suggests that NSAIDs and/or acetaminophen should be used after carpal tunnel release for postoperative pain management.

Quality of Evidence: High

Strength of Recommendation: Strong ★★★★

Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Rationale

One high-quality article (Husby 2001) showed no significant differences in observed outcomes for patients who underwent surgery for CTS treated with acetaminophen vs. patients that were given matching placebo pills. Three high-quality articles (Husby 2001 and Ilyas, 2018/2019) showed no significant differences in observed outcomes for patients who underwent surgery for CTS treated with acetaminophen vs. those who were given non-steroidal anti-inflammatory drugs (NSAIDs) (Naproxen or ibuprofen). Ilyas (2018) also showed that the patients who took acetaminophen or ibuprofen after mini-open carpal tunnel repair had statistically significantly lower Worst Daily Pain (0-10 scale) than those who took Oxycodone – 2.5 and 3.4 respectively. Ilyas (2019) again showed that the patients who underwent CTS surgery who took acetaminophen or ibuprofen also had less VAS Worst Daily Pain than patients who took Oxycodone – 2.5, 2.5, and 2.9 respectively; these differences reached statistical significance. Adverse events were also significantly less common in patients taking NSAIDs or acetaminophen in comparison to Oxycodone. Ilyas 2018 reported 11% of the oxycodone group reported adverse events compared to 3% in the acetaminophen group; Ilyas 2019 adverse events were reported in 15% of the oxycodone group, 1.6% of the acetaminophen group, and 1.6% in the NSAID group.

Benefits/Harms of Implementation

The benefit of having two non-opioid medications for postoperative pain management is that pain can still be managed despite concomitant conditions, which may preclude a patient from taking either NSAID or acetaminophen. In addition, this helps avoid the many adverse effects of opioids (overdose and addiction).

Outcome Importance

NSAIDs and acetaminophen are options to help control postoperative pain.

Acceptability

Accepted treatment for pain in the postoperative state as there are over-the-counter medications.

Feasibility

Feasible as these are over-the-counter medications that are familiar to patients and clinicians.

View background material via the CPG eAppendix 1
View data summaries via the CPG eAppendix 2

OPTIONS

Low quality evidence, no evidence, or conflicting supporting evidence have resulted in the following statements for patient interventions to be listed as options for the specified condition. Future research may eventually cause these statements to be upgraded to strong or moderate recommendations for treatment.

RISK FACTORS: KEYBOARDING, CLERICAL WORK

In the absence of reliable evidence, it is the opinion of the workgroup that there is no association between high keyboard use and carpal tunnel syndrome.

Quality of Evidence: Very Low
Strength of Option: Consensus ★☆☆☆

Description: Evidence there is no supporting evidence, or limited level evidence was downgraded due to major concerns addressed in the EtD framework. In the absence of reliable evidence, the guideline work group is making a recommendation based on their clinical opinion.

Rationale

No high- or moderate-quality studies were identified to address the question of the association of keyboard use and carpal tunnel syndrome. A single low-quality study that met inclusion criteria, (Eleftheriou et al. 2012), reported a statistically significant association between high keyboard use and carpal tunnel syndrome.

Benefits/Harms of Implementation

This recommendation is based upon a research question that was specifically focused on the association of high keyboard use and carpal tunnel syndrome. The potential harm in the CPG lies in the lack of recognition of keyboard use as a strong risk factor or causative variable for carpal tunnel syndrome which has implications for worker's compensation cases and physicians called upon to evaluate causation.

THERAPEUTIC ULTRASOUND

Evidence suggests therapeutic ultrasound does not provide long-term improvement of carpal tunnel syndrome.

Quality of Evidence: High

Strength of Option: Limited ★★☆☆ (Downgraded)

Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Option was downgraded based on EtD framework.

Rationale

There is limited standardization of the studies assessing the effectiveness of therapeutic ultrasound on carpal tunnel symptoms; this recommendation has been downgraded for inconsistency and heterogeneity of both treatments and outcomes. Studies were inconsistent with the use of constant versus pulsed-wave treatments as well as dosages and supplementing treatment with an orthosis. Only one study provided long term follow up (Jothi, 2019) and showed no significant difference between therapeutic ultrasound and sham ultrasound therapy. Two additional papers also showed no significant difference between treatment and control groups, although the follow up was only one to two months (Catalbas 2018 and Yildiz 2011). Only one paper favored the use of ultrasound for treatment of CTS (Dincer, 2009) while Ebenbichler et al. Showed more mixed results in 1998. Many studies evaluated therapeutic ultrasound against various other treatments, including, exercise, phonophoresis, pulsed radiofrequency, heat and laser therapy, however, ultrasound was not clearly superior. There was limited standardization of the use of therapeutic ultrasound on carpal tunnel symptoms, such as the use of constant versus pulsed-wave treatments as well as dosages.

Benefits/Harms of Implementation

Therapeutic ultrasound does not show any significant difference from placebo. Although it does not have any direct biological adverse reactions, ultrasound adds to the time and cost of treatment without established benefit to patients. There are no harms expected from this recommendation based on the evidence.

Cost Effectiveness/Resource Utilization

Given the lack of effectiveness of therapeutic ultrasound, it is not cost effective to use it as a therapy for CTS.

Acceptability

Due to lack of supporting evidence, this guidance is anticipated to be accepted by surgeons, patients, and therapists.

Feasibility

Readily available and feasible to not use this modality.

Future Research

More long-term follow up studies are required to confirm the lack of effectiveness of therapeutic ultrasound in the treatment of CTS.

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View data summaries via the CPG eAppendix 2

NON-OPERATIVE TREATMENTS VS. PLACEBO/CONTROL

Evidence suggests that the following non-operative treatments do not demonstrate superiority over control or placebo: acupressure, insulin injection, heat therapy, magnet therapy, nutritional supplementation, oral diuretic, oral NSAID, oral anticonvulsant, phonophoresis.

Quality of Evidence: High
Strength of Option: Limited ★★☆☆ (Downgraded)

Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Option was downgraded based on EtD framework.

Rationale

The overall strength was downgraded for this option given the heterogeneity in treatment modalities, study quality, control cohort utilized, and follow-up time periods. Single studies evaluating acupressure, insulin injection, heat therapy, immobilization, oral diuretic, and oral NSAID for the treatment of CTS showed no significant difference at short term follow up (Asgari, 2020, Kamel 2019, Mansiz Kaplan 2019, Kocak Ulucakoy 2020, Chang 2020). Two studies showed moderate evidence that there was no significant difference between patient treatment with magnet therapy and controls (Colbert 2010 and Baute 2018). Patients treated with nutritional supplementation did not show improvement over controls in two studies (Paolucci 2018 and Faig-Marti 2017), however, showed improvement in a single study with very short term follow up (Marvulli 2021). There is strong evidence that oral anticonvulsants are not effective in the treatment of CTS with three out of four articles showing no significant difference between treatment and placebo groups (Hui 2011, Eftekharsadat 2015, Mehmetoglu 2018, Hesami 2018). Lastly, there is strong evidence against the use of phonophoresis to treat CTS (Boohong 2020 and Haghighat 2021).

Benefits/Harms of Implementation

The above treatments do not show a consistent significant difference from control groups and add to the time and monetary expense for patients suffering from CTS and to the health system (low value care). Moreover, adverse reactions from oral diuretics, NSAIDs and anticonvulsants are well recognized and are discouraged for non-operative treatment of CTS through this guideline.

Outcome Importance

As the above treatments do not show a difference in symptom improvement for CTS, they should not be recommended.

Cost Effectiveness/Resource Utilization

Given the lack of effectiveness of the above treatments are not considered cost effective to treat CTS.

Future Research

No long-term follow up studies are available to confirm the lack of effectiveness of these therapies, however, are likely not necessary, given the lack of short-term benefits.

NON-OPERATIVE TREATMENTS: LONG-TERM

Evidence suggests the following non-operative treatments do not improve long-term patient reported outcomes for carpal tunnel syndrome: oral corticosteroid, hyaluronic acid injection, hydro dissection, kinesiotaping, laser therapy, peloid therapy, perineural injection therapy, topical treatment, shockwave therapy, exercise, ozone injection, massage therapy, manual therapy, pulsed radiofrequency.

Quality of Evidence: High

Strength of Option: Limited ★★☆☆ (Downgraded)

Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Option was downgraded based on EtD framework.

Rationale

The overall strength was downgraded for this option given the heterogeneity in treatment modalities, study quality, control cohort utilized, and follow-up time periods. One study evaluating oral corticosteroid (Chang 1998). Two studies evaluating hyaluronic acid injection demonstrate limited evidence in favor of hyaluronic acid injection at 6 months as compared to a normal saline injection (Wu 2022) and no difference between a hyaluronic acid and normal saline injection at 1-, 3-, and 6-mo follow up time points (Su 2021).

There are three studies that evaluated the utilization of hydro dissection for the treatment of carpal tunnel syndrome. Elawamy et al.2020 demonstrated improved pain and function 6 months after hydro dissection with Hyalase and 10 mL saline solution injection as compared to hydro dissection with 10mL of saline solution only. We et al.2018 demonstrated that hydro dissection resulted in improved function and symptom severity compared to subcutaneous injection at 6mo. He et al.2022 demonstrated that hydro dissection with 5% dextrose as an add on to a corticosteroid injection resulted in improved patient reported outcome scores at 3 mo.

Five studies evaluated kinesiotaping, two favoring kinesiotaping and three demonstrating no difference as compared to various treatment modalities including an orthosis, placebo kinesiotaping, nerve and tendon gliding exercises (Geler 2016, De Sire 2021, Aminian 2022, Mansiz 2019, Yildririn 2018).

Seven studies evaluated the utilization of laser therapy, four of which were either mixed or favored laser therapy whereas three demonstrated no difference in outcomes when comparing laser therapy to orthosis and/or placebo (Barbosa 2016, Chang 2008, Dincer 2009, Evic 2007, Fusakul 2014, Guner 2018, Yagci 2019). Metin et al.2017 evaluated peloid treatment with nighttime orthosis as compared to nighttime orthosis alone and demonstrated improvements in functionality at one month.

Wu et al.2017, when comparing perineural injection therapy with 5% dextrose to perineural injection therapy with normal saline, demonstrated clinical improvement in the former group at 6 months post injection. Five studies evaluated the use of topical treatments (e.g., lavender oil, chamomile oil) that demonstrated varied results as compared to placebo (Eftekharsadat 2018, Flondell 2017, Hashempur 2015, Karimi 2021, Hashempur 2017.

Ten studies evaluate short term (up to 6-month) effects of shockwave therapy, eight of which demonstrate benefits and two of which demonstrate no difference in outcomes as compared to sham treatment, (Habibzadeh 2022, Kocak 2020, Gesslbauer 2021, Chang 2020, Wu 2016, Vahdatpour 2016, Saglam 2022, Haghighat 2021,

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Raissi 2017, Karatas 2019). Six studies evaluated exercise therapy or neuromobilization for the treatment of carpal tunnel syndrome. There was great variation in the intervention protocols (Shem 2020, Zidkova 2019, Abdolrazaghi 2021, Hesami 2018, Salehi 2019). Shem 2020 showed symptom improvements after 6 weeks of self-myofascial stretching. Zidkova 2019 showed 9-week improved symptom scores after exercise with neuromobilization techniques. Abdorlrazaghi 2021 found that a 6-week gliding exercise with splinting protocol did not provide improvement in comparison to splinting alone. Hesami 2018 and Salehi similarly showed nerve and gliding tendon exercises provide benefit in comparison to splinting alone after 6-week protocols.

Bahrami (2019) evaluated ozone injection with splinting as compared to splinting alone and demonstrated clinical improvement in the intervention arm. Elbalawy 2020 compared sensory rehabilitation with physical therapy as compared to physical therapy alone for carpal tunnel syndrome and demonstrated no difference in cohorts.

Four studies evaluate various manual therapies for the treatment of carpal tunnel syndrome. Despite various therapy modalities and time periods of follow up, each study favors manual therapy as compared to the control cohort. Jimenez Del Barrio 2018 investigated diacutaneous fibrolysis; Wolny investigated neurodynamic techniques administered twice per week for ten weeks in both 2018 and 2019. Dinarvand 2017 compared hamate and scaphoid mobilization with splinting with splinting alone and found that while both groups improved significantly at ten-week follow-up, the degree of improvement was larger in the mobilization group. Chen 2015 compared ultrasound-guided pulsed radiofrequency treatment with night splinting as compared to night splinting alone and demonstrated improved pain and functional outcome scores in the intervention cohort. Weintraub et al. evaluated the use of static and pulsed electromagnetic fields for the treatment of carpal tunnel and noted improvements in pain as compared to sham treatment.

Benefits/Harms of Implementation

The above interventions do not demonstrate a consistently significant difference as compared to control cohorts. Each treatment is associated with its own time and monetary expense, as well as risk profile.

Cost Effectiveness/Resource Utilization

Given the lack of effectiveness of the above treatments, they are not considered cost effective for the treatment of carpal tunnel syndrome.

Acceptability

Due to lack of supporting evidence, this guideline is anticipated to be accepted by surgeons, patients, and therapists.

Future Research

Future research may include studies that compare non operative treatment options to carpal tunnel release and/or with a more consistently defined intervention and/or control cohort.

COMPARISON OF NON-OPERATIVE TREATMENTS

Evidence suggests no significant difference in patient reported outcomes between non operative treatment techniques for carpal tunnel syndrome.

Quality of Evidence: High

Strength of Option: Limited ★★☆☆ (Downgraded)

Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Option was downgraded based on EtD framework.

Rationale

Numerous articles compared various therapies for carpal tunnel against other therapies. Not only were the treatments and their comparisons very heterogeneous, but no long-term follow also up was described either – as such, this recommendation has been downgraded. The majority of the studies did not demonstrate any significant difference between the treatment arms. When comparing corticosteroid injection versus shockwave therapy, the results were equivocal with one study out of four favoring ESWT, another favoring CSI, and two showing no significant difference between the treatment groups. When comparing ESWT with various treatments, three studies showed a slight benefit in ESWT.

Benefits/Harms of Implementation

The above non operative treatments do not show a consistent significant difference from other treatments and add to the time and monetary expense for patients suffering from CTS.

Outcome Importance

As there is limited data with mixed quality of evidence, any particular non-operative treatment cannot be recommended over another non-operative treatment.

Cost Effectiveness/Resource Utilization

None of the non-operative treatments have shown long-term success in the treatment of CTS and therefore, are not considered cost-effective options.

Acceptability

Due to lack of supporting evidence, this guideline is anticipated to be accepted by surgeons, patients, and therapists.

Feasibility

Readily available and feasible to not use these modalities.

Future Research

No long-term follow up studies are available to confirm the lack of effectiveness of these therapies, however, are likely not necessary, given the lack of short-term benefits.

View background material via the CPG eAppendix 1
View data summaries via the CPG eAppendix 2

SITE OF SERVICE

Limited evidence suggests carpal tunnel release may be safely conducted in the office setting.

Quality of Evidence: Low

Strength of Option: Limited ★★☆☆

Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale

No high- or moderate-quality studies were identified to address the question related to the association of site of carpal tunnel release on outcomes. Five low-quality studies were identified, most of which were single-surgeon, single-institution and/or retrospective or database studies evaluating carpal tunnel release conducted in the office setting as compared to the operating room setting (Halvorson 2020, Miller 2022, Moscato 2021, Randall 2021, Stephens 2021). These studies consistently demonstrated that carpal tunnel release in the office setting results in no increased risk of complications with higher ratings of patient experience and satisfaction when compared to surgical release in the operating room.

When examining surgical site infection (SSI) rates, Halvorson et al. (2020) discerned no significant disparity between clinic-based procedure rooms (PR) and traditional operating rooms (OR). In terms of patient experience and satisfaction, Miller (2022) highlighted the advantages of office-based procedures utilizing wide awake local anesthesia (WALANT). Patients in the office reported heightened enjoyment, reduced anxiety, and an overall more positive experience compared to those in the OR. Exploring patient satisfaction in relation to anesthesia and surgical settings, Moscato's study (2021) illuminated the superiority of office-based CTR surgeries with WALANT over hospital-based procedures with regional anesthesia and sedation. This was underscored by consistent correlations between WALANT anesthesia and enhanced patient satisfaction across settings. Regarding medical complications, Randall (2021) revealed comparable safety profiles for office-based procedure rooms (PR) and OR settings. Notably, no substantial differences were found in major medical, surgical site, or iatrogenic complications between office and OR environments, underscoring the safety of CTR procedures regardless of the chosen setting.

Lastly, Stephens' study (2021) evaluated long-term outcomes after open CTR procedures. The transition from OR to PR in 2014 did not yield discernible discrepancies in patient demographics or postoperative outcomes measured using the Boston Carpal Tunnel Questionnaire (BCTQ), highlighting the enduring clinical effectiveness of CTR procedures across various procedural environments.

Benefits/Harms of Implementation

The benefits of surgical release in the office as compared to the operating room include potential time and cost savings for patients and hospital systems. There are also potential improvements in the patient experience with office based carpal tunnel release. Notably, patients eligible for office-based procedures should be appropriately chosen and willing to undergo surgical release awake with limited anesthesia.

Future Research

Future research should include randomized controlled trials of office vs OR based carpal tunnel release and cost effectiveness analyses of moving cases from the OR to the office.

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View data summaries via the CPG eAppendix 2

SURGICAL DRAPING

In the absence of reliable evidence, it is the opinion of the workgroup that limited draping is an option for carpal tunnel release.

Quality of Evidence: Consensus
Strength of Option: Consensus ★☆☆☆

Description: Evidence there is no supporting evidence, or limited level evidence was downgraded due to major concerns addressed in the EtD framework. In the absence of reliable evidence, the guideline work group is making a recommendation based on their clinical opinion.

Rationale
There are no randomized trials of draping options or field sterility relevant to this question. Multiple case series of WALANT surgeries, including carpal tunnel release, have shown low infection rates using field sterility. Given the well-documented cost savings of in-office carpal tunnel release using field sterility and the low reported infection rates for carpal tunnel release in general, it is our opinion that field sterility should be considered adequate for performance of carpal tunnel release surgery.

Benefits/Harms of Implementation
Given the low risk of infection in CTR overall, the harms are minimal. Benefits apply largely to efficiency and cost of in-office or surgical suite CTR surgery where full operative draping may not be feasible.

Cost Effectiveness/Resource Utilization
Field sterility or minimal draping is less expensive than full operative draping and contributes to the cost-effectiveness of CTR.

Acceptability
Well accepted approach in the literature in multiple health system settings.

Feasibility
No feasibility issues are expected as this approach minimizes the use of potentially unnecessary draping.

Future Research
Randomized controlled trials of field sterility in hand surgery are lacking and would strengthen the evidence against their use.

ANTICOAGULATION

Limited evidence suggests anticoagulation medication may be safely continued for carpal tunnel release.

Quality of Evidence: Low

Strength of Option: Limited ★★☆☆

Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale

Two low quality studies provide limited evidence suggesting that anticoagulation medication may be safely continued for carpal tunnel release. Kaltenborn (2019) utilized propensity score matching to evaluate the association of bleeding complications with acetylsalicylic acid use in patients undergoing carpal tunnel release and demonstrated no difference in bleeding outcomes between the acetylsalicylic acid cohort and the control cohort. Brunetti (2013) similarly demonstrated no difference in complications between cohorts undergoing carpal tunnel release taking acetylsalicylic acid and those not taking acetylsalicylic acid. Although not included in the guideline given the lack of results specific to carpal tunnel syndrome, a single-center, prospective cohort trial (Bogunovic 2015) evaluated the impact of uninterrupted Warfarin use on hand and wrist surgery. When case matched to those not prescribed Warfarin, those prescribed Warfarin (with an INR<3.5) demonstrated an infrequent risk of bleeding complications requiring reoperation.

Benefits/Harms of Implementation

The benefits and harms of continuing anticoagulation vary based upon the indication for the specific anticoagulation. From a surgical perspective, the harm in continuing anticoagulation may include complications related to bleeding, however this has not been definitively demonstrated in the literature.

Cost Effectiveness/Resource Utilization

Continuation of anticoagulation medication may prevent unnecessary visits to a patient's cardiologist and/or medical team to inquire and/or obtain counseling related to pausing or bridging medications.

Acceptability

Use of anticoagulants is accepted practice but may vary based upon type of anticoagulation, patient factors, and surgeon preference.

Feasibility

No issues related to feasibility beyond the anticipated discussion on risks of bleeding/hematoma when continuing on anticoagulation medication.

Future Research

Future research should be conducted to explore various types of anticoagulation and to increase the quality of evidence.

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View data summaries via the CPG eAppendix 2

PROPHYLACTIC PERIOPERATIVE ANTIBIOTICS

Limited evidence suggests perioperative prophylactic antibiotics are not indicated for the prevention of surgical site infection following carpal tunnel release.

Quality of Evidence: Low

Strength of Option: Limited ★★☆☆

Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale

Four low quality studies demonstrate limited evidence suggesting that perioperative prophylactic antibiotics are not indicated for the prevention of surgical site infection following carpal tunnel release. Multiple retrospective reviews have demonstrated that the use of prophylactic antibiotics for carpal tunnel release does not decrease the rate of infection, even in patients with diabetes (Harness 2010, Mehta 2022, Tosti 2012, Vasconcelos 2017). A claims database study evaluating the effectiveness of perioperative antibiotics for common soft tissue hand procedures that controlled for several patient demographic factors through propensity score matching demonstrated no difference in infection rates between cohorts with and without perioperative prophylactic antibiotics (Li, 2018). Notably, this study, despite including over 60,000 patients undergoing carpal tunnel release (>50% of included patients) was not included in the evidence as the infection rate was not detailed by condition.

Benefits/Harms of Implementation

The benefit of perioperative prophylactic antibiotics is the prevention of surgical site infection; however, this has not been demonstrated in the literature. The harm of perioperative prophylactic antibiotics includes risks related to the side effects of antibiotics (allergic reactions, development of drug-resistant organisms, and Clostridium difficile infection) without the proven benefit of reducing infections.

Cost Effectiveness/Resource Utilization

There are costs associated and resources utilized in the delivery of perioperative antibiotics and the treatment of downstream adverse effects.

Acceptability

It is accepted practice to limit the overuse of antibiotics although not strictly practiced by all surgeons due to other guidelines for major surgery that support the routine administration of preoperative antibiotics (e.g., total joint arthroplasty).

Feasibility

There are no feasibility issues with the implementation of this recommendation as it suggests limited unnecessary care.

Future Research

Future research should address the strength of recommendation through more condition-specific analyses for the use of preoperative antibiotics.

PREOPERATIVE TESTING

In the absence of sufficient evidence specific to carpal tunnel, it is the opinion of the workgroup that routine pre-operative testing (e.g., labs, CXR, EKG) is not indicated.

Quality of Evidence: Very Low
Strength of Option: Consensus ★☆☆☆

Description: Evidence there is no supporting evidence, or limited level evidence was downgraded due to major concerns addressed in the EtD framework. In the absence of reliable evidence, the guideline work group is making a recommendation based on their clinical opinion.

Rationale

There are no studies evaluating the utilization of pre-operative testing (e.g., labs, CXR, EKG) for carpal tunnel patients only. One study evaluated the use of pre-operative testing for patients with common hand conditions (including carpal tunnel) and demonstrated increased generation of downstream tests, procedures, and costs. Studies outside of hand surgery consistently demonstrate that pre-operative testing for healthy patients undergoing minor procedures leads to delays in care, unnecessary downstream testing and care, and added costs.

Benefits/Harms of Implementation

The potential benefits of this recommendation include decreasing the utilization of unnecessary testing that has the potential to lead to increased costs, delays in care, and downstream care cascades. The potential harm is missing a critical test result that may impact care or the patient's health. In healthy patients, this risk and thus potential harm is low. As such, the working group recommends that peri-operative testing not be performed routinely on healthy patients before carpal tunnel release and may be utilized on a case-by-case basis for non-healthy patients when it may impact their anesthetic type or peri-operative care.

View background material via the CPG eAppendix 1
View data summaries via the CPG eAppendix 2

ADJUNCTIVE TESTING

In the absence of reliable evidence, it is the opinion of the workgroup that, when multiple risk factors for amyloidosis are present, pathological analysis of tenosynovium may be performed.

Quality of Evidence: Consensus
Strength of Option: Consensus ★☆☆☆

Description: Evidence there is no supporting evidence, or limited level evidence was downgraded due to major concerns addressed in the EtD framework. In the absence of reliable evidence, the guideline work group is making a recommendation based on their clinical opinion.

Rationale

Amyloidosis has various clinical manifestations that can include cardiac dysfunction. Carpal tunnel is often one of the earliest clinical manifestations of amyloidosis (Nakagawa 2016). A recent cross-sectional study of patients with carpal tunnel syndrome undergoing carpal tunnel release showed that 10.2% exhibited amyloid deposits on tenosynovial biopsy, leading 4% to disease-modifying treatment. Although the diagnosis of amyloidosis is rare, given the lack of high-quality evidence to guide the decision to perform pathological analysis of tenosynovium, it is the opinion of the workgroup that this decision should be guided by patient preference and risk factors (Sood 2021).

Benefits/Harms of Implementation

The benefits of tenosynovial analysis include the possible detection and possible treatment of amyloidosis. The harms include the downstream care cascade that may result from a positive biopsy (e.g., lab testing, echocardiograms) that may be negative.

Cost Effectiveness/Resource Utilization

There are costs associated and resources utilized in the pathological analysis of tenosynovium. There are also downstream care cascades that may result from a positive sampling.

Acceptability

Accepted practice but may vary based upon risk factors and patient preference.

Feasibility

No feasibility issues beyond limitations in access to appropriate labs.

Future Research

Future research should involve the cost effectiveness of pathological analysis of tenosynovium based upon various risk profiles and the impact of downstream care cascades that may result from a positive sample.

POSTOPERATIVE PAIN: TRAMADOL

In the absence of reliable evidence, it is the opinion of the workgroup that Tramadol may be considered over other opioids for postoperative pain management.

Quality of Evidence: Very Low
Strength of Option: Consensus ★☆☆☆

Description: Evidence there is no supporting evidence, or limited level evidence was downgraded due to major concerns addressed in the EtD framework. In the absence of reliable evidence, the guideline work group is making a recommendation based on their clinical opinion.

Rationale

Miller et al. (2017) conducted a prospective cohort study to compare the effectiveness of opioids (i.e., hydrocodone, codeine, oxycodone) and tramadol. The results showed that patients that took opioids postoperatively had more medication-related side-effects and pill-consumption than those who took Tramadol. A multivariate regression analysis demonstrated that a tramadol prescription was an independent predictor of decreased total pill consumption. Moreover, patients with opioid prescriptions consumed only 28% of the filled prescription, compared to 36% consumption for tramadol. As this is the only article that met inclusion criteria and was low-quality due to its observational study design, the workgroup has provided the opinion consensus statement above.

Benefits/Harms of Implementation

The use of Tramadol over opioids for postoperative pain management has benefits as it avoids the many adverse effects of opioids (overdose and addiction).

Outcome Importance

Tramadol remains an option to help control postoperative pain.

Acceptability

Accepted treatment for pain in the postoperative state.

Future Research

There are no high-quality studies comparing the use of tramadol versus opioids in the control of postoperative pain after carpal tunnel release.

View background material via the CPG eAppendix 1
View data summaries via the CPG eAppendix 2

APPENDICES

Appendix I: References

Introduction References

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Appendix II: PICO Questions Used to Define Literature Search

PICO Questions

1. In patients with symptoms and signs concerning for CTS, how can CTS be diagnosed?
2. Do occupations that involve keyboard typing or clerical work lead to increased development to CTS?
3. In patients presenting with CTS, do the selected non-operative treatments lead to improved outcomes in comparison to control or each other?
4. For patients undergoing surgical release for the treatment of CTS, what release techniques lead to better outcomes?
5. For patients undergoing surgical treatment for CTS, do outcomes differ between various modes of anesthesia?
6. For patients undergoing surgical treatment for CTS, do outcomes differ between Sites of Service?
7. For patients undergoing surgical treatment for CTS, does limited surgical draping lead to similar infection rates in comparison to full draping?
8. For patients undergoing surgical treatment for CTS, do various post-operative outcomes significantly differ between those who undergo continuation of anticoagulation prior to surgery and those without continuation of anticoagulation prior to surgery?
9. For patients undergoing surgical treatment for CTS, are there significant differences in infection rates or other complications between those treated with prophylactic antibiotics and those not treated with prophylactic antibiotics peri-operatively.
10. For patients who have been treated with a surgical intervention for CTS, is therapy indicated? If so, who, when, what (certain treatments), and how long (duration of therapy)?
11. For patients who have been treated with a surgical intervention for CTS, does post-operative immobilization result in significant differences in symptom relief and functional improvement, as compared to those who undergo early mobilization or unrestricted movement.
12. For patients undergoing surgical treatment for CTS, does preoperative testing (e.g., lab, EKG) influence or affect outcomes?
13. For patients undergoing surgical treatment for CTS, should patients have testing for amyloid?
14. For patients undergoing surgery for CTS, what postoperative pain management modalities lead to better PROs, complication rates?

Inclusion Criteria

To be included in our systematic reviews (and hence, in this guideline) an article had to meet the following criteria:

- Study must be of a CTS injury or prevention thereof.
- Study must be published in or after 1966 for surgical treatment, rehabilitation, bracing, prevention and MRI.
- Study must be published in or after 1966 for x rays and non-operative treatment.
- Study must be published in or after 1966 for all others non specified.
- Study should have 10 or more patients per group.
- For surgical treatment a minimum of 3 months follow up duration.
- Antibiotic prophylaxis, anti-coagulations, mode of anesthesia: all follow-ups
- For non-operative treatment a minimum of 1 month.

Standard Criteria for all CPGs

- The article must be a full article report of a clinical study.
- Retrospective non-comparative case series, medical records review, meeting abstracts, historical
- articles, editorials, letters, and commentaries are excluded.
- Confounded studies (i.e., studies that give patients the treatment of interest AND another treatment)
- are excluded.
- Case series studies that have non-consecutive enrollment of patients are excluded.
- Controlled trials in which patients were not stochastically assigned to groups AND in which there was either a difference in patient characteristics or outcomes at baseline AND where the authors did not statistically adjust for these differences when analyzing the results are excluded.
- All studies of "Very Low" Quality of evidence are excluded.
- All studies evaluated as Level V will be excluded.
- Composite measures or outcomes are excluded even if they are patient oriented.
- Study must appear in a peer-reviewed publication.
- For any included study that uses "paper-and-pencil" outcome measures (e.g., SF-36), only those outcome measures that have been validated will be included.
- For any given follow-up time point in any included study, there must be ≥ 50% patient follow-up (if the follow-up is >50% but <80%, the study quality will be downgraded by one Level)
- Study must be of humans.
- Study must be published in English.
- Study results must be quantitatively presented.
- Study must not be an in vitro study.
- Study must not be a biomechanical study.
- Study must not have been performed on cadavers.

*We will only evaluate surrogate outcomes when no patient-oriented outcomes are available.

Best Available Evidence

When examining primary studies, we will analyze the best available evidence regardless of study design. We will first consider randomized controlled trials identified by the search strategy. In the absence of two or more RCTs, we will sequentially search for prospective controlled trials, prospective comparative studies, retrospective comparative studies, and prospective case-series studies. Only studies of the highest level of available evidence are included, assuming that there were 2 or more 100 studies of that higher level. For example, if there are two Level II studies that address the recommendation, Level III and IV studies are not included.

We will only evaluate surrogate outcomes when no patient-oriented outcomes are available. We did not include systematic reviews or meta-analyses compiled by others or guidelines developed by other organizations. These documents are developed using different inclusion criteria than those specified by the AAOS work group. Therefore, they may include studies that do not meet our inclusion criteria. We recalled these documents, if the abstract suggested they might provide an answer to one of our recommendations and searched their bibliographies for additional studies to supplement our systematic review *2022 literature search for all PICOs will be performed from last search date of 2017 CPG.

View background material via the CPG eAppendix 1
View data summaries via the CPG eAppendix 2

Appendix III: Literature Search Strategy

Database:	MEDLINE
Interface:	Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions ® 1946 to March 22, 2022
Date of Initial Search:	3/23/2022
Date of Updated Search:	11/17/2022
Search	Carpal Tunnel 2022
Line	**Search Strategy**
1	English.lg.
2	(exp Animals/ NOT Humans/) OR exp Cadaver/ OR cadaver*.ti,ab. OR in-vitro.ti. OR ((comment OR editorial OR letter OR historical article) NOT clinical trial).pt. OR address.pt. OR news.pt. OR newspaper article.pt. OR pmcbook.af. OR case reports.pt. OR (case report? OR abstracts OR editorial OR reply OR comment? OR commentary OR letter).ti. OR (animal* OR dog OR dogs OR sheepdog OR canine OR cats OR feline OR horse* OR equine OR donkey* OR mice OR murin?e OR woodmouse OR rat OR rats OR cottonrat* OR rodent* OR hamster* OR squirrel* OR chipmunk* OR otter* OR weasel* OR badger* OR beaver* OR llama* OR alpaca* OR rabbit* OR hare OR hares OR sheep OR ovine OR lamb* OR goat* OR porcine OR swine* OR pig OR pigs OR piglet* OR boar OR boars OR hog OR hogs OR cow OR cows OR cattle* OR bull OR bulls OR bovine OR bison* OR buffalo* OR monkey* OR ape OR apes OR baboon* OR gibbon* OR bonobo* OR gorilla* OR lemur* OR chimp* OR orangutan* OR macaque* OR marmoset* OR primate* OR bear OR bears OR avian OR bird* OR hen OR hens OR duck? OR goose OR geese OR fowl? OR turkey* OR deer OR doe OR reindeer OR dolphin OR (fish* NOT fisher*) OR pisces OR trout* OR zebrafish* OR catfish* OR goldfish* OR seahorse* OR shark* OR salmon* OR whitefish* OR reptil* OR snake* OR lizard* OR alligator* OR crocodile* OR turtle* OR amphibian* OR frog* OR toad* OR eel? OR salamander* OR veterinar*).ti.
3	1 NOT 2
4	limit 3 to yr=2015-Current
5	Carpal-Tunnel-Syndrome/ OR ((carpal AND tunnel) OR ((median ADJ6 nerve?) AND (compression OR entrapment OR neuropath*)) OR (((compression OR entrapment OR median OR peripheral) AND neuropath*) AND (carpal OR wrist?))).ti,ab.
6	4 AND 5
7	Extracorporeal-Shockwave-Therapy/ OR Ultrasonic-Therapy/ OR (shockwave OR shock-wave OR ((ultraso* OR US) ADJ5 (therap* OR puls*)) OR hydrodissect* OR Graston).ti,ab. OR exp Stem-Cell-Transplantation/ OR exp Stem-Cells/ OR (stem-cell? OR autologous).ti,ab.
8	exp *Health-Facilities/ OR Ambulatory-Surgical-Procedures/ OR (clinic? OR (hospital AND cost)).ti. OR ((surgical OR surgery OR operat* OR clinic OR outpatient* OR inpatient* OR procedur* OR office) ADJ (room* OR setting* OR center* OR department* OR theatre*)).ti,ab.
9	Surgical-Drapes/ OR drap*.ti,ab.
10	((Preoperative-Care/ OR ((before OR pre?) ADJ6 (surg* OR procedur* OR operat* OR postoperative* OR release OR decompress*)).ti,ab.) AND (test* OR lab? OR laboratory OR evaluat* OR screen* OR study OR studies OR X-ray? OR assess* OR examination).ti,ab.) OR ((preoperative* OR pre-operative* OR presurg*) ADJ6 (test* OR lab? OR laboratory OR evaluat* OR screen* OR study OR studies OR X-ray? OR assess* OR examination)).ti,ab.
11	exp Amyloidosis/ OR (amyloid* OR TTR).ti,ab.
12	Pain-Postoperative/ OR Postoperative-Care/ OR exp Postoperative-Period/ OR (postoperative* OR post-operative* OR postsurg* OR post-surg* OR ((following OR after OR post) ADJ5 (surg* OR procedur* OR operat* OR release OR decompress*))).ti,ab.
13	Anesthesia/ OR exp Anesthesia-Conduction/ OR exp Anesthesia-General/ OR exp Anesthetics/ OR (an?esthesia OR an?esthetic? OR analgesi*).ti,ab. OR (lidocaine OR ropivacaine OR bupivacaine OR lignocaine).ti,ab.
14	Pain-Management/ OR (((multimodal* OR multi-modal*) AND (pain OR therapy)) OR (pain ADJ3 manag*)).ti,ab.
15	Acetaminophen/ OR (acetaminophen OR paracetamol OR Tylenol OR propacetamol).ti,ab.
16	exp Narcotics/ OR Tramadol/ OR (narcotic* OR opioid* OR opiate* OR papaver* OR oxycodone OR Oxycontin OR Oxy-ER OR Oxy-CRF OR OxyIR OR Oxy-IR OR Percodan OR Percocet OR Roxicet OR hydrocodone OR dihydrocodeinone OR Vicodin OR Vicoprofen OR Norco OR Lortab OR Lorcet OR oxymorphone OR Opana OR morphine OR Kadian OR Avinza OR MS Contin OR Duramorph OR Roxanol OR codeine OR fentanyl OR Duragesic OR Actiq OR Sublimaze OR hydromorphone OR Dilaudid OR meperidine OR Demerol OR tramadol OR Ultram OR buprenorphine OR propoxyphene OR Darvocet OR Omnopon OR methadone OR Dolophine OR Methadose OR suboxone OR nalbuphine OR propoxyphene OR pentazocine).ti,ab.
17	Pregabalin/ OR Gabapentin/ OR (gabapentin* OR Neurontin OR Gralise OR Horizant OR pregabalin OR Lyrica).ti,ab.

18	exp Anti-Inflammatory Agents, Non-Steroidal/ OR (NSAID* OR non-steroidal OR nonsteroidal OR meloxicam OR Mobic OR naproxen OR Aleve OR ibuprofen OR Advil OR flurbiprofen OR ketorolac OR Toradol OR COX-2-inhibitor* OR COX2-inhibitor* OR celecoxib OR Celebrex OR diclofenac OR misoprostol OR sulindac OR ketoprofen OR tolmetin OR etodolac OR fenoprofen OR piroxicam OR indomethacin OR nabumetone OR aspirin).ti,ab.
19	exp Adrenal-Cortex-Hormones/ OR (corticosteroid* OR (steroid* NOT (non-steroid*)) OR corticoid* OR prednisone OR prednisolone OR methylprednisolone OR triamcinolone OR dexamethasone OR glucocorticoid*).tw.
20	6 OR (3 AND 5 AND (7 OR 8 OR 9 OR 10 OR 11 OR (12 AND (13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19))))

View background material via the CPG eAppendix 1
View data summaries via the CPG eAppendix 2

Database:	Embase
Interface:	Elsevier
Date of Initial Search:	3/23/2022
Date of Updated Search	11/17/2022
Search	Carpal Tunnel 2022
Query #	**Search**
1	[english]/lim
2	abstract-report/de OR book/de OR editorial/de OR editorial:it OR note/de OR note:it OR letter/de OR letter:it OR case-study/de OR case-report/de OR chapter:it OR conference-paper/exp OR conference-paper:it OR conference-abstract:it OR conference-review:it OR (abstracts OR editorial OR reply OR comment$ OR commentary OR letter):ti OR cadaver/de OR in-vitro-study/exp OR cadaver*:ti,ab OR in-vitro:ti OR animal-experiment/exp OR (animal* OR dog OR dogs OR sheepdog OR canine OR cats OR feline OR horse* OR equine OR donkey* OR mice OR murin$e OR woodmouse OR rat OR rats OR cottonrat* OR rodent* OR hamster* OR squirrel* OR chipmunk* OR otter* OR weasel* OR badger* OR beaver* OR llama* OR alpaca* OR rabbit* OR hare OR hares OR sheep OR ovine OR lamb* OR goat* OR porcine OR swine* OR pig OR pigs OR piglet* OR boar OR boars OR hog OR hogs OR cow OR cows OR cattle* OR bull OR bulls OR bovine OR bison* OR buffalo* OR monkey* OR ape OR apes OR baboon* OR gibbon* OR bonobo* OR gorilla* OR lemur* OR chimp* OR orangutan* OR macaque* OR marmoset* OR primate* OR bear OR bears OR avian OR bird* OR hen OR hens OR duck$ OR goose OR geese OR fowl$ OR turkey* OR deer OR doe OR reindeer OR dolphin OR (fish* NOT fisher*) OR pisces OR trout* OR zebrafish* OR catfish* OR goldfish* OR seahorse* OR shark* OR salmon* OR whitefish* OR reptil* OR snake* OR lizard* OR alligator* OR crocodile* OR turtle* OR amphibian* OR frog* OR toad* OR eel$ OR salamander* OR veterinar*):ti
3	#1 NOT #2 AND [2015-3000]/py
4	carpal-tunnel-syndrome/de OR ((carpal AND tunnel) OR ((median ADJ6 nerve$) AND (compression OR entrapment OR neuropath*)) OR (((compression OR entrapment OR median OR peripheral) AND neuropath*) AND (carpal OR wrist?))):ti,ab
5	#3 AND #4
6	((#1 AND #4) NOT #2)
7	shock-wave-therapy/de OR extracorporeal-shock-wave-lithotripsy/de OR ultrasound-therapy/exp OR (shockwave OR shock-wave OR ((ultraso* OR US) NEAR/5 (therap* OR puls*)) OR hydrodissect* OR Graston):ti,ab OR stem-cell-transplantation/exp OR stem-cell/exp OR (stem-cell* OR autologous):ti,ab
8	health-care-facility/exp/mj OR (clinic$ OR (hospital AND cost)):ti OR ((surgical OR surgery OR operat* OR clinic OR outpatient* OR inpatient* OR procedur* OR office) NEXT/1 (room* OR setting* OR center* OR department* OR theatre*)):ti,ab
9	surgical-drape/exp OR drap*:ti,ab
10	((preoperative-care/de OR ((before OR pre$) NEXT/6 (surg* OR procedur* OR operat* OR postoperative* OR release OR decompress*)):ti,ab) AND (test* OR lab$ OR laboratory OR evaluat* OR screen* OR study OR studies OR X-ray* OR assess* OR examination):ti,ab) OR ((preoperative* OR pre-operative* OR presurg*) NEAR/6 (test* OR lab? OR laboratory OR evaluat* OR screen* OR study OR studies OR X-ray* OR assess* OR examination)):ti,ab
11	amyloidosis/exp OR (amyloid* OR TTR):ti,ab
12	postoperative-pain/de OR postoperative-period/exp OR (postoperative* OR post-operative* OR postsurg* OR post-surg* OR ((following OR after OR post) NEXT/5 (surg* OR procedur* OR operat* OR release OR decompress*))):ti,ab
13	anesthesia/de OR general-anesthesia/exp OR regional-anesthesia/exp OR local-anesthesia/exp OR anesthetic-agent/exp OR local-anesthetic-agent/exp OR analgesia/exp OR analgesic-agent/exp OR (an$esthesia OR an$esthetic$ OR analgesi*):ti,ab OR (lidocaine OR ropivacaine OR bupivacaine OR lignocaine):ti,ab
14	(((multimodal* OR multi-modal*) AND (pain OR therapy)) OR (pain ADJ3 manag*)):ti,ab
15	paracetamol/exp OR propacetamol/exp OR (acetaminophen OR paracetamol OR propacetamol OR tylenol):ti,ab

16	narcotic-agent/exp OR narcotic-analgesic-agent/exp OR (narcotic* OR opioid* OR opiate* OR papaver* OR oxycodone OR Oxycontin OR Oxy-ER OR Oxy-CRF OR OxyIR OR Oxy-IR OR Percodan OR Percocet OR Roxicet OR hydrocodone OR dihydrocodeinone OR Vicodin OR Vicoprofen OR Norco OR Lortab OR Lorcet OR oxymorphone OR Opana OR morphine OR Kadian OR Avinza OR MS-Contin OR Duramorph OR Roxanol OR codeine OR fentanyl OR Duragesic OR Actiq OR Sublimaze OR hydromorphone OR Dilaudid OR meperidine OR Demerol OR tramadol OR Ultram OR buprenorphine OR propoxyphene OR Darvocet OR Omnopon OR methadone OR Dolophine OR Methadose OR suboxone OR nalbuphine OR propoxyphene OR pentazocine):ti,ab
17	pregabalin/exp OR gabapentinoid/exp OR gabapentin/exp OR (pregabalin OR gabapentin* OR Lyrica OR Neurontin OR Gralise OR Horizant):ti,ab
18	nonsteroid-antiinflammatory-agent/exp OR cyclooxygenase-2-inhibitor/exp OR (NSAID* OR non-steroidal OR nonsteroidal OR meloxicam OR mobic OR naproxen OR aleve OR ibuprofen OR advil OR flurbiprofen OR ketorolac OR toradol OR cox-2-inhibitor* OR cox2-inhibitor* OR celecoxib OR celebrex OR diclofenac OR misoprostol OR sulindac OR ketoprofen OR tolmetin OR fenoprofen OR piroxicam OR etodolac OR indomethacin OR nabumetone OR aspirin):ti,ab
19	corticosteroid/exp OR (corticosteroid* OR (steroid* NOT (non-steroid*)) OR corticoid* OR prednisone OR prednisolone OR methylprednisolone OR triamcinolone OR dexamethasone OR glucocorticoid*):ti,ab
20	#5 OR (#6 AND (#7 OR #8 OR #9 OR #10 OR #11 OR (#12 AND (#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19))))

Database:	Cochrane Central Register of Controlled Trials (CENTRAL)
Interface:	Wiley (https://www.cochranelibrary.com/central)
Date of Initial Search:	3/23/2022
Date of Updated Search:	11/17/2022
Search	Carpal Tunnel 2022
Query #	**Search**
1	((carpal AND tunnel) OR ((median NEAR/6 nerve$) AND (compression OR entrapment OR neuropath*)) OR (((compression OR entrapment OR median OR peripheral) AND neuropath*) AND (carpal OR wrist?))):ti,ab
2	"conference abstract":pt OR (abstracts OR editorial OR reply OR comment? OR commentary OR letter OR biomechanic*):ti OR cadaver*:ti,ab OR "in vitro":ti OR (animal* OR dog OR dogs OR sheepdog OR canine OR cats OR feline OR horse* OR equine OR donkey* OR mice OR murin?e OR woodmouse OR rat OR rats OR cottonrat* OR rodent* OR hamster* OR squirrel* OR chipmunk* OR otter* OR weasel* OR badger* OR beaver* OR llama* OR alpaca* OR rabbit* OR hare OR hares OR sheep OR ovine OR lamb* OR goat* OR porcine OR **swine*** OR pig OR pigs OR piglet* OR boar OR boars OR hog OR hogs OR cow OR cows OR cattle* OR bull OR bulls OR bovine OR bison* OR buffalo* OR monkey* OR ape OR apes OR baboon* OR gibbon* OR bonobo* OR gorilla* OR lemur* OR chimp* OR orangutan* OR macaque* OR marmoset* OR primate* OR bear OR bears OR **avian OR bird*** OR hen OR hens OR duck? OR goose OR geese OR fowl? OR turkey* OR deer OR doe OR reindeer OR dolphin OR (fish* NOT fisher*) OR pisces OR trout* OR zebrafish* OR catfish* OR goldfish* OR seahorse* OR shark* OR salmon* OR whitefish* OR reptil* OR snake* OR lizard* OR alligator* OR crocodile* OR turtle* OR amphibian* OR frog* OR toad* OR eel? OR salamander* OR veterinar*):ti
3	#1 NOT #2 *with Publication Year from 2015 to 2022, in Trials*
4	#1 NOT #2 *with Cochrane Library publication date from Feb 2015 to Mar 2022, in Cochrane Reviews*
5	#3 OR #4
6	(shockwave OR shock-wave OR ((ultraso* OR US) NEAR/5 (therap* OR puls*)) OR hydrodissect* OR Graston):ti,ab OR (stem-cell$ OR autologous):ti,ab
7	(clinic? OR (hospital AND cost)):ti OR ((surgical OR surgery OR operat* OR clinic OR outpatient* OR inpatient* OR procedur* OR office) NEXT/1 (room* OR setting* OR center* OR department* OR theatre*)):ti,ab
8	drap*:ti,ab
9	(((before OR pre?) NEXT/6 (surg* OR procedur* OR operat* OR postoperative* OR release OR decompress*)):ti,ab AND (test* OR lab? OR laboratory OR evaluat* OR screen* OR study OR studies OR X-ray? OR assess* OR examination):ti,ab) OR ((preoperative* OR pre-operative* OR presurg*) NEAR/6 (test* OR lab? OR laboratory OR evaluat* OR screen* OR study OR studies OR X-ray? OR assess* OR examination)):ti,ab
10	(amyloid* OR TTR):ti,ab
11	(postoperative* OR post-operative* OR postsurg* OR post-surg* OR ((following OR after OR post) NEXT/5 (surg* OR procedur* OR operat* OR release OR decompress*))):ti,ab
12	(an$esthesia OR an$esthetic$ OR analgesi*):ti,ab OR (lidocaine OR ropivacaine OR bupivacaine OR lignocaine):ti,ab
13	(((multimodal* OR multi-modal*) AND (pain OR therapy)) OR (pain NEAR/3 manag*)):ti,ab
14	(acetaminophen OR paracetamol OR propacetamol OR tylenol):ti,ab
15	(narcotic* OR opioid* OR opiate* OR papaver* OR oxycodone OR Oxycontin OR Oxy-ER OR Oxy-CRF OR OxyIR OR Oxy-IR OR Percodan OR Percocet OR Roxicet OR hydrocodone OR dihydrocodeinone OR Vicodin OR Vicoprofen OR Norco OR Lortab OR Lorcet OR oxymorphone OR Opana OR morphine OR Kadian OR Avinza OR MS-Contin OR Duramorph OR Roxanol OR codeine OR fentanyl OR Duragesic OR Actiq OR Sublimaze OR hydromorphone OR Dilaudid OR meperidine OR Demerol OR tramadol OR Ultram OR buprenorphine OR propoxyphene OR Darvocet OR Omnopon OR methadone OR Dolophine OR Methadose OR suboxone OR nalbuphine OR propoxyphene OR pentazocine):ti,ab
16	(pregabalin OR gabapentin* OR Lyrica OR Neurontin OR Gralise OR Horizant):ti,ab

17	(NSAID* OR non-steroidal OR nonsteroidal OR meloxicam OR mobic OR naproxen OR aleve OR ibuprofen OR advil OR flurbiprofen OR ketorolac OR toradol OR ((cox-2 OR cox2) NEXT/1 inhibitor*) OR celecoxib OR celebrex OR diclofenac OR misoprostol OR sulindac OR ketoprofen OR tolmetin OR fenoprofen OR piroxicam OR etodolac OR indomethacin OR nabumetone OR aspirin):ti,ab
18	(corticosteroid* OR (steroid* NOT (non-steroid*)) OR corticoid* OR adrenal-cortex-hormone* OR prednisone OR methylprednisolone OR triamcinolone OR glucocorticoid* OR cortisone OR hydrocortisone OR dexamethasone OR prednisolone OR betamethasone OR budesonide OR mineralocorticoid*):ti,ab
19	#1 NOT #2
20	#5 OR (#19 AND (#6 OR #7 OR #8 OR #9 OR #10 OR (#11 AND (#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18))))

View background material via the CPG eAppendix 1
View data summaries via the CPG eAppendix 2

Appendix IV: Guideline Development Group Disclosures

Prior to the development of this clinical practice guideline, clinical practice guideline development group members disclose conflicts of interest (COI). They disclose COIs in writing to the American Academy of Orthopaedic Surgeons via a private on-line reporting database and also verbally at the recommendation approval meeting.

Robin Neil Kamal, MD, FAAOS
AAOS: Board or committee member ($0) EBQV(Self)
Acumed, LLC: Paid consultant ($30,000) general consulting(Self)
American Society for Surgery of the Hand: Board or committee member ($0) Quality Metrics Committee (Self)

Lauren Michelle Shapiro, MD
(This individual reported nothing to disclose)

Noah Matthew Raizman, MD, FAAOS
(This individual reported nothing to disclose)

Jason Strelzow, MD, FAAOS
Acumed, LLC: Paid presenter or speaker ($2,000) Number of Presentations: 2 Acumed(Self)
Acumed, LLC: Paid consultant ($9,000) Consulting Services(Self)
American Society for Surgery of the Hand: Board or committee member ($0) N/A(Self)
BoneSupport: Paid presenter or speaker ($2,500) Number of Presentations: 2 N/A(Self)
BoneSupport: Paid consultant ($2,000) BoneSupport(Self)
Journal of Bone and Joint Surgery - American: Editorial or governing board ($0) JBJS Reviews(Self)
Journal of Hand Surgery - American: Editorial or governing board ($0) N/A(Self)
Orthopaedic Trauma Association: Board or committee member ($0) N/A(Self)
Stryker: Other financial or material support ($300) N/A(Self)

Mia Erickson, PT
American Physical Therapy Association: Board or committee member ($0) Board of Directors(Self)
SLACK Incorporated: Publishing royalties, financial or material support ($7,000) I have published 2 textbooks on physical therapy documentation for SLACK inc. and I am a consultant for a book series for the physical therapist assistant(Self)

Karen Chi-Lynn Chen, MD
(This individual reported nothing to disclose)

Jeff Steven Brault, DO
American Academy for Cerebral Palsy and Developmental Medicine: Board or committee member ($0) Wife on Board for this group (Family)

Douglas W Martin, MD
ACOEM Practice Guidelines: Editorial or governing board ($0) I serve on the Disability Evaluation Chapter Panel(Self)
American College of Occupational & Environmental Medicine: Board or committee member ($0) President Elect - will be President in May 2022(Self)
Interstate Postgraduate Medical Association: Board or committee member ($0) Vice Chair(Self)
Iowa Academy of Family Physicians: Board or committee member ($0) Board of Directors(Self)
ODG Treatment in Workers Compensation: Editorial or governing board ($0) I serve on the Editorial Advisory Board(Self)

Mohammad Kian Salajegheh, MD
(This individual reported nothing to disclose)

Nash H Naam, MD
American Association for Hand Surgery: Board or committee member ($0)
Journal of Hand Surgery - American: Editorial or governing board ($0)

View background material via the CPG eAppendix 1
View data summaries via the CPG eAppendix 2

2027 CPT Code Review Transcutaneous Neuromodulation

Plain Language Summary:

Nerve stimulation treatment (transcutaneous neuromodulation) uses low-level electrical signals applied to a painful area to reduce the brain's pain response.

Because this therapy has not been well studied, HERC staff do not recommend adding coverage.

This Issue summary appeared on the March 19 meeting materials and is unchanged.

Staff Analysis Summary:

Significant proposed changes or discussion items:

1. Do not add coverage for transcutaneous neuromodulation

Code:

CPT *97XX5 transcutaneous neuromodulation

Note: Since the advance meeting materials were published, the AMA withdrew this code from publication. Therefore staff recommend no change to the Prioritized List.

Similar codes:

CPT *0278T (Transcutaneous electrical modulation pain reprocessing (e.g., scrambler therapy), each treatment session (includes placement of electrodes)) is on Excluded Services Guideline E2. The last 2 reviews for procedures in that E2 entry were for TENS and cranial electrical stimulation and did not include Scrambler therapy.

Background:

Scrambler Therapy/Calmare device is also known as transcutaneous electrical modulation pain reprocessing (TEMPR). Scrambler therapy is a noninvasive pain modifying technique that utilizes transcutaneous electrical stimulation of pain fibers with the intent of re-

organizing maladaptive signaling pathways. It is used to treat various types of chronic pain. Treatment is performed by applying electrodes corresponding to the dermatome on the skin just above and below the area of pain. The device provides electrical signals via the electrodes presenting non pain information to the painful area using continuously changing, variable, nonlinear waveforms. This is purported to modify how the brain senses pain with the aim of reducing the pain a patient experiences.

Previous HSC/HERC reviews:

The last review of this technology was in September 2017. A 2016 systematic review of Scrambler therapy was included in that review, which found possible benefit but called for larger randomized controlled trials to be conducted. The HERC staff summary read: "The evidence base regarding the benefits of transcutaneous electrical modulation pain reprocessing (i.e., scrambler therapy) as a treatment for pain from any etiology is extremely limited. Early, pilot studies with small numbers of patients treated for short periods of time are promising, but larger, well conducted, randomized trials are needed. There are no clinical practice guidelines that recommend scrambler therapy and major insurers are not covering this therapy. Based on the limited literature, scrambler therapy appears to be investigational". Based on this review, CPT *0278T was added to what is now Excluded Services Guideline E2.

Current Prioritized List/Coverage status:

EXCLUDED SERVICES GUIDELINE E2, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

The following Interventions are unproven, have no clinically important benefit or have harms that outweigh benefits and should be excluded from coverage

Procedure Code	Intervention Description	Rationale	Last Review
* 97014, 97032, 0278T, E0720, E0730, G0283	Transcutaneous electrical nerve stimulation (TENS), frequency specific microcurrent therapy, microcurrent electrical stimulation, and all similar therapies; Scrambler therapy; all similar transcutaneous electrical neurostimulation therapies	Insufficient evidence of effectiveness for chronic pain and all other indications	January, 2020 for TENS; October, 2021 for cranial electrical stimulation

Evidence:

1) **Jin 2022:** Efficacy of Scrambler Therapy (ST) for Management of Chronic Pain: A Meta-Analysis of Randomized Controlled Trials
    a. N=7 RCTs
        i. "The included trials have a small sample size and low methodological quality"
        ii. Control group: conventional medical therapy (2), TENS (1) or sham (4)
        iii. Pain conditions were chemotherapy-induced peripheral neuropathy (CIPN) in 4 trials, postsurgical neuropathic pain in 2 trials, post-herpetic neuralgia in 2 trials, pain due to spinal stenosis in 2 trials, cancer pain in one trial, and persistent nonspecific low back pain in one trial
        iv. The pain was assessed by using a VAS, NRS, BPI-short form (SF), NAS, and BPI-CIPN
    b. In the random-effects model meta-analysis of 7 RCTs, ST marginally decreased pain after the end of the treatment compared with the control group (SMD, −0.85; 95% CI, −1.66 to −0.03; I2 = 89.5%)
    c. No severe adverse events reported
    d. Authors conclusions: In summary, we found that ST is effective in reducing pain in the short term in adults with chronic pain. However, there are several important limitations to prove its efficacy due to the small sample size of the

included trials (10 to 80 study patients), low methodological quality, inappropriate methods, and use of sham procedure. Further large-scale trials with at least several hundreds of study patients are warranted to confirm our findings on the efficacy of the ST in the management of chronic pain.

2) **Karri 2022**: The Use of Scrambler Therapy in Treating Chronic Pain Syndromes: A Systematic Review
    a. N=21 studies
        i. N=8 RCTs, 10 prospective observational studies and 3 retrospective observational studies
        ii. Most studies included small study populations, with only six studies including >50 patients.
    b. Most studies defined treatment success as ≥50% reduction in average pain scores relative to preprocedural baseline, and many reported average pain reductions of up to 80% to 90%. The duration of follow-up for most studies ranged from ten to 14 days (the completion of a standard ST treatment protocol) to three months. Significant pain reduction was reported extensively in nearly all studies, but ST was found to be equivalent to sham therapy in two studies
    c. Unfortunately, long-term follow-up data are significantly lacking.
    d. No significant adverse effects
    e. Authors conclusions: ST is a safe intervention with significant potential benefit for analgesia and quality of life. The duration of analgesia for ST remains unclear and requires further study but may range for months since the last treatment. There is preliminary evidence that ST may decrease pain medication requirements (eg, opioids), and may potentially reduce nonpainful neuropathic symptoms, but more studies are necessary to confirm these findings
3) **Wang 2022**: Evaluating the safety, feasibility, and efficacy of non-invasive neuromodulation techniques in chemotherapy-induced peripheral neuropathy (CIPN): A systematic review
    a. Studies on Scrambler: 6 studies (2 RCTs and 4 single arm pretest-posttest studies)
    b. Overall severity of CIPN

i. A comparable effect between scrambler therapy and TENS or sham stimulation on the patient-reported overall severity of CIPN was identified in two RCTs (Loprinzi et al., 2020b; Smith et al., 2020). Similarly, it was shown in two RCTs (Tonezzer et al., 2017; Song et al., 2020), respectively, that TENS and low-frequency electrostimulation did not contribute to bringing about a greater improvement in patient-reported CIPN compared with a placebo or sham stimulation. However, the results were just the opposite in quasi-experimental studies, which suggested that scrambler therapy (Coyne et al., 2013) and TENS (Wong et al., 2016; Gewandter et al., 2019) can help to reduce the overall severity of CIPN.

c. Pain and symptoms
    i. In a crossover RCT (Loprinzi et al., 2020b; Childs et al., 2021), it was shown that there was no significant difference between scrambler therapy and TENS in the proportion of patients achieving a ≥50% reduction in pain scores. Smith et al. (2020), in their RCT, also found no statistically significant difference between scrambler therapy and sham stimulation in alleviating pain related to CIPN. In contrast, all four single-arm studies (Smith et al., 2010; Coyne et al., 2013; Pachman et al., 2015a; Lee et al., 2016) indicated that scrambler therapy can help to relieve the pain and sensory symptoms associated with CIPN
d. Quality of life
    i. A crossover RCT showed that in the initial phase (Loprinzi et al., 2020b), patients treated with scrambler therapy had a greater subjective impression of an improvement in their quality of life compared with patients treated with TENS, whereas no significant differences between the two groups were identified at the 8-week follow-up. In the crossover phase (Childs et al., 2021), it was also shown graphically that patients treated with scrambler therapy had a greater subjective impression of an improvement in their quality of life. Similarly, Pachman et al.'s (2015b) single-arm study graphically depicted a persistent subjective impression of an improvement in quality of life throughout the ten weeks of follow-up after scrambler

therapy, although no statistical analysis was conducted. In contrast, Smith et al.'s (2010) single-arm study showed that scrambler therapy failed to improve the quality of life of patients over a longer follow-up period of 12 weeks.

e. Author's conclusions: Scrambler therapy and TENS are of limited or no efficacy in the management of CIPN

Submitted literature:

None received to date

Expert guidelines:

1) **Loprinzi 2020**: Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: ASCO Guideline Update
    a. Outside the context of a clinical trial, no recommendations can be made on the use of the following interventions for the treatment of CIPN: • Scrambler therapy
        i. Note: While recent preliminary evidence suggests a potential for benefit from exercise, acupuncture, and scrambler therapy, larger sample-sized definitive studies are needed to confirm efficacy and clarify risks

Other payer policies:

1) Premara BCBS 2025: Transcutaneous electrical modulation pain reprocessing (TEMPR) (also called Scrambler therapy or Calmare pain therapy) is considered investigational for the treatment of cancer pain, chronic pain, neuropathic pain and all other indications (0278T)
2) Aetna 2025:
    a. The following durable medical equipment (DME) and supplies are considered experimental, investigational, or unproven because the effectiveness of these approaches for the specified indication(s) has not been established
        i. Scrambler Therapy/The Calmare Therapy Device (also known as transcutaneous electrical modulation pain reprocessing (TEMPR)) for the treatment of cancer pain, chronic pain, Dejerine-Roussy

syndrome, neuropathic pain associated with chemotherapy-induced peripheral neuropathy, post-mastectomy pain, and other indications

3) United HealthCare 2025: considers Scrambler therapy to be experimental
4) Providence Health Plan 2025
    a. Not medically necessary for any indication:
        i. Transcutaneous electrical modulation pain reprocessing (also known as scrambler therapy)
5) Connecticut Medicaid: considers 0278U to be experimental

Expert input:

None received to date

HERC staff summary:

Transcutaneous neuromodulation with systems like the Scrambler system has a limited evidence based consisting mainly of small poorly conducted studies. There are mixed findings on whether this therapy can reduce pain in the short term; no research exists on long term impacts. No expert group recommends this therapy and no surveyed payer is currently covering it.

Based on this review, HERC staff recommend continued non-coverage of transcutaneous neuromodulation.

HERC staff recommendation:

1) Update the entry in Excluded Services Guideline E2 as relating to transcutaneous neuromodulation as shown below

EXCLUDED SERVICES GUIDELINE E2, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

The following Interventions are unproven, have no clinically important benefit or have harms that outweigh benefits and should be excluded from coverage

Procedure Code	Intervention Description	Rationale	Last Review
* 97014, 97032, 0278T, E0720, E0730, G0283	Transcutaneous electrical nerve stimulation (TENS), frequency specific microcurrent therapy, microcurrent electrical stimulation, and all similar therapies; Scrambler therapy; all similar transcutaneous electrical neurostimulation therapies	Insufficient evidence of effectiveness for chronic pain and all other indications	January, 2020 for TENS; October, 2021 for cranial electrical stimulation March 2026 for Scrambler therapy/transcutaneous neuromodulation

Pain Physician 2022; 25:E931-E939 • ISSN 2150-1149

Meta-Analysis

Efficacy of Scrambler Therapy for Management of Chronic Pain: A Meta-Analysis of Randomized Controlled Trials

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Disclaimer: There was no external funding in the preparation of this manuscript.

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 01-21-2022
Revised manuscript received: 05-05-2022
Accepted for publication: 06-02-2022

Free full manuscript: www.painphysicianjournal.com

Background: Although several randomized controlled trials (RCTs) have reported the efficacy of scrambler therapy (ST) for the management of chronic pain, those findings remain inconsistent.

Objectives: This meta-analysis aimed to investigate the efficacy of ST for the management of chronic pain.

Study Design: A meta-analysis of RCTs.

Methods: We searched core databases including PubMed, EMBASE, and the Cochrane library for RCTs in October 2021. Standardized mean differences (SMDs) with 95% confidence intervals (CIs) for pain reduction were calculated using a random-effects model meta-analysis.

Results: Out of 348 studies, a total of 7 RCTs (n = 287 patients) that met the inclusion criteria were included in the final analysis. Overall, ST marginally decreased pain scores after the end of the treatment compared with the control group, with substantial heterogeneity (SMD, –0.85; 95% CI, –1.66 to –0.03; I^2 = 89.5%, n = 7). A subgroup meta-analysis found that the use of ST significantly reduced analgesic consumption compared to the control group (SMD, –0.54; 95% CI, –0.93 to –0.14; I^2 = 0.0%; n = 2). However, no significant efficacy was observed in the subgroup meta-analyses by methodological quality, type of diseases causing pain, and follow-up period.

Limitations: The included trials have a small sample size and low methodological quality.

Conclusions: ST seems to be effective in the management of patients with chronic pain. However, further, large RCTs are warranted to confirm our findings.

Key words: Scrambler therapy, Calmare therapy, chronic pain, meta-analysis, randomized controlled trials

Pain Physician 2022: 25:E931-E939

Chronic pain has emerged as a major health problem and has contributed to high health care costs and lost productivity (1-3). Some studies estimate that the prevalence of chronic pain is between 11% and 40% in the general population (4). Clinical trials and guidelines recommend a multimodal, interdisciplinary therapeutic approach that includes pharmacologic therapy, cognitive and behavioral modifications, rehabilitation therapy, and nonpharmacological interventions (5). Pharmacologic

therapy includes the use of nonsteroidal anti-inflammatory drugs (NSAIDs), antidepressants, anticonvulsants, musculoskeletal agents, opioids, or combinations of those medications (6). A mechanistic, reasonable approach to pharmacotherapy is an important component in the management of chronic pain (7). Opioids are commonly used for acute pain management. However, the evidence on the efficacy and risk-benefit profiles for the treatment of chronic pain is weak (8). The use of opioid drugs to treat pain is associated with serious adverse events such as sedation, respiratory depression, physical dependence, and addiction (9). Besides opioids, pharmacological agents involved in the treatment of chronic pain are associated with a risk of various systemic adverse events (10). Because of the substantial adverse events of the long-term multi-pharmacological therapies, there has been a growing interest in non-pharmacological approaches for sustained pain management (11).

Scrambler therapy (ST), which was introduced in 2003 by Giuseppe Marineo, is a noninvasive electrocutaneous stimulation therapy using 5 artificial neurons. It generates 16 different synthetic action potentials designed to convey "non-painful" information to the central nervous system (12,13). He hypothesized that ST works through the plasticity of the pain system under the control of information (12). In other words, the concept of ST is to modulate neuroplasticity to convert chronic pain signals into normal non-pain signals through scrambled electrical stimulation, not to suppress the noxious stimulation itself (12,14). Several clinical trials have been conducted to investigate the efficacy of ST in the treatment of chronic pain due to various diseases. In 2003, the inventor of ST introduced a small clinical trial investing its use in the management of chronic visceral cancer pain in 11 study patients (13). In this trial, all patients experienced a significant decrease in pain scores (13). Since then, various types of relatively small sample size studies such as randomized controlled trials (RCTs), prospective single-arm trials, clinical practice experiences, and retrospective studies have reported some beneficial effects of ST in various types of pain such as chemotherapy-induced peripheral neuropathy, chronic low back pain, post-herpetic neuralgia, and bone and visceral metastases (15,16). ST was approved by the US Food and Drug Administration (FDA) in 2009 for the symptomatic relief of acute and chronic pain, including acute post-surgical pain and post-traumatic pain, and has been widely used in clinical practice (17).

However, subsequent RCTs have reported inconsistent findings regarding the efficacy of ST in the management of pain (18-24). No meta-analysis has been published regarding the efficacy of the ST on chronic pain so far.

The current study aimed to evaluate the efficacy of ST for the management of chronic pain compared to the control groups such as placebos or other conventional treatments by using a meta-analysis of RCTs.

Methods

Scrambler Therapy

Theoretical Model

A well-known leading concept regarding the mechanism of pain perception and transmission is the gate control theory, which postulates a gate composed of excitatory and inhibitory synapses present in the dorsal horn of the spinal cord (25). It proposes that reinforcing input of A-beta fibers shuts the gate, thereby inhibiting transmission of nociceptive information that leads to pain perception (25). This theory serves as the scientific basis for the efficacy of transcutaneous electrical nerve stimulation (TENS) in pain reduction (26). Although TENS is widely used as an adjuvant to pharmacological or non-pharmacological pain management, the scientific data supporting its efficacy are still lacking and have not consistently demonstrated benefits, highlighting the need for new treatment options (27,28).

Figure 1 shows the theoretical model of ST. The principle of ST is based on Shannon's information theory, which is different from the gate control theory (12,29). Shannon's information theory proposes that "scrambled" artificial waveforms are assembled into dynamic strings of information (14,16,30) which are calibrated to synchronize surface receptors on C-fibers, converting endogenous pain information into synthetic "nonpain" information (12). Loss of a causal, linear relationship in the pain pathway may contribute to new, non-linear dynamical systems of chronic pain (12). This theoretical model provides a multidimensional understanding of chronic pain, making some phenomena that are difficult to explain with the gate control theory more intuitive and explainable (12).

Mechanism of Action

The functioning mechanism of ST is to control the neuroplasticity in chronic pain through informa-

tion control (12,16). It transmits coded information from painful nociceptors to "non-pain" signals by generating 256 types of dynamically assembled and modulated strings of information using 16 different synthetic action potentials (12,16). There are 4 main variables concerning the dynamically modifying algorithm that generates each new string: 1) 16 different synthetic action potentials, 2) packet frequency (43-52 Hz), 3) packet time duration (0.7-10 seconds), and 4) amplitude of modulation (18). The electrical stimulation intensity of ST ranges from 10 to 70 (18). The average amperage of ST does not exceed a maximum of 5.5 mA even at the highest "70" setting (18). Therefore, the average emission intensity is much lower than that of the conventional TENS (30-150mA) (12,18).

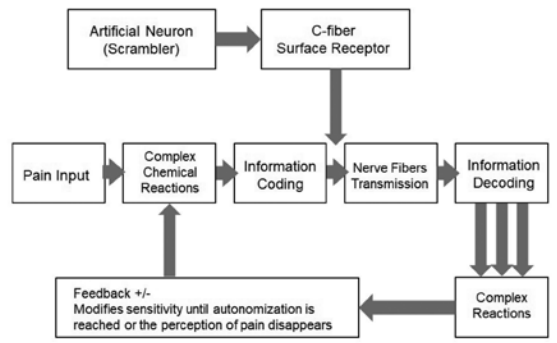

Fig. 1. *Theoretical model of Scrambler therapy. Adapted from Marineo G. Inside the Scrambler Therapy, a Noninvasive Treatment of Chronic Neuropathic and Cancer Pain (12).*

Fig. 2. *Device for Scrambler therapy. The first industrialized original equipment manufacturer version device for Scrambler therapy, Scrambler Therapy® MC-5A, also known as its commercial brand name "Calmare."*

Device

The first industrialized original equipment manufacturer (OEM) version marketed in the US is the Scrambler Therapy® MC-5A, also known as its commercial brand name "Calmare" (Fig. 2). The second OEM version is the Scrambler Therapy® Technology MC-5A (12,31). In 4 of the 7 articles (18-20,24), the first or second OEM version of ST was used, whereas the remaining 3 articles (21-23) did not clarify which specific device of the ST was used.

Eligibility Criteria

This meta-analysis was conducted based on the criteria of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (32,33). We included RCTs that met the following criteria: (1) Population - adult patients aged 18 years or older suffering from chronic pain lasting more than 3 months; (2) Intervention - ST using a standard Calmare device; (3) Comparisons - sham procedure, conventional medication, active comparator, or no treatment; (4) Outcome - pain assessment using a Numeric Rating Scale (NRS), a Visual Analog Scale (VAS), or a Brief Pain Inventory (BPI). If a study was duplicated, we selected the more comprehensive one.

Search Strategy

Two authors (YHJ and DHK) independently retrieved relevant studies from electronic databases (Cochrane Library, MEDLINE, EMBASE, CINAHL, and Scopus) in October 2021. The key words were: "Scrambler therapy" or "Calmare therapy." Because there were no Medical Subject Headings (MeSH) related to the following search terms, we used those free text words. The bibliographies of related articles were reviewed to identify additional publications in previous review articles and reference lists. There were no restrictions on the language of the publications.

Data Extraction and Quality Assessment

Two independent authors (YHJ and DHK) assessed the eligibility of studies, obtained data in a blinded manner, and assessed the methodological quality of the RCTs. If there were any discrepancies between the researchers, an agreement was reached through discussion and consultation with a third author (SKM). We extracted the name of the author, year of publication, sample size, the mean age of patients, disease type, outcome evaluation, follow-up interval, study type, and treatment type. We also investigated adverse event reports. The risk of bias was assessed based on the Cochrane risk of bias tool (34). Trials with a low risk of bias ≥ 5 items were considered as an overall low risk of bias study in this analysis.

Statistical Analysis

The primary endpoint was pain score after the treatment with ST. The time and frequency for the post-treatment pain assessments and the intervals between the baseline pain assessment and the post-treatment pain assessments are different across the studies. Thus, in the main analysis, we used the pain score for the post-treatment closest to the final treatment date in each study: prior to or immediately after the final treatment in 5 studies, a week after the final treatment in a study, and a month after the final treatment in a study. The secondary endpoints were analgesic consumption and adverse events.

In order to calculate a pooled standardized mean difference (SMD) with a corresponding 95% confidence interval (CI), we used an SMD with a 95% CI, which is calculated by subtracting the mean value in the control group from the mean value in the intervention group in each trial. Median (interquartile range or range) values were converted to mean (standard deviation) values. Because individual trials were performed in the different populations, we used a random-effects model meta-analysis based on the DerSimonian and Laird method (34,35). Study-wide heterogeneity was evaluated using Higgins I^2 to measure the overall variance (36). An I^2 value exceeding 50% was considered as substantial heterogeneity (36). The statistical analyses were performed using Stata/MP version 17.0 software package (StataCorp, College Station, TX).

Results

Study Selection

A flow chart of the selection process for this study is shown in Fig. 3. A total of 348 articles were identified

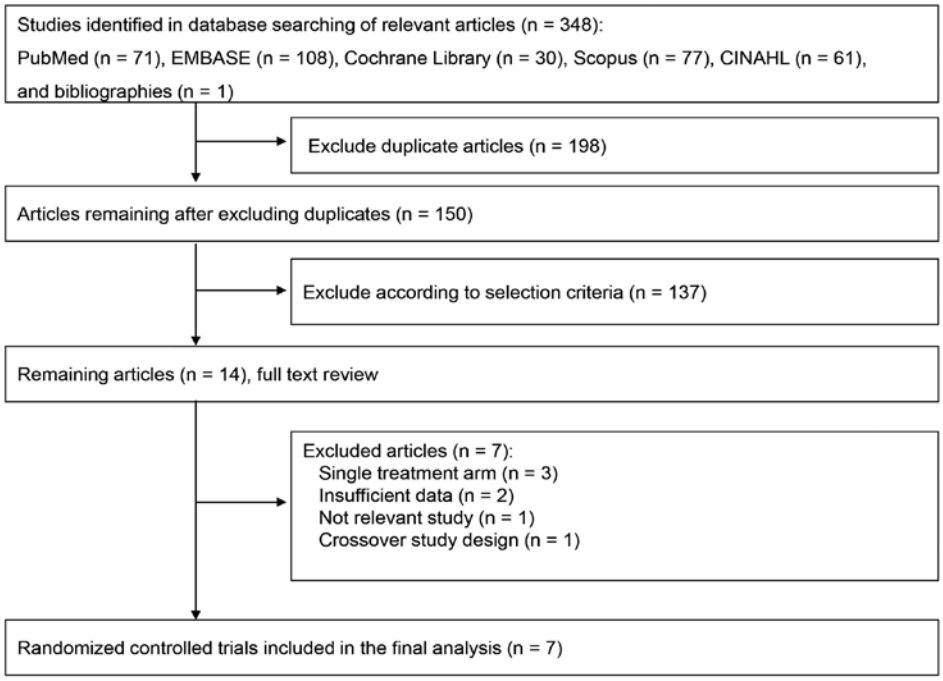

Fig. 3. *Flow diagram for identification of relevant studies.*

through electronic searches of 4 databases and manual searches of relevant bibliographies. After removing 198 duplicated articles, the 2 independent authors assessed the eligibility of all articles based on their titles and abstracts, and additional 137 articles that did not meet the predefined selection criteria were excluded. Fourteen full-text articles were then reviewed for the final selection. Seven articles were excluded for the following reasons: single treatment arm (n = 3), insufficient data (n = 2), not relevant study (n = 1), and crossover study design (n = 1). The remaining 7 RCTs were included in the final analysis (18-24).

Study Characteristics

Table 1 shows the general characteristics of the RCTs included in the final analysis. The publication years were between 2012 and 2020; a total of 287 patients (142 in the intervention group and 145 in the control group) were

Table 1. *Characteristics of trials included in the final analysis (n = 7).*

	Source	Number of patients (S/C)	Pain condition	Scrambler therapy group	Control group	Pain assessment	Follow-up	Main findings
1	Marineo 2012 (18)	26/26	Postsurgical neuropathic pain, PHN, and SS	45 minutes for 10 days up to maximal tolerable intensity (70 U)	Conventional medical treatment	VAS	1 month, 2 month, and 3 months	Significant reduction in pain score at 1 month from 8.0 to 0.7 in the Scrambler therapy group, compared with 8.1 to 5.8 in the control group ($P < 0.0001$)
2	Campbell 2013 (19)	5/5	CIPN	50 minutes for 10 days	Sham	Verbal-NRS	10 days	No significant difference in changes in pain score change between both groups ($P = 0.57$)
3	Starkweather 2015 (20)	15/15	Persistent nonspecific low back pain	30 minutes for 10 days up to maximal tolerable intensity (70 U)	Sham: one set of electrodes placed above painful dermatome, under nontherapeutic threshold	BPI-SF	1 week and 3 weeks after the end of the treatment	Significant reduction in worst pain score at 1 week from 5.40 to 4.34 in the Scrambler therapy group, compared with 4.98 to 5.76 in the sham group ($P = 0.01$).
4	Kashyap 2020 (21)	40/40	Cancer pain	40 minutes for 10 days up to maximal tolerable intensity	Conventional medical treatment	NRS	1 week after the end of the treatment	Significant difference in pain score reduction between the Scrambler therapy group (6.19) and the control group (3.1) at 1 week after the end of the treatment ($P < 0.001$)
5	Loprinzi 2020 (22)	15/19	CIPN	30 minutes for 10 days up to maximal tolerable intensity	TENS	NAS	Daily for 2 weeks and then weekly for 8 additional weeks	At least a 50% documented improvement during the 2 treatment weeks in the Scrambler therapy group, compared with the TENS group
6	Nayback-Beebe 2020 (23)	25/23	PHN, CIPN, SS, and postsurgical neuropathic pain	30 minutes for 10 days,	Sham: nontherapeutic threshold, placing leads outside painful dermatomes	NRS	Post-treatment (after last treatment session) and 4 weeks post-treatment)	No significant difference in changes in pain score reduction at 4 weeks post-treatment between both groups ($P = 0.494$)
7	Smith 2020 (24)	16/17	CIPN	30 minutes on 10 days up to maximal tolerable intensity	Sham: placed in an "X" across the L2-5 or C5-8 region	BPI-CIPN	Days 10, 28, 60, and 90	No significant difference in pain score reduction on day 10 ($P = 0.296$)

Abbreviations: S, Scrambler therapy group; C, control group; PHN, post-herpetic neuralgia; CIPN, chemotherapy induced peripheral neuropathy; SS, spinal stenosis; TENS, transcutaneous electrical nerve stimulation; VAS, visual analogue scale; NRS, numeric rating scale; BPI-SF, Brief Pain Inventory – Short Form; NAS, numerical analog scale

included in this meta-analysis. Pain conditions were chemotherapy-induced peripheral neuropathy (CIPN) in 4 trials (19,22-24), postsurgical neuropathic pain in 2 trials (18,23), post-herpetic neuralgia (18,23), pain due to spinal stenosis (18,23), cancer pain (21) in one trial, and persistent nonspecific low back pain in one trial (20). Treatment time and period were approximately 30 to 50 minutes per session over 10 working days. The control groups were conventional medical treatment, sham treatment, and TENS. The pain was assessed by using a VAS, NRS, BPI-short form (SF), NAS, and BPI-CIPN. Follow-up periods ranged between 10 days and 3 months from baseline. In the main findings, 3 trials showed no significant difference in changes in pain score (19,23,24), whereas 3 trials showed a significant reduction in pain score between the ST group and the control group (18,20,21). The remaining one did not report a statistical significance (22).

Methodological Quality

In the assessment of the methodological quality score based on the Cochrane risk-of-bias tool, 2 trials demonstrating the low risk of bias ≥ 5 items were categorized as having high quality (20,24), while the remaining 5 low-quality trials had a low risk of bias < 5 items (18,19,21-23) (Table 2). The included trials were generally of low quality, mostly related to lack of blinding. Due to the small number of studies (< 10), we could not rule out publication bias by performing funnel plots (37).

Efficacy of Scrambler Therapy on Pain Relief

In the random-effects model meta-analysis of 7 RCTs, ST marginally decreased pain after the end of the treatment compared with the control group (SMD, –0.85; 95% CI, –1.66 to –0.03; I^2 = 89.5%; Fig. 4). All the included studies reported different follow-up periods ranging from immediately to 3 months after the treatment.

Subgroup Meta-Analysis

Tables 3 shows the efficacy of ST for the management of chronic pain in the random-effects model subgroup meta-analysis by various factors. Subgroup meta-analysis showed that the use of ST significantly reduced analgesic consumption after the intervention compared to the control group (SMD, –0.54; 95% CI, –0.93 to –0.14; I^2 = 0.0%; n = 2). In the subgroup meta-analysis by type of control group, ST showed superior effects in relieving chronic pain than conventional medical treatment (SMD, –2.28; 95% CI, –2.80 to –1.76; I^2 = 24.5%; n = 2), whereas there was no significant difference, compared to the sham group (SMD, –0.22; 95% CI, –0.64 to 0.19; I^2 = 19.7%; n = 4). No significant association was observed in the remaining subgroup meta-analyses by methodological quality, type of diseases causing pain (CIPN or noncancerous origin), and follow-up period.

Adverse Events

Five out of 7 trials investigated the adverse events of ST (18-22). Among them, 2 (19,22) reported 2 adverse events: small bowel obstruction in a patient in the sham group (19) and minor ecchymosis at the site of the electrode placement in a patient (22). No severe adverse event was reported from all the included studies.

Table 2. *Summary of risk of bias assessment for the included trials (n = 7).*

Source	Random Sequence Generation	Allocation Concealment	Blinding of Patients, and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Bias	No. of Low Risk of Bias
Marineo 2012 (18)	Low	High	High	High	Low	Low	Unclear	3
Campbell 2013 (19)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	0
Starkweather 2015 (20)	Low	Low	Low	Unclear	Low	Low	Unclear	5
Kashyap 2020 (21)	Low	Low	High	High	Unclear	Low	Low	4
Loprinzi 2020 (22)	Low	Low	High	High	Unclear	Low	Low	4
Nayback 2020 (23)	Unclear	High	Unclear	Unclear	Unclear	Unclear	Unclear	0
Smith 2020 (24)	Low	Low	Unclear	Low	Unclear	Low	Low	5

[a]Based on the Cochrane Risk of Bias Tool.

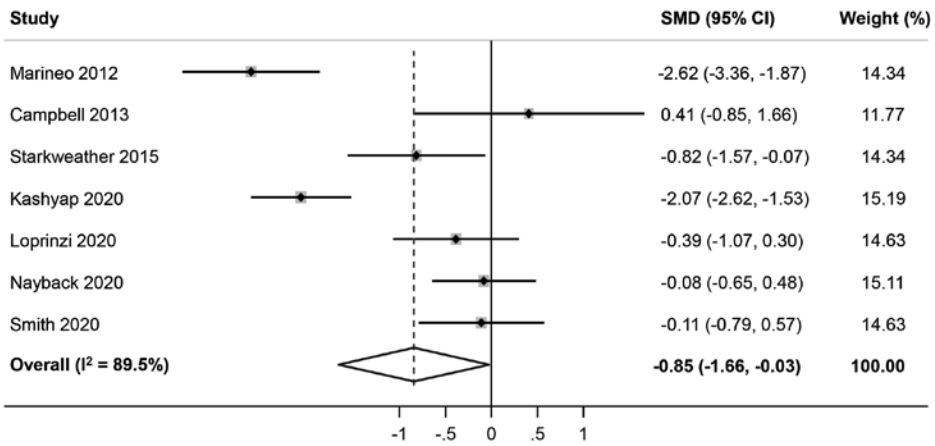

Fig. 4. *Use of Scrambler therapy and change of pain score based on the initial evaluation after the end of the treatment in a random-effects meta-analysis of randomized controlled trials (n = 7).*
SMD, standardized mean difference; CI, confidence interval.

Table 3. *Efficacy of scrambler therapy for management of chronic pain in random-effects model subgroup meta-analyses by various factors.*

Factor	Number of studies	Number of patients	SMD (95% CI)	Heterogeneity, I^2
All**	7	287	-0.85 (-1.66 -0.03)	89.5%
Analgesics dose*	2 (21,23)	103	-0.54 (-0.93, -0.14)	0.0%
Methodological quality				
High-quality (Low risk of bias in ≥ 5 items) Post-immediate follow-up 1 month follow-up	 2 (20,24) 2 (20,24)	 63 63	 -0.45 (-1.14, 0.24) -0.45 (-2.01, 1.12)	 46.6% 88.8%
Low-quality (Low risk of bias in ≤ 4 items)	5 (18,19,21,22,23)	224	-0.99 (-2.10, 0.11)	92.0%
Type of diseases				
CIPN	3 (19,22,24)	77	-0.16 (-0.62, 0.29)	0.0%
Non-cancer pain	2 (18,20)	82	-1.72 (-3.48, 0.04)	91.0%
Follow-up period				
1 month	3 (18,23,24)	133	-0.69 (-2.45, 1.06)	95.2%
2 months	2 (18,24)	85	-0.93 (-2.72, 0.87)	93.1%
3 months	2 (18,24)	85	-0.60 (-2.24, 1.04)	92.2%
Type of control group				
Sham	4 (19,20,23,24)	121	-0.22 (-0.64, 0.19)	19.7%
Conventional medical treatment*	2 (18,21)	132	-2.28 (-2.80, -1.76)	24.5%

*Statistically significant, **Marginally significant. SMD, standardized mean difference; CIPN, chemotherapy-induced peripheral neuropathy; RR, relative risk; CI, confidence interval

Discussion

In the current meta-analysis of 7 RCTs, ST showed marginally significant reductions in pain scores and significant reductions in analgesic consumption scores compared to the control group. The incidence of adverse events in the ST group was not higher than that in the control group.

However, we found that there are a lot of limitations in investigating the efficacy of ST in pain manage-

ment. First, most RCTs showed a high risk of bias in the assessment of methodological quality, which is due to a limitation for blinding of study patients and research personnel. The appropriate use of operator-dependent ST does not allow complete double-blind trial designs (31). When conducting ST, the optimal electrode position and stimulation intensity should be determined through interaction with a patient, thereby aiming for complete pain relief (31). Attempting a complete double-blind clinical trial would automatically distort the standard treatment protocol prominently (31).

Second, there was substantial heterogeneity in the main analysis. There were several reasons which may account for the heterogeneity between studies: different pain assessment scale, pain condition, sample size, follow-up period, type of control group, and procedural protocol across trials.

Third, specific diseases causing pain were not well documented. All the included trials (18-24) did not present a reliable, standardized criteria for the diagnosis of a specific disease that the study patients had.

Fourth, there were lots of differences in the placement and number of electrodes between the ST group and the sham group. For example, in Starkweather et al's (20) study, the placement and number of electrodes were different between the ST and sham groups, and the settings involved a nontherapeutic range in the sham group. In Nayback-Beebe et al's (23) study, leads were placed outside the affected dermatome and at the nontherapeutic threshold. Smith et al's (24) study used the different electrode arrangement between the ST group and the sham group and the same maximum threshold.

Fifth, procedural problems were also observed in several RCTs. In general, the electrodes should not be applied directly to the site of pain but to the dermatome above and below the site (18). After the primary pain site and its borders have been identified, the electrodes placement should surround the proximal to the distal border of the skin at the pain site (38). It is not recommended to place the electrodes at the site of numbness or sensory changes (24). Neural pathways that cause numbness or sensory changes due to structural or functional impairments may not effectively transmit or even degrade the synthetic "nonpain" information (12).

Sixth, given that the effect of ST is practice-dependent and improves with follow-up training, there is inevitably a difference in the skill levels of practitioners performing the ST, which further affects the results of the trial (16,39,40).

Lastly, we included only 7 studies involving 287 patients in the main analysis. The number of study patients in each trial ranged between 10 and 80, which is considered very small.

Conclusions

To the best of our knowledge, this is the first meta-analysis to evaluate the efficacy of ST for the management of chronic pain. In summary, we found that ST is effective in reducing pain in the short term in adults with chronic pain. However, there are several important limitations to prove its efficacy due to the small sample size of the included trials (10 to 80 study patients), low methodological quality, inappropriate methods, and use of sham procedure. Further large-scale trials with at least several hundreds of study patients are warranted to confirm our findings on the efficacy of the ST in the management of chronic pain.

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Check for updates

Received: January 26, 2022 Revised: April 5, 2022 Accepted: April 22, 2022

https://doi.org/10.1016/j.neurom.2022.04.045

The Use of Scrambler Therapy in Treating Chronic Pain Syndromes: A Systematic Review

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ABSTRACT

Background: Scrambler therapy (ST) is a noninvasive method of transcutaneous neuromodulation that has 510(K) clearance from the United States Food and Drug Administration for treating acute pain, postoperative pain, and intractable chronic pain. Since its inception, ST has been used to treat many chronic pain syndromes in a variety of patient populations. We synthesized the available literature for ST to delineate its overall evidence basis.

Materials and Methods: We performed a systematic review based on conventional Preferred Reporting Items for Systematic Reviews and Meta-Analyses methods by surveying multiple data sources from January 1950 through October 2021. Two review authors, independently and in a standardized, unblinded fashion, conducted a systematic review to identify relevant studies and extract the necessary outcome measures. A conservative search strategy was implemented to identify all ST studies for the treatment of chronic pain syndromes. Primary outcome parameters collected were analgesic benefit, adverse effects, and other metrics such as sensorimotor testing.

Results: A total of 21 studies met the final criteria for study inclusion and comprised randomized controlled trials ($n = 8$), prospective observational studies ($n = 10$), and retrospective cohort studies ($n = 3$). Nearly all the reported studies explored the use of ST for the treatment of neuropathic pain, with chemotherapy-induced peripheral neuropathy being the most studied condition. Most studies were limited by small cohorts but reported ST being safe, well tolerated, and providing clinically meaningful pain reduction. The duration of posttreatment follow-up ranged from ten to 14 days (concordant with completion of typical ST protocols) to three months. Secondary benefits such as medication reduction and improvement of sensory and motor symptoms were noted by some studies.

Conclusions: ST is regarded as a safe intervention with potential for significant analgesic benefit for neuropathic pain conditions. Although the available evidence is most robust for treating chemotherapy-induced peripheral neuropathy, ST has also been shown to be effective in treating other neuropathic pain syndromes. Evidence for ST use in nociceptive pain conditions is limited but appears promising. The favorable safety profile and increasing evidence basis for ST warrant more extensive recognition and consideration for use in clinical care.

Keywords: Calmare, cancer pain, neuromodulation, neuropathic pain, scrambler

Conflict of Interest: The authors reported no conflict of interest.

BACKGROUND

In the United States alone, chronic pain is thought to affect approximately 100 million individuals resulting in >$560 billion of health care expenses.[1] There is a significant societal burden associated with chronic pain, given the high prevalence of disability and lost productivity in affected persons and secondary burdens placed on families and caregivers.[1,2]

Chronic pain syndromes are largely categorized as nociceptive, which is characterized by actual or potential damage to nonneural tissue, or neuropathic, which is characterized by a lesion to the somatosensory neuraxis.[3–5] Irrespective of the precise mechanistic

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For more information on author guidelines, an explanation of our peer review process, and conflict of interest informed consent policies, please see the journal's Guide for Authors.

Source(s) of financial support: The authors reported no funding sources.

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etiology, chronic pain treatments are typically multimodal and incorporate conservative measures, physical therapy modalities, behavioral and psychologic conditioning, pharmacologic therapies, and nonsurgical and surgical interventions. Given that pain transmission occurs through the ascending spinothalamic pathway, the use of electrical neuromodulation for targeted treatment has gained significant clinical interest in recent years. Neuromodulation represents a nonpharmacologic treatment paradigm that allows for the modulation of ascending noxious signaling, either peripherally or centrally, for the treatment of pain.[5] In particular, peripheral nerve stimulation can be favorable for treating focal pain conditions because it allows for the targeted treatment of peripheral neuropathic pain.[6]

Invented by Dr. Guiseppe Marineo in Italy, scrambler therapy (ST), which is also referred to as Calmare© therapy (derived from the Italian word for "soothe or ease"), is a noninvasive method of neuromodulation distinct from transcutaneous electrical nerve stimulation (TENS).[7,8] In 2009, ST was granted 510(K) clearance by the United States Food and Drug Administration for treating acute pain, postoperative pain, and chronic intractable pain.[9] The gate control theory serves as the mechanistic foundation for other neuromodulation interventions, such as spinal cord stimulation or TENS. These devices are designed to activate Aβ fibers and thereby attenuate the transmission of noxious stimuli by ascending C-fibers. In contrast, ST does not attenuate nociceptive signaling, but rather administers synthetic "nonpain" information through C-fibers with the goal of reconditioning supraspinal pain centers.[8] This reconditioning through "nonpain" transmission is thought to reprogram dysfunctional pain-mediated neuroplasticity and help reestablish physiological responses to noxious stimuli. ST signals are delivered to C-fibers through adhesive cutaneous electrodes that are placed around the area of pain.[9–11]

Since its inception, ST has been used worldwide to treat chronic pain in heterogeneous populations and contexts.[9,10] Reports on its appropriate indications, clinical use, benefits, and adverse effects are thought to be inconsistent. This systematic review aims to summarize the available evidence regarding the use of ST in treating chronic pain syndromes, as well as its analgesic benefits, adverse effects, procedure-specific variables, and other metrics such as sensorimotor tests, medication reduction, and effect on circulation neuropeptides.

MATERIALS AND METHODS

We performed a systematic review based on conventional methods described by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[12] Multiple data sources, including PubMed, EMBASE, Google Scholar, reference lists, and the clinicaltrials.gov website, were searched from January 1950 through October 2021. A conservative search strategy was implemented for optimal capture of relevant literature. The search across all data sources included the following keywords: (scrambler OR MC5-A OR calmare) AND pain.

Inclusion criteria were original studies that detailed the use of ST to treat various chronic pain syndromes in humans and included case series, case-control studies, cohort studies (retrospective and prospective), or randomized trials.

Exclusion criteria were studies that were written in languages other than English, explored the use of ST for nonanalgesic indications, limited to <10 cases, or failed to clearly report outcome parameters.

The primary outcome parameters collected were analgesic benefit, adverse effects, and other metrics such as sensorimotor testing. Procedure-specific variables including stimulation intensity, duration, delivery modes, and number of treatments were also collected, when and as reported. However, there existed a large variance in the degree of reporting of procedure-specific stimulation and treatment variables, presumably because most studies adopted and used manufacturer-recommended protocols. All articles were independently screened by two authors (JK and AM) based on the inclusion and exclusion criteria. The same two authors independently assessed the full text of all included studies and extracted the relevant outcome measures. A risk of bias assessment was also performed independently by the same two review authors, with all disagreements resolved with a secondary screen of implicated studies. The five major evaluated risk of bias domains included selection, performance, detection, reporting, and other biases (eg, financial or other conflicts of interest) and were graded per the latest Cochrane recommendations.[11]

RESULTS

Studies and Patient Populations

We identified a total of 21 studies that met the final criteria for inclusion into our systematic review (Fig. 1). These studies consisted of randomized controlled trials (RCTs) (n = 8),[13–20] prospective observational studies (n = 10),[21–30] and retrospective cohort studies (n = 3)[31–33] (Tables 1–3). Most studies included small study populations, with only six studies including >50 patients. Most of the high-quality evidence explored the use of ST in treating cancer-associated chronic pain, with chemotherapy-induced peripheral neuropathy (CIPN) being more commonly studied than nonmalignant pain syndromes. Nearly all the included studies explored the use of ST for the treatment of neuropathic pain. Notably, the level of evidence for this relatively novel therapy seems to be increasing, with nearly all the included RCTs (n = 6) being published after 2019.[13–15,17–19]

Study Limitations and Sources of Bias

Most of the included studies clearly identified their study populations and outcomes. However, nearly all the studies were found to have performance and detection biases (Fig. 2). Because ST requires direct feedback between the operator and the patient for proper device titration, blinding is challenging, and there is no standard "sham" treatment as a comparison.[9,12] In practice, the nervous system acclimates to the stimulation signal, thus requiring the operator to increase the intensity every 5 to 10 minutes to the new tolerance threshold. The use of only stable stimulation intensity across the ST treatment is thought to be ineffective and has been used as a sham control.[20] Most studies also failed to explore additional outcomes aside from pain reduction and/or lacked clarity in reporting their results. Lastly, the authors of several studies reported industry affiliations with the manufacturer of the ST device, and the inventor of the ST device himself is an author of several studies.

Interventions and Outcomes

ST Parameters

Most studies reference and use the same ST treatment protocol.[9,10,12] This entails the placement of up to five pairs of adhesive cutaneous electrodes, such as those used for an electrocardiogram, on the skin proximally and distally to the region of pain, along the

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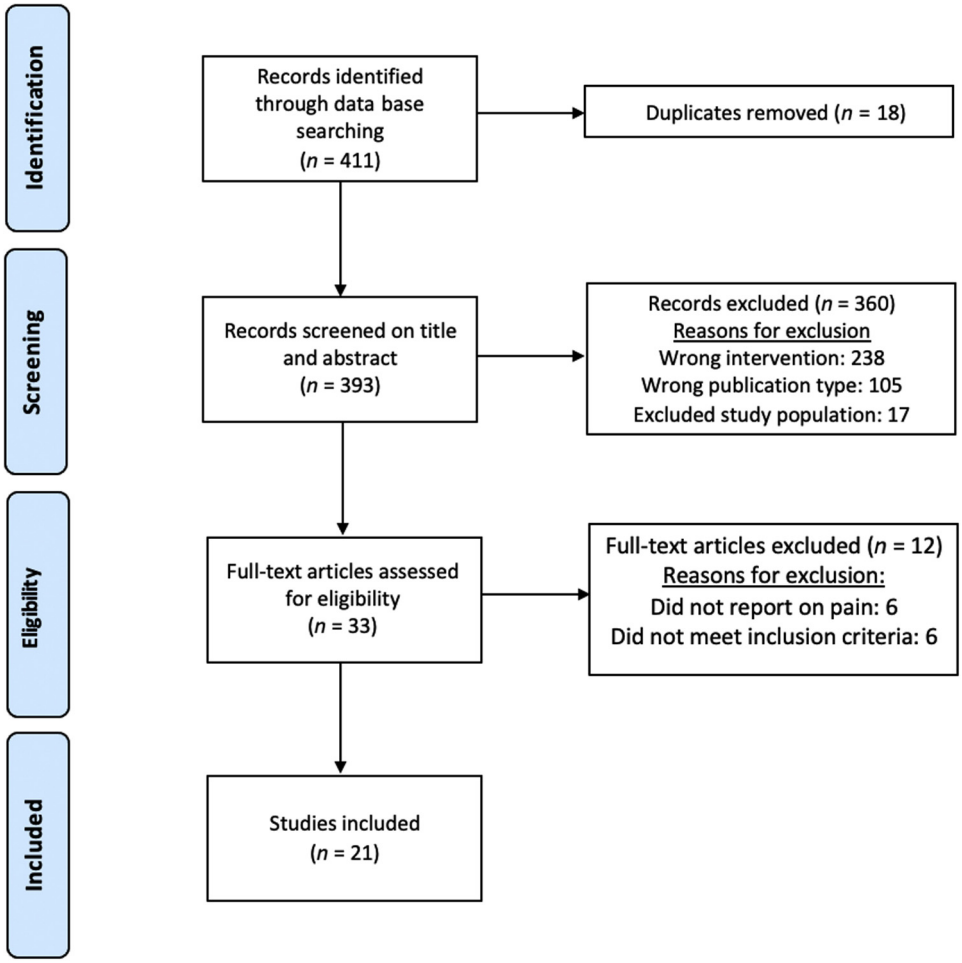

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart for study selection. [Color figure can be viewed at www.neuromodulationjournal.org]

dermatome that most closely corresponds to the distribution of pain symptoms. The electrodes are connected to the ST device, which acts as an external pulse generator and is operated by a health care professional trained in ST use. The device administers electrical signals organized into 16 unique waveforms and combined into 256 dynamic strings of information packets, which the device software algorithm constantly changes. The physician then modulates the stimulation intensity such that it is above the perceptive threshold ("tell me when you feel something") but below the nociceptive threshold ("tell me when enough is enough"), as reported by the patient through direct verbal feedback. This modulation can occur per individual "channel" or electrode pair. The maximum current of 5.5 mA and stimulation intensity of 12.5 V correspond to a maximum current density of 0.0002009 W/cm^2, which is similar to the stimulation intensities generated by TENS devices. ST pulse duration typically ranges between 6.8 and 10.9 milliseconds, with a frequency of 43 to 52 Hz. Nearly all studies described once-a-day ST treatments across ten to 14 consecutive days, depending on site-specific protocols, with each treatment session typically lasting between 30 and 45 minutes. The full ten-to-14-day treatment protocol is recommended when there is meaningful pain reduction with the initial treatment sessions. Treatment sessions were discontinued when patients reported >24 hours of complete pain relief, the maximum number of sessions in the protocol had been administered, or there was a lack of efficacy. It should be noted that fewer than ten sessions may be performed if the patient is found to be completely pain-free for 24 hours after the last ST treatment.[8–10]

Analgesic Benefit

Most studies defined treatment success as ≥50% reduction in average pain scores relative to preprocedural baseline, and many reported average pain reductions of up to 80% to 90%. The duration of follow-up for most studies ranged from ten to 14 days (the completion of a standard ST treatment protocol) to three months. Significant pain reduction was reported extensively in nearly all studies, but ST was found to be equivalent to sham therapy in two studies.[18,19] A study by Smith et al[19] reported improved sensory nerve testing with both ST and sham therapy and no statistically significant improvement in pain relief from ST compared with sham therapy. The authors noted that the small sample size and misplaced electrodes may have contributed to the lack of demonstrated effect, but could not rule out a placebo effect from both ST

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Table 1. Randomized Controlled Trials Exploring ST Treatment for Chronic Pain.

Author, year	Study population (sample size, pain syndrome)	Intervention	ST parameters (no. of sessions, duration in min)	Outcome time frame	Outcomes (a. Pain reduction) (b. Other benefits, if specified)
Loprinzi et al,[15] 2020	46 CIPN; patients weaned off gabapentin and pregabalin	ST vs TENS	10 sessions ST vs 14 sessions TENS over 2 wk, 30-min treatments each	2-wk treatment plus 8-wk follow-up	a. Although % change from baseline scores for average numbness, tingling, and pain did not yield significant differences at 2 or 10 wk, they did show a trend of ST achieving better relief compared to TENS. At the end of the 8-wk observation period, numbness, tingling, and pain scores were reduced by 28%, 41%, and 33% from baseline, respectively. b. When evaluated for Global Impression of Change scores, neuropathy ($p = 0.001$), pain ($p = 0.005$), and quality of life ($p = 0.005$) scores for ST were significantly improved vs TENS during the 2-wk treatment period* but not significantly different during the 8-wk follow-up. EORTC QLQ CIPN-20 showed no significant difference between the two arms.
Childs et al,[13] 2021	46 precrossover (same as Loprinzi et al[15]), 22 postcrossover CIPN	ST vs TENS in crossover design	10 sessions ST vs 14 sessions TENS over 2 wk with 30-min treatments	2-wk and 8-wk follow up	a. Patients who received ST are twice as likely to have 50% reduction in primary symptom (pain or tingling) at 14 d as patients who received TENS. This trend is consistent after crossover treatment. b. ST appears better than TENS when assessed by Global Impression of Change for overall quality of life.
Kashyap and Bhatnagar,[14] 2020	80 Head, neck, and thoracic cancer pain (40 participants in intervention arm, 40 participants in control arm)	ST and opioid medications vs opioid medications alone	10 sessions, 40-min treatments	10-d treatment plus 1-wk follow-up	a. On day 10, the mean NRS-11 score in the ST group was significantly lower than in the control group (0.74 ± 0.75 vs 3.15 ± 1.00).* At 1-wk follow-up, ST group scores remained significantly lower than the control group (0.46 ± 0.55 vs 3.47 ± 1.12).* b. Compared with the control group, morphine doses were significantly lower in the ST group at days 7, 8, 9, and 10 and at the 1-wk follow-up (1-wk follow-up: 43.65 ± 24.48 mg vs 78.27 ± 59.10 mg).* However, tramadol dosage did not change significantly.
Marineo et al,[16] 2012	Neuropathic pain (28 postsurgical neuropathic pain, 16 postherpetic neuralgia, and 8 spinal canal stenosis)	ST + medications vs medications alone	10 sessions, 45-min treatments	2-wk treatment	a. At 1 mo, mean VAS pain scores fell from 8.1 to 5.8 in the control group and from 8.0 to 0.7* in the ST group ($p < 0.0001$). At 2 mo and 3 mo, control group scores were 5.7 and 5.9, whereas ST group scores were 1.4* and 2.0* ($p < 0.0001$), respectively.
Mealy et al,[17] 2020	22 Neuromyelitis optica spectrum disorder	ST vs sham control (with TENS) and continued maintenance medications	10 sessions, 35-min treatments	10-d treatment with follow-up at 30-d and 60-d intervals	a. ST resulted in a significant reduction of median NRS pain scores from 5.0 to 1.5* while sham (TENS) scores did not significantly change. NRS pain scores for ST remained significantly decreased at 4 wk* but not at 8 wk. b. ST resulted in significant reduction in median depression scores ($p = 0.03$),* but had no significant effect on anxiety, sleep disturbance, or pain interference. Sham (TENS) had no significant effect on any of these scores.
Nayback-Beebe et al,[18] 2020	47 Chronic neuropathic pain; 97% of patients had low back pain with radiculopathy	ST vs sham therapy (leads placed outside the affected dermatomes at a nontherapeutic threshold)	10 sessions ST or sham sessions over 2 wk, 30-min treatments for each	2-wk treatment plus 4-wk follow-up.	a. ST group experienced a 42% reduction and sham group experienced a 33% reduction in pain intensity posttreatment. And, at 4-wk follow-up, reduction from baseline pain was 39% and 33% for ST and sham groups, respectively. There were no

(Continued)

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Table 1. *Continued*

Author, year	Study population (sample size, pain syndrome)	Intervention	ST parameters (no. of sessions, duration in min)	Outcome time frame	Outcomes (a. Pain reduction) (b. Other benefits, if specified)
					significant between-group differences found in pain intensity. b. No significant between-group difference found for analgesic medication use or mental or physical quality of life scores.
Smith et al,[19] 2020	35 CIPN	ST vs sham (leads placed outside the affected dermatomes); anticonvulsant drugs including gabapentinoids were stopped in both groups	10 sessions, 30-min treatments	10-d treatment with follow-up at 28-d, 60-d, and 90-d intervals.	a. No significant changes to pain scores in either group at any follow-up interval. Significant sensory score reductions* were observed each week in both ST and sham, but differences between the two were not statistically significant.
Starkweather et al,[20] 2015	30 Persistent nonspecific lower back pain	Sham-controlled (leads placed outside affected dermatomes, stimulation at a nontherapeutic threshold)	10 sessions, 30-min treatments	2-wk treatment plus 1-wk and 3-wk follow-up	a. At 3-wk follow-up, compared with sham, ST group reported significantly lower scores in "worst pain" (3.32 ± 1.27 vs 5.81 ± 1.75),* pain interference (1.92 ± 1.36 vs 2.89 ± 1.19),* heat pain threshold (44.34 vs 41.41 °C),* and pressure pain threshold (479.16 vs 354.25 kPa) scores.

EORTC QLQ CIPN-20, European Organization for Research and Treatment of Cancer quality of life questionnaire for CIPN; NRS, numerical rating scale; VAS, visual analog scale.
*Statistically significant difference.

and sham therapy. They later noted that electrode placement had been incorrect by being placed over the areas of damaged nerve endings, because chemotherapy-induced neuropathy extends much farther up the leg than the pain sensation.[34] There must be sufficient normal nerves to carry the "nonpain" signal to the brain for the therapy to be effective.[8]

Unfortunately, long-term follow-up data are significantly lacking. However, several authors suggest that the effects of ST may persist for several months.[16,17,21,30] Although not included in our systematic review, there are some case reports noting ST-specific pain relief lasting for several years.[35,36]

Sensory and Motor Testing, and Other Metrics

Aside from pain reduction, six studies further explored ST effects on sensory and motor neuropathy.[15,19–21,26,28] Five of these studies performed sensory and motor testing with neuropathy questionnaires such as the European Organization for Research and Treatment of Cancer quality of life questionnaire for CIPN.[15,19,21,26,28] Four studies found benefit of ST in reducing symptoms of sensory neuropathy such as tingling or numbness.[15,21,26,28] This is in contradistinction to the best drug available for CIPN, duloxetine, that had no effect on numbness or tingling in a large randomized trial.[35] Notably, Coyne et al[21] and Loprinzi et al[15] found these improvements in sensory neuropathy scores to persist for two months and three months, respectively. In addition, Coyne et al[21] reported motor improvements in their cohort across three months.

Only one study explored ST effects on sensory and motor neuropathy using objective measures.[20] Starkweather et al,[20] in an RCT, explored objective measures alongside clinical effect against low back pain and found that three weeks after ten days of ST, "worst" pain scores were significantly reduced by >50%. In addition, the ST group had higher (improved) thresholds to heat and pressure pain on both the treated back area and the untreated forearm than the sham group. The messenger RNA expression of 84 genes involved in the transduction, maintenance, and modulation of pain responses was tested at baseline and three weeks after the treatment ended. The ST group had significant reductions in 17 key pain genes, many of which code for proteins involved in the potentiation of afferent nerves (nerve growth factors and glial cell line–derived neurotrophic factor) or that mediate nociceptive signaling and/or inflammation.

Nearly half of the included studies reported quality-of-life metrics but used heterogenous scoring methods. Metrics included the Patient Global Impression of Change scale (two studies),[13,15] mental and physical quality of life (one study),[18] and the European Organization for Research and Treatment of Cancer quality of life questionnaire (two studies).[15,21] Overall, ST appeared to improve these quality-of-life metrics, but conclusions are limited by the heterogeneity of study populations and follow-up durations. Regarding medication use, four studies reported reductions in opioid use with adjunct use of ST.[14,16,21,23]

Adverse Effects

Of the 22 studies included, only 17 explored adverse effects with ST. ST was universally considered to be safe and well tolerated. There were no substantial side effects reported in the original 2297 cases reported for European Euromark certification for safety.[8] There was only one reported adverse effect published in the literature of contact dermatitis in the study by Min et al.[25] However,

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Table 2. Prospective Observational Studies Exploring ST Treatment for Chronic Pain.

Author, year	Study population (sample size, pain syndrome)	ST (no. of sessions, duration in min)	Outcome time frame	Outcomes (a. Pain reduction) (b. Other benefits, if specified)
Coyne et al,[21] 2013	39 Cancer-associated chronic neuropathic pain (33 patients with CIPN)	10 sessions, 45-min treatments	2-wk treatment with follow-up at 1-mo, 2-mo, and 3-mo intervals.	a. Pain scores decreased from 6.6 to 4.5 at 14 d and to 4.6, 4.8, 4.6 at 1, 2, and 3 mo respectively ($p < 0.001$).* b. EORTC CIPN-20 showed significant improvements for both sensory* and motor components.* Opioid use did not change significantly.
Kashyap et al,[22] 2017	20 Patients with cancer with bony, neuropathic, or mixed type pain	12 sessions, 40-min treatments	10-d treatment plus 1-wk and 2-wk follow-ups, with an extra ST session during each for a total of 12 sessions.	a. Pain scores significantly reduced from 8.4 ± 1.4 to 2.9 ± 1.5 ($p = 0.008$) after ST.* b. There were significant improvements in physical, psychologic, social, and environmental health domain scores after the therapy.*
Lee et al,[23] 2016	20 Cancer-associated neuropathic pain (7 bony metastatic pain, 7 postsurgical pain, 6 CIPN)	10 sessions, 30-min treatments Highest setting: 3.5–5.5 mA, 6.5–12.5 V w/ phase duration 6.8–10.9 s w/ pulse rate 43–52 Hz	2-wk treatment plus 2-wk follow-up	a. Mean NRS pain score was significantly decreased from 7.4 to 3.7.* b. There was no change in opioid consumption.
Marineo et al,[24] 2003	11 Medication refractory visceral pain from terminal abdominal cancer	10 sessions, 45-min treatments	10-d treatment	a. Mean VAS pain scores decreased significantly by 82.3 ± 10.9 points from a mean baseline score of 86 points ($p < 0.001$).* b. 9 of 11 patients stopped requesting unspecified "painkillers" between the second and fifth treatment sessions, and the remaining two patients reduced dosage considerably.
Min et al,[25] 2021	25 Drug-resistant neuropathic pain from peripheral nerve or spinal cord lesions	10 sessions, 30-min treatments Highest setting: 5.5 mA	2-wk treatment plus 2-wk follow-up	a. Overall 15% decrease* in NRS pain scores from baseline at 2 wk. Clustering based on the NPSI profile resulted in three clusters with distinct neuropathic pain phenotypes. Clusters showed a differential response to ST,* indicating more favorable outcomes in patients with paroxysmal pain rather than persistent pain.
Pachman et al,[26] 2015	37 patients enrolled initially and decreased to 20 patients by day 10 Chronic CIPN	10 sessions, 30-min treatments	10-d treatment plus 10 wk of weekly follow-up	a. After 10 d, pain decreased 53%,* tingling decreased 44%,* and numbness decreased 37%.*
Ricci et al,[27] 2019	219 total 83 patients with cancer-associated pain 136 patients with various unspecified noncancer-associated chronic pain conditions (118 from both groups with neuropathic pain)	10 sessions, 30-min treatments	2-wk treatment plus 2-wk follow-up	a. NRS pain scores decreased from 6.44 ± 2.11 at baseline to 3.22 ± 2.2 at 2 wk and to 3.19 ± 2.34 at 4 wk. This pain reduction from baseline to week 2 was maintained at week 4 ($p < 0.0001$).* For patients with neuropathic pain, mean NRS scores decreased from 6.56 ± 2.07 at baseline to 3.38 ± 2.48 at 4 wk ($p < 0.0001$).*
Russo et al,[28] 2018	45 Neuropathic pain from multiple etiologies (top 3 diagnoses include: 17 radiculopathy, 12 postherpetic neuralgia, 8 peripheral neuropathy)	10 sessions (flexible), 45 min	10-d treatment (stopped if pain disappeared at any point, and continued until complete resolution or until stable condition)	a. Median of 10.5 (range 5–20) ST sessions. NRS pain scores decreased significantly.* 40 of 45 patients responded to treatment and experienced a pain intensity reduction of ≥50%. Neuropathic Pain Diagnostic Questionnaire (DN4) scores decreased by 50.3% from 5.67 ± 1.43 at baseline to 2.82 ± 2.18 after 10 d.* There was a significant correlation between treatment responders and change in DN4 scores.*

(Continued)

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Table 2. *Continued*

Author, year	Study population (sample size, pain syndrome)	ST (no. of sessions, duration in min)	Outcome time frame	Outcomes (a. Pain reduction) (b. Other benefits, if specified)
				ST can resolve somatosensory signs and symptoms related to neuropathic pain.
Sabato et al,[29] 2005	226 Medication refractory neuropathic pain from multiple etiologies (~20% failed back surgery, ~20% other neuropathies, ~15% sciatic and lumbar pain, ~9% post herpetic neuralgia, ~9% trigeminal neuralgia)	5 sessions, 30-min treatments	5-d treatment	a. 80% of patients were responders and had pain relief ≥50%. VAS pain scores at 5 d were decreased significantly for all groups when compared with baseline.*
Smith and Marineo,[30] 2018	10 Postherpetic neuropathy	10 sessions, 30-min treatments	10-d treatment with follow-up at 1-mo, 2-mo, and 3-mo intervals.	a. Pain scores decreased from 7.64 ± 1.46 at baseline to 0.42 ± 0.89 at 1 mo, with continued relief at 2 mo and 3 mo. Most patients stopped or reduced their pain medications.

EORTC CIPN-20, European Organization for Research and Treatment of Cancer quality of life questionnaire for CIPN; NPSI, Neuropathic Pain Symptom Inventory; NRS, numerical rating scale; VAS, visual analog scale.
*Statistically significant difference.

it is unclear whether this adverse effect was caused by the ST signals or the cutaneous adhesive electrodes.

DISCUSSION

ST for Treating Neuropathic Pain in Patients With Cancer

Chronic neuropathic pain is common in the population with cancer and can be a sequela of tumor burden, surgical resection, radiation therapies, and/or neurotoxic chemotherapies.[37] CIPN is one of the most common causes of chronic pain among patients with cancer and may affect up to 30% to 40% of all patients who have received chemotherapy.[37,38] Unfortunately, the only treatment for painful CIPN supported by the 2020 American Society of Clinical Oncology (ASCO) guidelines is duloxetine,[37] which may only provide modest relief, and its use may be limited by adverse effects or impaired renal function.[39] In addition, it has no effect on nonpainful sensory neuropathy symptoms, such as numbness and tingling, which can often be as bothersome as pain itself.[39] Regarding ST, the ASCO guidelines state that there is insufficient evidence establishing a clear treatment benefit, but note that it does appear to be a safe modality. Notably, the ASCO guidelines only assessed two prospective studies regarding ST,[15,19] and several additional RCTs have been published thereafter.

Smith et al[19] in 2020 found no meaningful superiority of ST over sham therapy in 33 patients with CIPN at one-month, two-month, and three-month follow-up intervals. However, the method of electrode placement was later reported to be faulty by the authors themselves, as noted by the earlier discussion of lead placement on damaged nerves being improper.[19,34] Childs et al[13] and Loprinzi et al[15] in 2020 both provided data to support that ST was superior to TENS in yielding pain reduction at eight-week follow-up. In addition, both studies supported a superiority for ST in improving Patient Global Impression of Change scores, with Loprinzi et al[15] demonstrating a reduction of nonpainful neuropathy symptoms as well. Coyne et al[21] in 2013 and Pachman et al[26] in 2015 similarly reported reductions in sensory and motor parameters of neuropathy. Coyne et al[21] additionally noted that the 30% pain reduction in their cohort at four-month follow-up far surpasses the 10% benefit with duloxetine, the only ASCO recommended treatment for CIPN, which was supported by a large RCT by Smith et al.[39] It should be noted that no study was able to definitively describe the mechanisms of how ST may reduce or reverse signs and symptoms of neuropathy.

None of the included studies reported significant adverse effects with ST. Therefore, it appears that ST is at worst ineffective or equivalent to sham treatment, but at best a safe and beneficial intervention for providing pain relief, improving quality of life, and reducing nonpainful neuropathy symptoms.

Use of ST in Treating Other Neuropathic Pain Syndromes

In 2015, the neuropathic pain special interest group of the International Association for the Study of Pain published updated guidelines regarding pharmacologic treatments for neuropathic pain.[40] Gabapentinoids (eg, gabapentin and pregabalin), selective norepinephrine reuptake inhibitors (eg, duloxetine), and tricyclic antidepressants (eg, nortriptyline and amitriptyline) received the strongest recommendation based on the available evidence. However, the group noted that the usage of these first-line medications may be limited by adverse effects.

An RCT by Marineo et al[16] in 2012 compared the safety and effectiveness of ST with antineuropathic medications with that of

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Table 3. Retrospective Studies Exploring ST Treatment for Chronic Pain.

Author, year	Study population (sample size, pain syndrome)	ST (no. of sessions, duration in min, electrical dose)	Outcome time frame	Outcomes (a. Pain reduction) (b. Other benefits, if specified)
Compagnon et al,[31] 2015	201 Chronic pain from multiple etiologies; approximately 90% of patients had neuropathic pain	10 sessions of ST, 45-min treatments	2-wk treatment	a. Numerical rating scale pain scores decreased from 7.41 ± 2.06 to 1.60 ± 2.22 after ST treatment.
Moon et al,[32] 2015	147 Various pain conditions; approximately 50% of patients had neuropathic pain	Minimum of 3 consecutive sessions or 5 total sessions; patients underwent an average of 20.3 ± 18.4 sessions, 40–60-min treatments Highest setting: 3.5–5.5 mA, 6.5–12.5 V w/ phase duration 6.8–10.9 s w/ pulse rate 43–52 Hz	1-mo follow-up minimum	a. ≥50% pain relief persisting for longer than 1 mo was counted as a successful outcome. Overall success rate was 38.1%; however, the most prominent factor was study site, with 2 sites achieving 57.8% and 55.6% and the third only 23.8%. Treatment success was correlated with the presence of neuropathic (OR = 24.78; $p = 0.006$) or mixed (OR = 10.52; $p = 0.042$) pain, and treatment at either Walter Reed (OR = 6.87; $p = 0.010$) or Seoul National University (OR = 12.29; $p = 0.012$). Treatment failure was correlated with disease (OR = 0.04; $p = 0.020$) or traumatic/surgical etiologies (OR = 0.05; $p = 0.015$) and antidepressant use (OR = 0.47; $p = 0.056$).
Notaro et al,[33] 2016	25 Chronic refractory pain from bony (68%) and visceral (32%) metastases	10 sessions of ST, 30–40-min treatments	10 d	a. 100% of patients experienced pain relief ≥50%. Mean pain scores were reduced significantly at the end of 10 d from 8.4 ± 1.4 to 2.9 ± 1.5 ($p = 0.008$).* The duration of pain control by ST was 7.7 ± 5.3 wk. b. Sleeping hours increased from 4.4 ± 1.2 to 7.5 ± 1.1 ($p = 0.004$).*

*Statistically significant difference.

antineuropathic medications alone in a cohort of patients with postsurgical neuropathic pain, postherpetic neuralgia, or spinal canal stenosis. As per the standard of care described in the European Federation for Neurologic Science, most patients were treated with a combination of amitriptyline, gabapentin, clonazepam, tramadol, and oxycodone across the study.[16,41] Specific drug utilization parameters, such as patient selection and medication titration, were not described. Patients in the ST treatment arm had significantly lower pain across three months, as measured by average pain scores and allodynia prevalence, and did not report any adverse effects. In addition, patients in the ST group were found to have a significant dose reduction and/or discontinuation of amitriptyline, gabapentin, and tramadol medications across three months. On the contrary, patients in the control group were found to have no change in their amitriptyline, oxycodone, or clonazepam usage across the same period.

In 226 patients with neuropathic pain from various syndromes that was refractory to medication management, Sabato et al[29] found that as few as five ST sessions were significantly effective in yielding meaningful pain reduction in 80% of patients. Similarly, Min et al[25] found that ST was effective in yielding pain reduction in 25 patients with drug-resistant neuropathic pain from peripheral nerve or spinal cord lesions. Most importantly, they found that the phenotype of pain may influence the overall effectiveness of ST in reducing pain. By categorizing patients by neuropathic pain symptom inventory profiles, they found that patients with paroxysmal pain achieved the greatest reduction in average baseline pain. Of note, they report the only listed adverse event in the ST literature we observed, with one patient developing contact dermatitis on the eighth day of treatment.[25]

In a cohort with various neuropathic pain syndromes (eg, radiculopathy and postherpetic neuralgia), Russo et al[28] found that ST yielded analgesic superiority to sham treatment across ten days. In addition, they found that ST reduced sensory symptoms such as tingling and numbness across the same time span. These reductions in sensory neuropathy symptoms also were reported by several other studies, including those by Coyne et al[21] and Pachman et al,[26] which explored ST benefits in patients with CIPN as discussed earlier.

However, an RCT from Nayback-Beebe et al[18] found that ST was equivalent to sham therapy in facilitating pain reduction and quality-of-life decrement after four weeks in patients with lumbar radiculopathy. Of note, the sham therapy group achieved a 33% reduction in pain scores, leading the authors to suggest that the electrical stimulation used as the sham therapy may have been therapeutic in itself, in addition to placebo effects. The inventor of ST critiqued the double-blinded method of the study because the operator was made unaware of which treatment was being used.[42] This procedural approach to ST precludes effective placement of the electrodes and interaction with the patient to appropriately modulate the stimulation intensity. In addition, the researchers apparently had no experience with ST before attempting the study.

Collectively, these studies suggest that ST may be beneficial for reducing medication requirements, or even serve as a safe monotherapy if medications are ineffective or lead to adverse effects. Further studies focusing on the specific mechanism of ST may provide insight into optimal stimulation parameters and electrode placement protocols, especially when sham therapy, such as that used by Nayback-Beebe et al,[18] may itself be therapeutic.

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Figure 2. Risk of bias assessment for all included studies. [Color figure can be viewed at www.neuromodulationjournal.org]

ST for Treating Nonneuropathic Cancer Pain

ST has also been used for treating cancer-associated nociceptive pain. Marineo et al[24] in 2003 recruited 11 patients with advanced intraabdominal cancers in the palliative care setting. After ten sessions of ST, pain scores were reduced by as much as 90% from baseline; all 11 patients reported no pain by the end of the tenth session. In addition, nine of 11 patients discontinued their unspecified pain medications by the fifth treatment, and the remaining two patients significantly reduced their pain medication dose requirements. All 11 patients experienced enough benefit with ST to elect to receive treatments until their death.

Notaro et al[33] in 2015 recruited 25 patients with cancer pain from metastatic disease, of whom 17 patients (68%) had bony metastases. In addition to a significant pain decrease of 89% on average across ten ST treatment sessions, six patients deferred further offered ST treatments, given that there was no longer any limiting pain reported. Most patients also reported improved duration of sleep. On average, these patients reported a duration of effect from ST lasting 7.7 weeks.

Most recently, Kashyap and Bhatnagar[14] in 2020 performed an open-label RCT exploring the benefit of ST and opioids vs opioids alone in 80 patients with pain from the head, neck, and thoracic cancers. Similarly to previously mentioned studies, they too demonstrated a decrease in pain scores and opioid use across ten treatments. Patients in the ST arm had significantly lower pain scores and opioid requirements than patients who received opioids alone. At the one-week post-treatment follow-up, the control arm was found to have approximately 50% higher pain scores and required an average of 78 morphine milliequivalents compared with 46 morphine milliequivalents in patients in the ST arm. These results are particularly promising for patients with head and neck cancer because many suffer from dysphagia and have limited tolerance for oral medications.

ST for Treating Noncancer-Associated Nociceptive Pain

There is limited evidence available for ST in treating noncancer-associated nociceptive pain. In a double-blinded RCT, Starkweather et al[20] in 2015 used ST to treat 30 patients with chronic, non-radicular low back pain. There was a significant reduction in average pain scores and pain sensitivity, as defined by heat and pressure thresholds, in the intervention cohort across three weeks. Of note, ST was associated with a reduced expression of seven genes implicated in pain expression. However, the authors note that causality between reduction in pain gene expression and ST could not be established.

In contrast, Moon et al[32] retrospectively explored the benefit of ST in 147 predominantly military patients with various unspecified chronic pain syndromes. This population comprised patients with pain that was refractory to "usual modalities" and included a subset of 45 patients with nociceptive pain. Among this heterogeneous patient population, only 38% of patients of the full cohort achieved a successful outcome, which was defined as >50% pain relief lasting more than one month after the last treatment. Multivariate regression analyses found that patients with neuropathic (odds ratio [OR] = 24.78) or mixed (OR = 10.52) pain, rather than nociceptive pain, were much more likely to have positive ST treatment outcomes.

Overall, the evidence for ST for nociceptive pain remains limited, and studies have yielded mixed results. Additional controlled trials with well-defined patient subgroups are needed to clarify if particular types of nociceptive pain are more likely to be successfully treated with ST.

CONCLUSIONS

ST is a safe intervention with significant potential benefit for analgesia and quality of life, especially in neuropathic pain conditions. Although the available evidence is most robust for treating CIPN, ST also appears to be effective in other neuropathic pain

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conditions. Evidence of benefit for ST use in nociceptive pain conditions is limited but appears positive. With a highly favorable safety profile, ST may be a valuable treatment for patients with neuropathic pain that is refractory to first-line medications and other modalities. The duration of analgesia for ST remains unclear and requires further study but may range for months since the last treatment. There is preliminary evidence that ST may decrease pain medication requirements (eg, opioids), and may potentially reduce nonpainful neuropathic symptoms, but more studies are necessary to confirm these findings.

Authorship Statements

Jay Karri and Eric J. Wang designed and oversaw the execution of the study. Jay Karri and Anuj Marathe performed the systematic review and most of the writing. Jay Karri, Thomas J. Smith, and Eric J. Wang provided final edits. All authors approved the final manuscript.

How to Cite This Article

Karri J., Marathe A., Smith T.J., Wang E.J. 2023. The Use of Scrambler Therapy in Treating Chronic Pain Syndromes: A Systematic Review.
Neuromodulation 2023; 26: 1499–1509.

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COMMENTS

The authors provide an excellent overview of scrambler therapy for neuropathic pain. There have been multiple publications that have provided data supporting the utility of scrambler therapy for this problem, and it is nice to have the present overview of this approach. Hopefully, funding will become available to support

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randomized clinical trials to further our knowledge regarding scrambler therapy.

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Despite years of research on chronic neuropathic pain, we have more doubts than certainties about the pathophysiological bases that perpetuate the pathology (Kim YR, Kim SJ. Altered synaptic connections and inhibitory network of the primary somatosensory cortex in chronic pain. *Korean J Physiol Pharmacol*. 2022;26:69–75.). As pointed out in numerous publications, the social impact of this pathology is enormous. Numerous guidelines address the treatment of this pathology (Moulin D, Boulanger A, Clark AJ, et al. Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society. *Pain Res Manag*. 2014;19:328–335; and Attal N, Cruccu G, Baron R, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol*. 2010;17:1113.e88.). However, many patients do not respond or partially respond to treatment. The Scrambler is another treatment possibility that presents exciting results and many limitations. The authors of this article list the evidence available at the moment. It is limited but with exciting developments. It is improbable that a single treatment will solve the problem magically. But continuing to look for alternatives and collaboration with the different specialties that treat these patients is the best alternative (Szewczyk AK, Jamroz-Wisniewska A, Haratym N, Rejdak K. Neuropathic pain and chronic pain as an underestimated interdisciplinary problem. *Int J Occup Med Environ Health*. 2022;35:249-264.).

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European Journal of Oncology Nursing 58 (2022) 102124

Contents lists available at ScienceDirect

European Journal of Oncology Nursing

journal homepage: www.elsevier.com/locate/ejon

Evaluating the safety, feasibility, and efficacy of non-invasive neuromodulation techniques in chemotherapy-induced peripheral neuropathy: A systematic review

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ARTICLE INFO

Keywords:
Cancer
Chemotherapy-induced peripheral neuropathy
Non-invasive neuromodulation
Pain
Symptom management
Systematic review

ABSTRACT

Purpose: This systematic review was conducted to evaluate the best available evidence regarding the use of non-invasive neuromodulation techniques for managing chemotherapy-induced peripheral neuropathy (CIPN).
Methods: A systematic literature search of the following databases from their inception to October 17, 2021 was performed and was updated on March 2, 2022: AMED via Ovid, CINAHL via the EBSCO Host, Cochrane Library, Embase, PEDro, PubMed, and Web of Science. Randomized controlled trials (RCTs) and quasi-experimental studies examining the safety, feasibility, and efficacy of non-invasive neuromodulation techniques for managing established CIPN were identified. Narrative synthesis was used to analyze data collected from the included studies.
Results: Nine RCTs and nine quasi-experimental studies were included. A variety of non-invasive peripheral and central neuromodulation techniques were investigated in those studies, including scrambler therapy, electrical stimulations, photobiomodulation, magnetic field therapy, therapeutic ultrasound, neurofeedback, and repetitive transcranial magnetic stimulation. Non-invasive neuromodulation techniques for the management of established CIPN are generally safe and feasible. The efficacy of peripheral neuromodulation techniques such as scrambler therapy and transcutaneous electrical nerve stimulation was mostly unsatisfactory, while central neuromodulation techniques such as neurofeedback and repetitive transcranial magnetic stimulation were promising.
Conclusions: The use of non-invasive neuromodulation techniques for managing CIPN is still in its infancy. Non-invasive central neuromodulation techniques have significant potential for relieving chronic pain and neuropathic symptoms related to CIPN, meriting further exploration.

1. Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a disabling side effect that often occurs in patients who have received an anti-cancer treatment with neurotoxic agents, including the widely used platinum compounds, taxanes, vinca alkaloids, protease inhibitors, or anti-angiogenesis (Staff et al., 2017). Although CIPN improves in most patients over time, long-term follow-up data have shown that 27%–58% of patients with cancer still suffered from CIPN five years after the end of chemotherapy (Shah et al., 2018; Bennedsgaard et al., 2020a, 2020b). Persistent and severe CIPN can cause anxiety and depression, and increase the risk of falling, hence jeopardizing the functions and quality of life of patients (Kolb et al., 2016; Winters-stone et al., 2017). Unfortunately, no prophylaxis or cure for CIPN is available at present (Loprinzi et al., 2020a). Given that cancer survival rates are increasing (Allemani et al., 2018), pain and symptom management for patients with CIPN has become an important topic.

In the National Cancer Institute's Clinical Trials Planning Meeting, experts encouraged further research into non-pharmacological interventions for relieving CIPN-related pain and symptoms, taking patient preferences into consideration, in order to address accompanying functional impairments and improve the quality of life of patients (Dorsey et al., 2019). Currently, numerous studies have tested an array of non-pharmacological interventions for CIPN, such as acupuncture (Chien et al., 2019; Molassiotis et al., 2019a), exercise (Lin et al., 2021; Tanay et al., 2021), and behavioral therapy (Tanay et al., 2021);

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https://doi.org/10.1016/j.ejon.2022.102124
Received 7 March 2022; Received in revised form 16 March 2022; Accepted 17 March 2022
Available online 29 March 2022
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however, no consensus has been reached on their effectiveness due to conflicting results, the heterogeneity of the study interventions and participants, underpowered sample sizes, a lack of sham controls, and/or unclear mechanisms of action. Therefore, in addition to conducting more rigorous trials to verify these interventions, exploring novel treatment options is of equal importance.

Studies have shown that CIPN-related pain and symptoms result from peripheral nerve deficits (Kroigard et al., 2020; Bennedsgaard et al., 2020a) and central maladaptive plasticity (Boland et al., 2014; Nudelman et al., 2016). This implies that neuromodulation, an approach that can directly modify neurological function through the delivery of physical stimuli (i.e., electrical, magnetic, optical, thermal, and acoustic) (North et al., 2021), could be a promising strategy. Neuromodulation can be invasive (i.e., surgical procedures are needed) or non-invasive (i.e., surgical procedures are not needed). Non-invasive neuromodulation techniques applying electrical or electromagnetic pulses as stimuli are common in pain research and treatments, which include transcutaneous electrical nerve stimulation (TENS), interferential current therapy, and scrambler therapy targeting the peripheral nervous system, as well as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) targeting the central nervous system (Pacheco-barrios et al., 2020; Knotkova et al., 2021).

Hypothetically, TENS and interferential current therapy were developed based on the gate control theory, with the aim of inhibiting the transmission of pain signals by stimulating A-beta fibers, while scrambler therapy involves applying artificial neurons to mimic non-pain signals, following the Active Principle of Information. These signals can be transmitted to the brain through C fibers to produce an analgesic effect (Marineo, 2019; Min et al., 2021; Tella et al., 2021). As for the two non-invasive central neuromodulation techniques, i.e., rTMS and tDCS, they were developed based on the neuromatrix theory, to modulate the processing of pain by the brain (Plow et al., 2012). Other novel non-invasive neuromodulation techniques, including low-level light therapy or photobiomodulation (Cheng et al., 2021), focused therapeutic ultrasound (Blackmore et al., 2019), and neurofeedback (Patel et al., 2020) also demonstrated efficacy in relieving pain.

Despite the growing number of studies on non-invasive neuromodulation, these techniques remain novel in the field of CIPN. Although current systematic reviews have evaluated evidence on the use of pharmacological and non-pharmacological interventions in CIPN (Jones et al., 2022; Tamburin et al., 2021), they only consider randomized controlled trials (RCTs) for inclusion, which means that some newly emerging techniques might not have been identified. This systematic review was conducted to summarize the best available evidence on the use of non-invasive neuromodulation techniques in patients with CIPN.

2. Methods

The protocol of this systematic review is registered in PROSPERO (CRD42021264187). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021) were followed in reporting the review.

2.1. Eligibility criteria

Inclusion criteria were described following the participants (P), interventions (I), comparisons (C), outcomes (O), and study design (S) formula, as presented below:

- **P:** patients (age ≥18) with cancer who have developed CIPN after receiving chemotherapy with neurotoxic agents. The diagnostic criteria of CIPN can be either pertinent pain and symptoms reported by patients or neurological signs assessed by clinicians.
- **I:** non-invasive peripheral (TENS, interferential current therapy, scrambler therapy, magnetic field therapy, low-level light therapy/photobiomodulation, and focused ultrasound) and central (rTMS, and neurofeedback) neuromodulation techniques. Studies involving acupuncture and electroacupuncture were excluded, as these approaches are invasive.
- **C:** passive comparison (usual care or wait-list without treatment), active comparison (sham or alternative intervention), or no comparison.
- **O:** safety, feasibility, acceptability, and/or efficacy of non-invasive neuromodulation techniques. Safety outcomes included a number of adverse events that were reported as relevant to non-invasive neuromodulation techniques. Feasibility outcomes included eligibility rate, recruitment rate, retention rate, attrition rate, adherence rate, and satisfaction. Efficacy outcomes included the overall severity of CIPN, pain and other related symptoms, function, and quality of life.
- **S:** experimental studies, i.e., parallel or crossover RCTs and pilot studies with a randomized controlled design, and quasi-experimental studies, i.e., non-RCTs and single-arm pretest-posttest studies.

2.2. Information sources and search strategy

Seven electronic databases, namely AMED via Ovid, CINAHL via EBSCO Host, the Cochrane Library, Embase, PEDro, PubMed, and the Web of Science were searched for original reports published in peer-reviewed journals from the date of inception of the database up to the search date (October 17, 2021). The terms used for the search included "chemotherapy", "neuropathy", "non-invasive neuromodulation", and synonyms that represented the population and intervention of interest. The relevant subject headings and keywords were used in combination to build the search string. A full description of the search strategies is presented in the online Appendix I. The reference lists of the retrieved studies that were included for an appraisal of their methodological quality were manually searched for additional relevant studies. No limits on date and language of publication were set for the search. The literature search was updated on March 2, 2022.

2.3. Study selection

Duplicate checking of full records from the initial search was performed by a reviewer (MW) using EndNote X9 software (Clarivate Analytics, PA, USA). Two independent reviewers (MW and ZP) then screened the titles and abstracts of the remaining records against the eligibility criteria. The full text was obtained of studies that were considered eligible for inclusion by at least one of the reviewers. The full-text reports were read by the two reviewers (MW and ZP) independently to determine which ones merited inclusion. In cases of disagreement between the two reviewers, a third reviewer (AM) was consulted to achieve consensus.

2.4. Risk of bias assessment

The second version of the Cochrane tool (RoB 2.0) was used to assess the risk of bias in the included RCTs in terms of randomization process, intended interventions, completeness of outcome data, outcome measurement, and selective reporting, using grades of low, high, or some concerns (Sterne et al., 2019). The results were visualized using robvis (McGuinness and Higgins, 2021). The Critical Appraisal Checklists of the Joanna Briggs Institute (JBI) were used to assess the methodological risk of bias of the included quasi-experimental studies (Aromataris and Munn, 2020). The assessment was independently conducted by three reviewers (MW, YY, and HY). In cases of disagreement, discussions were held between all members of the review team in order to reach a consensus.

2.5. Data extraction

Data extraction was completed by one reviewer (MW) and independently checked by the other two reviewers (YY and HY). Data extracted from the included studies were: first author, year and country of publication, study design, sample size and characteristics, components of the intervention and the comparator, outcome measures, and main findings. Discrepancies were addressed through discussions among the review team.

2.6. Data synthesis

Feasibility, acceptability, and safety outcomes were summarized using number and percentage according to the documented data. A narrative synthesis of efficacy outcomes was used given the heterogeneity of the included studies in terms of participants, interventions, comparators, and measurements. The results were tabulated and analyzed according to similarities in the types of interventions and/or outcomes.

3. Results

3.1. Study inclusion

The search entries returned a total of 2,264 records, from which 19 reports involving 17 studies were identified (Fig. 1). To avoid over-reporting, this systematic review refers to studies instead of reports. Two studies (Coyne et al., 2013; Lee et al., 2016) enrolled patients with pain whether or not related to CIPN; this review only considers data from those with pain related to CIPN. One RCT (Argenta et al., 2017) allowed participants in the control group to cross over to receive photobiomodulation plus physiotherapy after the main trial period; this review only included data from the main trial. In addition, one more study (Gabrys, 2004) was identified from manually searching the reference lists of the included studies. In the end, a total of 18 studies were included in this systematic review. The updated search did not identify any more eligible studies.

3.2. Methodological characteristics of the included studies

The methodological characteristics of the included studies are shown in Table 1. Nine (50%) of the 18 studies adopted an RCT design (Lindblad et al., 2016; Argenta et al., 2017; Rick et al., 2017; Prinsloo et al., 2017, 2018; Tonezzer et al., 2017; Loprinzi et al., 2020b; Childs et al., 2021; Smith et al., 2020; Song et al., 2020; Al Onazi et al., 2021), while nine (50%) adopted a quasi-experimental design (Smith et al., 2010; Coyne et al., 2013; Pachman et al., 2015a; Geiger et al., 2015; Lee et al., 2016; Wong et al., 2016; Gewandter et al., 2019; Gabrys, 2004; Goto et al., 2020). Nevertheless, four of the nine RCTs (44%) were found to be pilot studies (Al Onazi et al., 2021; Childs et al., 2021; Loprinzi et al., 2020b; Prinsloo et al., 2017, 2018; Smith et al., 2020). One study (Tonezzer et al., 2017) actually adopted a randomized controlled design, yet was labeled a "preliminary case-control study" in the title. Of the nine quasi-experimental studies, seven (39%) adopted a single-arm pretest-posttest design (Smith et al., 2010; Coyne et al., 2013; Pachman et al., 2015a; Geiger et al., 2015; Lee et al., 2016; Gewandter et al., 2019; Gabrys, 2004), one used randomization to address the possibility of selection bias on the part of the participants for the intervention of interest (i.e., acupuncture-like transcutaneous nerve stimulation, ALTENS), rather than to facilitate comparisons of treatment efficacy between the two arms of the study (Wong et al., 2016). The remaining study used randomization to allocate the sequence of the intervention sessions (Goto et al., 2020).

A total of 688 patients with CIPN were involved in the included

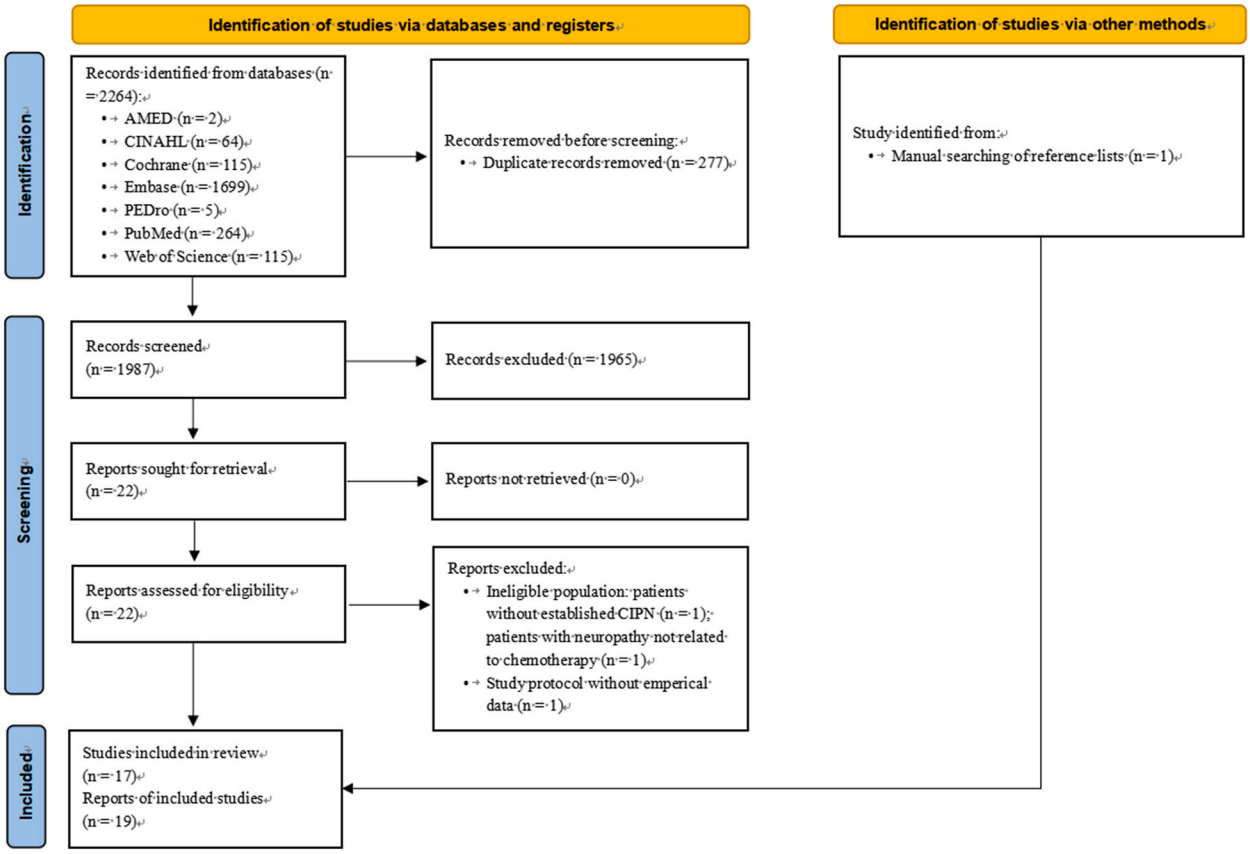

Fig. 1. PRISMA flow diagram of the study selection process.

Table 1
Methodological characteristics of the included studies.

Study/ country	Design	Sample size	Median age	Female sex	Cancer type	Neurotoxic agent:	Chemotherapy status	CIPN criteria	Intervention	Comparator
Al Onazi et al. (2021) Canada	Pilot RCT	EG: 16 CG: 15	60.5 y	EG: 10 (63%) CG: 9 (60%)	Colorectal	Oxaliplatin	EG: 12 (75%) ended CG: 10 (67%) ended	NCI-CTCAE grades 1–3	**Therapeutic ultrasound** • 3 MHz frequency, 0.7 to 0.8 w/cm^2 intensity, 5 min/ location, 10 consecutive daily sessions (Monday to Friday) in 2 weeks • Target: the fingers and toes/base of the feet with CIPN **Standard care** • Home exercise and balance training, 15–20 min/day, for 6 weeks	**Standard care** • Home exercise and balance training, 15–20 min/day, for 6 weeks
Argenta et al. (2017) [aa] United States	RCT	EG: 30 CG: 40	≥18 y	70 (100%)	Mixed	Taxanes, platinum compounds	100% ended	Self-reported symptoms	**Photobiomodulation** • 1 cm from the skin for 1–12 min, 6.75–12 W power, 20,000 Hz pulsed waveforms or continuous waveforms with 800–970 nm wavelengths, 3 times/ week for 6 weeks, with a total of 18 treatments • Target: the lumbar and sacral spine, legs, and feet with CIPN	**Sham** • Delivered in an identical manner using a ceramic heat probe
Childs et al. (2021) [†] United States	Crossover analysis of a pilot RCT	EG: 10 CG: 12	61 y	EG: 8 (80%) CG: 9 (75%)	NR	Paclitaxel, oxaliplatin, other	100% ended	≥4 on 0–10 NRS of tingling/pain in 7 days before enrollment	**Scrambler therapy** • Greatest tolerable intensity, 30 min/ session, 10 consecutive daily sessions (Monday to Friday) in 2 weeks • Target: extremities with CIPN	**TENS** • Administered by participants at the most symptomatic areas, 30 min/ day, for 14 days
Coyne et al. (2013) [b] United States	Single-arm pilot trial	33	NR	NR	NR	NR	NR	>5 on 0–10 NRS of pain or at least "a little bit" numbness on EORTC QLQ-CIPN20 for ≥2 weeks	**Scrambler therapy** • Greatest tolerable intensity, 60 min/ session, 10 consecutive daily sessions (Monday to Friday) in 2 weeks • Target: extremities with CIPN	N/A
Gabrys (2004) Germany	Single-arm pilot trial	44	NR	NR	Mixed	Taxanes, cisplatin, vinca alkaloids	100% ended	Self-reported symptoms	**Magnetic field therapy** • ≤ 33 mT intensity, 3 sessions (morning and evening)/day, for 4 weeks • Target: lower extremities with CIPN	N/A
Geiger et al. (2015) Germany	Single-arm pilot trial	20	59 y	5 (25%)	NR	Taxanes, platinum compounds	100% ended	NCI-CTCAE grade 1-3	**Magnetic field therapy** • 4–12 Hz and 200 mT intensity, 5 min/ session, 2 sessions (morning and evening)/day, for 10–28 days • Target: extremities with CIPN	N/A
Gewandter et al.		29	56 y	17 (59%)	NR	Taxanes, platinum	100% ended	≥4 on 0–10 NRS of pain,	**TENS**	N/A

(*continued on next page*)

Table 1 (*continued*)

Study/ country	Design	Sample size	Median age	Female sex	Cancer type	Neurotoxic agent:	Chemotherapy status	CIPN criteria	Intervention	Comparator
(2019) United States	Single-arm feasibility study					compounds, other		tingling, numbness, or cramping in 7 days before enrollment	• Stimulation intensity as 2 times the participant's sensation threshold, 60 min/session, 2 sessions (morning and evening)/day, for 6 weeks, or continuously wear the device in the 1-h treatment and 1-h rest format, 3–12 h/day, from week 4–6 • Target: lower extremities with CIPN	
Goto et al. (2020) Japan	Single-arm Four-way crossover study	11	65 y	11 (100%)	Mixed	Taxanes, oxaliplatin	100% ended	NCI-CACAE grade ≥2 and ≥30 mm on 0–100 mm VAS of pain or dysesthesia	**rTMS** • Figure-8 coil at lateral-medial direction, 90% resting motor threshold intensity, 5 Hz frequency, 10 trains of 10-s biphasic pulses, 50 s intertrain interval, a total of 500 pulses per session • Target: primary motor cortex contralateral to the most affected extremity	**rTMS** • Figure-8 shape coil at posterior-anterior directions with 90% or 100% resting motor threshold intensity, 5 Hz frequency, 10 trains of 10-s biphasic pulses, 50 s intertrain interval, a total of 500 pulses per session • Target: primary motor cortex contralateral or ipsilateral to the most affected extremity
Lee et al. (2016) [b] South Korea	Single-arm pilot study	6	62 y	3 (50%)	Mixed	Oxaliplatin, vincristine, thalidomide	100% ended	painDETECT score ≥19 and ≥4 on 0–10 NRS of average daily pain for ≥6 months but stable ≥2 weeks	**Scrambler therapy** • Greatest tolerable intensity, 40 min/ session, 10 consecutive daily sessions (Monday to Friday) in 2 weeks • Target: extremities with CIPN	N/A
Lindblad et al. (2016) Sweden	RCT	IG: 34 CG: 33	64 y	EG: 17 (50%) CG: 17 (52%)	Mixed	Taxanes, platinum compounds, vinca alkaloids, capecitabine	100% ended	Self-reported symptoms and clinical assessment	**ITH** • 0–100 Hz frequency interferential currents, strong but tolerable intensity, 15 min/lower extremity, for 12 weeks • High-power long-wave diathermy, 6 min/session for 12 weeks • Target: lower extremities with CIPN	**Placebo** • Low-power long-wave diathermy 6 min/session for 12 weeks
Loprinzi et al. (2020) [†] United States	Pilot RCT	EG: 24 CG: 22	61.5 y	EG: 17 (71%) CG: 17 (77%)	NR	Taxanes, platinum compounds, bortezomib, other	100% ended	≥4 on 0–10 NRS of tingling/pain in 7 days before enrollment	**Scrambler therapy** • Greatest tolerable intensity, 30 min/ session, 10 consecutive daily sessions (Monday to Friday) in 2 weeks • Target: extremities with CIPN	**TENS** • Administered by participants at the most symptomatic areas, 30 min/ day, for 14 days
Pachman et al. (2015)	Single-arm pilot trial	37	58 y	25 (68%)	Mixed	Taxanes, platinum	100% ended	≥4 on 0–10 NRS of tingling/pain in	**Scrambler therapy**	N/A

(*continued on next page*)

Table 1 (*continued*)

Study/ country	Design	Sample size	Median age	Female sex	Cancer type	Neurotoxic agent:	Chemotherapy status	CIPN criteria	Intervention	Comparator
United States						compounds, vincristine		7 days before enrollment	• Greatest tolerable intensity, 30 min/ session, 10 consecutive daily sessions (Monday to Friday) in 2 weeks • Target: extremities with CIPN	
Prinsloo et al. (2017) ‡ United States	Wait-list pilot RCT	EG: 35 CG: 36	62.5 y	EG: 31 (89%) CG: 31 (86%)	Mixed	Taxanes, platinums, other	100% ended	NCI-CTCAE grade 3 or ≥ 4 on 0–10 NRS of pain	**Scrambler therapy** • Participants were guided to maintain the reward EEG waveform and reduce other EEG waveforms through a game with visual and auditory feedback based on the quantitative EEG results, 45 min/ session, at least 2 times/week, 20 sessions in total, for a maximum of 10 weeks • Target: brain	**Usual care (wait list)**
Prinsloo et al. (2018) ‡ United States	Long-term follow-up of a wait-list pilot RCT	EG: 35 CG 36	62.5 y	EG: 31 (89%) CG: 31 (86%)	Mixed	Taxanes, platinums, other	100% ended	NCI-CTCAE grade 3 or ≥ 4 on 0–10 NRS of pain	**Neurofeedback** • Participants were guided to maintain the reward EEG waveform and reduce other EEG waveforms through a game with visual and auditory feedback based on the quantitative EEG results, 45 min/ session, at least 2 times/week, 20 sessions in total, for a maximum of 10 weeks • Target: brain	**Usual care (wait list)**
Rick et al. (2017) Germany	Phase-III RCT	EG: 21 CG: 23	58 y	EG: 15 (71%) CG: 16 (70%)	Mixed	Taxanes, platinum compounds, vinca alkaloids, other	100% ended	NCI-CTCAE grades 1–4	**Magnetic field therapy** • 4–12 Hz and 420 mT intensity, 5 min/ session, 2 sessions (morning and evening)/day, for 3 months • Target: extremities with CIPN	**Placebo** • Delivered in an identical manner using an identical device, except without a magnetic part
Smith et al. (2010) United States	Single-arm pilot trial	18	59 y	14 (78%)	Mixed	Taxanes, platinum compounds, bortezomib, thalidomide, vincristine, other	100% ended	Self-reported average daily pain score ≥5 of 10 for ≥1 month	**Scrambler therapy** • Greatest tolerable intensity, 60 min/ session, 10 consecutive daily sessions (Monday to Friday) in 2 weeks • Target: extremities with CIPN	N/A
Smith et al. (2020) United States	Pilot RCT	EG: 17 CG: 18	59.5 y	EG: 11 (65%) CG: 15 (83%)	Mixed	NR	100% ended	>4 on 0–10 NRS of average daily CIPN symptoms over the past week	**Scrambler therapy** • Greatest tolerable intensity, 30 min/ session, 10 consecutive daily sessions (Monday to Friday) in 2 weeks • Target: extremities with CIPN	**Sham** • Delivered using an identical manner except for the positioning of electrodes across the L2-5 region for leg pain and C5-8 for hand/ arm pain in an "X" shape

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Table 1 (*continued*)

Study/ country	Design	Sample size	Median age	Female sex	Cancer type	Neurotoxic agent:	Chemotherapy status	CIPN criteria	Intervention	Comparator
Song et al. (2020) South Korea	RCT	EG: 36 CG: 36	50 y	72 (100%)	Breast	Docetaxel, paclitaxel	100% ended	≥5 on 0–10 NRS of average pain within the first week after completion of chemotherapy	**Low-frequency electrostimulation** • 100 μA intensity, 40 Hz frequency, ≥ 2 times/day, ≥ 120 min (including a 60 min continuous stimulation), for over 14 days • Target: unilateral PC6 acupoint above the wrist crease	**Sham** • Delivered in an identical manner with an identical device
Tonezzer et al. (2017) Brazil	RCT	EG: 11 CG: 13	49.5 y	EG: 3 (27%), CG: 2 (15%)	Mixed	Paclitaxel, oxaliplatin	100% ongoing	NCI-CACAE grade 1 or 2 and ≥2 on 0–10 VAS of paresthesia/ pain	**TENS** • Symmetrical biphasic waveform, 7–65 Hz frequency, 200 μs pulse width, delivered at the greatest tolerable intensity, 60 min/day, for 45 days • Target: extremities with CIPN	**Placebo** • Device produced a stimulation current for only 30s, then decreased to 0 intensity in 15s
Wong et al. (2016) [c] Canada	Quasi-experimental study	30	58 y	NR	Mixed	Taxanes, platinum compounds, vinorelbine	100% ended	Self-reported symptoms	**Acupuncture-like TENS** • Square electrical pulses, 250 ms duration, 4 Hz repetition rate, random switching among electrodes every 10 s 20 min/ session, for a total of 12 sessions over 6–8 weeks • Target: acupoints including T7, L3, LI 4, LIV 3, LI 11, and/or ST 36	N/A

Note. CG = control group; CIPN = chemotherapy-induced peripheral neuropathy; EG = experimental group; N/A = not applicable; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NRS = numerical rating scale; NR = not reported; RCT = randomized controlled trial; TENS = transcutaneous electrical nerve stimulation.

[†] Reports from the same RCT.

[‡] Reports from the same RCT.

[a] Only included data from the main trial.

[b] Only included data from patients with chemotherapy-induced peripheral neuropathy.

[c] Only included data from the acupuncture-like transcutaneous electrical nerve stimulation group.

studies, with the number ranging from 24 to 72 in the RCTs, and from 6 to 44 in the quasi-experimental studies. These studies were conducted between 2004 and 2018 in the United States (n = 8), Canada (n = 2), Germany (n = 3), Sweden (n = 1), Japan (n = 1), South Korea (n = 2), and Brazil (n = 1). Most (17/18, 94%) were published in English, while one was published in German.

3.3. Risk of bias within the included studies

Among the included RCTs, a risk of bias was identified in all domains (Fig. 2). Two of the included RCTs (Lindblad et al., 2016; Rick et al., 2017) did not provide sufficient information regarding randomization and allocation concealment. In one RCT (Tonezzer et al., 2017) there were more participants with a lower performance status (Eastern Cooperative Oncology Group Performance Status scale score = 2) in the control group (n = 5) than in the experimental group (n = 0) at baseline. The blinding of the participants, intervention provider, and outcome assessor was a major concern, with only two RCTs (Tonezzer et al., 2017; Song et al., 2020) meeting all of the criteria. One RCT (Lindblad et al., 2016) did not provide sufficient information on the reasons why some participants withdrew from the study. Two RCTs (Prinsloo et al., 2017, 2018; Loprinzi et al., 2020b; Childs et al., 2021) did not use an intention-to-treat analysis, although some participants dropped out of the study after randomization.

Overall, the methodological risk of bias of the quasi-experimental studies was low because most of the assessment criteria were met (Table 2). However, none of these studies adopted an independent control group. Wong et al.'s (2016) study included an acupuncture group; however, direct comparisons were not made between the tested neuromodulation technique (i.e., ALTENS) and acupuncture. Goto et al. (2020) used multiple self-controlled observations to evaluate the efficacy of different modes of rTMS. Statistical methods were not clearly presented in Geiger et al.'s (2015) study. Gabrys' (2004) study only used descriptive statistics to present the proportion of responders among the participants.

3.4. Characteristics of the participants

In the studies with relevant data, the mean age of the included participants ranged from 50 to 65 years. In most (11/18, 61%) of the

included studies, there were more female than male participants, while three studies only enrolled female participants (Argenta et al., 2017; Goto et al., 2020; Song et al., 2020). There were a variety of types of cancer and neurotoxic agents among the participants in most (15/18, 83%) of the studies. Remarkably, Tonezzer et al. (2017) enrolled a larger proportion of male patients with breast cancer than female patients. Gabrys (2004) provided no detailed information regarding the demographic and clinical characteristics of the study participants, although the researcher stated that the participants were mainly patients who had been diagnosed with breast or gynecological cancer and had been treated with taxane- or cisplatin-based chemotherapy. There were also patients who had been diagnosed with lymphoma and had been treated with vinca alkaloids.

A quasi-experimental study involving patients with different pain conditions also did not report demographic and clinical characteristics specific to those with CIPN (Coyne et al., 2013). Of the remaining two studies, one focused on patients with breast cancer who had been treated with taxanes (i.e., docetaxel or paclitaxel) (Song et al., 2020), while the other only included patients with colon or rectal cancer who had been treated with oxaliplatin (Al Onazi et al., 2021). Participants had completed neurotoxic chemotherapy in the majority (n = 15, 83%) of the included studies, except for three studies that either included patients who were undergoing neurotoxic chemotherapy (Tonezzer et al., 2017; Al Onazi et al., 2021) or lacked relevant information (Coyne et al., 2013). The criteria for the inclusion of participants with CIPN were based on patient-reported symptoms in 11 (61%) studies (Argenta et al., 2017; Loprinzi et al., 2020b; Childs et al., 2021; Smith et al., 2010, 2020; Song et al., 2020; Coyne et al., 2013; Pachman et al., 2015a; Lee et al., 2016; Wong et al., 2016; Gewandter et al., 2019; Gabrys, 2004), and on a clinical assessment in three studies (Rick et al., 2017; Al Onazi et al., 2021; Geiger et al., 2015). One study (Prinsloo et al., 2017, 2018) used either patient-reported symptoms or a clinical assessment, while three studies (Lindblad et al., 2016; Tonezzer et al., 2017; Goto et al., 2020) used a combination of patient-reported symptoms and a clinical assessment to select participants with CIPN. The course of CIPN varied from 3 to 228 months among the studies that provided relevant data. Detailed characteristics of the participants are presented in Table 1.

3.5. Characteristics of interventions and comparators

There was considerable variation in the types of non-invasive neuromodulation techniques investigated by the studies, with the majority (n = 15, 88%) targeting the peripheral nerves. Scrambler therapy, a non-invasive peripheral neuromodulation technique, was used in two RCTs (Loprinzi et al., 2020b; Childs et al., 2021; Smith et al., 2020) and four single-arm pretest-posttest studies (Smith et al., 2010; Coyne et al., 2013; Pachman et al., 2015a; Lee et al., 2016). Transcutaneous electrical nerve stimulation was used as the study intervention in one RCT (Tonezzer et al., 2017) and two quasi-experimental studies (Wong et al., 2016; Gewandter et al., 2019). In two of the studies TENS was delivered in the symptomatic area of the extremities (Tonezzer et al., 2017; Gewandter et al., 2019), while in one study TENS was delivered at acupoints (i.e., ALTENS) (Wong et al., 2016). Other electrical stimulation modalities used in the included studies were interferential currents, combined with long-wave diathermy (Lindblad et al., 2016) and low-frequency electrostimulation (Song et al., 2020). Magnetic field therapy, a pulsed electromagnetic technique, was used in two single-arm pretest-posttest studies (Gabrys, 2004; Geiger et al., 2015) and one RCT (Rick et al., 2017). Photobiomodulation (a light-based neuromodulation technique) and therapeutic ultrasound were used in the RCTs of Argenta et al. (2017) and Al Onazi et al. (2021), respectively. Only two studies examined non-invasive modulation techniques targeting the central nervous system (CNS), including neurofeedback and rTMS.

In terms of comparators, six of the nine included RCTs (Argenta et al., 2017; Lindblad et al., 2016, Rick et al., 2017; Smith et al., 2020; Song et al., 2020; Tonezzer et al., 2017) used sham or placebo stimulation, while one RCT (Childs et al., 2021; Loprinzi et al., 2020b) used TENS as a comparator. Another RCT (Al Onazi et al., 2021) used standardized care that included home-based exercise and balance training. The remaining one RCT (Prinsloo et al., 2017, 2018) used the usual care as the wait-list control. Detailed characteristics of the interventions and comparators are presented in Table 1.

3.6. Safety

In general, non-invasive neuromodulation techniques are safe for use in managing CIPN. Four studies reported adverse events related to the study interventions. The RCT conducted by Loprinzi et al. (2020b) reported mild skin reactions in two participants after receiving the scrambler therapy, while two participants in the control group experienced sensations of discomfort such as a burning feeling or restlessness in the treated extremities after receiving TENS. However, safety data were not reported in the crossover phase of the study (Childs et al., 2021). In the studies of Gewandter et al. (2019) and Wong et al. (2016) dermatitis or sensations of discomfort were also found in a few participants after receiving TENS. One participant in Gabrys' (2004) study experienced a slight cardiac sensation at the beginning of receiving pulsed magnetic field therapy. Nevertheless, all of the adverse events reported in included studies were mild and were likely to diminish once the interventions were terminated. Eight studies reported no adverse events related to the study intervention, while six studies did not provide safety data. Detailed results of the safety outcomes are presented in Table 3.

3.7. Feasibility and acceptability

All of the included studies provided data on at least one feasibility outcome, although in the study of Coyne et al. (2013) the data were not specifically for patients with CIPN. Eight of the included studies reported a recruitment rate of 59%–100% (Table 3). The low recruitment rate reported by Childs et al. (2021) was because it involved the crossover phase of an RCT, in which a considerable proportion (24/46, 52%) of the participants no longer met the inclusion criteria or could not be reached after the initial phase of the RCT. Retention rates in the included studies ranged from 44% to 100%. The main reasons for participant attrition were deviations from the protocol, withdrawal of consent, low adherence, logistics issues, and a worsening health condition. One study (Gewandter et al., 2019) reported that two participants withdrew due to worsening symptoms after receiving TENS.

Seven studies provided information on the acceptability of the study

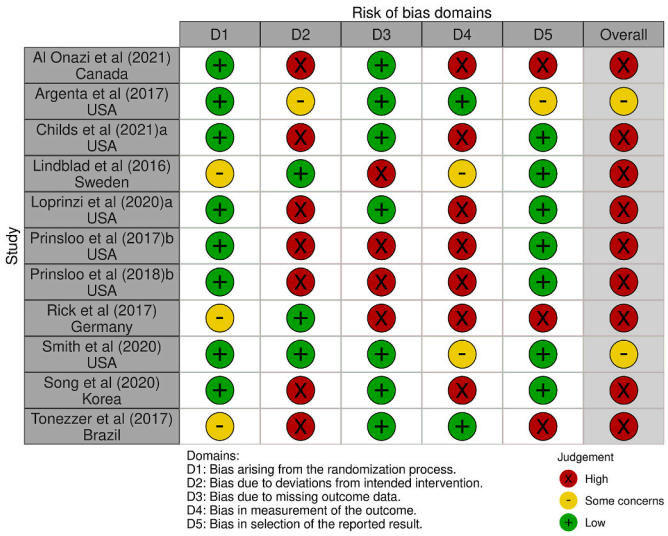

Fig. 2. Risk of bias in the included randomized controlled trials.

Table 2
Critical appraisal of included quasi-experimental studies.

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
Gabrys (2004)	Y	Y	N/A	N	Y	Y	Y	Y	N
Smith et al. (2010)	Y	Y	N/A	N	Y	Y	Y	Y	Y
Coyne et al. (2013)	Y	Y	N/A	N	Y	Y	Y	Y	Y
Pachman et al. (2015)	Y	Y	N/A	N	Y	Y	Y	Y	Y
Geiger et al. (2015)	Y	Y	N/A	N	Y	Y	Y	Y	U
Lee et al. (2016)	Y	Y	N/A	N	Y	Y	Y	Y	Y
Gewandter et al. (2019)	Y	Y	N/A	N	Y	Y	Y	Y	Y
Wong et al. (2016)	Y	Y	N/A	N	Y	Y	Y	Y	Y
Goto et al. (2020)	Y	Y	Y	N	Y	Y	Y	Y	Y
Total %	100	100	100	0	100	100	100	100	78

Note. Y = yes; N = no; U = unclear.
JBI critical appraisal checklist for quasi-experimental studies: Q1 = Is it clear in the study what is the "cause" and what is the "effect" (i.e., there is no confusion about which variable comes first)? Q2 = Were the participants who were included in any comparisons similar to each other? Q3 = Were the participants who were included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest? Q4 = Was there a control group? Q5 = Were there multiple measurements of the outcome both prior to and after the intervention/exposure? Q6 = Was the follow-up complete and if not, were differences between the groups in terms of their follow-up adequately described and analyzed? Q7 = Were the outcomes of the participants included in any comparisons measured in the same way? Q8 = Were outcomes measured in a reliable way? Q9 = Was an appropriate method of statistical analysis used?.

intervention. Gewandter et al.'s (2019) study demonstrated that TENS was generally acceptable to the participants. Two studies (Loprinzi et al., 2020b; Smith et al., 2020) indicated that scrambler therapy also has good acceptability and was more likely to be recommended by participants than TENS. Good adherence among the participants to photobiomodulation (Argenta et al., 2017), therapeutic ultrasound (Al Onazi et al., 2021), neurofeedback (Prinsloo et al., 2017), and rTMS (Goto et al., 2020) was shown in four other studies. Detailed results of the feasibility outcomes are presented in Table 3.

3.8. Efficacy

3.8.1. Overall severity of CIPN

A total of 11 studies reported the efficacy of non-invasive neuromodulation techniques on the overall severity of CIPN, including seven RCTs and four quasi-experimental studies. The detailed results are summarized in Table 3.

A comparable effect between scrambler therapy and TENS or sham stimulation on the patient-reported overall severity of CIPN was identified in two RCTs (Loprinzi et al., 2020b; Smith et al., 2020). Similarly, it was shown in two RCTs (Tonezzer et al., 2017; Song et al., 2020), respectively, that TENS and low-frequency electrostimulation did not contribute to bringing about a greater improvement in patient-reported CIPN compared with a placebo or sham stimulation. However, the results were just the opposite in quasi-experimental studies, which suggested that scrambler therapy (Coyne et al., 2013) and TENS (Wong et al., 2016; Gewandter et al., 2019) can help to reduce the overall severity of CIPN.

In one RCT (Argenta et al., 2017) it was found that, compared with sham stimulation, photobiomodulation significantly improved the compositely measured CIPN, and the significance persisted to the 16-week follow-up. That magnetic field therapy can reduce the patient-reported severity of CIPN was found in one RCT (Rick et al., 2017) and one single-arm study (Geiger et al., 2015). In one RCT (Al Onazi et al., 2021) it was found that adding therapeutic ultrasound to home exercise contributed to a greater improvement than home exercise alone in patient-reported CIPN, but the difference had not persisted at the 6-week follow-up.

3.8.2. Pain and symptoms

The efficacy of non-invasive neuromodulation techniques for pain and relevant symptoms was reported in a total of 15 studies, including seven RCTs and eight quasi-experimental studies. The detailed results are summarized in Table 3.

In a crossover RCT (Loprinzi et al., 2020b; Childs et al., 2021), it was shown that there was no significant difference between scrambler therapy and TENS in the proportion of patients achieving a ≥50% reduction in pain scores. Smith et al. (2020), in their RCT, also found no statistically significant difference between scrambler therapy and sham stimulation in alleviating pain related to CIPN. In contrast, all four single-arm studies (Smith et al., 2010; Coyne et al., 2013; Pachman et al., 2015a; Lee et al., 2016) indicated that scrambler therapy can help to relieve the pain and sensory symptoms associated with CIPN.

Tonezzer et al.'s (2017) RCT showed that the effects of TENS on pain and sensory symptoms related to CIPN were not significantly different to those of a placebo, whereas Gewandter et al.'s (2019) single-arm study supported the efficacy of TENS on pain and sensory symptoms related to CIPN. In their quasi-experimental study, Wong et al. (2016) did not find that ALTENS can significantly relieve general pain in patients with CIPN. Song et al.'s (2020) RCT showed that low-frequency electrostimulation was no better than sham stimulation for symptoms related to CIPN. Lindblad et al. (2016) demonstrated in their RCT that there was no significant difference between the effects of interferential therapy plus high-power long-wave diathermy and placebo on pain and sensory symptoms related to CIPN.

In a single-arm study (Gabrys, 2004), 27% (n = 12/44) of the participants had a >50% reduction in their pain score after undergoing magnetic field therapy. However, the analgesic effect of magnetic field therapy on pain related to CIPN was neither supported by an RCT (Rick et al., 2017) nor by another single-arm study (Geiger et al., 2015).

Prinsloo et al.'s (2017, 2018) RCT showed that compared with a wait-list control, neurofeedback could significantly relieve pain and sensory symptoms associated with CIPN, with a moderate to large effect size. The between-group difference remained significant at the first and fourth months of follow-up (Prinsloo et al., 2018). In addition, subjects receiving neurofeedback experienced greater improvements in general cancer-related symptoms and fatigue than did the wait-list group at the fourth-month follow-up (Prinsloo et al., 2018). In a quasi-experimental study, Goto et al. (2020) found that 5 Hz excitatory rTMS delivered in the posterior-anterior and lateral-medial directions over the primary motor cortex with an intensity of 90% in the resting motor threshold can significantly relieve pain and dysesthesia related to CIPN in the target extremity.

3.8.3. Nerve function and balance

A total of seven studies reported the efficacy of non-invasive neuromodulation techniques on nerve function, including two RCTs and five quasi-experimental studies. The detailed results are summarized in Table 3. In a single-arm study (Pachman et al., 2015a), no significant improvement in vibration sensitivity was found after scrambler therapy. Another single-arm study (Gewandter et al., 2019) demonstrated that TENS could significantly restore large fiber function and tactile

Table 3
Safety, feasibility, and efficacy of non-invasive neuromodulation techniques.

Neuromodulation (vs. comparator)	Study	Relevant AE	Feasibility	Efficacy			
				Overall severity of CIPN	Pain and symptoms	Function	Quality of life
Scrambler therapy (vs. TENS)	Loprinzi et al. (2020) †	2 (vs. 2)	• Retention: 46/50 (92%) • Attrition: scrambler therapy = 1/25 (4%), TENS = 3/25 (12%) • Satisfaction: participants who received scrambler therapy were more willing to recommend their treatment than those who received TENS ($p < 0.001$)	**Follow-up (8 weeks)** • EORTC QLQ-CIPN20 sensory ($p = 0.13$)	**After intervention (2 weeks)** • ≥ 50% reduction in 0–10 NAS primary symptoms (40% vs. 20%, $p = 0.12$) • PGIC neuropathy symptoms ($p = 0.001$) and pain ($p = 0.005$) **Follow-up (8 weeks)** • PGIC neuropathy symptoms ($p = 0.09$) and pain ($p = 0.16$)	N/A	**After intervention (2 weeks)** • PGIC ($p = 0.005$) **Follow-up (8 weeks)** • PGIC ($p = 0.11$)
Scrambler therapy (vs. TENS)	Childs et al. (2021) †	NR	• Eligibility: 37/46 (80%) • Recruitment: 22/37 (59%) • Retention: 21/22 (95%) • Attrition: scrambler therapy = 0/10 (0%), TENS = 1/12 (8%)	N/A	**After intervention (2 weeks)** • ≥ 50% reduction in 0–10 NAS primary symptom (60% vs. 25%, $p = 0.11$) • PGIC neuropathy symptoms and pain (graphically, scrambler therapy better than TENS) **Follow-up (8 weeks)** • PGIC neuropathy symptoms and pain (graphically, scrambler therapy better than TENS)	N/A	**Follow-up (8 weeks)** • PGIC (graphically, scrambler therapy better than TENS)
Scrambler therapy (vs. sham)	Smith et al. (2020)	NR	• Retention: 35/35 (100%) • Satisfaction: scrambler therapy = 11/14 (79%), sham = 9/14 (64%)	**After intervention (10 days)** • EORTC QLQ-CIPN20 sensory ($p = 0.16$) and motor ($p = 0.25$) **Follow-up (28 days)** • EORTC QLQ-CIPN20 sensory ($p = 0.24$) and motor ($p = 0.45$) **Follow-up (2 months)** • EORTC QLQ-CIPN20 sensory ($p = 0.14$) and motor ($p = 0.31$) **Follow-up (3 months)** • EORTC QLQ-CIPN20 sensory ($p = 0.62$) and motor ($p > 0.9$)	**After intervention (10 days)** • 0–10 NRS pain ($p = 0.3$) **Follow-up (28 days)** • 0–10 NRS pain ($p = 0.61$) **Follow-up (2 months)** • 0–10 NRS pain ($p = 0.59$) **Follow-up (3 months)** 0-10 NRS pain ($p = 0.88$)	N/A	N/A

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Table 3 (*continued*)

Neuromodulation (vs. comparator)	Study	Relevant AE	Feasibility	Efficacy			
				Overall severity of CIPN	Pain and symptoms	Function	Quality of life
Scrambler therapy	Smith et al. (2010)	0	• Retention: 15/18 (83%)	N/A	**After intervention (10 days)** • ≥ 20% reduction in 0–10 NRS (94%, $p < 0.001$) • 0–10 NRS pain ($p < 0.001$)	N/A	**Follow-up (12 weeks)** • Uniscale ($p > 0.05$)
Scrambler therapy	Coyne et al. (2013)	0	• NR for CIPN subgroup	**After intervention (14 days)** • EORTC QLQ-CIPN20 sensory ($p < 0.001$) and motor ($p = 0.014$) **Follow-up (1 month)** • EORTC QLQ-CIPN20 sensory ($p < 0.001$) and motor ($p = 0.1$) **Follow-up (2 months)** • EORTC QLQ-CIPN20 sensory ($p < 0.001$) and motor ($p = 0.009$) **Follow-up (3 months)** • EORTC QLQ-CIPN20 sensory ($p < 0.001$) and motor ($p = 0.004$)	**After intervention (14 days)** • NRS ($p < 0.001$) • BPI worst pain ($p = 0.007$), least pain ($p = 0.38$), average pain ($p = 0.067$), pain now ($p = 0.003$), pain interference (all $p < 0.05$) **Follow-up (1 month)** • NRS ($p = 0.007$) • BPI worst pain ($p = 0.017$), least pain ($p = 0.79$), average pain ($p = 0.062$), pain now ($p = 0.005$), pain interference (all $p < 0.05$) **Follow-up (2 months)** • NRS ($p = 0.009$) • BPI worst pain ($p = 0.004$), least pain ($p > 0.9$), average pain ($p = 0.03$), pain now ($p = 0.009$), pain interference (all $p < 0.05$) **Follow-up (3 months)** • NRS ($p = 0.002$) • BPI worst pain ($p = 0.089$), least pain ($p = 0.9$), average pain ($p = 0.18$), pain now ($p = 0.001$), pain interference (all $p < 0.05$)	N/A	N/A
Scrambler therapy	Pachman et al. (2015)	0	• Retention/completion rate: 20/37 (54%)	N/A	**After intervention (10 days)** • 0–10 NRS average pain (−53%, $p < 0.001$), tingling (−44%, $p < 0.001$), and numbness (−37%, $p < 0.001$) • 0–10 NRS worst pain (51%, $p < 0.001$), tingling (40%, $p < 0.001$), and numbness (41%, $p < 0.001$)	**Follow-up (10 weeks)** • Vibration sensitivity (+0.53, $p = 0.06$)	**Follow-up (10 weeks)** • PGIC quality of life improved

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Table 3 (*continued*)

Neuromodulation (vs. comparator)	Study	Relevant AE	Feasibility	Efficacy			
				Overall severity of CIPN	Pain and symptoms	Function	Quality of life
					• PGIC neuropathy symptoms improved during the 10 days of the intervention but regressed during 10 weeks of follow-up		
Scrambler therapy	Lee et al. (2016) [a]	0	• NR for CIPN subgroup	N/A	**Follow-up (4 weeks)** • 0–10 NRS pain (p = 0.027)	N/A	N/A
TENS (vs. placebo)	Tonezzer et al. (2017)	NR	• Retention: 24/24 (100%)	**After intervention (45 days)** • CINQ frequency (p = 0.59) and interference (p = 0.86)	**After intervention (45 days)** • VAS pain, numbness, and paresthesia (all p > 0.05)	N/A	N/A
Low-frequency electrostimulation (vs. sham)	Song et al. (2020)	0	• Eligibility: 72/72 (100%) • Recruitment: 72/72 (100%) • Retention: 64/72 (89%) • Attrition: low-frequency electrostimulation = 6/36 (17%), sham = 4/36 (11%)	**After intervention (2 weeks)** • TNS (p = 0.083) • EORTC QLQ-CIPN20 sensory (p = 0.89), motor (p = 0.29), and autonomic (p = 0.35)	**After intervention (2 weeks)** • 0–10 NRS CIPN symptoms (p = 0.27)	N/A	**After intervention (2 weeks)** • FACT-B (p = 0.24)
TENS	Gewandter et al. (2019)	6	• Eligibility: 36/64 (56%) • Recruitment: 29/64 (81%) • Retention: 22/29 (76%) at week 6, 15/29 (52%) at 6 months • Acceptability: confirmed by qualitative interview	**After intervention (6 weeks)** • EORTC QLQ-CIPN20 (p = 0.004)	**After intervention (6 weeks)** • SF-MPQ-2 (p = 0.002) • 0–10 NRS pain (p < 0.001), tingling (p = 0.002), numbness (p < 0.001), and cramping (p = 0.005)	**After intervention (6 weeks)** • UENS large fiber function (p = 0.04) • Tactile sensitivity (p < 0.001)	N/A
ALTENS	Wong et al. (2016) [b]	4	• Retention: 40/47 (85%)	**Follow-up (6 months)** • mTNS (p < 0.001)	**Follow-up (6 months)** • ESAS general pain (p = 0.14)	**Follow-up (6 months)** • Tactile sensitivity in palms (p = 0.007), fingers (p = 0.001), feet (p = 0.002), and toes (p = 0.004)	**Follow-up (6 months)** • ESAS general well-being (p = 0.16)
ITH (vs. placebo)	Lindblad et al. (2016)	NR	• Eligibility: 67/73 (92%) • Recruitment: 67/73 (92%) • Retention: 59/67 (88%) at week 12, 50/67 (75%) at week 37 • Attrition: ITH = 5/34 (15%) at week 12, 5/29 (17%) at week 37; Placebo = 3/33 (9%) at week 12, 4/30 (13%) at week 37	N/A	**After intervention (12 weeks)** • 0–100 NRS pain (p = 0.8) and discomfort (p = 0.5) • Pain-drawing sketch (p > 0.9) **Follow-up (37 weeks)** • 0–100 NRS pain (p = 0.89) and discomfort (p = 0.82) • pain-drawing sketch (p = 0.83)	**After intervention (12 weeks)** • DHI (p = 0.49), Tightened Romberg test (p = 0.24), and One-legged stance test (p > 0.9) for balance **Follow-up (37 weeks)** • DHI (p > 0.9), Tightened Romberg test (p = 0.3), One-legged stance test	N/A

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Table 3 (*continued*)

Neuromodulation (vs. comparator)	Study	Relevant AE	Feasibility	Efficacy			
				Overall severity of CIPN	Pain and symptoms	Function	Quality of life
						(p = 0.78) for balance	
Photobiomodulation (vs. sham)	Argenta et al. (2017) [c]	NR	• Recruitment: 70/70 (100%) • Retention: 68/70 (97%) • Attrition: photobiomodulation = 2/30 (7%), sham = 0/40 (0%) • Adherence (completed at least 95% treatment sessions): IG = 29/30 (97%), CG = 40/40 (100%)	**4 weeks into intervention** • mTNS (−4.2 [−32.4%] vs. −0.1 [−0.7%], p < 0.001) **Follow-up (8 weeks)** • mTNS (−6.8 [−52.6%] vs. +0.2 [+1.5%], p < 0.001) **Follow-up (16 weeks)** • mTNS (−5.0 [38.8%] vs. 0 [0%], p < 0.001)	N/A	N/A	N/A
Magnetic field therapy	Gabrys (2004)	1	• Retention: 44/44 (100%)	N/A	**After intervention (4 weeks)** • ≥ 50% reduction in VAS (n = 12/44, 27%)	**After intervention (4 weeks)** • ≥ 50% improvement in vibration sensitivity (n = 6/44, 14%)	N/A
Magnetic field therapy	Geiger et al. (2015)	NR	• Retention: 20/20 (100%)	**After intervention** • NCI-CTC sensory ataxia (p < 0.001) • NCI-CTC motor (p = 0.23) • NCI-CTC sensory (p = 0.003)	**After intervention** • painDETECT (p > 0.05)	**After intervention** • Ulnar and sural NCV (all p > 0.05)	N/A
Magnetic field therapy (vs. placebo)	Rick et al. (2017)	NR	• Retention rate: 41/44 (93%) at week 3, 31/44 (70%) at month 3 • Attrition rate: magnetic field therapy = 1/21 (5%) at week 3, 3/20 (15%) at month 3; placebo = 2/23 (9%) at week 3, 7/21 (33%) at month 3	**3 weeks into intervention** • NCI-CTCAE (p = 0.042) **After intervention (3 months)** • NCI-CTCAE (p = 0.04)	**3 weeks into intervention** • painDETECT (p = 0.25) **After intervention (3 months)** • painDETECT (p = 0.12)	**3 weeks into intervention** • Ulnar (p > 0.14) and peroneal (p > 0.9) NCV **After intervention (3 months)** • Ulnar (p > 0.28) and peroneal (p = 0.015) NCV	N/A
Therapeutic ultrasound (vs. standard care)	Al Onazi et al. (2021)	0	• Recruitment: 31/37 (84%) • Retention: 31/31 (100%) • Adherence: completed 100% treatment sessions	**After intervention (2 weeks)** • FACT/GOG-NtxS (p = 0.003) • EORTC QLQ-CIPN20 (p = 0.75) **Follow-up (6 weeks)** • FACT/GOG-NtxS (p = 0.14) • EORTC QLQ-CIPN20 (p = 0.51)	N/A	**After intervention (2 weeks)** • Tactile sensitivity (p > 0.9) • Temperature sensitivity (p = 0.35) • Vibration sensitivity (p = 0.23) • Tendon reflex (p = 0.03) • mCTSIB for balance (p > 0.9) • Single leg balance (p = 0.6)	**After intervention (2 weeks)** • FACT-G (p = 0.09) **Follow-up (6 weeks)** • FACT-G (p = 0.8)

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Table 3 (*continued*)

Neuromodulation (vs. comparator)	Study	Relevant AE	Feasibility	Efficacy			
				Overall severity of CIPN	Pain and symptoms	Function	Quality of life
						Follow-up (6 weeks) • Tactile sensitivity (p = 0.74) • Temperature sensitivity (p = 0.53) • Vibration sensitivity (p = 0.43) • Tendon reflex (p = 0.21) • mCTSIB for balance (p = 0.3) • Single leg balance (p = 0.56)	
Neurofeedback (vs. usual care wait-list)	Prinsloo et al. (2017) ‡	0	• Recruitment: 71/75 (84%) • Retention: 62/71 (100%) • Attrition: neurofeedback = 5/35 (14%), wait-list = 4/36 (11%) • Adherence: completed 100% treatment sessions	N/A	**After intervention** • BPI-SF (p = 0.001–0.042) • PQAS (p = 0.001–0.017)	N/A	N/A
Neurofeedback (vs. usual care wait-list)	Prinsloo et al. (2018) ‡	N/A	• Retention rate: 31/71 (44%) at 1-month follow-up after treatment, 51/71 at 3-month follow-up after treatment	N/A	**After intervention** • MDASI (all p < 0.001) • BFI (p < 0.05) • PSQI (p > 0.05) **Follow-up (1 month)** • BPI-SF (most p < 0.05) • PQAS (most p < 0.05) • MDASI (all p > 0.05) • BFI (p > 0.05) • PSQI (p > 0.05) **Follow-up (4 months)** • BPI-SF (most p < 0.05) • PQAS (most p < 0.05) • MDASI (all p < 0.05) • BFI (p < 0.05) • PSQI (p > 0.05)	N/A	**After intervention** • SF-36 (all p < 0.05) **Follow-up (1 month)** • SF-36 (all p > 0.05) **Follow-up (4 months)** • SF-36 (all p > 0.05)
rTMS	Goto et al. (2020)	0	• Recruitment rate: 11/15 (73%) • Retention rate: 11/11 (100%) • Compliance: 100% completed all treatment sessions	N/A	**After intervention (LM 90%)** • VAS pain (p = 0.03) and dysesthesia (p = 0.04) related to the targeted extremity **After intervention (PA 90%)** • VAS dysesthesia (p = 0.03) and SF-MPQ-2 (p = 0.01) related to the targeted extremity	N/A	N/A

Note. BFI = Brief Fatigue Inventory; BPI/BPI-SF = Brief Pain Inventory-Short Form; CG = control group; CIPN = chemotherapy-induced peripheral neuropathy; DHI = Dizziness Handicap Inventory; EEG = Electroencephalography; EG = experimental group; EORTC QLQ-CIPN20 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-CIPN20; FACT-B = Functional Assessment of Cancer Therapy-Breast scale; FACT-G = Functional Assessment of Cancer Therapy-General scale; FACT/GOG-NtxS = Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity subscale; ITH = interferential therapy and long-wave diathermy at high power; mCTSIB = modified Clinical Test of Sensory Interaction and Balance; MDASI = MD Anderson Symptom

Inventory; mTNS = modified total neuropathy score; N/A = not applicable; NAS = Numerical Analogue Scale; NCI-CTC/CTCAE = National Cancer Institute-Common Toxicity Criteria/Common Terminology Criteria for Adverse Events; NCS = nerve conduction studies; NRS = numerical rating scale; PGIC = Patient Global Impression of Change scale; PQAS = Pain Quality Assessment Scale; PSQI = Pittsburgh Sleep Quality Index; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SF-36 = 36-Item Short Form Survey Instrument; SF-MPQ-2 = Short form McGill Pain Questionnaire 2; TENS = transcutaneous electrical nerve stimulation; TRT = Tightened Romberg test; VAS = visual analogue scale.

[†] Reports from the same RCT.

[‡] Reports from the same RCT.

[a] Only included data from patients with chemotherapy-induced peripheral neuropathy.

[b] Only included data from the acupuncture-like transcutaneous electrical nerve stimulation group.

[c] Only included data from the main trial.

sensitivity in patients with CIPN. Similarly, Wong et al.'s (2016) quasi-experimental study suggested that TENS delivered at acupoints could improve tactile sensitivity in patients.

A single-arm study (Gabrys, 2004) showed that 14% (6/44) of participants achieved a >50% improvement in vibration sensitivity after magnetic field therapy. Another single-arm study (Geiger et al., 2015) involving magnetic field therapy did not find it to be efficacious in improving ulnar and sural nerve conduction velocity (NCV). Similarly, Rick et al.'s (2017) RCT demonstrated that magnetic field therapy did not significantly improve ulnar NCV compared with a placebo, but did significantly improve peroneal NCV.

In their RCT, Al Onazi et al. (2021) showed that, compared with those treated with home exercise, patients with CIPN treated with therapeutic ultrasound experienced greater improvement in their Achilles' tendon reflex at the end of the intervention, whereas there was no significant difference between the two groups in terms of improvements in tactile, temperature, and vibration sensitivity.

In terms of balance, one RCT (Lindblad et al., 2016) showed no significant improvements in patients with CIPN from interferential therapy plus high-power long-wave diathermy compared to a placebo, whether in self-reported or objective measurements. In another RCT (Al Onazi et al., 2021), adding therapeutic ultrasound to home exercise was not found to lead to any significant improvements in the balance of patients with CIPN compared with the use of home exercise alone.

3.8.4. Quality of life

A total of seven studies (four RCTs and three quasi-experimental studies) reported that non-invasive neuromodulation techniques were efficacious at improving quality of life (Table 3). A crossover RCT showed that in the initial phase (Loprinzi et al., 2020b), patients treated with scrambler therapy had a greater subjective impression of an improvement in their quality of life compared with patients treated with TENS, whereas no significant differences between the two groups were identified at the 8-week follow-up. In the crossover phase (Childs et al., 2021), it was also shown graphically that patients treated with scrambler therapy had a greater subjective impression of an improvement in their quality of life. Similarly, Pachman et al.'s (2015b) single-arm study graphically depicted a persistent subjective impression of an improvement in quality of life throughout the ten weeks of follow-up after scrambler therapy, although no statistical analysis was conducted. In contrast, Smith et al.'s (2010) single-arm study showed that scrambler therapy failed to improve the quality of life of patients over a longer follow-up period of 12 weeks.

In Song et al.'s (2020) RCT, no significant difference was identified between patients who received low-frequency electrostimulation and those who received sham stimulation in quality of life at the end of the 2-week intervention. In their quasi-experimental study, Wong et al. (2016) also did not find that ALTENS had a significant effect on the general well-being of patients. Al Onazi et al.'s (2021) RCT suggested that therapeutic ultrasound may have limited efficacy in improving patients' quality of life.

Prinsloo et al. (2018) found in their RCT that patients allocated to receive neurofeedback achieved a significantly better quality of life than the wait-list control group after completing 20 sessions of the intervention. However, the difference was not significant at the first and fourth months of follow-up (Prinsloo et al., 2018).

4. Discussion

This systematic review was conducted to evaluate the best available evidence regarding the safety, feasibility, and efficacy of non-invasive neuromodulation techniques for managing CIPN. The results suggest that non-invasive peripheral and central neuromodulation techniques are safe for use in patients with CIPN. In addition, the majority of participants were able to complete the planned intervention sessions, and the available data also showed that the neuromodulation techniques were well accepted by patients, indicating good feasibility. However, no definite conclusions can be drawn due to the insufficient data. Only a few participants who were treated with the non-invasive peripheral neuromodulation techniques experienced mild discomfort, which could be resolved immediately after treatment ended. No adverse effects were identified in relation to non-invasive central neuromodulation techniques, although the number of relevant studies was small. Only the studies involving peripheral neuromodulation techniques evaluated the overall severity of CIPN. Quasi-experimental studies mostly demonstrated significant effects from scrambler and TENS, whereas RCTs did not support their efficacy. This could be because in most patients CIPN would automatically be resolved after the completion of chemotherapy (Pachman et al., 2015b, 2016; Molassiotis et al., 2019b). The lack of a well-matched control group could lead to an overestimation of the effects of an intervention. Both RCTs and quasi-experimental studies involving magnetic field therapy showed a significant mitigation effect on patient-reported CIPN (Geiger et al., 2015; Rick et al., 2017); however, the CIPN grading method used in the RCT was not clear. The results of the study should be independently verified given the role of the sponsor in the study.

Photobiomodulation demonstrated efficacy for relieving the overall severity of CIPN (Argenta et al., 2017); however, the single RCT was conducted with a medium sample size of 70 female patients. Interestingly, the efficacy of therapeutic ultrasound was found to differ between two measurements, i.e., the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity subscale (FACT/-GOG-NtxS) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-CIPN20 (EORTC QLQ-CIPN20) (Al Onazi et al., 2021). A longitudinal study compared the psychometric properties of these two measurements and found that compared with EORTC QLQ-CIPN20, FACT/GOG-NtxS is more responsive to clinical changes in CIPN severity and is therefore more applicable to research and practice (Cheng and Molassiotis, 2019). Since this study did not have a sham control, the actual treatment effect requires further verification. The overall severity of CIPN was not evaluated in the studies involving non-invasive central neuromodulation techniques.

Most of the included studies examined the efficacy of neuromodulation techniques for managing pain and sensory symptoms related to CIPN. Similar to overall CIPN outcomes, the efficacy of scrambler therapy and TENS was inconsistent between the RCT and quasi-experimental studies, suggesting a placebo effect. Other non-invasive peripheral neuromodulation techniques also did not demonstrate significant effects on pain and symptoms related to CIPN. This implies that these techniques rely on the peripheral nerves to deliver the therapeutic

electrical signals. Once the damaged peripheral nerves are unable to transmit therapeutic signals, their efficacy would be compromised (Smith et al., 2020). In contrast, two non-invasive central neuromodulation techniques, i.e., neurofeedback and rTMS, showed a significant effect on pain and symptom reduction (Goto et al., 2020; Prinsloo et al., 2017, 2018). Similarly, a recent systematic review demonstrated that central neuromodulation techniques are superior to peripheral neuromodulation techniques for managing pain related to diabetic neuropathy (Zeng et al., 2020). Given the growing evidence supporting the critical role of the brain in the development of CIPN symptoms, directly modulating the relevant brain activity following the neuromatrix theory might be a more effective way to manage CIPN (Omran et al., 2021). However, the size of the effect is not comparable between different interventions due to the considerable heterogeneity in methodology, participant characteristics, and outcome measures among the included studies.

Although all of the participants in both the neurofeedback study and rTMS study completed the full intervention sessions, less effort from the patients would be required in receiving rTMS than neurofeedback (Jensen et al., 2014), making rTMS more likely to be applied to patients in poor health. However, the neurofeedback and the rTMS studies lacked a sham control group, which may have exaggerated the actual treatment effect. The preliminary findings should be verified with high-quality studies.

Except in a few single-arm studies, non-invasive peripheral neuromodulation techniques have not been found to be effective in improving sensory nerve function. Previous studies have shown that peripheral neuromodulation mainly acts on motor nerves (Zeng et al., 2020). However, the included studies have not demonstrated that peripheral neuromodulation is effective at improving the balance of patients with CIPN. It might be interesting to see if an intervention of longer duration can reduce the incidence of falls. Although the photobiomodulation study used the testing of functions such as pin sensitivity, vibration sensitivity, tendon reflex, and muscle strength as components in the overall CIPN outcome assessment (Argenta et al., 2017), the researchers did not perform an exploratory analysis of the changes in each individual item. Therefore, the benefit of photobiomodulation on peripheral nerve functions remains unclear. Studies involving non-invasive central neuromodulation techniques did not assess functional outcomes, which warrants further exploration.

There were a limited number of studies evaluating the efficacy of non-invasive neuromodulation techniques on the quality of life of patients with CIPN. The results were mixed, suggesting potential benefits. However, these preliminary data are insufficient to support definitive conclusions. The quality of life outcome measurements used in these studies were mostly non-specific to patients with cancer, which may lead to a low responsiveness to the effects of the intervention. As quality of life is a complex construct, future studies may consider adopting a qualitative approach to explore the impact of non-invasive neuromodulation techniques on the quality of life of patients with CIPN (Mccarron et al., 2020).

4.1. Limitations

There are several limitations to this systematic review. Although a meta-analysis was planned in the review protocol, the heterogeneity of the included studies prevented the conducting of a pooled analysis of data from those studies. Therefore, the overall effect size of the neuromodulation techniques for managing CIPN could not be estimated. However, the adoption of broader eligibility criteria in terms of the study design ensured the inclusion in the systematic review of very preliminary studies involving novel neuromodulation techniques. These can provide more information for future research. Additionally, in this systematic review only English terms were used for the literature search, potentially causing studies indexed in databases in other languages to be overlooked. However, the researchers did not place limitations on the language of publication, which meant that studies from non-English speaking countries that were not published in English were considered.

4.2. Implications for practice and research

The efficacy of non-invasive neuromodulation techniques for CIPN and related symptoms, function, and quality of life in patients with cancer remain inconclusive due to the lack of high-level evidence from double-blinded randomized sham-controlled trials. Therefore, no recommendation can be made for routine clinical practice. In terms of managing chronic pain and neuropathic symptoms related to CIPN, neuromodulation techniques targeting CNS, such as neurofeedback and rTMS, appear to be more promising than those targeting PNS, although relevant research is still in its infancy.

It should be noted that the one study on rTMS that was included in this review used a single-session rTMS protocol, which is distinct from the multi-session mode often used in clinical practice. The 5Hz stimulation frequency used in the study was lower than the 10–20 Hz typically used in pain management. The limited stimulation session and the low stimulation frequency would make it difficult to maintain the efficacy of the protocol in the longer term.

Due to insufficient knowledge of CIPN and its impact on patients, most existing studies did not cover outcomes most relevant to the clinical phenotype of CIPN, leading to inconclusive results. The internal and external validity of those studies might also have been affected. Future research is needed to establish a clear theoretical framework to achieve a better understanding of CIPN and to develop an optimal neuromodulation protocol.

5. Conclusion

Non-invasive neuromodulation techniques are safe and feasible for managing CIPN. Due to the lack of high-level evidence, however, recommendations cannot be made for routine clinical use at present. Scrambler therapy and TENS are of limited or no efficacy in the management of CIPN. Non-invasive central neuromodulation techniques may be more promising for relieving chronic pain and neuropathic symptoms related to CIPN. These are worthy of further exploration in studies with a more rigorous design.

Author contributions

MW and AM contributed to the conceptualization and design of the systematic review. MW and ZP conducted the literature search and screening. MW, YY, and HY contributed to the extraction of data and assessment of the risk of bias. MW and AM contributed to the interpretation of the data and writing of the manuscript. All authors approved the content of the final manuscript.

Declaration of competing interest

Prof. Alex Molassiotis reports research grants from Helsinn, outside of the submitted work; the other authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejon.2022.102124.

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ASCO special articles

Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: ASCO Guideline Update

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abstract

PURPOSE To update the ASCO guideline on the recommended prevention and treatment approaches in the management of chemotherapy-induced peripheral neuropathy (CIPN) in adult cancer survivors.

METHODS An Expert Panel conducted targeted systematic literature reviews to identify new studies.

RESULTS The search strategy identified 257 new references, which led to a full-text review of 87 manuscripts. A total of 3 systematic reviews, 2 with meta-analyses, and 28 primary trials for prevention of CIPN in addition to 14 primary trials related to treatment of established CIPN, are included in this update.

RECOMMENDATIONS The identified data reconfirmed that no agents are recommended for the prevention of CIPN. The use of acetyl-L-carnitine for the prevention of CIPN in patients with cancer should be discouraged. Furthermore, clinicians should assess the appropriateness of dose delaying, dose reduction, substitutions, or stopping chemotherapy in patients who develop intolerable neuropathy and/or functional impairment. Duloxetine is the only agent that has appropriate evidence to support its use for patients with established painful CIPN. Nonetheless, the amount of benefit from duloxetine is limited.

Additional information is available at www.asco.org/survivorship-guidelines.

J Clin Oncol 38:3325-3348. © 2020 by American Society of Clinical Oncology

ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on May 15, 2020 and published at ascopubs.org/journal/jco on July 14, 2020: DOI https://doi.org/10.1200/JCO.20.01399

Clinical Practice Guidelines Committee approval: May 5, 2020

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INTRODUCTION

Chemotherapy-induced neuropathy is a serious clinical problem caused by a substantial number of cytotoxic drugs, including taxanes, platinums, vinca alkaloids, epothilones, eribulin, and bortezomib; these drugs cause different pathologic insults to neurons. Although there are differences and similarities between the neuropathies caused by these agents, historically, they have not been well defined. Inconsistent measurement methods have often been used to characterize the variations in neuropathy caused by different chemotherapy drugs. However, the same validated neuropathy measurement tools have been recently used in several clinical studies. The data arising from these studies allow for a more detailed comparison of neuropathy clinical manifestations caused by two of the most prominent neurotoxic chemotherapy agents, paclitaxel and oxaliplatin.[1-4]

Both oxaliplatin and paclitaxel cause acute neuropathy. Oxaliplatin-induced acute neuropathy is characterized by cold sensitivity, throat discomfort, discomfort swallowing cold liquids, and muscle cramps. Although some of these symptoms can occur within the time of drug infusion, their severity usually peaks 2 to 3 days after each dose of oxaliplatin. With subsequent treatment cycles, symptom severities double in magnitude over that seen for the first treatment cycle. Oxaliplatin-induced acute neuropathy does not return to baseline between cycles when oxaliplatin is administered once every 2 weeks. There is no good information to delineate how long acute symptoms last after the last dose of oxaliplatin.

Paclitaxel also frequently causes a pain syndrome that occurs in the days following each dose. These symptoms, in the past, had been labeled as being arthralgias or myalgias. However, newer data support that they are a manifestation of an acute neuropathy.[2,5] These acute neuropathy symptoms from paclitaxel present with a similar time pattern as oxaliplatin acute neuropathy symptoms, peaking approximately 2 to 3 days after each dose of paclitaxel. The symptom complex, however, is different than that seen with oxaliplatin, in that it is primarily a pain, classically occurring in a truncal/hip distribution. In comparison

THE BOTTOM LINE

Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: ASCO Guideline Update

Guideline Question

What are the recommended prevention and treatment approaches in the management of chemotherapy-induced neuropathies in adult cancer survivors?

Target Population

Adult cancer survivors with, or at risk for developing, chemotherapy-induced neuropathies

Target Audience

Health care practitioners who provide care to cancer survivors; patients and their caregivers

Methods

An Expert Panel was convened to update clinical practice guideline recommendations based on a systematic review of the medical literature.

Updated Recommendations

The following recommendations are evidence based, informed by randomized trials, and guided by clinical experience. The recommendations were developed by a multidisciplinary group of experts.

Prevention of chemotherapy-induced peripheral neuropathy.

1.1 Clinicians should assess the risks and benefits of agents known to cause CIPN among patients with underlying neuropathy and with conditions that predispose to neuropathy such as diabetes and/or a family or personal history of hereditary neuropathy (Type of recommendation: Informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

1.2 Clinicians should not offer, and should discourage use of, acetyl-L-carnitine for the prevention of CIPN in patients with cancer (Type of recommendation: evidence based, harms outweigh benefits; Evidence quality: high; Strength of recommendation: strong).

1.3 Outside the context of a clinical trial, no recommendations can be made on the use of the following interventions for the prevention of CIPN:

- Acupuncture
- Cryotherapy
- Compression therapy
- Exercise therapy
- Ganglioside-monosialic acid (GM-1)

(Type of recommendation: no recommendation; Evidence quality: low; Strength of recommendation: not applicable).

Note: While preliminary evidence suggests a potential for benefit from these interventions, larger sample–sized definitive studies are needed to confirm efficacy and clarify risks.

1.4 Clinicians should not offer the following agents for the prevention of CIPN to patients with cancer undergoing treatment with neurotoxic agents:

- All-trans retinoic acid
- Amifostine
- Amitriptyline
- Calcium magnesium
- Calmangafodipir
- Cannabinoids
- Carbamazepine
- L-carnosine
- Diethyldithiocarbamate (DDTC)
- Gabapentin/pregabalin
- Glutamate
- Glutathione (GSH) for patients receiving paclitaxel/carboplatin chemotherapy
- Goshajinkigan (GJG)
- Metformin

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THE BOTTOM LINE (CONTINUED)

- Minocycline
- *N*-acetylcysteine
- Nimodipine
- Omega-3 fatty acids
- Org 2766
- Oxcarbazepine
- Recombinant human leukemia inhibitory factor
- Venlafaxine
- Vitamin B
- Vitamin E

(Type of recommendation: evidence based, no benefits; Evidence quality: intermediate; Strength of recommendation: moderate).

Treatment of chemotherapy-induced peripheral neuropathy that develops while patients are receiving neurotoxic chemotherapy.

2.1 Clinicians should assess, and discuss with patients, the appropriateness of dose delaying, dose reduction, or stopping chemotherapy (or substituting with agents that do not cause CIPN) in patients who develop intolerable neuropathy and/or functional nerve impairment (Type of recommendation: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

Treatment of chemotherapy-induced peripheral neuropathy for patients who have completed neurotoxic chemotherapy.

3.1 For patients with cancer experiencing painful CIPN, clinicians may offer duloxetine (Type of recommendation: evidence based, benefits equal harms; Evidence quality: intermediate; Strength of recommendation: moderate).

3.2 Outside the context of a clinical trial, no recommendations can be made on the use of the following interventions for the treatment of CIPN:

- Exercise therapy
- Acupuncture
- Scrambler therapy
- Gabapentin/pregabalin
- Topical gel treatment containing baclofen, amitriptyline HCL, plus/minus ketamine
- Tricyclic antidepressants
- Oral cannabinoids

(Type of recommendation: no recommendation; Evidence quality: low; Strength of recommendation: not applicable).

Note: While recent preliminary evidence suggests a potential for benefit from exercise, acupuncture, and scrambler therapy, larger sample-sized definitive studies are needed to confirm efficacy and clarify risks.

Additional Resources

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/survivorship-guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

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with oxaliplatin-related symptoms, these symptoms tend to resolve more between doses of paclitaxel, and the symptoms are not worsened, on average, in subsequent cycles.

The chronic neuropathies related to these 2 drugs share several similarities. The neuropathy associated with each drug is primarily sensory, as opposed to motor or autonomic. The most common descriptors of this sensory neuropathy are numbness, tingling, and pain. Numbness and tingling appear earlier and are generally more prominent problems than pain. A stocking-glove distribution of symptoms typically begins distally in the fingers and toes and can progress proximally as the condition worsens.

When comparing chronic neuropathy distribution patterns between the 2 drugs, paclitaxel-induced chronic neuropathy symptoms are more prominent in the lower extremities than upper extremities during treatment. In contrast,

oxaliplatin-induced symptoms experienced during treatment are more severe in the upper extremities than in the lower extremities.

After completion of chemotherapy treatments, paclitaxel neuropathy, on average, improves over the ensuing several months. In contrast, oxaliplatin-induced neuropathy, on average, worsens for 2-3 months after cessation of therapy (labeled as coasting phenomenon); after approximately 3 months, neuropathy tends to improve.[3] Neuropathy in the hands improves faster than in the feet, so that, months after completion of oxaliplatin, neuropathy is worse in the feet than in the hands. Although neuropathy caused by both drugs tends to improve over time, neuropathy can remain as a substantial debilitating problem in a subset of patients for years.[6,7]

The diagnosis of the more chronic chemotherapy-induced peripheral neuropathy can generally be made by clinical history. If a patient receiving neurotoxic chemotherapy develops new or worsening numbness, tingling, and/or pain in their hands and/or feet, and there is no other good reason for them to have developed these symptoms, then the diagnosis is made. Neurologic physical examination can be abnormal in a patient with chemotherapy-induced peripheral neuropathy. Neurologic tests, such as electromyography (EMG), can be used but are not usually necessary. There are data supporting that nerve conduction studies in asymptomatic patients who are receiving neurotoxic chemotherapy can predict the development or worsening of chemotherapy-induced peripheral neuropathy (CIPN).[8-10] These tests, however, are not routinely used.

Chemotherapy-induced peripheral neuropathy can markedly affect the quality of life (QOL) of patients. In addition, it may be detrimental to their cancer outcomes, as it may limit the amount of chemotherapy that clinicians can give.

The purpose of this guideline update is to systematically review new evidence reported in the literature since the original guideline was published, compare outcomes among trials, and provide updated guidance on the effectiveness of prevention and treatment options for CIPN in adults with a history of cancer.

GUIDELINE QUESTIONS

This clinical practice guideline addresses 2 overarching clinical questions: What are the recommended (1) prevention and (2) treatment approaches in the management of chemotherapy-induced neuropathies in adult cancer survivors?

METHODS

Guideline Update Development Process

This systematic review-based guideline was developed by a multidisciplinary expert panel, which included a patient representative and an ASCO guidelines staff member with health research methodology expertise (Appendix Table A1, online only). The Expert Panel met via webinar and corresponded through e-mail. On the basis of the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. The guideline recommendations were made available for an open comment period of 2 weeks, allowing the public to review and comment on the recommendations after submitting a confidentiality agreement. The full guideline was shared with 2 external reviewers. Comments were taken into consideration while finalizing the recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of the guideline, which was then circulated for external review and submitted to *Journal of Clinical Oncology* for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Clinical Practice Guidelines Committee before publication. All funding for the administration of the project was provided by ASCO.

The recommendations were developed using a systematic review and informed by expert clinical experience. PubMed was searched for randomized controlled trials (RCTs) and meta-analyses published between January 1, 2013, and August 28, 2019. An updated search was conducted in February 2020. Search terms are provided in the Data Supplement. Randomized trial articles were selected for inclusion in the systematic review of the evidence if they (1) focused on chemotherapy-induced neuropathy, (2) included cancer survivors, and (3) considered neuropathy as an important outcome of the study. Articles were excluded from the systematic review if they (1) were phase I studies, other noncomparative studies, case reports, editorial letters, or newspaper articles; (2) only involved individuals $<$ 18 years of age; (3) were published in a language other than English; (4) included $<$ 10 participants; or (5) focused on radiation therapy–related neuropathy or stem-cell transplantation–related neuropathy.

The updated search was guided by the "signals"[11] approach that is designed to identify only new, potentially practice-changing data—signals—that might translate into revised practice recommendations. The approach relies on targeted routine literature searching and the expertise of ASCO Expert Panel members to help identify potential signals. Before publication, a review of guideline implementability was also conducted. Ratings for the type and strength of the recommendation and the quality of evidence are provided with each recommendation, using standardized criteria that are applied to all ASCO guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline update.

The ASCO Expert Panel and guidelines staff will continue to work with co-chairs in the future to keep abreast of the need

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for any substantive updates to the guideline. On the basis of formal review of the emerging literature, ASCO will determine the need to update.

Guideline Disclaimer

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Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/rwc). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

The review of prevention and treatment of CIPN identified a total of 31 prevention and 14 treatment publications that met eligibility criteria and form the evidentiary basis for the guideline updated recommendations. Characteristics and key results of these publications, by clinical question, are provided in Tables 1 and 2. Studies that were particularly pertinent to the development of the recommendations are discussed in the Literature Review Update and Analysis sections.

Study Quality Assessment

Study quality was formally assessed for the 45 intervention studies identified. Systematic reviews and meta-analyses were assessed for quality using the AMSTAR tool.[12] Design elements such as blinding, allocation concealment, sufficient sample size, intention to treat, and funding sources were assessed for RCTs. AMSTAR scores ranged from 8 to 9 out of a possible 11 points. Overall, the included systematic reviews were conducted in a rigorous fashion; however, many of the primary studies included in these reviews suffered from flaws in study design. Additional RCTs identified and included in this guideline ranged from low to high overall risk of bias. Many of these trials also had flaws in the study design, mainly around blinding; had small sample sizes and/or high attrition rates; and lacked statistical power, thus lowering the confidence in the findings. The included studies were also heterogeneous with respect to patient populations, sample size, methodological quality, treatment duration, and outcome measures. The primary outcomes varied across studies and, in the majority of cases, were not directly comparable because of different outcomes, measurements, and instruments used at different time points. This diversity precluded a quantitative analysis and, as such, only a qualitative review was performed. Refer to the Data Supplement for quality rating scores and the Methodology Manual (http://www.asco.org/guideline-methodology) for definitions of ratings for overall potential risk of bias.

UPDATED RECOMMENDATIONS

CLINICAL QUESTION

What are the recommended prevention and treatment approaches in the management of chemotherapy-induced neuropathies in adult cancer survivors?

Prevention of Chemotherapy-Induced Peripheral Neuropathy

1.1 Clinicians should assess the risks and benefits of agents known to cause CIPN among patients with underlying neuropathy and with conditions that

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TABLE 1. New Randomized Controlled Trials Regarding the Prevention of CIPN Since the Initial ASCO Guideline

Investigational Agent /Authors	Study Design	Neurotoxic Chemotherapy Agent	Evaluable Patients (No.)	Intervention Dose	Incidence/Severity of Neuropathy	Other
Acetyl-L-carnitine						
Hershman et al[7]	Double-blind, randomized phase III study	Taxane-based chemotherapy	409	1,000 mg 3 times a day	ALC group had a statistically significantly ($P = .01$) greater worsening of NTX scores of −1.39 points (95% CI, −2.48 to −0.30).	
Campone et al[14]	Double-blind, randomized phase II study	Sagopilone	150	1,000 mg every 3 days	No significant differences between the 2 treatment arms for peripheral neuropathy overall; median duration of neuropathy was similar.	
Alpha-lipoic acid						
Guo et al[17]	Phase III randomized, double-blind, placebo-controlled trial	Cisplatin or oxaliplatin	243	600 mg 3 times a day	No significant differences between the 2 treatment arms for peripheral neuropathy	Only 70 of 243 patients (29%), completed the study
Calcium and magnesium						
Jordan et al[18]	Systematic review and meta-analysis	Oxaliplatin	694 patients from 5 trials	CaMg infusions	Incidence of grade ≥ 2 neuropathy: RR, 0.81; 95% CI, 0.60 to 1.11. Incidence of chronic neurotoxicity for all grades: pooled RR of 0.95 (95% CI, 0.69 to 1.32).	Concluded that CaMg was not beneficial for decreasing oxaliplatin-induced neuropathy
Han et al[21]	Randomized, pilot, double-blind, placebo-controlled, crossover trial	Oxaliplatin	19	1 g of each IV before and after chemotherapy	No acute neuropathy differences between the 2 study arms. No differences in EMG motor nerve hyperexcitability scores between arms.	
Calmangafodipir						
Glimelius et al[22]	Placebo-controlled randomized phase II study	Oxaliplatin	173	Calmangafodipir was given as a 5-minute infusion 10 minutes before oxaliplatin	Calmangafodipir-treated patients (all 3 doses pooled) did not have significantly less physician-graded neurotoxicity (OR, 0.62; 90% CI, 1-sided upper level, 1.15; $P = .16$) but had significantly fewer sensory symptoms in the Leonard scale (cycle 1-8 mean, 1.9 *v* 3.0; $P < .05$ and during follow-up after 3 and 6 months, mean 3.5 *v* 7.3; $P < .01$).	
L-carnosine						
Yehia et al[23]	Randomized controlled pilot trial	Oxaliplatin	65	Arm A, 31 patients received FOLFOX-6 regimen (oxaliplatin, FU, and leucovorin); arm B, 34 patients received FOLFOX-6 regimen and daily oral L-carnosine (500 mg) along the treatment period	Neuropathy grade 2: arm A: 19 patients (61.3%); arm B: 1 patient (3.3%)	

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TABLE 1. New Randomized Controlled Trials Regarding the Prevention of CIPN Since the Initial ASCO Guideline (continued)

Investigational Agent /Authors	Study Design	Neurotoxic Chemotherapy Agent	Evaluable Patients (No.)	Intervention Dose	Incidence/Severity of Neuropathy	Other
Cryotherapy, compression therapy, cryo-compression therapy						
Hanai et al[25]	Prospective, self-controlled clinical trial	Paclitaxel	36	Each patient wore flexible FGs and socks on the dominant hand and foot from 15 minutes before paclitaxel administration to 15 minutes after the infusion was complete (90 minutes in total). FGs were replaced after the first 45 minutes. The nondominant side acted as the untreated control.	Incidence of objective and subjective CIPN signs was clinically and statistically significantly lower on the intervention side than on the control. Hand: OR, 20.00; 95% CI, 3.20 to 828.96; $P < .001$; foot: OR, infinite; 95% CI, 3.32 to infinite; $P < .001$; warm sense: hand: OR, 9.00; 95% CI, 1.25 to 394.48; $P = .02$; foot: OR, 5.00; 95% CI, 1.07 to 46.93; $P = .04$	No withdrawals for toxicity
Beijers et al[26]	Prospective, randomized trial	Paclitaxel, docetaxel, or oxaliplatin	180	Patients were randomly assigned between wearing FGs on both hands during treatment or not wearing FGs.	ITT analyses, EORTC CIPN20 subscales: no statistically significant differences between intervention and control groups. In cryotherapy arm: less tingling in fingers/hands ($P = .005$); less trouble opening a jar ($P = .04$); EORTC QLQ-C30 quality of life better ($P = .03$)	34% discontinued the FGs before end of chemotherapy mainly due to discomfort. The EORTC CIPN20 subscales include data on lower extremities, which were not cooled in this trial.
Ruddy et al[27]	Prospective, randomized pilot, phase II study	Paclitaxel	42	Hands and feet were cooled starting 15 minutes before each paclitaxel dose and continued for 15 minutes after each dose was complete.	No difference in CIPN20 scores between the study arms, but cross-study comparisons suggested benefit from cryotherapy	
McCarthy et al[28]	Prospective, randomized study	Docetaxel	53	Participants acted as their own control, with the frozen gel glove worn on 1 randomly assigned hand starting 15 minutes before infusion and continuing until 15 minutes after completion of treatment.	No significant differences were determined between hand conditions in terms of time to event or in terms of toxicity in gloved and nongloved hands.	60% withdrawal rate due to patient discomfort with the intervention
Bandla et al[31]	Internally controlled pilot trial	Paclitaxel	20	Patients underwent limb hypothermia of 1 leg for a duration of 3 hours with every paclitaxel infusion, with the contralateral limb used as control.	Grade 3 PN occurred in 2 patients (10%), grade 2 in 2 (10%), and grade 1 in 12 (60%). Significant correlation was observed between amount of skin cooling and motor nerve amplitude preservation at 6 months ($P < .0005$). Sensory velocity and amplitude in the cooled limbs were less preserved than in the control limbs, but the difference did not attain statistical significance.	Well tolerated, with no premature termination of cooling due to intolerance.
Kanbayashi et al[34]	Phase II, self-controlled clinical trial	Paclitaxel	38	During chemotherapy, patients wore an FG on one hand and 2 SGs of the same size (ie, 1 size smaller than the size that best fits the hand) on the other hand.	Frequencies of CTCAE grade ≥ 2 was 18.4% in both groups. Frequencies of PNQ grade ≥ D peripheral neuropathies was 2.6% in both groups. No difference was identified between FG and SG groups in PNQ sensory neuropathy ($P = .32$-1.0), PNQ motor neuropathy ($P = .51$-1.0), or total FACT-T score ($P = .67$-$.93$) at each evaluation time.	Authors concluded that both approaches appeared to have similar benefits.

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TABLE 1. New Randomized Controlled Trials Regarding the Prevention of CIPN Since the Initial ASCO Guideline (continued)

Investigational Agent /Authors	Study Design	Neurotoxic Chemotherapy Agent	Evaluable Patients (No.)	Intervention Dose	Incidence/Severity of Neuropathy	Other
Tsuyuki et al[33]	Self-controlled clinical trial	Paclitaxel	42	Each patient wore 2 SGs on the dominant hand; both were 1 size smaller than the size that would normally fit the patient's hand. The nondominant hand served as the control (ie, did not wear SGs or anything else).	Compared with the control hands, the SG-protected hands: maintained significantly lower incidences of grade 2 or higher PN over time, despite the increase in nab-PTX treatment cycles ($P < .0001$); significantly decreased the overall occurrence of CTCAE grade ≥ 2 PN from 76.1% to 21.4% for sensory neurotoxicity and from 57.1% to 26.2% for motor neurotoxicity; sensory and motor incidences of grade ≥ 4 PNQ responses were significantly higher (ie, more interference with activities of daily living) for control hands than for SG-protected hands (sensory 38.1% *v* 7.1%; motor 23.8% *v* 2.4%).	During the administration of nab-PTX, 9 patients (21.4%) were permitted to take additional medications, such as goshajinkigan, pregabalin, and/or duloxetine, because PN grade ≥ 2 affected their control hands and/or feet.
Griffiths et al[29]	Randomized, self-controlled clinical trial	Paclitaxel	29	Patients wore a glycerin-containing Elasto-Gel glove and sock over a disposable glove and sock liner maintained at −25 to −30°C in a freezer for 3 hours before application. To maintain the appropriate cold, the study coordinator replaced the glove and sock every 45 to 50 minutes during the treatment of a total duration of 210 minutes.	There was no significant difference in NPSI scores between treated and untreated hands (all $P > .15$) or feet (all $P > .30$) at any assessment point; this remained true even when limiting analysis to the subset of 7 participants who had data for the final post-chemotherapy assessment.	Ten (34%) participants could not tolerate the cryotherapy, and 6 (21%) declined further participation at some point during the trial. Only 7 participants (24%) were available for the final post-chemotherapy QST and questionnaires.
Exercise						
Zimmer et al[36]	Randomized controlled trial	Various regimens for patients with metastatic colorectal cancer	30	Intervention included 8-week supervised exercise program, including endurance, resistance, and balance training (2×/wk for 60 minutes) *v* control group received written standard recommendations for physical fitness.	Neuropathic symptoms remained stable in the intervention group over time, while CIPN significantly worsened in the control group from baseline to 8 weeks and from baseline to 4 weeks postintervention completion follow-up. The intervention group also significantly improved in strength and balance function compared with the controls. Changes in CIPN correlated with changes in balance.	
Kleckner et al[35]	Randomized controlled trial	Taxane-, platinum-, or vinca alkaloid–based chemotherapy	355	Intervention included chemotherapy plus EXCAP, a standardized, individualized, moderate-intensity, home-based, 6-week progressive walking and resistance exercise program.	Exercise significantly reduced CIPN symptoms of: hot/coldness in hands/feet (−0.46 units; $P = .045$); numbness and tingling (−0.42 units; $P = .061$) was not statistically significantly reduced compared with the control.	This trial was developed to study fatigue, but CIPN data were also collected.

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TABLE 1. New Randomized Controlled Trials Regarding the Prevention of CIPN Since the Initial ASCO Guideline (continued)

Investigational Agent /Authors	Study Design	Neurotoxic Chemotherapy Agent	Evaluable Patients (No.)	Intervention Dose	Incidence/Severity of Neuropathy	Other
GM-1						
Zhu et al[39]	Randomized trial	Oxaliplatin	120	100 mg once daily IV	Less neuropathy in the investigational treatment arm, compared with the control group.	Clinician-reported neuropathy, not patient-reported. Lack of a placebo arm introduces a potential bias
Su et al[38]	Randomized trial	Taxanes	206	80 mg, day −1 to day 2	Functional Assessment of Cancer Treatment Neurotoxicity subscale GM-1: 43.3 (95% CI, 43.1 to 43.5). Placebo: 34.3 (95% CI, 33.8 to 34.9); mean difference, 8.96 (95% CI, 8.4 to 9.5; $P < .001$). Grade ≥ 1 peripheral neurotoxicity in CTCAE v4: GM-1: 14.3%; placebo: 100.0%; $P < .001$. Incidence of grade ≥ 1 neurotoxicity by ECOG. Sensory neuropathy: GM1: 26.4% *v* placebo: 97.8%; $P < .001$. Motor neuropathy: GM-1: 20.9%; placebo: 81.5%; $P < .001$	Peculiar total reversal of CIPN 3 months after taxane completion, which has not been observed in other trials.
Goshajinkigan						
Kuriyama et al[41]	Systematic review and meta-analysis	—	397, from 5 trials	—	Reduced incidence of CIPN grade ≥ 1: RR, 0.43; 95% CI, 0.27 to 0.66. Reduced incidence of CIPN grade ≥ 2: not statistically significant. Reduced incidence of CIPN grade 3: RR, 0.42; 95% CI, 0.25 to 0.71.	Authors concluded that, given the low quality and insufficient amount of the evidence, use of goshajinkigan as standard of care is not currently recommended.
Metformin						
El-Fatatry et al[42]	Randomized controlled trial	Oxaliplatin	40	Patients in the metformin group received the same chemotherapeutic regimen as the control group in addition to metformin 500 mg 3 times daily after meals throughout the 12 cycles of chemotherapy.	NCI-CTCAE peripheral neuropathy grading: at the end of 12th cycle, there were significantly fewer patients with grade 2-3 neuropathy in metformin arm compared with control arm (60% *v* 95%; $P = .009$). The Ntx-12 questionnaire: at the end of the 6th cycle and on to 12th cycle, metformin group showed significantly higher mean scores than control group (37.8 *v* 34.5; $P = .0001$ and 24.0 *v* 19.2; $P < .0001$, respectively). The BPI-SF "worst pain": At the end of 11th and 12th cycles, metformin group showed significantly lower mean pain scores than control group (6.4 *v* 6.9; $P = .01$ and 6.7 *v* 7.3; $P = .001$, respectively).	

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TABLE 1. New Randomized Controlled Trials Regarding the Prevention of CIPN Since the Initial ASCO Guideline (continued)

Investigational Agent /Authors	Study Design	Neurotoxic Chemotherapy Agent	Evaluable Patients (No.)	Intervention Dose	Incidence/Severity of Neuropathy	Other
Pregabalin						
de Andrade et al[44]	Randomized, double-blind, placebo-controlled trial	Oxaliplatin	143	3 days before and 3 days after each oxaliplatin infusion.	Pain intensity: pregabalin: 1.03 (95% CI, 0.79 to 1.26); placebo: 0.85 (95% CI, 0.64 to 1.06). Not significant. Scores from the BPI, MPQ, DN-4, NPSI, and NCS and side-effect profiles and incidence of death did not differ between groups. QOL score: pregabalin group: 79.4 ± 20.6; placebo, 76.9 ± 23.1	
Shinde et al[43]	Pilot randomized, double-blind, placebo-controlled trial	Paclitaxel	46	75 mg/d	Not enough positive evidence to support a phase III trial.	
Gabapentin						
Aghili et al[45]	Randomized, placebo-controlled trial	Paclitaxel	40	300 mg 3 times a day	Difference in neuropathy grading between the gabapentin and control group were statistically significantly in favor of gabapentin in each treatment cycle ($P <$ .004). Change in baseline nerve conduction velocity after 4 cycles of paclitaxel was statistically significantly lower in the gabapentin group compared with placebo (sural nerve: 17.7% ± 37.2% *v* 61.0% ± 48.0%; P = .004; peroneal nerve: 21.9% ± 41.5% *v* 62.5% ± 53.5%; P = .016).	
Venlafaxine						
Zimmerman et al[47]	Pilot randomized, double-blind, placebo-controlled trial	Oxaliplatin	50	37.5 mg twice a day	Not enough positive evidence to support a phase III trial.	
Vitamin B						
Schloss et al[49]	Pilot, randomized, placebo-controlled trial	Oxaliplatin or vincristine	47	1 capsule, twice a day, of B vitamin complex, which included 50 mg of thiamine, 20 mg of riboflavin, 100 mg of niacin, 163.5 mg of pantothenic acid, 30 mg of pyridoxine, 500 μg of folate, 500 μg of cyanocobalamin, 500 μg of biotin, 100 mg of choline, and 500 μg of inositol.	TNS demonstrated that the B vitamin group did not significantly reduce the incidence of CIPN compared with placebo (P = .73). Statistical significance was achieved for patient perceived sensory peripheral neuropathy (12 weeks, P = .03; 24 weeks, P = .005; 36 weeks, P = .021). The risk estimate for the PNQ was also statistically significant (OR, 5.78; 95% CI, 1.63 to 20.5). EORTC QOL, total pain score, and pain interference showed no significance (P = .46, P = .9, P = .37, respectively).	

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TABLE 1. New Randomized Controlled Trials Regarding the Prevention of CIPN Since the Initial ASCO Guideline (continued)

Investigational Agent /Authors	Study Design	Neurotoxic Chemotherapy Agent	Evaluable Patients (No.)	Intervention Dose	Incidence/Severity of Neuropathy	Other
Vitamin E						
Huang et al[50]	Systematic review and meta-analysis	Platinum-based therapy, paclitaxel-based therapy, and various other chemotherapeutic agents	353 from 6 studies	300 mg daily (1 study); 300 mg twice daily (3 studies); 400 mg daily (1 study)	Incidence of CIPN: RR, 0.55; 95% CI, 0.29 to 1.05; P = .07). RR in high-quality trials with low bias risk, 1.03; 95% CI, 0.59 to 1.80; P = .92. Subgroup analysis of cisplatin-related neurotoxicity: RR, 0.31; 95% CI, 0.17 to 0.58; P = .0002.	Four of the 6 included studies assessed the safety of vitamin E during chemotherapy and no adverse events were observed
Salehi et al[51]	Prospective, randomized controlled study	Oxaliplatin	65	400 mg daily	Mean peripheral neuropathy score changes (mean difference after to before) after sixth course of the oxaliplatin base regimen: vitamin E group: 6.37 ± 2.85; control group, 6.57 ± 2.94; P = .78).	
Acupuncture						
Greenlee et al[13]	Randomized sham-controlled trial	Taxanes	63	Selected acupuncture points were attached to 2 leads connected to an electro-stimulator that generated 2 Hz of mixed pulsatile intervals for a total of 30 minutes. Needles not attached to the electro-stimulator were manipulated manually to elicit de qi once during the treatment.	Week 12, increase in mean BPI-SF worst pain score: EA: 2.6; sham EA: 2.8; P = .86. Week 16, mean BPI-SF worst pain score: EA: 3.4; sham EA: 1.7; P = .03. The increase in BPI-SF worst pain score was 1.62 points higher in the EA group than in the sham EA group at week 16 (P = .04).	
Minocycline						
Wang et al[84]	Phase II randomized clinical trial	Oxaliplatin	66	Intervention included 100 mg twice daily minocycline	There was no observed significant symptom reduction on numbness/tingling in either arm, nor was there a difference in levels of serum proinflammatory or antiinflammatory markers between arms.	No grade 3 adverse events were observed
Pachman et al[85]	Randomized pilot study	Paclitaxel	47	Intervention included minocycline 200 mg on day 1 followed by 100 mg twice daily	There were no remarkable differences noted between the minocycline and placebo groups for the overall sensory neuropathy score of the EORTC QLQ-CIPN20 or its individual components, which evaluate tingling, numbness and shooting/burning pain in hands and feet. Patients taking minocycline had a reduction in the daily average pain score attributed to P-APS (P = .02).	

Abbreviations: ALC, acetyl-L-carnitine; BPI-SF, Brief Pain Inventory–Short Form; CIPN, chemotherapy-induced peripheral neuropathy; CTCAE, Common Terminology Criteria for Adverse Events; DN-4, Douleur Neuropathique 4 Questions; EA, electro-acupuncture; EMG, electromyography; EORTC, European Organization for Research and Treatment of Cancer; EXCAP, Exercise for Cancer Patients; FACT-T, Functional Assessment of Cancer Therapy-Taxane; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; FG, frozen glove; FU, fluorouracil; GM-1, ganglioside-monosialic acid; ITT, intention to treat; IV, intravenous; MPQ, McGill Pain Questionnaire; nab-TPX, nanoparticle albumin-bound paclitaxel; NCI, National Cancer Institute; NCS, nerve conduction studies; NPSI, Neuropathic Pain Symptom Inventory; NTX, neurotoxicity; OR, odds ratio; P-APS, paclitaxel-associated acute pain syndrome; PN, peripheral neuropathy; PNQ, Patient Neurotoxicity Questionnaire; QLQ-C30, Quality of Life Questionnaire-Core 30; QOL, quality of life; QST, quantitative sensory testing; RR, relative risk; SG, surgical glove; TNS, Total Neuropathy Score.

predispose to neuropathy such as diabetes and/or a family or personal history of hereditary peripheral neuropathy (Type of recommendation: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

1.2 Clinicians should not offer, and should discourage use of, acetyl-L-carnitine for the prevention of CIPN in patients with cancer (Type of recommendation: evidence based, harms outweigh benefits; Evidence quality: high; Strength of recommendation: strong).

1.3 Outside the context of a clinical trial, no recommendations can be made on the use of the following interventions for the prevention of CIPN:

- Acupuncture
- Cryotherapy
- Compression therapy
- Exercise therapy
- Ganglioside-monosialic acid (GM-1)

(Type of recommendation: no recommendation; Evidence quality: low; Strength of recommendation: not applicable).

Note: While preliminary evidence suggests a potential for benefit from these interventions, larger sample–sized definitive studies are needed to confirm efficacy and clarify risks.

1.4 Clinicians should not offer the following agents for the prevention of CIPN to patients with cancer undergoing treatment with neurotoxic agents:

- All-trans retinoic acid
- Amifostine
- Amitriptyline
- Calcium magnesium
- Calmangafodipir
- Cannabinoids
- Carbamazepine
- L-carnosine
- Diethyldithiocarbamate (DDTC)
- Gabapentin/pregabalin
- Glutamate
- Glutathione (GSH) for patients receiving paclitaxel/carboplatin chemotherapy
- Goshajinkigan (GJG)
- Metformin
- Minocycline
- *N*-acetylcysteine
- Nimodipine
- Omega-3 fatty acids
- Org 2766
- Oxcarbazepine
- Recombinant human leukemia inhibitory factor
- Venlafaxine
- Vitamin B
- Vitamin E

(Type of recommendation: evidence based, no benefits; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature Review Update and Analysis on Prevention

Acupuncture. One small randomized, sham-controlled trial of weekly electro-acupuncture for the prevention of taxane-induced peripheral neuropathy in 63 patients did not show any differences in neuropathy between groups.[13] In this trial, the electro-acupuncture arm actually had a slower recovery of neuropathy than was seen in the sham group, after chemotherapy was stopped.

Acetyl-L-carnitine. Two trials evaluating acetyl-L-carnitine were identified. Campone et al[14] reported data on the use of acetyl-L-carnitine for preventing sagopilone-induced neuropathy in 150 patients randomly assigned to receive acetyl-L-carnitine or placebo. There were no significant differences between the 2 treatment arms for peripheral neuropathy overall, and the median duration of neuropathy was similar.[14] These data are consistent with older data from a previously reported trial in patients receiving paclitaxel, where neuropathy was actually worse in the patients who received acetyl-L-carnitine.[15,16] In a recent long-term follow-up analysis[7] of that trial, 24 weeks of acetyl-L-carnitine therapy resulted in statistically significantly worse CIPN ($P = .01$) over 2 years, as measured by the Functional Assessment of Cancer Therapy-Neurotoxicity (FACT-Ntx) Questionnaire.

Alpha-lipoic acid. One randomized, double-blinded clinical trial that evaluated oral alpha-lipoic acid (ALA) for the prevention of platinum-induced peripheral neuropathy was identified. Patients received 600 mg ALA acid 3 times daily for 24 weeks while receiving chemotherapy. This trial enrolled 243 patients, but only 70 of them (29%) completed the trial. The study authors reported that the high dropout rate may have been related, in part, to the requirement that patients take the drug 3 times per day. Data indicated that neuropathy scores increased significantly from baseline for both groups at 24 weeks ($P < .001$ for each group), with no statistically significant ameliorating effect from ALA in the treatment arm being observed from the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) tool, from pain scores, or from functional test scores. The study results suggest that ALA is not tolerated well and does not prevent neuropathy.[17]

Calcium and magnesium. One systematic review and 1 pilot trial not included in the systematic review evaluating the utility of intravenous calcium and magnesium were identified. The systemic review, which included 694 patients from 5 trials published between 2010 and 2014, confirmed that there was no beneficial effect in terms of the incidence of grade ≥ 2 neuropathy (relative risk [RR], 0.81; 95% CI, 0.60 to 1.11) or chronic neurotoxicity (RR, 0.95; 95% CI, 0.69 to 1.32) from CaMg infusions for the prevention of oxaliplatin-induced peripheral neuropathy.[18] Two older pooled analyses identified from Xu et al[19] and Wen et al[20], which did not come to the same conclusion, should be

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TABLE 2. Randomized Controlled Trials for the Treatment of Established CIPN

Investigational Agent/ Authors	Study Design	Neurotoxic Chemotherapy Agent	Evaluable Patients (No.)	Neuropathy Outcomes	Methods	Comments
Duloxetine and pregabalin						
Farshchian et al[48]	Randomized clinical trial of duloxetine *v* venlafaxine	Various	156	Grades of neuropathy outcomes decreased significantly in venlafaxine and duloxetine groups. Reduction was more considerable in duloxetine group compared with venlafaxine group ($P < .05$).	Patient-reported outcomes and clinical neurologic assessments	
Hirayama et al[58]	Open-label, randomized, crossover study	Various	34	Significant decreased VAS score in duloxetine pain ($P = .04$), numbness ($P = .03$). AEs: no AEs grade > 2 by CTCAE	Patient-reported outcome	Vitamin E was used in the control arm. Crossover data, after a wash-out period, also supported duloxetine benefit.
Salehifar et al[59]	Randomized clinical trial of duloxetine *v* pregabalin	Taxanes	82	Both arms showed statistically significantly decreased CIPN from baseline, and pregabalin was reported to be significantly better than duloxetine.	Patient-reported outcomes and CTCAE evaluations.	Most patients were started on this therapy while they were receiving chemotherapy. Confirmation of these results needed, given other results of other reported gabapentinoid trials.
Topical amitriptyline/ketamine						
Gewandter et al64	Phase III randomized, double-blind, placebo-controlled trial	Various	462	No observed benefit from treatment.	Patient-reported outcome	
Oral mucosal cannabinoid extract						
Lynch et al[63]	Randomized, placebo-controlled crossover pilot study	Various	16	No statistically significant difference between the treatment and the placebo groups on the NRS-PI.	11-point numerical rating scale, patient-reported	Low power
Scrambler therapy						
Loprinzi et al[61]	Randomized phase II pilot trial	Variety	46	Baseline pain, tingling and numbness scores: compared with TENS-treated patients, twice as many scrambler-treated patients had ≥ 50% documented improvement during the 2 treatments. Patients in the scrambler group were more likely than those in the TENS group to recommend their treatment to other patients during both the 2-week treatment period and the 8-week follow-up period ($P < .0001$).	Patient-reported outcomes	Minimal toxicity was observed.
Smith et al[60]	Randomized sham-controlled phase II trial	Variety	46	Average pain, the BPI, and EORTC CIPN-20: no significant differences between the sham and the "real" ST group at day 10, 28, 60, or 90. There was improvement in the sensory subscale of the CIPN-20 at 2 months in the "real" group ($P = .14$).	Patient-reported outcomes	
Acupuncture						
Lu et al[54]	Randomized controlled trial	Taxanes	40	At 8 weeks: PNQ sensory scores: IA, -1.0 ± 0.9; wait-list control group (control): -0.3 ± 0.6; $P = .01$. FACT-NTX summary score: IA, 8.7 ± 8.9; control, 1.2 ± 5.4, $P = .002$; BPI-SF pain severity score: IA: -1.1 ± 1.7; control: 0.3 ± 1.5; $P = .03$	Patient-reported outcomes	No serious adverse effects were observed.
Molassiotis et al[53]	Randomized controlled trial	Variety	87	At 8 weeks: statistically significant differences detected in pain (primary outcome), the clinical neurologic assessment, QOL domains, and symptom distress (all $P < .05$). Fourteen weeks: improvements in pain interference, neurotoxicity-related symptoms, and functional aspects of quality of life were sustained ($P < .05$). Twenty weeks: improvements in physical and functional well-being sustained ($P < .05$).	Patient-reported outcomes and clinical neurologic assessments	

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TABLE 2. Randomized Controlled Trials for the Treatment of Established CIPN (continued)

Investigational Agent/ Authors	Study Design	Neurotoxic Chemotherapy Agent	Evaluable Patients (No.)	Neuropathy Outcomes	Methods	Comments
D'Alessandro et al[55]	Randomized controlled pilot trial	NR	33	EORTC QLQ-C30: statistical differences in physical (P = .03) and function (P = .04) domains. NCI CTCAE Scale and neuropathy sensory symptoms pre- *v* post-treatment: statistically significantly better results in acupuncture group (P = .01) *v* control group, which showed no statistically significant differences after 5 weeks (P = .11).	Patient-reported outcomes and clinical neurologic assessments	Intervention included 10 sessions of acupuncture, 2 times per week
Han et al[57] (acupuncture plus methylcobalamin)	Randomized controlled trial		98	VAS pain scores: Met + Acu: decreased in 85.7% of patients; control: decreased in 77.6% of patients. VAS pain scores in the Met + Acu group decreased more significantly compared with the control group ($P < .01$). QOL FACT/GOG-Ntx: significant symptom improvement in Met + Acu group ($P < .001$) after therapy, but not in control group ($P > .05$), and the improvement was more significant in the Met + Acu group ($P < .05$). Nerve conduction velocity: after treatments, there was no significant difference in MCV improvement in the Met + Acu group compared with the control group ($P > .05$).	Patient-reported outcomes and clinical neurologic assessments	
Rostock et al[56] (electro-acupuncture)	Randomized controlled trial	Taxanes, platinum derivatives, or vinca alkaloids	60	CIPN perceived symptom severity on a 10-point numeric rating scale: compared with placebo (1.3 ± 1.3) electro-acupuncture showed worse effects (0.8 ± 1.2), resulting in a group difference of −0.3 (CI, −1.4 to 0.8; P = .705). No significant differences in sensory nerve conduction studies or quality of life (EORTC QLQ-C30) were found.	Patient-reported outcomes	Study was stopped early at interim analysis as no relevant superiority of electro-acupuncture was detected ($P\alpha_0 > 0.6$).
Exercise						
Kneis et al[86]	Randomized controlled trial	NR	50	At 12 weeks: ITT (n = 41) did not reveal a significant group for sway path in semi-tandem stance after intervention (primary end point). Per-protocol analysis of 37 patients with training compliance ≥ 70%: intervention group reduced their sway path during semi-tandem stance, improved the duration standing on 1 leg on instable surface and reported decreased motor symptoms on CIPN20 motor score.	Patient-reported outcomes	Intervention included endurance plus balance training *v* only endurance training in the control group (both groups did so twice weekly over 12 weeks). Neuropathy measures were not the primary outcome.
Dhawan et al[52]	Randomized controlled trial	Paclitaxel and carboplatin	45	At 10 weeks: significant reduction in neuropathic pain scores ($P <$ .0001) and improvement in Functional QOL (P = .0002), Symptom QOL (P = .0003), Global Health Status QOL (P = .004) scores were observed after intervention in the exercise group compared with the usual-care group.	Patient-reported outcomes and clinical neurologic assessments	Intervention included home-based muscle strengthening and balancing exercise for 10 weeks

Abbreviations: AE, adverse effect; BPI, Brief Pain Inventory; CIPN, chemotherapy-induced peripheral neuropathy; CTCAE, Common Terminology Criteria for Adverse Events; EORTC, European Organization for Research and Treatment of Cancer; FACT-NTX, Functional Assessment of Cancer Therapy-Neurotoxicity; FACT/GOG-Ntx, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity; IA, immediate acupuncture; ITT, intention to treat; MCV, motor conduction velocities; Met + Acu, methylcobalamin plus acupuncture; NCI, National Cancer Institute; NR, not reported; NRS-PI, Numerical Rating Scale-Pain Intensity; PNQ, Patient Neurotoxicity Questionnaire; QOL, quality of life; QLQ-C30, Quality of Life Questionnaire-Core 30; ST, scrambler therapy; TENS, transcutaneous electrical nerve stimulation; VAS, visual analogue scale.

TABLE 3. Summary of Recommendations

Interventions	Strength of Recommendation	Strength of the Evidence	Benefits	Harms[a]
Prevention				
Acetylcysteine	Moderate against	Intermediate	Low	Low
Acetyl-L-carnitine	Strong against	High	No evidence of efficacy	High
Acupuncture	No recommendation	Low	Low	Moderate
Amifostine	Moderate against	Intermediate	Low	Moderate
Amitriptyline	Moderate against	Intermediate	No evidence of efficacy	Moderate
Calcium and magnesium	Moderate against	Intermediate	Low	Low
Cannabinoids	Moderate against	Intermediate		
Calmangafodipir	Moderate against	Intermediate	Low	Low
Carbamazepine/oxcarbazepine	Moderate against	Intermediate	Low	Low
L-carnosine	Moderate against	Intermediate	Low	Low
Compression therapy	No recommendation	Low	Low	Low
Cryotherapy	No recommendation	Low	Low	Moderate
DDTC	Moderate against	Intermediate	No evidence of efficacy	High
Exercise	No recommendation	Low	Low	Low
Gabapentin/pregabalin	Moderate against	Intermediate	Low	Low
GM-1	No recommendation	Low	Low	Low
Glutamate/glutamine	Moderate against	Intermediate	Low	Low
GSH	Moderate against	Intermediate	Low	Low
GJG–Kampo medicine	Moderate against	Intermediate	Low	Low
Metformin	Moderate against	Intermediate	Low	Low
Minocycline	Moderate against	Intermediate	Low	Low
Nimodipine	Moderate against	Intermediate	No evidence of efficacy	Moderate
Omega 3	Moderate against	Intermediate	Low	Low
Org 2766	Moderate against	Intermediate	Low	Low
Retinoic acid	Moderate against	Intermediate	Low	Moderate
rhuLIF	Moderate against	Intermediate	No evidence of efficacy	Low
Venlafaxine	Moderate against	Intermediate	Moderate	Moderate
Vitamin B	Moderate against	Intermediate	Low	Low
Vitamin E	Moderate against	Intermediate	Low	Low
Treatment				
Acupuncture	No recommendation	Low	Low	Low
Duloxetine	Moderate for	Intermediate	Moderate	Low
Exercise	No recommendation	Low	Low	Low
Gabapentin/pregabalin	No recommendation	Low	Low	Low
BAK	No recommendation	Low	Low	Low
Oral cannabinoids	No recommendation	Low	Low	Low
Tricyclic antidepressants	No recommendation	Low	Low	Low
Scrambler therapy	No recommendation	Low	Low	Low

Abbreviations: BAK, topical amitriptyline, ketamine, ± baclofen; DDTC, diethyldithiocarbamate; GJG, goshajinkigan; GM-1, ganglioside-monosialic acid; GSH, glutathione.

[a]Harms are based only on the results of the specific clinical trials in the previous tables and not on any other evaluations of the safety of these treatments.

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discounted, as they did not include data from the largest and most recent definitive trial.

A small randomized, placebo-controlled, crossover trial of calcium/magnesium for prevention of oxaliplatin-induced acute neuropathy involved 20 patients and evaluated EMG motor nerve hyperexcitability scores.[21] The authors reported that there were no differences between those who received calcium and magnesium versus placebo in EMG outcomes (mean EMG score Ca/Mg, 6.5; standard deviation [SD], 4.31; and mean placebo score, 6.2; SD, 4.34) or for patient-reported acute neurotoxicity symptoms.[21]

Calmangafodipir. Calmangafodipir was studied in a placebo-controlled 3-arm phase II trial in patients receiving oxaliplatin-based chemotherapy.[22] This trial provided promising enough data to initiate 2 phase III, placebo-controlled clinical trials (ClinicalTrials.gov identifiers: NCT04034355 and NCT04034355), with results forthcoming.

L-Carnosine. A 61-patient randomized trial evaluated a nutraceutical product, L-carnosine, as an agent to try to decrease oxaliplatin-induced neuropathy.[23] Although the study reported remarkably positive results for the study agent over the control arm, there was no placebo used in this trial and it was not double-blinded. Clinicians judged neuropathy severity, as opposed to using patient-reported outcomes. Thus, additional data are necessary to understand the potential utility of this agent.

Cryotherapy/compression therapy/cryo-compression therapy. The first publication suggesting that cryotherapy was helpful for decreasing taxane-induced neuropathy came from Danish investigators, who noted that patients who received distal-extremity cryotherapy for decreasing onycholysis appeared to have reduced amounts of docetaxel-induced neuropathy by approximately 50%.[24] Five trials evaluating cryotherapy were identified. One prospective, self-controlled trial in 36 patients with breast cancer treated weekly with paclitaxel, who wore frozen gloves (FGs) and socks on the dominant side for 90 minutes but not the other side, reported that the development of subjective CIPN symptoms was clinically and statistically significantly delayed during the course of the paclitaxel treatment; the occurrence of subjective CIPN at a cumulative dose of 960 mg/m^2 was reported to be almost completely prevented (severe CIPN; hand: 2.8% *v* 41.7%; odds ratio [OR], infinite; 95% CI, 3.32 to infinite; $P < .001$; foot: 2.8% *v* 36.1%; OR, infinite; 95% CI, 2.78 to infinite; $P < .001$), and the CIPN incidence, as assessed by other objective modalities, was lower on the intervention side.[25] In a larger unblinded RCT, 180 patients started treatment with oxaliplatin, docetaxel, or paclitaxel and were randomly assigned to FGs on both hands during treatment or to usual care.[26] Self-reported CIPN and QOL were measured. Overall neuropathy scores, the primary outcome measure, were not significantly different between the groups, in part because the feet were not treated, and neuropathy in lower extremities is oftentimes more problematic than it is in upper extremities. This study's results did support that FGs reduced neuropathy symptoms in patients' hands and improved some QOL measures. A recently published randomized phase II trial, involving 42 patients, compared cryotherapy (performed with ice packs on hands and feet) to an untreated control group who was not treated with cryotherapy.[27] The area under the curve of the CIPN20 sensory scores over 12 weeks of paclitaxel was not found to differ between the study arms (mean difference, 3.45; 95% CI, −3.13 to 10.02; $P = .26$). However, when the cryotherapy arm was compared with a control arm made up of controls combined from 3 previous trials, the cryotherapy arm had less neuropathy (Wilcoxon rank-sum $P = .01$). The authors of this study reported that the data supported phase III trial testing of this approach.

In a trial that evaluated a unilateral FG in 53 patients receiving docetaxel, 60% of the patients stopped the cryotherapy, and there were no differences between the hands that were randomly assigned to receive it versus not.[28] Likewise, another study described similarly high drop-out rates and did not report positive findings.[29]

One trial evaluated continuous-flow limb hypothermia as a neuroprotective strategy in 20 patients receiving paclitaxel chemotherapy compared with usual care. Patients who received continuous limb hypothermia had less self-reported paclitaxel-induced neuropathy symptoms and had better nerve conduction studies.[30] The same group of researchers also conducted a subsequent proof-of-concept study in patients with cancer receiving taxane chemotherapy.[31] In this study, both cryotherapy and compression therapy (ie, cryo-compression therapy) were given to all 4 limbs in 13 subjects with each dose of paclitaxel. An analysis of nerve conduction studies with cryo-compression, administered at 16°C and a cyclic pressure of 5-15 mm Hg, illustrated preservation of motor amplitudes compared with baseline.[32] In a cross-study comparison with their previous group of patients who had been treated with cryotherapy alone, patients appeared to do better with the combination therapy.[32]

One trial evaluated compression therapy using a tight surgical glove during taxane chemotherapy infusion.[33] The intervention hand side was randomized within 43 patients. National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 2 sensory neuropathies were reported in 21% of the hands that wore the gloves versus 76% of hands that were not gloved.

A recently published small trial (38 patients) compared cryotherapy to compression therapy. This trial had patients use cryotherapy on one hand and compression therapy on the other and reported that similar results were seen with each approach.[34] Additional randomized trials investigating cryotherapy and cryo-compression are ongoing.

Exercise. Three RCTs that evaluated various exercise interventions for the prevention of CIPN were identified. In

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a large trial of patients with cancer receiving taxane-, platinum-, or vinca alkaloid–based chemotherapy,[35] 355 patients were randomly assigned to chemotherapy or chemotherapy plus Exercise for Cancer Patients (EXCAP), a standardized, individualized, moderate-intensity, home-based, 6-week progressive walking and resistance exercise program. This unblinded trial was developed to evaluate the effectiveness of exercise on fatigue. As a secondary analysis, data regarding CIPN were also collected; these results supported that, compared with the control, exercise significantly reduced CIPN symptoms of hot/coldness in hands/feet (P = .045) and numbness and tingling, although the latter was not statistically significantly reduced compared with the control arm (P = .06). The intervention group still developed neuropathy, but less than the control group—a difference of approximately half a point on a 0-10 scale. On the basis of these findings and other preliminary supportive evidence,[36,37] the NCI has recently approved a concept for a randomized cooperative oncology group trial to prospectively address the utility of exercise in this setting.

GM-1. GM-1 is a monosialo-glycosphingolipid that performs an important function in the processes of neurogenesis, nerve development and differentiation, cell recognition, and signal transduction.[38] Two randomized trials investigating GM-1 for CIPN prevention were identified. In the first trial, Zhu et al[39] reported on 120 patients with GI cancers who were treated with oxaliplatin-based chemotherapy randomly assigned to receive intravenous ganglioside-monosialic acid or to a control group that received no neuroprotective agents. Although the grade of neurotoxicity in the experimental group was significantly lower than in the control group ($P < .05$, Mann-Whitney U test), the lack of placebo control and the lack of patient-reported outcome data decrease the confidence of this finding.[39]

The second trial was a placebo-controlled, double-blinded study of intravenous GM-1, given to prevent taxane-induced CIPN in 183 patients with early-stage breast cancer. The study reported that treatment with GM-1 resulted in a statistically significant reduction in the severity and incidence of CIPN after 4 cycles of taxane-containing chemotherapy ($P < .001$).[38] A peculiar aspect of this trial is that the neuropathy appeared to be totally reversed in the placebo arm 3 months after chemotherapy completion, which is quite unusual in Western populations.[40] Despite this very positive report, a confirmatory trial is needed.

Goshajinkigan. Our systematic review found a meta-analysis that pooled data from 5 trials and included 397 patients. The review reported that goshajinkigan was not associated with a reduced incidence of CIPN when assessed with the CTCAE (RR, 0.99; 95% CI, 0.53 to 1.85 for CIPN ≥ grade 2).[41] Our systemic review did not find additional studies with goshajinkigan that were not included in this meta-analysis.

Metformin. One small randomized study (N = 40) that evaluated metformin as a means of preventing oxaliplatin-induced neuropathy compared with a control group was identified.[42] The authors reported that, at the end of the 12th FOLFOX-4 (fluorouracil, leucovorin, and oxaliplatin) regimen cycle, grade 2-3 neuropathy was lower in the metformin arm compared with the control arm (60% *v* 95%; P = .009), and the metformin arm had better NTX-12 scores (24.0 *v* 19.2; $P < .001$). Given the small sample size, more confirmatory studies are needed before recommending this approach for oxaliplatin-induced neuropathy.

Gabapentin/pregabalin. Two randomized placebo-controlled trials investigating pregabalin were identified. On the basis of pilot study information, which suggested that gabapentinoids could decrease paclitaxel-associated acute pain and chronic neuropathy, investigators developed a phase II placebo-controlled clinical trial (N = 46) to look at pregabalin for preventing these neuropathic problems. The results did not support that pregabalin was helpful for preventing the paclitaxel-associated acute pain syndrome or paclitaxel-induced peripheral neuropathy.[43]

In another double-blind, placebo-controlled trial, 143 pain-free, chemotherapy-naive patients with colorectal cancer receiving at least 1 cycle of modified FLOX (ie, fluorouracil, leucovorin, and oxaliplatin) were randomly assigned to receive either pregabalin or placebo for 3 days before and 3 days after each oxaliplatin infusion. After following patients for up to 6 months, the authors reported that preemptive use of pregabalin during oxaliplatin infusions did not decrease the incidence of chronic pain related to oxaliplatin, measured by pain intensity and QOL scales.[44] An additional randomized, double-blinded, placebo-controlled trial of pregabalin involving 64 patients who were receiving oxaliplatin chemotherapy was terminated early, as an interim analysis found that there were not sufficiently positive data to continue the trial.[15]

A small study (20 patients per arm) evaluating gabapentin 300 mg 3 times a day in a double-blind, randomized trial in patients receiving paclitaxel was identified.[45] Although the authors reported a significant reduction in CIPN, confirmation of this is needed in a subsequent trial.

Venlafaxine. One trial investigating the efficacy of venlafaxine on prevention of CIPN was identified. Pursuant to data from Durand et al[46] discussed in the initial ASCO CIPN guideline, this phase II randomized, placebo-controlled clinical trial was conducted to look at venlafaxine as a drug to decrease neuropathy associated with oxaliplatin.[47] Fifty patients were randomly assigned to venlafaxine or placebo, given continuously with initiation of the first or second cycle of oxaliplatin. The trial results did not support the use of venlafaxine in this setting, dampening enthusiasm for proceeding with a phase III trial.[47] Notably, the Durand et al[46] study started venlafaxine/placebo after

patients had received some oxaliplatin, in contrast to at oxaliplatin initiation. Given that there are now data that support that venlafaxine may decrease symptoms in patients with established neuropathy (although not as well as duloxetine),[48] it may be that in the Durand et al[46] trial venlafaxine was potentially acting as an agent that treated established neuropathy, as opposed to acting as a prevention agent.

Vitamin B. A 71-patient placebo-controlled 2-arm trial evaluated an oral vitamin B product in patients who were receiving a variety of neurotoxic drugs (taxanes, oxaliplatin, or vincristine).[49] Data were only available for 47 patients and, understandably with this small sample size and the variety of chemotherapy drugs, there was no suggestion that the primary end point was improved in the vitamin B arm.

Vitamin E. One systemic review and meta-analysis plus another trial not included in the meta-analysis were identified. The systematic review and meta-analysis of 6 studies that included 353 patients reported that the administration of vitamin E (at doses that included 300 mg daily, 300 mg twice daily, and 400 mg daily) did not decrease the incidence of CIPN (RR, 0.55; 95% CI, 0.29 to 1.05; P = .07.[50] The small study published subsequently to the meta-analysis[51] also concluded that vitamin E did not help to prevent oxaliplatin-induced peripheral neuropathy.

Clinical interpretation regarding efforts to prevent CIPN. The current review did not find studies supporting the recommendation of any neuropathy-preventative agent. Unlike the promising original guideline commentary regarding venlafaxine as a preventative agent, the updated guideline does not recommend it. A negative follow-up study with a similar number of patients, which treated patients for a longer time period and used a more accepted chemotherapy neuropathy patient-reported outcome measurement tool, backs this.[47]

Given the dearth of effective established agents for preventing chemotherapy-induced neuropathy and the limited effective therapy for treating established CIPN, patients/clinicians should weigh the benefits of using neuropathy-inducing agents against the risks of developing long-term, irreversible CIPN.

Although proof of benefit has not been established, available data support that exercise, cryotherapy, compression therapy, and/or cryo-compression therapy may, in part, prevent CIPN symptoms and appear to be reasonably safe, although clinicians and patients should be aware of frostbite risk. Ganglioside-monosialic acid seemed to be effective in preventing taxane-induced peripheral neuropathy in Chinese patients, but this should be confirmed in a large trial in a different ethnic group. Ongoing trials are attempting to better define whether one or more of these methods will safely prevent CIPN.

Treatment of Chemotherapy-Induced Peripheral Neuropathy That Develops While Patients Are Receiving Neurotoxic Chemotherapy

2.1 Clinicians should assess, and discuss with patients, the appropriateness of dose delaying, dose reduction, or stopping chemotherapy (or substituting with agents that do not cause CIPN) in patients who develop intolerable neuropathy and/or functional nerve impairment (Type of recommendation: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

Clinical interpretation. Although there are limited clinical trial data available to guide practice when patients develop CIPN during the course of neurotoxic chemotherapy, this is a common clinical practice situation. Scenarios vary from patients who are being treated with curative intent versus palliative-intent chemotherapy for advanced cancer. Clinicians and patients may make different decisions for continuing neurotoxic chemotherapy in patients suffering from significant neuropathy, based on whether the patient is receiving adjuvant chemotherapy that might improve survival probabilities by a percentage point or two, versus a patient receiving adjuvant chemotherapy expected to improve survival probabilities by many percentage points, versus a patient with metastatic disease. In these individual situations, clinicians may determine whether to reasonably use alternative chemotherapy regimens that do not cause neurotoxicity. Clinicians should obtain individual patient perspectives in all these situations.

Treatment of Chemotherapy-Induced Peripheral Neuropathy for Patients Who Have Completed Neurotoxic Chemotherapy

3.1 For patients with cancer experiencing painful CIPN, clinicians may offer duloxetine (Type of recommendation: evidence based, benefits equal harms; Evidence quality: intermediate; Strength of recommendation: moderate).

3.2 Outside the context of a clinical trial, no recommendations can be made on the use of the following interventions for the treatment of CIPN:

- Exercise therapy
- Acupuncture
- Scrambler therapy
- Gabapentin/pregabalin
- Topical gel treatment containing baclofen, amitriptyline HCL, plus/minus ketamine
- Tricyclic antidepressants
- Oral cannabinoids

(Type of recommendation: no recommendation; Evidence quality: low; Strength of recommendation: not applicable).

Note: While recent preliminary evidence suggests a potential for benefit from exercise, acupuncture, and scrambler therapy, larger sample–sized definitive studies are needed to confirm efficacy and clarify risks.

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Literature Review Update and Analysis for Treatment of CIPN

Exercise. Current data from an RCT mildly suggest that exercise is a feasible, safe, and promising supportive measure for patients with cancer experiencing CIPN. The trial randomly assigned 45 patients with established CIPN to a 10-week home-based muscle strengthening and balancing exercise program versus usual care. The patients in the exercise group experienced a significant reduction in neuropathic pain scores ($P < .0001$) and improvement in Functional QOL ($P = .0002$), Symptom QOL ($P = .0003$) and Global Health Status QOL ($P = .004$) compared with those randomly assigned to the usual-care group.[52] The lack of an active control group diminishes the strength of the findings. Another small trial evaluated patients with metastatic colorectal cancer randomly assigned to an exercise program versus a wait-list control group.[36] Those receiving exercise had relatively stable CIPN scores over time, while the wait-list control group's CIPN worsened.

Acupuncture. Five trials evaluating the efficacy of acupuncture for the treatment of CIPN were identified,[53-55] including 1 trial that evaluated electro-acupuncture[56] and another that evaluated acupuncture combined with methylcobalamin.[57] A randomized assessor-only–blinded controlled trial of acupuncture twice weekly for 8 weeks versus a wait-list control group involving 87 patients with cancer reported significant changes at 8 weeks in pain measured using the Brief Pain Inventory (BPI).[53] Significant improvements in clinical neurologic assessment, QOL domains, and symptom distress were also reported (all $P < .05$). Improvements in pain interference, neurotoxicity-related symptoms, and functional aspects of QOL were sustained in a 14-week assessment ($P < .05$), as were physical and functional well-being at a 20-week assessment ($P < .05$).

A pilot trial involving 40 women with stage I-III breast cancer and grade ≥ 1 CIPN after taxane-containing adjuvant chemotherapy investigated immediate acupuncture versus a wait-list control.[54] At 8 weeks, participants in the treatment arm experienced significant improvements in the Patient Neurotoxicity Questionnaire (PNQ) sensory score ($P = .01$), FACT-NTX summary score ($P = .002$), and BPI–Short Form pain severity score $P = .03$) compared with those in the control arm. No serious adverse effects were observed.

Another pilot trial randomly assigned 33 adult patients with cancer and CIPN into 2 groups (control and acupuncture: treated with 10 sessions, twice a week).[55] Statistically significant differences were reported in physical ($P = .03$) and function ($P = .04$) domains of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 when comparing between control and acupuncture groups. NCI CTCAE Scale and neuropathy sensory symptoms were also improved in the acupuncture group between pretreatment and 5 weeks post-treatment ($P = .01$), whereas no such differences were detected in the control group ($P = .11$). The use of electro-acupuncture was not superior to placebo in a randomized trial of 59 patients with CIPN.[56] The trial failed to show efficacy compared with placebo, as determined by using a predefined statistical threshold at the first interim analysis.

Another trial in 98 patients compared acupuncture combined with methylcobalamin to methylcobalamin alone and found that after 3 cycles of therapy the pain was significantly mitigated in the methylcobalamin plus acupuncture group.[57] Visual analogue scale (VAS) pain scores decreased more in the methylcobalamin plus acupuncture group than the methylcobalamin control group ($P < .01$).

Duloxetine and pregabalin. Two duloxetine trials were published after the initial ASCO CIPN guideline publication.[48,58] One trial randomly assigned patients with CIPN to 3 pharmacotherapy groups: venlafaxine, duloxetine, and placebo.[48] The authors reported decreased neuropathy in the venlafaxine and duloxetine groups, with a better reduction in the duloxetine group compared with venlafaxine group ($P < .05$). In another open-label, randomized, crossover study, 34 patients with cancer were randomly assigned to receive duloxetine (20 mg/d orally for the first week and 40 mg/d for the next 3 weeks) or vitamin B12 (1.5 mg/d orally for 4 weeks).[58] After a 2- to 4-week washout period, treatment was crossed over for another 4 weeks. Decreases in the mean VAS scores for numbness and pain were seen during the periods of duloxetine administration. Significant differences were observed between the duloxetine-first and the vitamin B12-first groups with respect to numbness ($P = .03$) and pain ($P = .04$) at 4 weeks after administration.

In January 2020, a trial was published that randomly assigned patients with paclitaxel- or docetaxel-associated CIPN to receive duloxetine versus pregabalin, with 40-42 patients per arm. They reported a ≥ 33% improvement of visual analog scores in the duloxetine and pregabalin arms at 6 weeks of 38% and 93%, respectively ($P < .001$).[59] The majority of the patients in both arms started their treatment while they were receiving chemotherapy, and some of this improvement may have been related to chemotherapy discontinuation.

Scrambler therapy. Two randomized trials evaluating scrambler therapy, an electrocutaneous treatment approach, were found.[60,61] One randomized sham-controlled phase II trial in 33 patients who received 30-minute sessions of scrambler therapy (ST) or sham treatment found no significant differences between the sham and the experimental ST group for BPI average pain or the EORTC CIPN-20.[60]

The second phase II trial randomly assigned patients with CIPN symptoms for at least 3 months to receive ST or transcutaneous electrical nerve stimulation (TENS) for 2 weeks. In 46 evaluable patients, twice as many ST-treated patients had at least a 50% documented improvement during the 2 treatment weeks from their baseline pain, tingling, and numbness scores when compared with the TENS-treated patients (from 36%-56% compared with

16%-28% for each symptom).[61] Global Impression of Change scores for "neuropathy symptoms," pain, and QOL improved similarly. Moreover, patients in the ST group were more likely than those in the TENS group to recommend their treatment to other patients, during both the 2-week treatment period and the 8-week follow-up period ($P < .0001$).[61] The publication did not report any substantial adverse events.[62]

Oral mucosal cannabinoid extract. A small, randomized, placebo-controlled clinical trial of 18 patients evaluated the role of nabiximols, an oral mucosal cannabinoid spray, for chemotherapy-induced neuropathic pain.[63] In this crossover clinical trial, 16 of the 18 randomly assigned patients completed the study. Noting the small number of patients, there was no suggestion of differential benefits in neuropathy scores between the active and placebo agents. Yet, there was more evidence of toxicity (fatigue, dry mouth, dizziness, and nausea) in the patients receiving the cannabinoid preparation, decreasing interest in this approach.

Topical amitriptyline/ketamine. A topical 4% amitriptyline/2% ketamine preparation was studied as a treatment of established chemotherapy neuropathy in a randomized, placebo-controlled trial involving 462 patients.[64] Patients with average 7-day pain, numbness, and tingling ratings of at least 4 on an 11-point numeric rating scale were eligible for enrollment in the study. Topical amitriptyline/ketamine showed no effect on 6-week CIPN scores (adjusted mean difference, −0.17; $P = .363$), and this trial did not support that using this topical preparation alleviated chemotherapy-induced pain, numbness, or tingling.

Clinical interpretation regarding the treatment of established CIPN. Additional data, which have become available since the previous ASCO CIPN guideline, further support the utility of duloxetine for treating established painful CIPN. Conversely, there have not been any further clinical trials to strongly support the utility of tricyclic antidepressants, gabapentinoids, or topical amitriptyline/ketamine/baclofen, decreasing the tepid support that was provided for these 3 therapeutic approaches in the initial ASCO CIPN guideline. In addition, newer published reports do not provide support for a topical amitriptyline/ketamine preparation or an oral mucosal cannabinoid product.

Although proof of benefit has not been provided, data suggestive of benefit support that 3 approaches (scrambler therapy, acupuncture, and exercise) may diminish established CIPN symptoms and appear to be reasonably safe. Further research is needed to better delineate the utility, or its lack thereof, of these approaches in treating established CIPN.

DISCUSSION

The current review found no additional studies supporting the use of any preventative approach for neuropathy. In contrast with the promising original guideline commentary regarding venlafaxine as a preventative agent, longer follow-up data do not support its use.[47]

For treatment of established painful neuropathy, duloxetine remains the sole recommended treatment. Along with the data demonstrating that duloxetine decreases CIPN pain, there is a suggestion from exploratory analyses that it also decreases nonpainful CIPN symptoms.[58,65] When patients stop duloxetine, it should be tapered slowly, as stopping abruptly can lead to withdrawal symptoms.

Acetyl-L-carnitine data were inconclusive for the treatment of established neuropathy at the time of the initial ASCO guideline publication. A new larger trial reported that there was no benefit for acetyl-L-carnitine for treating chemotherapy-induced neuropathy. Consequently, the current updated guideline recommends against acetyl-L-carnitine for the treatment of established chemotherapy-induced neuropathy.[14]

There were 3 treatments that were inconclusive in the original guideline but "reasonable to try in some situations," namely tricyclic antidepressants, gabapentinoids, and a topical gel treatment containing baclofen, amitriptyline, and ketamine. Although data regarding these 3 treatment options remain inconclusive, there is waning enthusiasm regarding them.

Regarding the tricyclic antidepressants, the previous guideline indicated that tricyclic antidepressant use was reasonable to try, primarily on the basis of their utility in other neuropathy situations, but not on the basis of any positive randomized clinical trials demonstrating any utility of this drug class for treating established CIPN. Currently, the use of tricyclic antidepressants does not appear to be common, because of their lack of established benefit and/or their unfavorable side effects.

Regarding topical baclofen, amitriptyline, and ketamine, the previous guideline noted that a placebo-controlled trial was promising. However, there are reasons to be less enthusiastic about this approach now: (1) no additional trials have been conducted; (2) there is not an US Food and Drug Administration–approved product available, and the only way to get this treatment is to have it compounded; and (3) there was a subsequent publication of a negative trial that studied topical amitriptyline and ketamine.[64] However, the lack of baclofen in this latter preparation may explain the negative finding of the study.

The suggestion in the initial ASCO CIPN guideline that gabapentinoids might be helpful and worth trying for chemotherapy-induced neuropathy was also primarily based on gabapentinoid efficacy against other types of neuropathies, like diabetic neuropathy. Presently, this endorsement is harder to support. With the 1 older placebo-controlled clinical trial that showed no benefit for gabapentin for the treatment of chemotherapy-induced peripheral neuropathy,[66] 2 subsequent trials investigating pregabalin as an agent to prevent chemotherapy-induced neuropathy (1 for paclitaxel[43] and 1 for oxaliplatin [ClinicalTrials.gov Identifier: NCT00380874]) failed to provide evidence of benefit. Although prevention trials are certainly

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different from treatment trials, if pregabalin was given continuously while the patient developed neuropathy in a prevention trial, one would have expected to see a decrease in the severity of neuropathic symptoms if it was truly beneficial for treating established neuropathy. In contrast to these negative gabapentinoid data, 1 trial[59] suggests that pregabalin was helpful. Confirmation of these data is necessary before endorsement of routine use of gabapentinoids for treating established CIPN.

Historically, the first known report on using gabapentin for chemotherapy-induced neuropathy came from Italian authors at the 2000 ASCO annual meeting, entitled "Oxaliplatin-induced Neuropathy: Could Gabapentin be the Answer?"[67] This report describes the use of gabapentin in 7 patients who developed neuropathy while receiving oxaliplatin. With the initiation of neuropathy, gabapentin was given at 100 mg twice per day. Clinicians could increase gabapentin to 100 mg 3 times daily if the lower daily dose did not resolve symptoms. The abstract reported there was a disappearance of neuropathy symptoms, which continued even with the use of up to 14 total oxaliplatin doses. This work is not available in manuscript form. In retrospect, it does not seem biologically plausible that this very low dose of gabapentin (given that target doses of this drug can be ≥ 3,000 mg/d) could have had such a dramatic benefit. A body of other published articles regarding gabapentin for treating CIPN (ranging from case reports to case series to 1 randomized placebo-controlled trial)[66,68-74] do not, on the whole, support the utility of gabapentin for treating established CIPN.

Notably, some insurance companies require that patients with CIPN receive a gabapentinoid agent before allowing the use of duloxetine.[75] Additional support for this contention comes from a recent article reporting that on insurance claims data the use of gabapentinoids (gabapentin or pregabalin) was more than 8-fold higher than was the use of duloxetine in patients who had recently received neurotoxic chemotherapy.[76] This contradicts the recommendations of the previous and current ASCO CIPN guidelines.

Although the current guideline is primarily focused on means of preventing CIPN and/or treating established CIPN, CIPN can involve physical dysfunction; patients with CIPN have balance troubles and a higher chance of falling.[77,78] Therefore, it is reasonable to consider physical therapy and/or occupational therapy approaches for patients with such CIPN-related disabilities.

A summary of the recommendations is provided in Table 3.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Each ASCO guideline includes a member from ASCO's Practice Guideline Implementation Network (PGIN) on the panel. The additional role of this PGIN representative on the guideline panel is to assess the suitability of the recommendations to implementation in the community setting and also to identify any other barrier to implementation a reader should be aware of. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and survivors of cancer and caregivers and also to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO PGIN. ASCO guidelines are posted on the ASCO website and most often published in *Journal of Clinical Oncology* and *Journal of Oncology Practice*.

LIMITATION OF THE RESEARCH AND FUTURE RESEARCH

Inconsistent subjective and objective outcome measures, choice of control group, and duration of exposure have resulted in challenges in interpreting some of the prior studies. NCI-sponsored studies are ongoing to better define the phenotype of CIPN, to ensure consistency in outcome measures from study to study going forward.

Better interventions are needed to prevent CIPN. Ongoing and planned trials will, likely, better clarify the role of exercise, compression therapy, cryotherapy, and other targeted interventions. Several planned and/or ongoing preclinical studies are evaluating the role of neuronal transport, neuroprotection, neuro-inflammation, serotonin-norepinephrine reuptake, nociceptor sodium channel inhibition, mitochondrial enzymes, and oxidative stress.[79-81] Many of the above agents target DNA damage related to inflammation, reactive oxygen species, and oxidative stress, supporting this as a thematic target for prevention of CIPN.

Better agents are also needed to treat established CIPN. Ongoing and planned clinical trials should better clarify the role of exercise, acupuncture, scrambler therapy, and other targeted interventions. Topical therapies such as capsaicin might also be further explored.[82]

Clinicaltrials.gov currently lists > 100 clinical trials related to CIPN that are actively accruing patients or in development. We hope that results from these trials will lead to new means of preventing and/or treating CIPN.

ADDITIONAL RESOURCES

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/survivorship-guidelines. Patient information is available at www.cancer.net.

RELATED ASCO GUIDELINES

- Patient-Clinician Communication[83] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)

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EDITOR'S NOTE

This American Society of Clinical Oncology (ASCO) Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/supportive-care-guidelines.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.20.01399.

ACKNOWLEDGMENT

We thank Ting Bao, MD, DABMA, MS, Zoneddy Dayao, MD, Emily Tonorezos, MD, MPH, and Jørn Herrstedt MD, DMSc, and the Clinical Practice Guidelines Committee for their thoughtful reviews and insightful comments on this guideline. All Appendices and Acknowledgment material (including the table of Expert Panel members) are online-only. They will appear on JCO website online but not in the print version.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: ASCO Guideline Update

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Patents, Royalties, Other Intellectual Property: I have a number of antibodies that have been licensed from Indiana University School of Medicine that are sold by various companies. The royalties come back to the school and I share in some of them. I receive some royalties from licensed technology to Apexian Pharmaceuticals and could eventually receive royalties from Ocuphire Pharma if milestones are met. Ocuphire is an eye company and not cancer related. I have not received any royalties from these units at this time beyond consulting as disclosed. Apexian licensed my IP and then sublicensed IP to Ocuphire for the eye.

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No other potential conflicts of interest were reported.

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APPENDIX

TABLE A1. Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers Guideline Update Expert Panel Membership

Name	Affiliation/Institution	Role/Area of Expertise
Charles L. Loprinzi, MD (co-chair)	Mayo Clinic, Rochester, MN	Medical oncology
Dawn L. Hershman, MD, MS (co-chair)	Columbia University Medical Center, New York, NY	Medical oncology
Maryam B. Lustberg, MD	Ohio State University, Columbus, OH	Medical oncology
Thomas J. Smith, MD	Johns Hopkins, Baltimore, MD	Medical oncology
Nina Wagner-Johnston, MD	Johns Hopkins, Baltimore, MD	Medical oncology
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Jonathan Bleeker, MD	Sanford USD Medical Center, Sioux Falls, SD	Medical oncology
Shelby Terstriep, MD	Sanford Health, Fargo, ND	Medical oncology
Judith A. Paice, PhD, RN	Northwestern University, Chicago, IL	Nursing/pain
Guido Cavaletti, MD, PhD	University of Milano-Bicocca, Monza, Italy	Neurology/pain
Daniel L. Hertz, PharmD, PhD	University of Michigan, Ann Arbor, MI	Clinical pharmacology
Mark R. Kelley, PhD	Indiana University School of Medicine, Indianapolis, IN	Translational research
Antoinette Lavino, RPh, BCOP	Oncology Pharmacist, PGIN Member, Mass General North Shore Cancer Center, Danvers, MA	Community oncology
Ellen M. Lavoie Smith, PhD	University of Michigan, Ann Arbor, MI	Nursing
Cynthia Chauhan, MSW, Patient Advocate	Wichita, KS	Patient representative
Mary Lou Smith, JD, MBA, Patient Advocate	Research Advocacy Network, Plano, TX	Patient representative
Christina Lacchetti, MHSc	ASCO, Alexandria, VA	ASCO Practice Guideline Staff (Health Research Methods)

Abbreviation: PGIN, Practice Guideline Implementation Network.

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Tumor Treating Fields for Pancreatic Cancer

Plain Language Summary:

Tumor Treating Fields is a device that uses electric signals to slow cancer growth. The device is approved by the FDA for a certain kind of advanced pancreas cancer.

One study suggests this device may help people live longer. Until other studies are available, HERC staff do not recommend adding coverage.

Staff Analysis Summary:

Significant proposed changes or discussion items:

1. Do not add coverage for electric tumor treating fields for pancreatic cancer

Changes after public comment period:

One public comment was received on this topic from an employee of Novocure. The commentor supported coverage and provided one article, which was previously included in this issue summary. This comment did not change the HERC staff assessment that this technology is experimental.

Coverage Question:

Should electric tumor treating fields (ETTF) be covered for pancreatic cancer?

Question source:

Novocure

Background:

The FDA recently approved a new therapy for locally advanced pancreatic cancer in adults called OpTune Pax, a form of electric tumor treating fields (ETTF or TTF) therapy. This TTF therapy is approved for use with concomitant gemcitabine and nab-paclitaxel. Novocure is requesting a review of this technology for possible addition to coverage on the Prioritized list.

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Tumor treating fields is a non-invasive treatment that uses low intensity alternating electric fields to disrupt cancer dell division. TTF is currently covered on the Prioritized List for glioblastoma.

Previous HSC/HERC reviews:

ETTF for treatment of glioblastoma was reviewed in August 2016. Pancreatic cancer was not included in this review.

Current Prioritized List/Coverage status:

HCPCS E0766 (Electrical stimulation device used for cancer treatment, includes all accessories, any type) is on line 292 CANCER OF BRAIN AND NERVOUS SYSTEM.

GUIDELINE NOTE 155, ELECTRIC TUMOR TREATMENT FIELDS FOR GLIOBLASTOMA

Line 292

Electric tumor treatment fields (HCPCS E0766) are included on this line only when

A) Used for the initial treatment of either a
    a. supratentorial glioblastoma OR
    b. supratentorial IDH-mutant WHO grade 4 astrocytoma; AND
B) Used in combination with temozolomide and standard radiation therapy; AND
C) The patient is age 22 or older.

Electric tumor treatment fields are not included on this line for recurrent glioblastoma or astrocytoma or any other indication.

ICD-10-CM C25 family (pancreatic cancer) is on line 313 CANCER OF PANCREAS

Evidence:

1) **Babiker 2025** Tumor Treating Fields With Gemcitabine and Nab-Paclitaxel for Locally Advanced Pancreatic Adenocarcinoma: Randomized, Open-Label, Pivotal Phase III PANOVA-3 Study
    a. Funded by Novocure; data analysis by sponsor-employed or sponsor-funded statisticians; all authors had significant conflicts of interest

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b. Adults aged 18 years and older with unresectable, locally advanced, biopsy-confirmed, and previously untreated pancreatic adenocarcinoma were eligible if they had a life expectancy ≥3 months and Eastern Cooperative Oncology Group performance status (ECOG PS) 0-2. Patients could not have implantable electronic medical devices
c. N=571 (274 TTFields with gemcitabine/nab-paclitaxel and 286 gemcitabine/nab-paclitaxel alone)
    i. Locally advanced pancreatic cancer (LA-PAC)
    ii. No sham arm
d. Survival
    i. Overall survival was statistically improved with TTFields with gemcitabine/nab-paclitaxel, with a median of 16.2 months (95% CI, 15.0 to 18.0) versus 14.2 months (95% CI, 12.8 to 15.4) with gemcitabine/nab-paclitaxel (HR, 0.82 [95% CI, 0.68 to 0.99]; log rank P = .039)
    ii. The 1-year survival rate was significantly improved with concomitant TTFields versus gemcitabine/nab-paclitaxel (68.1% [95% CI, 62.0 to 73.5] v 60.2% [95% CI, 54.2 to 65.7]; P 5 .029). Median OS was also significantly prolonged in the mITT population (18.3 v 15.1 months; HR, 0.73)
e. Progression free survival
    i. No significant difference in PFS was noted (median, 10.6 months [95% CI, 9.2 to 12.2] v 9.3 months [95% CI, 7.6 to 11.1]; HR, 0.85 [95% CI, 0.68 to 1.05]; log rank P = .137)
    ii. Local PFS was not significantly different between study arms in either population
f. Pain free survival
    i. Pain-free survival was significantly prolonged with TTFields with gemcitabine/nab-paclitaxel compared with gemcitabine/nab-paclitaxel (median, 15.2 months [95% CI, 10.3 to 22.8] v 9.1 months [95% CI, 7.4 to 12.7]; HR, 0.74 [95% CI, 0.56 to 0.97], log rank P = .027)
g. Adverse events

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i. AEs of any cause were experienced by 97.8% and 98.9% of patients in the TTFields with gemcitabine/nab-paclitaxel and gemcitabine/nab-paclitaxel arms, respectively (Table 3). Grade ≥3 AEs were experienced by 88.7% and 84.3% of patients, respectively; the most frequent AEs were neutropenia (47.8% and 47.7%) and anemia (21.9% and 22.3%;
ii. Device-related AEs were mainly mild-to-moderate skin reactions, which were experienced by 209 patients (76.3%); the most frequent events were dermatitis (n 5 76, 27.7%), rash (n 5 48, 17.5%), pruritus (n 5 41, 15.0%), maculopapular rash (n 5 33, 12.0%), and erythema (n 5 29, 10.6%).

h. Authors conclusions: In conclusion, PANOVA-3, the only phase III trial specifically in unresectable LA-PAC to show a significant OS benefit, establishes that TTFields with gemcitabine/nab-paclitaxel is an effective treatment of unresectable LA-PAC

Submitted literature:

1) Optune Pax physician instructions
    a. Included discussion of Babiker 2025 (see above) and Rivera 2019 (PANOVA 1, cohort feasibility study, N=47)

Expert guidelines:

1) **NCCN 2.2025** Pancreatic Adenocarcinoma
    a. Tumor treatment fields not mentioned in the locally advanced disease treatment pathway

Other payer policies:

1) United Health Care 2026
    a. Covers electric tumor treatment field therapy for glioblastoma
    b. Due to insufficient evidence of efficacy, the use of devices to generate electric TTF is unproven and not medically necessary when the criteria above are not met and for all other indications including but not limited to the following: • Treatment of tumors other than GBM • Use of electric TTF

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therapy with concurrent medical therapy [e.g., bevacizumab (BEV) or chemotherapy] for treatment of rGBM

2) Aetna 2026
    a. Covers ETTF for glioblastoma
    b. Experimental: Devices to generate ETTF for the treatment of other malignant tumors (e.g., breast, lung, melanoma, non-small cell lung cancer, osteosarcoma, ovarian cancer, pleural mesothelioma, pancreatic cancer, salivary gland tumors (e.g., parotid adenoid cystic carcinoma), and solid tumor brain metastases; not an all-inclusive list) and for all other indications
3) Premara BCBS 2025
    a. Covers ETTF for glioblastoma
    b. Considers use for any cancer other than glioblastoma to be experimental

Expert input:

None received to date

HERC staff summary:

The literature on tumor treating fields for locally advanced pancreatic cancer consists of a feasibly study of 47 patients and one RCT of 571 patients. The results appear promising, with a 2 month longer overall survival rate in the RCT with TTF. Reported adverse events of the device were not serious. HERC staff conclude that while promising, the results of a single study are not sufficient to add coverage.

TTF is not included in the NCCN guideline for locally advanced pancreatic adenocarcinoma and is not covered by surveyed private payers.

HERC staff recommend non-coverage of elective tumor treating fields for pancreatic cancer at this time. The HCPCS code already is included on line 292 CANCER OF BRAIN AND NERVOUS SYSTEM; therefore, no Excluded Services Guideline E2 note can be added.

HERC staff recommendation:

1) Do not add HCPCS E0766 (Electrical stimulation device used for cancer treatment, includes all accessories, any type) to the pancreatic cancer line

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Public Comment Disposition: Tumor Treating Fields for Pancreatic Cancer

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Commenters

Identification	Commenter
A	Patrick Liedtka, Novocure [Submitted April 14, 2026]

Public Comments

ID/#	Comment	Disposition
A1	Line 292 of the Oregon Health Authority's Prioritized List describes coverage of electric tumor treatment fields therapy for glioblastoma, and guideline note 155 details the criteria for coverage. On February 11, 2026, the U.S. Food and Drug Administration (FDA) approved Optune Pax®, a Tumor Treating Fields (TTFields) therapy, for use concomitant with gemcitabine and nab-paclitaxel (GnP) for the	Thank you for your comment. The Oregon Health Plan does not cover a treatment solely based on FDA approval. The HERC staff summary already

ID/#	Comment	Disposition
	treatment of adult patients with locally advanced pancreatic cancer (LAPC). Pancreatic cancer remains an area of substantial unmet medical need. The PANOVA-3 Phase 3 randomized clinical trial, published in 2025 by Babiker et al., demonstrated that the addition of TTFields therapy to gemcitabine and nab-paclitaxel resulted in a statistically significant improvement in overall survival (OS) compared with chemotherapy alone in patients with LAPC. Secondary and supporting endpoints included improvements in time to pain progression and quality of life (QoL), with the most reported TTFields related adverse events limited to localized skin reactions. Based on available published evidence and FDA review, PANOVA-3 represents a pivotal study demonstrating a clinically meaningful survival benefit in this patient population. The journal article summarizing the key findings from the PANOVA-3 trial is attached below. Novocure requests that the Health Evidence Review Commission consider the findings of the PANOVA-3 trial in its review and discussion of whether or not to modify Line 292 of the Prioritized List to include use of our therapy in Oregon for individuals with locally advanced pancreatic cancer. Thank you for your consideration. We recognize that TTFields therapy for LAPC is not currently addressed in your organization's medical coverage policy.	includes the submitted Babiker 2025 PANOVA-3 study.

References Provided by Commenters

ID	References
A	Hani M. Babiker et al. Tumor Treating Fields With Gemcitabine and Nab-Paclitaxel for Locally Advanced Pancreatic Adenocarcinoma: Randomized, Open-Label, Pivotal Phase III PANOVA-3 Study. J Clin Oncol 43, 2350-2360(2025). DOI:10.1200/JCO-25-00746

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Tumor Treating Fields With Gemcitabine and Nab-Paclitaxel for Locally Advanced Pancreatic Adenocarcinoma: Randomized, Open-Label, Pivotal Phase III PANOVA-3 Study

Hani M. Babiker, MD[1]; Vincent Picozzi, MD[2]; Sreenivasa R. Chandana, MD, PhD[3]; Bohuslav Melichar, MD, PhD[4]; Anup Kasi, MD[5]; Jin Gang, MD[6]; Javier Gallego, MD[7]; Andrea Bullock, MD[8,9]; Hao Chunyi, MD[10]; Lucjan Wyrwicz, MD, PhD[11]; Erika Hitre, PhD[12]; Arsen Osipov, MD[13]; Christelle de la Fouchardiere, MD[14]; Inmaculada Ales, MD[15]; Tomislav Dragovich, MD, PhD[16]; Woojin Lee, MD, PhD[17]; Kynan Feeney, MD[18]; Philip Philip, MD, PhD[19]; Makoto Ueno, MD[20]; Eric Van Cutsem, MD, PhD[21]; Thomas Seufferlein, MD[22]; and Teresa Macarulla, MD, PhD[23]; on behalf of the PANOVA-3 Study Investigators

DOI https://doi.org/10.1200/JCO-25-00746

ABSTRACT

PURPOSE Tumor treating fields (TTFields) use alternating electric fields to disrupt cancer cell proliferation. Feasibility of TTFields therapy with gemcitabine/nab-paclitaxel was previously demonstrated in patients with advanced pancreatic adenocarcinoma. PANOVA-3 was designed to confirm safety and efficacy of TTFields in patients with unresectable locally advanced pancreatic adenocarcinoma (LA-PAC).

METHODS In this global phase III trial, 571 patients with newly diagnosed LA-PAC were randomly assigned to receive gemcitabine 1,000 mg/m² and nab-paclitaxel 125 mg/m² by intravenous infusion once a day on days 1, 8, and 15 of a 28-day cycle with or without TTFields. The primary end point was overall survival (OS). Secondary end points included progression-free survival (PFS), local PFS, pain-free survival, and overall response rate (ORR). Distant PFS was analyzed post hoc.

RESULTS OS was significantly prolonged using TTFields with gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel (median, 16.2 months [95% CI, 15.0 to 18.0] *v* 14.2 months [95% CI, 12.8 to 15.4]; hazard ratio [HR], 0.82 [95% CI, 0.68 to 0.99]; $P = .039$). PFS, local PFS, and ORR were not improved. Pain-free survival was significantly prolonged with TTFields with gemcitabine/nab-paclitaxel (median, 15.2 months [95% CI, 10.3 to 22.8] *v* 9.1 months [95% CI, 7.4 to 12.7]; HR, 0.74 [95% CI, 0.56 to 0.97]; $P = .027$), as was distant PFS (median, 13.9 months [95% CI, 12.2 to 16.8] *v* 11.5 months [95% CI, 10.4 to 12.9]; HR, 0.74 [95% CI, 0.57 to 0.96]; $P = .022$). Device-related skin adverse events (AEs) were experienced by 76.3% of patients. Most device-related skin AEs were mild to moderate, with 7.7% of patients reporting a grade 3 AE.

CONCLUSION This study demonstrated significant OS, pain-free survival, and distant PFS benefits for TTFields with gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel in patients with unresectable LA-PAC, with no additive systemic toxicity.

ACCOMPANYING CONTENT

Editorial, p. 2339

Listen to the podcast by Dr Li and Dr O'Reilly at https://ascopubs.org/do/jco-asco-annual-meeting-ttfields-locally-advanced-pancreatic-adenocarcinoma

Appendix

Data Sharing Statement

Data Supplement

Protocol

Accepted May 1, 2025
Published May 31, 2025

J Clin Oncol 43:2350-2360
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INTRODUCTION

Most patients with pancreatic adenocarcinoma present with advanced disease at diagnosis,[1] which remains difficult to treat. With 5-year survival rates between 8% and 13%,[1,2] prognosis for patients with pancreatic adenocarcinoma is poor. The current standard of care for unresectable locally advanced pancreatic adenocarcinoma (LA-PAC) consists of chemotherapy with or without radiation[1,3] and is extrapolated from trials in metastatic or unspecified advanced disease.[4-8] Gemcitabine emerged as a standard of care in 1997[4]; the addition of nab-paclitaxel to gemcitabine improved median overall survival (OS) to 8.5 months.[7] First-line fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) increased OS to 11.1 months in metastatic disease but is recommended for patients with good performance status because of significant toxicities.[1,3,6] Novel therapies for advanced pancreatic adenocarcinoma have mostly been investigated in metastatic populations and less so in LA-PAC.[9-11] Targeted agents and immunotherapies such as erlotinib, olaparib, and

CONTEXT

Key Objective

Is the application of tumor treating fields (TTFields; electric fields that disrupt cancer cell processes, delivered by a portable device) concomitant with gemcitabine/nab-paclitaxel safe and effective in patients with unresectable locally advanced pancreatic adenocarcinoma (LA-PAC) compared with gemcitabine/nab-paclitaxel alone?

Knowledge Generated

In the phase III PANOVA 3 trial, TTFields therapy with gemcitabine/nab-paclitaxel significantly improved overall survival, pain-free survival, and distant progression-free survival compared with gemcitabine/nab-paclitaxel in patients with LA-PAC. The adverse events most commonly associated with TTFields therapy were skin events; TTFields therapy did not exacerbate the toxicity associated with chemotherapy or the disease itself.

Relevance *(E.M. O'Reilly)*

The combination of TTFields combined with chemotherapy in a population relatively understudied in clinical trials, locally advanced pancreas cancer, provides benefit and serves as a new standard paradigm in this patient population. The data are aligned with benefit observed from the use of this novel modality in other challenging to treat solid organ malignancies.*

*Relevance section written by *JCO* Associate Editor Eileen M. O'Reilly, MD, FASCO.

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pembrolizumab have limited benefit and/or only benefit patients harboring specific alterations.[5,12,13]

Tumor treating fields (TTFields) is a noninvasive therapy using low-intensity electric fields that disrupt cellular processes critical for cancer cell viability and tumor progression.[14] TTFields have shown significant activity in vitro and in vivo in pancreatic cancer models, with enhanced efficacy with chemotherapy.[15] TTFields therapy with gemcitabine ± nab-paclitaxel was feasible, safe, and active in patients with advanced pancreatic adenocarcinoma in the phase II PANOVA trial (ClinicalTrials.gov identifier: NCT01971281).[16]

We present the results of the pivotal phase III PANOVA-3 trial (ClinicalTrials.gov identifier: NCT03377491), which evaluated the efficacy and safety of TTFields with gemcitabine/nab-paclitaxel as first-line therapy for unresectable LA-PAC.

METHODS

Trial Design and Oversight

PANOVA-3 was a global, randomized, open-label, multicenter, phase III clinical trial in patients with LA-PAC (196 sites in 20 countries; Data Supplement, online only). The study was approved by relevant ethics committees and competent authorities at participating sites and conducted in adherence with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent. The study was designed by the sponsor (Novocure GmbH) and investigators. Data were collected by the investigators and analyzed by sponsor-employed or sponsor-funded statisticians. All authors contributed to data interpretation and vouch for completeness, accuracy, and fidelity of the study to the protocol.

Patients

Adults aged 18 years and older with unresectable, locally advanced, biopsy-confirmed, and previously untreated pancreatic adenocarcinoma were eligible if they had a life expectancy ≥3 months and Eastern Cooperative Oncology Group performance status (ECOG PS) 0-2.[3,17] Patients could not have implantable electronic medical devices, such as pacemakers, in the torso or known severe hypersensitivity to medical adhesives or hydrogel or to one of the chemotherapies used. Full inclusion and exclusion criteria are provided in the Data Supplement.

Random Assignment and Treatment

Patients were centrally randomly assigned using an Interactive Web Response System in a 1:1 ratio to receive TTFields with gemcitabine/nab-paclitaxel or gemcitabine/nab-paclitaxel alone. Patients were stratified by ECOG PS (0/1 *v* 2) and region (North America, Eastern Europe, Western Europe, Israel, and rest of the world). TTFields therapy (150 kHz) was delivered by the NovoTTF-200T System (Novocure, Baar, Switzerland) with a recommended average usage of ≥75% (≥18 hours/d). Device support specialists provided guidance on device usage and prevention and management of skin adverse events (AEs). TTFields array placement was adapted to individual patients (Data Supplement, Fig S1); arrays were replaced two to three times/wk and shifted approximately 2 cm to prevent skin reactions. Usage was tracked by the device and sent to investigators monthly.

Nab-paclitaxel 125 mg/m² was infused intravenously once per day, immediately followed by gemcitabine 1,000 mg/m² intravenously once per day on days 1, 8, and 15 of each 28-day cycle. Treatment continued until local disease progression according to RECIST v1.1,[18] lack of compliance, intolerable toxicity, pregnancy, or withdrawal of consent.

Follow-up visits were every 4 weeks. Chest and abdomen computed tomography (CT), brain CT, or magnetic resonance imaging (if indicated) were performed every 8 weeks to assess disease progression.

Objectives

The primary objective was to determine whether first-line TTFields with gemcitabine/nab-paclitaxel improves OS, defined as the time from random assignment to the date of death or censoring, compared with gemcitabine/nab-paclitaxel alone. Secondary end points included progression-free survival (PFS), local PFS (time from random assignment until the date of local disease progression or death), 1-year survival rate, pain-free survival (time from random assignment until ≥20-point increase from baseline in a patient-reported visual analog scale [VAS] for pain or death),[19-21] puncture-free survival (time from random assignment until the first need for paracentesis or death), overall response rate (ORR; percentage of evaluable patients with partial or complete response between the time of random assignment and death), resectability rate (percentage of patients whose tumors were deemed resectable by a multidisciplinary team consisting of at least 1 surgeon, 1 medical oncologist, and 1 radiologist, and who underwent surgery), and safety (frequency and severity of investigator-recorded AEs using Common Terminology Criteria for Adverse Events v4.03).[22] A modified grading system was used for device-related skin AEs (Data Supplement, Table S1). Distant PFS (time from the date of random assignment until distant disease progression or death) was analyzed post hoc.

Statistical Analysis

Efficacy end points were analyzed in the intention-to-treat (ITT) population (all randomly assigned patients). OS, PFS, and ORR were also analyzed in a modified ITT (mITT) population (patients who completed ≥1 treatment cycle). Safety data were analyzed in patients who received any amount of study treatment. A sample size of 556 patients in the ITT population, assuming 10% loss to follow-up, was required to provide 80% power to detect a hazard ratio (HR) of death of <0.75 with TTFields with gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel.

Kaplan-Meier survival curves were compared using a two-sided log-rank test stratified by region with $\alpha = .04794$ for OS and $\alpha = .05$ for other survival end points. After the primary end point was met, establishing the directionality of the treatment effect, 1-year survival rates were estimated using the Kaplan-Meier method and compared using a one-sided t-test.

To avoid statistical multiplicity, OS and PFS were analyzed hierarchically. Patients lost to follow-up or still in follow-up at the time of OS analyses were censored at the last date they were known to be alive. For PFS, local PFS, distant PFS, and pain-free survival analyses, patients who discontinued the study for any reason were censored at the last follow-up visit they were reported alive and event free or at study closure. For pain-free survival analysis, patients who had not experienced an event at study closure were censored at the date of their last VAS assessment. Deaths were considered events if they occurred within 8 weeks of the last VAS assessment. Patients with no VAS assessments were censored at the date of random assignment. ORR and resectability rate were assessed using one-sided Fisher exact test with $\alpha = .05$.

RESULTS

Patients and Treatment

Between May 2018 and March 2023, 571 patients were randomly assigned to either TTFields with gemcitabine/nab-paclitaxel (N = 285) or gemcitabine/nab-paclitaxel (N = 286; Fig 1). Patient baseline demographics and characteristics were balanced between study arms (Table 1). Overall, 52.4% of patients were female, with a higher proportion of them in the gemcitabine/nab-paclitaxel arm (Table 1). The number of patients who completed 1 treatment cycle and were included in the mITT analysis was 198 for the TTFields with gemcitabine/nab-paclitaxel arm and 207 for the gemcitabine/nab-paclitaxel arm; the reasons for patient discontinuation during the first cycle of treatment are presented in Figure 1.

At data cutoff on October 16, 2024, the median (range) duration of exposure to gemcitabine and nab-paclitaxel was 24.1 (0.1-232.4) and 23.0 (0.1-232.4) weeks, respectively, in the TTFields arm and 22.1 (0.1-134.1) and 21.4 (0.1-134.1) weeks, respectively, in the gemcitabine/nab-paclitaxel arm (Data Supplement, Table S2). The median duration of TTFields exposure was 27.6 weeks (range, 0.1-234.4); the median device usage was 62.1% (range, 0%-99.0%) of each day, and mean device usage was 59.3% (standard deviation, 21.2%) of each day.

A total of 146 patients (51.2%) in the TTFields with gemcitabine/nab-paclitaxel arm and 134 patients (46.9%) in the gemcitabine/nab-paclitaxel arm received salvage therapy (Data Supplement, Table S3). Distribution of salvage therapies administered was similar between treatment arms. By study end, 201 and 230 deaths had occurred in the TTFields with gemcitabine/nab-paclitaxel and gemcitabine/nab-paclitaxel arms, respectively.

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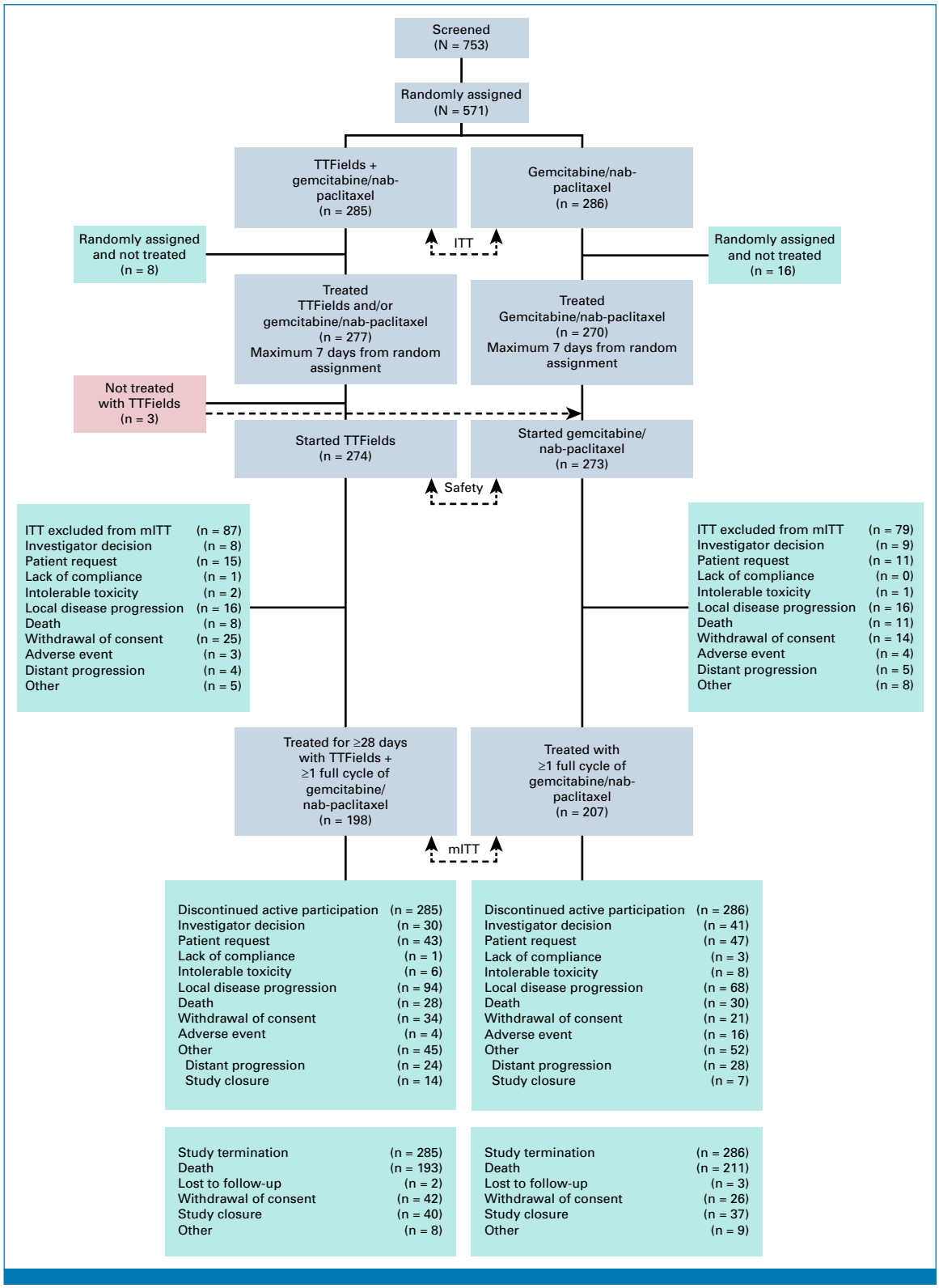

FIG 1. CONSORT diagram of enrolled patients. ITT, intention-to-treat; mITT, modified ITT; TTFields, tumor treating fields.

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Primary Efficacy End Point

OS was statistically improved with TTFields with gemcitabine/nab-paclitaxel, with a median of 16.2 months (95% CI, 15.0 to 18.0) versus 14.2 months (95% CI, 12.8 to 15.4) with gemcitabine/nab-paclitaxel (HR, 0.82 [95% CI, 0.68 to 0.99]; log rank P = .039; Fig 2). The 1-year survival rate was significantly improved with concomitant TTFields

TABLE 1. Baseline Patient and Tumor Characteristics

Characteristic	TTFields With Gemcitabine/Nab-Paclitaxel (n = 285)	Gemcitabine/Nab-Paclitaxel (n = 286)	Overall (n = 571)
Age, years, median (range)	67 (31-90)	67.5 (40-88)	67 (31-90)
Sex, No. (%)			
Male	147 (51.6)	125 (43.7)	272 (47.6)
Female	138 (48.4)	161 (56.3)	299 (52.4)
Race, No. (%)			
American Indian or Alaska Native	9 (3.2)	4 (1.4)	13 (2.3)
Asian	44 (15.4)	44 (15.4)	88 (15.4)
Black	16 (5.6)	14 (4.9)	30 (5.3)
White	202 (70.9)	204 (71.3)	406 (71.1)
Other	3 (1.1)	5 (1.7)	8 (1.4)
Not reported	11 (3.9)	15 (5.2)	26 (4.6)
Region, No. (%)			
North America	123 (43.2)	125 (43.7)	248 (43.4)
Eastern Europe	43 (15.1)	42 (14.7)	85 (14.9)
Western Europe and Israel	62 (21.8)	61 (21.3)	123 (21.5)
Rest of the world	57 (20.0)	58 (20.3)	115 (20.1)
ECOG PS, No. (%)			
0	109 (38.2)	111 (38.8)	220 (38.5)
1	166 (58.2)	163 (57.0)	329 (57.6)
2	10 (3.5)	12 (4.2)	22 (3.9)
BMI, kg/m^2, No. (%)			
<25	166 (58.2)	174 (60.8)	340 (59.5)
≥25	117 (41.1)	108 (37.8)	225 (39.4)
Target lesion site, No. (%)			
Head of the pancreas	143 (50.2)	148 (51.7)	291 (51.0)
Body of the pancreas	79 (27.7)	80 (28.0)	159 (27.8)
Tail of the pancreas	9 (3.2)	18 (6.3)	27 (4.7)
Other	79 (27.7)	63 (22.0)	142 (24.9)
CA 19-9, No. (%)			
Low (≤37 U/mL)	48 (16.8)	44 (15.4)	92 (16.1)
Moderate (38-1,000 U/mL)	140 (49.1)	152 (53.1)	292 (51.1)
High (>1,000 U/mL)	88 (30.9)	79 (27.6)	167 (29.2)
Untested	9 (3.2)	11 (3.8)	20 (3.5)

Abbreviations: CA 19-9, carbohydrate antigen 19-9; ECOG PS, Eastern Cooperative Oncology Group performance status; TTFields, tumor treating fields.

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versus gemcitabine/nab-paclitaxel (68.1% [95% CI, 62.0 to 73.5] *v* 60.2% [95% CI, 54.2 to 65.7]; $P = .029$). Median OS was also significantly prolonged in the mITT population (18.3 *v* 15.1 months; HR, 0.73; Data Supplement, Fig S2A).

Secondary Efficacy End Points

No significant difference in PFS was noted (median, 10.6 months [95% CI, 9.2 to 12.2] *v* 9.3 months [95% CI, 7.6 to 11.1]; HR, 0.85 [95% CI, 0.68 to 1.05]; log rank $P = .137$; Fig 3A). However, the 1-year PFS rate was higher with TTFields than with gemcitabine/nab-paclitaxel alone (43.9% [95% CI, 36.9 to 50.6] *v* 34.1% [95% CI, 27.1 to 41.2]; $P = .026$). Similar results were observed in the mITT population (Data Supplement, Fig S2B).

Local PFS was not significantly different between study arms in either population (Fig 3B; Data Supplement, Fig S2C). Pain-free survival was significantly prolonged with TTFields with gemcitabine/nab-paclitaxel compared with gemcitabine/nab-paclitaxel (median, 15.2 months [95% CI, 10.3 to 22.8] *v* 9.1 months [95% CI, 7.4 to 12.7]; HR, 0.74 [95% CI, 0.56 to 0.97], log rank $P = .027$; Fig 3C). In the TTFields with gemcitabine/nab-paclitaxel and gemcitabine/nab-paclitaxel arms, 244 and 243 patients were evaluable for response, respectively. ORR with TTFields with gemcitabine/

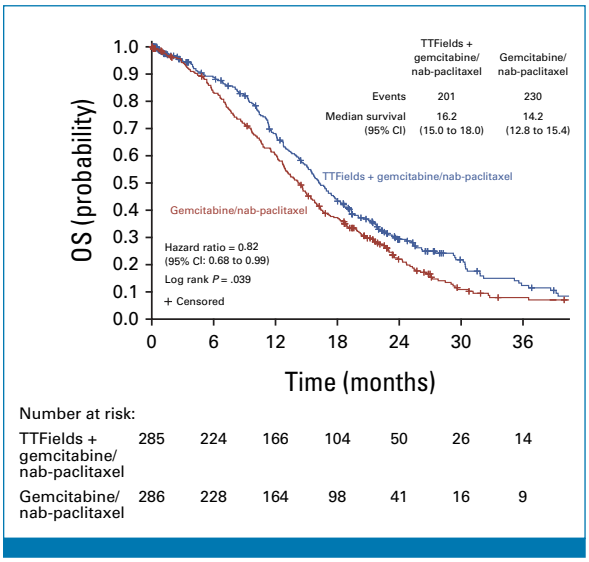

FIG 2. OS analysis for the ITT population. ITT, intention-to-treat; OS, overall survival; TTFields, tumor treating fields.

nab-paclitaxel was 36.1% (95% CI, 30.0 to 42.4) versus 30.0% (95% CI, 24.3 to 36.2) with gemcitabine/nab-paclitaxel (P = .094; Table 2).

No significant difference in resectability rate between patients receiving TTFields with gemcitabine/nab-paclitaxel and gemcitabine/nab-paclitaxel was observed (7.0% [95% CI, 4.3 to 10.6] *v* 10.1% [95% CI, 6.9 to 14.2]). Puncture-free survival was also not significantly different between study arms (75 and 78 events, respectively; P = .128).

Post Hoc Efficacy End Point

Distant PFS was significantly improved with TTFields with gemcitabine/nab-paclitaxel compared with gemcitabine/nab-paclitaxel (median, 13.9 months [95% CI, 12.2 to 16.8] *v* 11.5 months [95% CI, 10.4 to 12.9]; HR, 0.74 [95% CI, 0.57 to 0.96]; log rank P = .022; Fig 3D). Results were similar for the mITT population (Data Supplement, Fig S2D).

Safety

AEs of any cause were experienced by 97.8% and 98.9% of patients in the TTFields with gemcitabine/nab-paclitaxel and gemcitabine/nab-paclitaxel arms, respectively (Table 3). Grade ≥3 AEs were experienced by 88.7% and 84.3% of patients, respectively; the most frequent AEs were neutropenia (47.8% and 47.7%) and anemia (21.9% and 22.3%; Table 3).

Serious AEs (SAEs) occurred in 147 patients (53.6%) receiving TTFields with gemcitabine/nab-paclitaxel and 131 patients (48.0%) receiving gemcitabine/nab-paclitaxel (Table 3). The most common SAEs were sepsis (6.9% *v* 9.5%), cholangitis (5.8% *v* 3.7%), bile duct obstruction (5.5% *v* 3.3%), and pneumonia (5.1% *v* 3.3%; Data Supplement, Table S4). Most SAEs were related to chemotherapy or the underlying disease.

Device-related AEs were mainly mild-to-moderate skin reactions (Data Supplement, Table S5), which were experienced by 209 patients (76.3%); the most frequent events were dermatitis (n = 76, 27.7%), rash (n = 48, 17.5%), pruritus (n = 41, 15.0%), maculopapular rash (n = 33, 12.0%), and erythema (n = 29, 10.6%). Twenty-six patients (7.7%) experienced grade ≥3 device-related AEs, most frequently dermatitis (n = 8, 2.9%), rash (n = 4, 1.5%), and maculopapular rash (n = 3, 1.1%).

Device-related AEs leading to TTFields discontinuation occurred in 23 patients (8.4%); 47 (17.2%) and 43 (15.8%) patients discontinued chemotherapy because of chemotherapy-related AEs in the TTFields with gemcitabine/nab-paclitaxel arm and gemcitabine/nab-paclitaxel arm, respectively. No patient died due to AEs related to TTFields. Overall, four patients (0.7%) died due to chemotherapy-related AEs (Table 3). One patient receiving TTFields with gemcitabine/nab-paclitaxel experienced a SAE of diarrhea judged by the investigator to be related to gemcitabine/nab-paclitaxel and probably related to TTFields.

DISCUSSION

Improving OS in LA-PAC using a multidisciplinary approach has seen little progress in the past decade, with 5-year survival rates remaining low.[1,2] To date, the standard of care for this patient population has been extrapolated from phase III trials in metastatic cancer or mixed populations. Gemcitabine/nab-paclitaxel was established as the standard of care in 2013[7] in patients with metastatic disease. Since then, the single-arm phase II LAPACT trial[23] of gemcitabine/nab-paclitaxel showed OS of 18.8 months in the locally advanced population, while all phase III trials conducted in patients with unresectable locally advanced disease failed, notably the LAP-07 study[24] and the recent LAPIS trial of FOLFIRINOX or gemcitabine/nab-paclitaxel with or without pamrevlumab.[11] This may be explained in part by the numerous challenges in the design and conduct of controlled clinical trials in this population, including the lack of uniform criteria and observer variability in assessing vascular involvement, potential peritoneal carcinomatosis, and risk of complications due to biliary obstruction, which all affect patient suitability for surgical resection. In this context, it is particularly noteworthy that PANOVA-3 demonstrates for the first time, to our knowledge, significantly improved OS in unresectable LA-PAC.

Results for the key secondary end point pain-free survival and post hoc analysis of distant PFS support the benefit of TTFields with gemcitabine/nab-paclitaxel. PANOVA-3 is, to our knowledge, the first phase III trial to demonstrate a clinically and statistically meaningful improvement in pain-free survival (median, 15.2 *v* 9.1 months). Pain is a common and debilitating morbidity in patients with advanced

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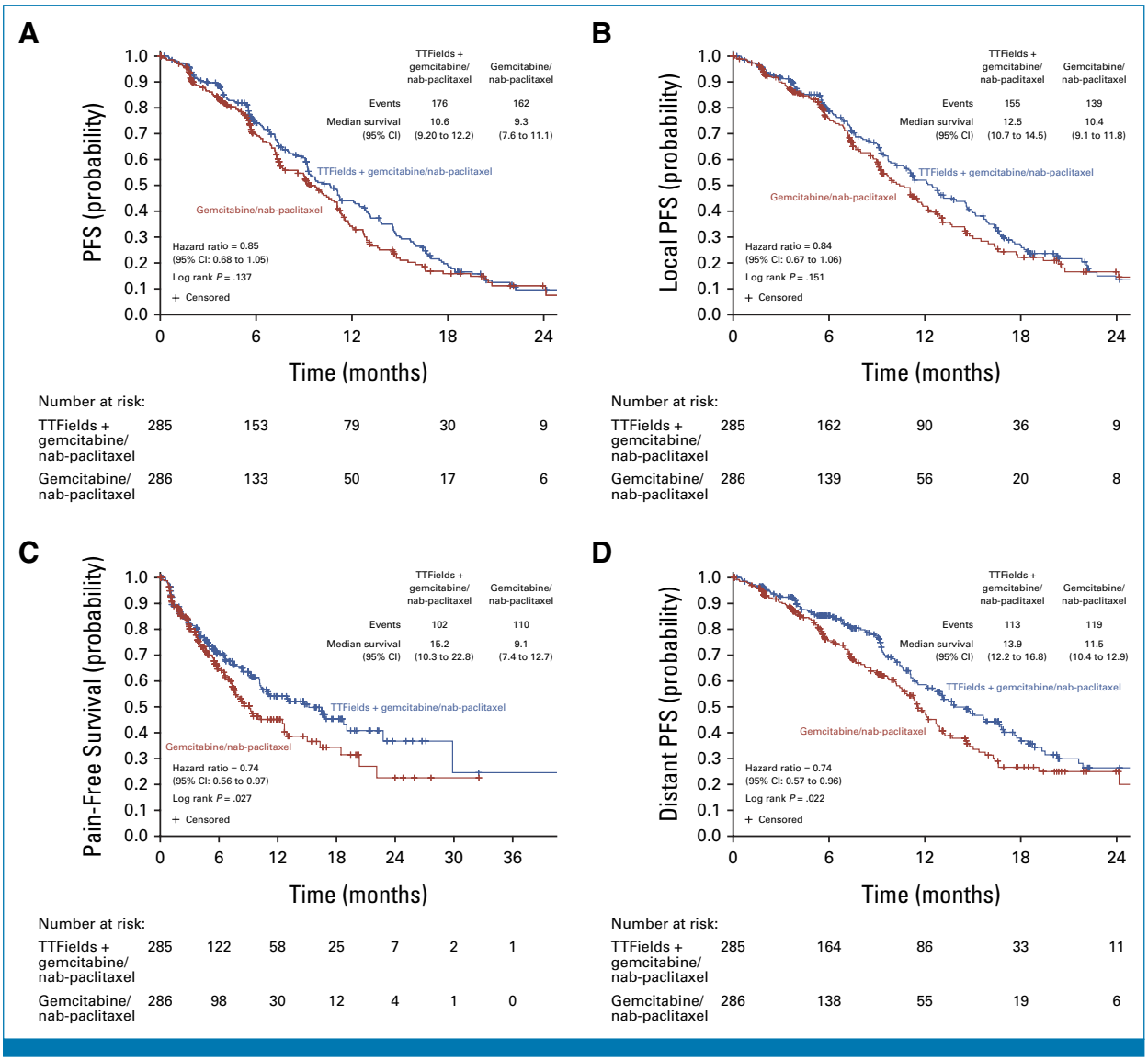

FIG 3. Survival analysis for the ITT population: (A) PFS, (B) local PFS, (C) pain-free survival, (D) distant PFS. ITT, intention-to-treat; PFS, progression-free survival; TTFields, tumor treating fields.

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TABLE 2. ORR in the ITT Population

Variable	TTFields With Gemcitabine/Nab-Paclitaxel (n = 244)	Gemcitabine/Nab-Paclitaxel (n = 243)
Best overall response, No. (%)		
Complete response	3 (1.2)	0
Partial response	85 (34.8)	73 (30.0)
Stable disease	142 (58.2)	150 (61.7)
Progressive disease	14 (5.7)	20 (8.2)
ORR, % (95% CI)	36.1 (30.0 to 42.4)	30.0 (24.3 to 36.2)
Mean difference in ORR, % (95% CI)	6.0 (−2.4 to 14.4)	
One-sided *P*	.094	

Abbreviations: ITT, intention-to-treat; ORR, overall response rate; TTFields, tumor treating fields.

TABLE 3. Summary of AEs in the Safety Analysis Population

	TTFields With Gemcitabine/Nab-Paclitaxel (n = 274), No. (%)		Gemcitabine/Nab-Paclitaxel (n = 273), No. (%)	
Event	All Grades	Grade ≥3	All Grades	Grade ≥3
Any AE	268 (97.8)	243 (88.7)	270 (89.9)	230 (84.2)
Serious AE	147 (53.6)	143 (52.2)	131 (48.0)	130 (47.6)
AE leading to device discontinuation	23 (8.4)		NA	
AE leading to chemotherapy discontinuation	47 (17.2)		43 (15.8)	
Serious AE leading to death	17 (6.2)		16 (5.9)	
AEs occurring in ≥20% of patients by system organ class and preferred term				
Blood and lymphatic system disorders				
Neutropenia	172 (62.8)	131 (47.8)	180 (65.9)	130 (47.6)
Anemia	161 (58.8)	60 (21.9)	158 (57.9)	61 (22.3)
Thrombocytopenia	122 (44.5)	39 (14.2)	133 (48.7)	32 (11.7)
Leukopenia	85 (31.0)	47 (17.2)	98 (35.9)	42 (15.4)
GI disorders				
Diarrhea	119 (43.4)	11 (4.0)	125 (45.8)	15 (5.5)
Nausea	107 (39.1)	11 (4.0)	121 (44.3)	7 (2.6)
Vomiting	82 (29.9)	7 (2.6)	79 (28.9)	15 (5.5)
Abdominal pain	73 (26.6)	11 (4.0)	83 (30.4)	12 (4.4)
Constipation	65 (23.7)	1 (0.4)	57 (20.9)	0
General disorders and administration site				
Fatigue	165 (60.2)	29 (10.6)	148 (54.2)	21 (7.7)
Edema peripheral	107 (39.1)	5 (1.8)	99 (36.3)	2 (0.7)
Pyrexia	74 (27.0)	6 (2.2)	64 (23.4)	2 (0.7)
Investigations				
Hepatic enzyme increased	75 (27.4)	35 (12.8)	72 (26.4)	24 (8.8)
Metabolism and nutrition disorders				
Anorexia	94 (34.3)	8 (2.9)	101 (37.0)	10 (3.7)
Hypokalemia	63 (23.0)	12 (4.4)	70 (25.6)	20 (7.3)
Musculoskeletal and connective tissue				
Musculoskeletal pain	70 (25.5)	3 (1.1)	79 (28.9)	5 (1.8)
Nervous system disorders				
Neuropathy peripheral	112 (40.9)	20 (7.3)	81 (29.7)	18 (6.6)
Skin and subcutaneous tissue disorders				
Alopecia	71 (25.9)	0	86 (31.5)	2 (0.7)
Rash	71 (25.9)	5 (1.8)	23 (8.4)	1 (0.4)
Dermatitis	82 (29.9)	8 (2.9)	8 (2.9)	0
Pruritus	61 (22.3)	0	23 (8.4)	0

Abbreviations: AE, adverse event; NA, not applicable; TTFields, tumor treating fields.

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pancreatic adenocarcinoma and a predictor of survival.[25,26] Thus, by mitigating cancer pain, TTFields may preserve the quality of life of patients with LA-PAC, further supporting TTFields' utility as first-line treatment of this disease.

With a 27.6-week median treatment duration and 62% median daily usage, TTFields were well tolerated and not associated with systemic AEs in addition to those of chemotherapy. Most device-related AEs were mild-to-moderate skin reactions, consistent with previous trials of TTFields and real-world evidence[16,27-31] and can be managed with topical steroids and calcineurin cream, in addition to appropriate skin-care routines.[32] Additionally, the 8% discontinuation rate because of AEs and minimal systemic AEs indicate good tolerability.

Although the benefit observed here is clinically meaningful in this challenging patient population, the OS in both study arms was lower than recently reported in LAPIS[11] and LAPACT.[23] This is potentially attributable to differences in patient selection criteria and trial conduct. PANOVA-3 was conducted in globally distributed community and academic

centers during the COVID-19 pandemic. Although the OS benefit of 2 months (TTFields with gemcitabine/nab-paclitaxel: 16.2 months; gemcitabine/nab-paclitaxel: 14.2 months; HR, 0.82) might be considered modest in the ITT population, it was more pronounced in the mITT population, with a benefit of 3.2 months (18.3 *v* 15.1 months; HR, 0.77). The relatively high number of discontinuations in both arms during the first 28 days after inclusion was reportedly related mostly to disease progression or patients' decision which may be indicative of a higher number of patients with more advanced disease and/or micrometastases in PANOVA-3 than in LAPIS or LAPACT (eg, patients with ECOG PS of 2 and patients with high baseline carbohydrate antigen 19-9). In addition, it should be noted that the recent NAPOLI 3 trial showed clinically relevant OS benefit with liposomal irinotecan, fluorouracil, leucovorin, and oxaliplatin in patients with metastatic disease compared with gemcitabine/nab-paclitaxel (11.1 *v* 9.2 months), with a comparable HR of death of 0.83 to that reported for PANOVA-3.[33] Finally, the imbalance between male and female patients between the two treatment arms may have biased OS favorably in the control arm, as women with pancreatic cancer have been reported to have better survival than men in several studies or meta-analyses.[34-38]

Although OS and distant PFS were extended with TTFields and gemcitabine/nab-paclitaxel, ORR and PFS were not improved. Radiologic response to treatment in LA-PAC is difficult to assess as the distinction between local inflammation, fibrotic tissue, and true tumor progression may be challenging on CT scans.[39] In pancreatic cancer, OS is connected to the ability to systemically control the disease, highlighting the importance of the improvement in distant PFS observed in this study. Further analyses are needed to explore the lack of difference in ORR and local PFS, characterize progression patterns in patients treated with TTFields, and identify prognostic and predictive factors of TTFields benefit.

In addition to the antimitotic effects of TTFields,[40] preclinical evidence has shown induction of adaptive immunity through activation of inflammasomes in glioblastoma,[41] while in lung cancer, models have shown that TTFields induce immunogenic cell death.[42] Furthermore, TTFields application reduced the spread, seeding, and growth of lung metastases from solid tumors in rabbits, an effect accompanied by extensive immune cell infiltration of the primary tumor.[43] Thus, TTFields may exert a systemic immune effect, potentially limiting metastatic spread and/or controlling already existing micrometastases, which is consistent with the observed improvement in distant PFS.

There is preclinical evidence that TTFields impair DNA damage repair[44] and induce DNA replication stress[40] as well as ER stress, triggering immunogenic cell death.[42] Future development of TTFields in pancreatic adenocarcinoma includes concomitant use of TTFields with FOLFIRINOX and other novel therapies. Whether the proimmunogenic effects of TTFields can sensitize pancreatic adenocarcinoma to immunotherapy is currently being investigated in an ongoing trial of TTFields concomitant with first-line gemcitabine/nab-paclitaxel and the PD-L1 inhibitor atezolizumab in metastatic pancreatic adenocarcinoma (PANOVA-4; ClinicalTrials.gov identifier: NCT06390059).

The survival benefit observed in this study was achieved with a median daily device usage of 62%, which is below the 75% recommended in the study protocol on the basis of data from a phase III study of TTFields in patients with glioblastoma.[45] However, usage requirements may vary according to the region of the body where the therapy is applied. Consistent with these findings, in the LUNAR study in patients with metastatic non–small cell lung cancer that has progressed on or after platinum-based therapy, adding TTFields therapy to either a PD-(L)1 inhibitor or docetaxel significantly extended OS with a median device usage of 56% over the first 3 months.[28] Additional analyses are needed to determine optimal usage recommendations for pancreatic cancer.

Limitations of the PANOVA-3 trial include investigator assessment of CT scans, which may have influenced patient selection as well as interpretation of PFS and ORR. The open-label study design and lack of a sham device in the control arm could have affected objective assessments despite rigorous data collection methodologies aimed at minimizing bias. While postprogression chemotherapy was permitted in both arms, neither cross-over to TTFields at progression in the control arm nor continuation of TTFields beyond local progression was permitted. This limits insights into TTFields' potential benefits in later-line treatment.

Although the study protocol included objective criteria for defining unresectable disease, no objective criteria were defined for assessing resectability during the treatment phase. Additionally, staging laparoscopy and centralized imaging review were not mandated across all sites during screening, potentially leading to the inclusion of patients with Stage IV disease or borderline resectable cases. Similarly, during treatment, the lack of a centralized approach to evaluate response and resectability introduced variability. These limitations may affect the ability to draw definite conclusions about the impact of TTFields on resectability. Despite these challenges, resectability rates were consistent with the existing literature and there was no difference between the two treatment arms.

However, potential imbalances because of the lack of systematic centralized multidisciplinary review were mitigated by the large size of this study, which reflects real-world practice and validates the clinical significance of the survival benefit observed in the TTFields arm. While the implementation of the TTFields therapy delivery system is home based, with integrated patient support from the manufacturer, carrying the device may be an obstacle for some patients. Caregivers' assistance as well as skin prophylaxis guidelines will be essential to help patients adopt this new treatment.

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In conclusion, PANOVA-3, the only phase III trial specifically in unresectable LA-PAC to show a significant OS benefit, establishes that TTFields with gemcitabine/nab-paclitaxel is an effective treatment of unresectable LA-PAC. With clinically meaningful improvements in OS, pain-free survival, and distant PFS and no exacerbation of systemic toxicity, TTFields therapy offers a potential treatment advance in the management of LA-PAC. The PANOVA-3 trial may have implications beyond LA-PAC, because it further supports the potential of concomitant use of TTFields therapy with the existing standard of care in solid tumors across a range of therapeutic settings.

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DISCLAIMER

The sponsor was involved in the study design, collection, analysis, and interpretation of data, as well as data checking of information provided in the manuscript. However, ultimate responsibility for opinions, conclusions, and data interpretation lies with the authors

EQUAL CONTRIBUTION

H.M.B. and V.P. contributed equally to the PANOVA-3 and the development of this manuscript.

PRIOR PRESENTATION

Presented at the ASCO Annual Meeting, Chicago, IL, May 30-June 4, 2025.

SUPPORT

Supported by Novocure Inc. H.M.B. acknowledges support under a grant awarded under the K-12 NCI grant program (K12CA090628) to study TTFields.

CLINICAL TRIAL INFORMATION

NCT03377491 PANOVA-3

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO-25-00746.

DATA SHARING STATEMENT

A data sharing statement provided by the authors is available with this article at DOI https://doi.org/10.1200/JCO-25-00746.

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ACKNOWLEDGMENT

The authors thank the patients, their families, and all investigators involved in this study. We thank Professor Daniel Von Hoff for inspiring the design of the study and supporting the development of the clinical protocol, and for serving as the first lead for the PANOVA-3 study and for pancreatic cancer research in general. We thank him for his trust and continued guidance during the entire study period. Statistical analysis was performed by sponsor-funded personnel, including Stav Edelstein, PhD; Avital Shalom, PhD; and Gitit Lavy-Shahaf, PhD; Novocure Ltd, Israel, and John Shin, MD, PhD, and Novocure Inc, USA. Medical writing support under the direction of the authors was provided by Janin Knop, PhD; Novocure GmbH, Switzerland; Chelsea Higgins, PhD, CMPP, Novocure Inc, USA; Christine Mormont, PhD; Novocure Canada Inc; Christine el Jundi, PhD; and Andrew Noble, CMPP, Bioscript Group Ltd, UK. Writing and editorial support provided by the Bioscript Group was funded by Novocure Inc and conducted according to Good Publication Practice guidelines (GPP 2022). The PANOVA-3 Study Investigators are listed in Appendix Table A1 (online only).

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Tumor Treating Fields With Gemcitabine and Nab-Paclitaxel for Locally Advanced Pancreatic Adenocarcinoma: Randomized, Open-Label, Pivotal Phase III PANOVA-3 Study

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Consulting or Advisory Role: Endocyte, Celgene, Idera, Myovant Sciences, Novocure, Ipsen, Caris MPI, Incyte, Guardant Health
Speakers' Bureau: Guardant Health
Research Funding: Spirita Oncology (Inst), Novocure (Inst), AstraZeneca (Inst), JSI (Inst), Incyte (Inst), Qurient (Inst), HiFiBiO Therapeutics (Inst), Revolution Health Care (Inst), Elevation Oncology (Inst), Dragonfly Therapeutics (Inst), Zelbio (Inst), BMS (Inst), Mirati Therapeutics (Inst), Strategia (Inst)

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Stock and Other Ownership Interests: Amgen, Johnson & Johnson, McKesson, Thermo Fisher Scientific, Cigna, Iovance Biotherapeutics, Lilly, Merck, United Health Group
Consulting or Advisory Role: TriSalus Life Sciences, Revolution Medicines
Research Funding: FibroGen (Inst), Ipsen (Inst), AbbVie (Inst), Novocure (Inst), PanTher Therapeutics (Inst), Amal Therapeutics (Inst), Panther Biotechnology (Inst), Verastem (Inst), Arcus Biosciences (Inst), Merus (Inst), AIM ImmunoTech (Inst)

Sreenivasa R. Chandana
Leadership: The Cancer & Hematology Centers
Consulting or Advisory Role: Ipsen, AstraZeneca
Speakers' Bureau: Natera
Research Funding: AbbVie (Inst), Merck (Inst), Pfizer (Inst), BMS (Inst), Exact Sciences (Inst), Zymeworks (Inst), AstraZeneca (Inst), Mirati Therapeutics (Inst), Elevation Oncology (Inst), Adcentrx Therapeutics (Inst), Amgen (Inst), Cardiff Oncology (Inst), Dicephera Pharmaceuticals, Inc (Inst), Genentech/Roche (Inst), IDEAYA Biosciences (Inst), IgM Biosciences (Inst), Incyte (Inst), Ipsen (Inst), Novocure (Inst), Qualigen Therapeutics (Inst), Janssen (Inst)

Bohuslav Melichar
Honoraria: Roche, Pfizer, Bristol Myers Squibb, Astellas Pharma, Novartis, MSD, Merck Serono, AstraZeneca, Eisai, Lilly
Consulting or Advisory Role: Roche, Pfizer, Bristol Myers Squibb, Astellas Pharma, Novartis, MSD, Merck Serono, AstraZeneca, Eisai, Lilly
Travel, Accommodations, Expenses: Bristol Myers Squibb, Merck Serono, AstraZeneca, MSD

Anup Kasi
Consulting or Advisory Role: Ipsen, Cardinal Health
Research Funding: Tesaro (Inst), Astellas Pharma (Inst), Rafael Pharmaceuticals (Inst), Geistlich Pharma (Inst), Cardiff Oncology (Inst), FibroGen (Inst), Bavarian Nordic (Inst), Novocure (Inst), Cend Therapeutics (Inst), Ability Pharma (Inst), Novita Pharmaceuticals (Inst), Boundless Bio (Inst)

Javier Gallego
Consulting or Advisory Role: Amgen, Bayer, Roche, Bristol Myers Squibb, Celgene, Lilly, Eisai Europe, AAA HealthCare, Merck Serono
Speakers' Bureau: Amgen, Ipsen, Lilly, Novartis
Research Funding: Lilly (Inst), Bristol Myers Squibb (Inst), Astellas Pharma (Inst)
Expert Testimony: Lilly, Bayer
Travel, Accommodations, Expenses: Amgen, Novartis, Roche
Other Relationship: Amgen, Bristol Myers Squibb, Amgen, Merck

Andrea Bullock
Stock and Other Ownership Interests: Medtronic
Consulting or Advisory Role: Sirtex Medical, Agenus
Research Funding: Geistlich Pharma (Inst), Agenus (Inst), Ipsen (Inst), Panova (Inst), Oncomatryx (Inst), AstraZeneca (Inst), Seagen (Inst)
Travel, Accommodations, Expenses: Agenus

Lucjan Wyrwicz
Honoraria: BeiGene, BMS, MSD, Servier
Consulting or Advisory Role: GlaxoSmithKline, Servier, AstraZeneca, Agenus
Speakers' Bureau: BMS, Servier, MSD
Travel, Accommodations, Expenses: Servier, Amgen

Arsen Osipov
Honoraria: Ipsen
Consulting or Advisory Role: Ipsen

Christelle de la Fouchardiere
Consulting or Advisory Role: Bristol Myers Squibb, Amgen, Servier, Pierre Fabre, MSD Oncology, Roche/Genentech, Daiichi Sankyo, Astellas Pharma, Gilead Sciences, BeiGene, Jazz Pharmaceuticals, Takeda, AbbVie
Research Funding: Pierre Fabre (Inst), Servier (Inst), MSD (Inst), Agenus (Inst)
Travel, Accommodations, Expenses: Pierre Fabre, Servier, MSD Oncology, Amgen, AstraZeneca

Inmaculada Ales
Consulting or Advisory Role: BMSi, Merck, AstraZeneca Spain
Speakers' Bureau: BMSi, AstraZeneca Spain, Servier
Travel, Accommodations, Expenses: AstraZeneca, Roche

Kynan Feeney
Travel, Accommodations, Expenses: BMS GmbH & Co KG

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Philip Philip
Honoraria: Bayer, Ipsen, Incyte, Taiho Pharmaceutical, Astellas Pharma, BioNTech SE, Novocure, TriSalus Life Sciences, Servier, Seagen
Consulting or Advisory Role: Celgene, Ipsen, Merck, TriSalus Life Sciences, Daiichi Sankyo, SynCoreBio, Taiho Pharmaceutical
Speakers' Bureau: Incyte
Research Funding: Bayer (Inst), Incyte (Inst), Merck (Inst), Taiho Pharmaceutical (Inst), Novartis (Inst), Regeneron (Inst), Genentech (Inst), Halozyme (Inst), Lilly (Inst), Merus (Inst), BioNTech SE (Inst)
Uncompensated Relationships: Rafael Pharmaceuticals, Caris MPI

Makoto Ueno
Honoraria: Taiho Pharmaceutical, AstraZeneca, MSD, Ono Pharmaceutical, Servier, Chugai Pharma, Incyte, Takeda, Novartis, Daiichi Sankyo/UCB Japan, J-Pharma, Boehringer Ingelheim, Eisai, Takada Pharm, Viatris, Asca
Consulting or Advisory Role: Boehringer Ingelheim
Research Funding: Taiho Pharmaceutical (Inst), Eisai (Inst), AstraZeneca (Inst), Ono Pharmaceutical (Inst), MSD (Inst), Incyte (Inst), Astellas Pharma (Inst), Chugai Pharma (Inst), Delta-Fly Pharma (Inst), Chiome Bioscience (Inst), Novartis (Inst), Boehringer Ingelheim (Inst), J-Pharma (Inst), Amgen (Inst), Jazz Pharmaceuticals (Inst), Novocure (Inst), Revolution Medicines (Inst), Amgen (Inst)

Eric Van Cutsem
Consulting or Advisory Role: Bayer, Lilly, Servier, Bristol Myers Squibb, Merck Sharp & Dohme, Merck KGaA, Novartis, AstraZeneca, Daiichi Sankyo, Pierre Fabre, Taiho Pharmaceutical, Astellas Pharma, GlaxoSmithKline, Nordic Group, Pfizer, Takeda, ALX Oncology, AbbVie, BeiGene, Boehringer Ingelheim, Mirati Therapeutics, Seagen, Ipsen, Agenus, Amgen, Arcus Biosciences, BioNTech SE, Debiopharm Group, ElmediX, Eisai, Simcere, Bexon Clinical Consulting, Cantargia AB, Fosum, Galapagos NV, ITeos Therapeutics, Microbial Machines, Novocure, Sanofi, Trishula Therapeutics

Thomas Seufferlein
Honoraria: Falk Foundation, Servier, Pierre Fabre, BMS GmbH & Co KG, AstraZeneca, Takeda
Consulting or Advisory Role: Servier, Pierre Fabre, Cantargia AB, Boehringer Ingelheim, Mirati Therapeutics, Scandion Oncology, Olympus Medical Systems, BioNTech SE, Silexion, Novocure, Arcus Biosciences, Amgen
Research Funding: Lilly/ImClone (Inst)
Travel, Accommodations, Expenses: Takeda

Teresa Macarulla
Consulting or Advisory Role: Sanofi/Aventis, Celgene, Roche, QED Therapeutics, Baxter, Incyte, Servier, Lilly, Ipsen, AstraZeneca, MSD, Eisai, Prime Oncology, Ability Pharma, Advance Medical, BioLineRX, Zymeworks, Aptitude Health, Basilea, Medscape, Novocure, Paraxel, Ellipses Pharma, Janssen, MFAR, Marketing Farmacéutico & Investigación Clínica, Amgen, Esteve, Arcus Biosciences, Boehringer Ingelheim, Taiho/Keylates, Alligator Bioscience, PEGASCY, Astellas Pharma, Revolution Medicines
Research Funding: Celgene (Inst), Agios (Inst), ASLAN Pharmaceuticals (Inst), Bayer (Inst), Roche (Inst), Genentech (Inst), AstraZeneca (Inst), Immunomedics (Inst), Lilly (Inst), Merrimack (Inst), Millennium (Inst), Novocure (Inst), Pfizer (Inst), Pharmacyclics (Inst), AbbVie (Inst), Ability Pharma (Inst), Amc Medical Research (Inst), Amgen (Inst), Armo Biosciences (Inst), Basilea Pharmaceutica International (Inst), Beigene (Inst), Keralty Group (Inst), BiolineRx (Inst), Blueprint Medicines (Inst), Boston Biomedical (Inst), Bristol Myers Squibb (BMS) (Inst), Cantargia AB (Inst), Eisai (Inst), Erytech Pharma (Inst), Fibrogen (Inst), Halozyme (Inst), Incyte (Inst), Ipsen (Inst), Loxo (Inst), Medimmune (Inst), Merck Sharp & Dohme (Inst), Nelum Corp (Inst), Novartis (Inst), OncoMed (Inst), VCN Biosciences (Inst), Zymeworks (Inst)
Travel, Accommodations, Expenses: Merck, H3 Biomedicine, Sanofi, Celgene, Servier, Prime Oncology, Incyte, AstraZeneca

No other potential conflicts of interest were reported.

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APPENDIX

TABLE A1. Study Sites and Principal Investigators

Site Name	Location	Principal Investigator
United States		
Tennessee Oncology	Nashville, TN	David Spigel (formerly Joanna Bendell)
Cedars Sinai	Los Angeles, CA	Arsen Osipov (formerly Andrew Hendifar)
Ochsner Clinic Foundation	New Orleans, LA	Marc Matrana
Associated Neurologists of Southern Connecticut	Fairfield, CT	Nicholas Blondin
University of Minnesota	Minneapolis, MN	Emil Lou
The University of Arizona Cancer Center	Tucson, AZ	Rachna Shroff (formerly Hani Babiker)
Texas Oncology	Dallas, TX	Douglas Orr (formerly Carlos Becerra)
Comprehensive Cancer Center of Nevada	Las Vegas, NV	Michael Anderson (formerly Fadi Braiteh)
Karmanos Cancer Center	Detroit, MI	Anthony Shields (formerly Philip Philip)
Norton Cancer Institute	Louisville, KY	John Hamm
Beth Israel Deaconess Medical Center (BIDMC)	Boston, MA	Andrea Bullock (Interim PI is Mary Peters; formerly Benjamin Schlecter)
Erlanger Health System	Chattanooga, TN	Sumana Nagireddy
West Virginia University	Morgantown, WV	Joanna Kolodney
Banner MD Anderson Cancer Center	Gilbert, AZ	Tomislav Dragovich
Seattle Cancer Care Alliance	Seattle, WA	Andrew Coveler
Pacific Cancer Medical Center	Anaheim, CA	Ajit Maniam
Virginia Mason Medical Center	Seattle, WA	Vincent Picozzi
Novant Health Oncology Specialists	Winston-Salem, NC	Judith Sears
HCA Midwest Division of Sarah Cannon Research Institute	Kansas City, MO	Joseph Stilwill (formerly Peter Van Veldhuizen, Jaswinder Singh)
Laura and Issac Perimutter Cancer Center at NYU Langone	Lake Success, NY	Francis Arena
Mount Sinai Comprehensive Cancer Center (MSCCC)	Miami Beach, FL	Mike Cusnir
Vita Medical Associates	Bethlehem, PA	Anna Niewiaroska
Loyola University Chicago	Maywood, IL	William Small
University of Kansas Cancer Center (KUCC)	Fairway, KS	Anup Kasi
Boca Raton Clinical Research Medical Center	Plantation, FL	Jason Tache
Florida Hospital Tampa	Tampa, FL	Sharona Ross (formerly Alexander Rosemurgy)
Dignity Health Cancer Institute	Carmichael, CA	Samer Shihabi
Florida Cancer Specialists	Petersburg, FL	Sunil Gandhi
Florida Cancer Specialists	Myers, FL	James Reeves
Renown Regional Medical Center	Reno, NV	Garrett Green
Piedmont Cancer Institute (PCI)	Atlanta, GA	Trevor Feinstein
Nebraska Methodist Hospital	Omaha, NE	Timothy Huyck
Geisinger Medical Center	Danville, PA	Nadia Ramdin (formerly Anand Mahadevan)
North Shore University Health	Evanston IL	Robert Marsh (formerly Marisa Hill)
University of Maryland Comprehensive Cancer Center	Baltimore, MD	Yixing Jiang
University of Oklahoma Health Sciences Center	Oklahoma City, OK	Hassan Hatoum
Arizona Oncology Associates	Tucson, AZ	Sudhir Manda
Oncology and Hematology Associates of Southwest Virginia	Roanoke, VA	Mark Kochenderfer
Texas Oncology—Bedford	Bedford, TX	Henrik Illum
Texas Oncology—Tyler	Tyler, TX	Donald Richards
Texas Oncology—El Paso Cancer	El Paso, TX	Panagiotis Valilis
Baylor, Scott and White Medical Center	Temple, TX	Lucas Wong

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TABLE A1. Study Sites and Principal Investigators (continued)

Site Name	Location	Principal Investigator
Cancer & Hematology Centers of Western Michigan	Grand Rapids, MI	Sreenivasa Chandana
Florida Hospital Cancer Institute	Orlando, FL	Herbert Newton
Houston Methodist Cancer Center and Institute of Academic Medicine	Houston, TX	Maen Abdelrahim
Cotton O'Neil Cancer Center Stormont Vail Health Care	Topeka, KS	David Einspahr
Illinois Cancer Specialist	Arlington Heights, IL	Richard Siegel
Texas Oncology—Beaumont Mamie	Beaumont, TX	Scott McKenney
Maryland Oncology Hematology	Columbia, MD	Mohit Narang
Willamette Valley Cancer Institution	Eugene, OR	Marc Uemura
NY Presbyterian Queens	Flushing, NY	Higinia Cardenes (formerly Steven DiBiase)
Infirmary Health	Mobile, AL	Kannan Thanikachalam (Formerly John Russell)
White Plains Hospital	White Plains, NY	Joshua Raff
Vista Oncology Group	Olympia, WA	Joseph Ye
Sutter Institute for Medical Research	Sacramento CA	Deepti Behl
Rush University Medical Center	Chicago, IL	Audrey Kam (formerly Ashiq Masood)
Methodist Richardson Cancer Center	Dallas, TX	Paul DeRose
Umass Memorial Hospital	Worcester, MA	Ali Tasneem (formerly Venu Bathini)
Lynn Cancer Institute, Boca Raton Regional Hospital	Boca Raton, FL	Warren Brenner
Grandview Health	Birmingham, AL	Jennifer De Los Santos
General Physician Cancer Care—Williamsville	Williamsville, NY	James Wang
Hematology Oncology Central Maine Medical Center (CMMC)	Lewiston ME	Daniel Rausch
Cancer Specialist of North Florida	Fleming Island, FL	Gaurav Trikha
Providence Medical Foundation	Fullerton, CA	David Park
Gabrail Cancer Center Research	NW Canton, OH	Nashat Gabrail
Toledo Clinic Cancer Center	Toledo, OH	Rex Mowat
OptumCare	Las Vegas, NV	Khawaja Jahangir
Tennessee Cancer Specialists	Knoxville, TN	Robert Schumaker
Princeton Radiation Oncology (Regional Cancer Care Associates LLC)	Plainsboro, NJ	Edward Soffen
Bassett Cancer Institute	Cooperstown, NY	Eric Bravin
Ridley Tree Cancer Center	Santa Barbara, CA	Mukul Gupta
Mayo Clinic Jacksonville	Jacksonville, FL	Hani Babiker
St Elizabeth Healthcare	Edgewood, KY	Ivan Bedoya-Apraez
St Helena Healthcare—Martin O'Neil Cancer Center	St Helena, FL	Tyler Kang
Canada		
Centre Hospitalier Universitaire de Sherbrooke CIUSSS de l'Estrie—CHUS	Sherbrooke, Québec	Frederic Lemay
London Health Science Center, London Regional Cancer Program	London, ON	Mark Vincent
Centre Hospitalier de l'Universite de Montreal—CHUM CIUSSS de l'Estrie—CHUS	Montreal, QC	Richard Letourneau
Germany		
Klinik München Bogenhausen	München	Martin Fuchs
Universitätsklinikum Ulm	Ulm	Thomas Theodor Werner Seufferlein
Carl-von-Basedow-Klinikum Saalekreis	Merseburg	Christine Doehring (formerly Jorn Russel)
Frau Dr med Ursula Vehling-Kaiser	Dingolfing	Mike Haberkorn
Medizinische Hochschule Hannover, Klinik fur Gastroenterologie, Hepatologie und Endokrinologie	Hannover	Arndt Vogel
Bonifatius Hospital Hematology and Oncology Lingen	Lingen (Ems)	Karen Russwurm
Klinikum Chemnitz gGmbH	Chemnitz	Jack Chater

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TABLE A1. Study Sites and Principal Investigators (continued)

Site Name	Location	Principal Investigator
Switzerland		
Fribourg Hôpital	Fribourg	Marc Küng
Winterthur Kantonsspital	Winterthur	Sabine Schacher
Israel		
Haifa Rambam Medical Center	Haifa	Maria Passhak (formerly Valeriya Semenisty)
Tel Aviv Sourasky Medical Center	Tel Aviv	Ravit Geva
Hadassah Medical Center	Jerusalem	Ayala Hubert
Rabin Medical Center	Petah Tikva	Salomon Stemmer
Sheba Pancreatic Cancer Center		Talia Golan
France		
Institut de Cancérologie de l'Ouest (ICO)	St Herblain	Hélène Senellart
Hopital Saint-Antoine	Saint-Antoine	Isabelle Trouilloud
Centre Léon Bérard	Lyon	Christelle de la Fouchardière (formerly Pauline Rochefort)
Hopital haut-Léveque CHU Bordeaux—Service d'Hépato-Gastroentérologie et d'Oncologie digestive	Bordeaux	Jean-Frederic Blan
Strasbourg Oncologie Liberale	Strasbourg	Luis-Marie Dourthe
Hospital Group Bretagne Sud	Lorient	Florence Le Roy (formerly Marie Clemence Daniel; formerly Joelle Egreteau)
Centre Armoricain d'Oncologie—CARIO	Plerin	Jerôme Martin-Babau
Centre de Lutte Contre le Cancer (CLCC)—Centre Paul Strauss	Strasbourg	Meher Ben Abdelghani
Austria		
Salzburg Uniklinik fur Innere Medizin	Salzburg	Richard Greil
Landes-Krankenhaus Steyr	Steyr	Georg Schreil
Medical University of Graz	Graz	Armin Gerger
Klinikum Klagenfurt am Wörthersee	Wörthersee	Wolfgang Eisterer
Spain		
BARCELONA: Vall d'Hebron	Barcelona	Teresa Macarulla Mercadé
Madrid, HM Hospitales CIOCC	Madrid	Antonio Cubillo
Instituto Oncologico Dr Rosell	Barcelona	Francesc Valladares Pons
Hospital Universitario Ramon Y Cajal Carretera de Colmenar Viejo	Madrid	Carmen Guillen Ponce
Hospital Regional Universitario de Málaga	Málaga	Inmaculada Ales Diaz (formerly Manuel Benavides Orgaz)
Marqués de Valdecilla University Hospital	Santander	Fernando Rivera
Elche Hospital General Universitario	Elche	Javier Gallego Plazas
Inst. Valenciano de Oncologia	Valencia	Ricardo Yaya
Pamplona Clinica Universidad de Navarra	Pamplona	Mariano Ponz Sarvise
Italy		
Università Campus Bio-Medico	Rome	Bruno Vincenzi
Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino	Torino	Mario Airoldi
Ospedale Civile Ss. Antonio e Biagio e Cesare Arrigo	Alessandria	Giovanna Bellotti
Ospedale San Giovanni	Rome	Domenico Cristiano Corsi
Azienda Ospedaliero-Universitaria Careggi	Firenze	Lorenzo Antonuzzo
Czech Republic		
Olomouc Fakultni Nemocnice	Olomouc	Bohuslav Melichar
Nemocnice Na Bulovce	Prague	Petra Holeckova

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TABLE A1. Study Sites and Principal Investigators (continued)

Site Name	Location	Principal Investigator
General University Hospital in Prague	Prague	Lubos Petruzelka
Nemocnice Novy Jicin	Novy Jicin	Rostislav Kotasek
Masaryk Institute of Oncology	Brno	Radim Nemecek
Belgium		
University of Leuven	Leuven	Eric van Cutsem
Research UZ/KU Leuven	Leuven	Jean-Luc van Laethem
Clinique Universutaire Saint Luc—Institut Roi Albert	Woluwe-Saint-Lambert	Ivan Borbath
South Korea		
Chonnam National University Hwasun Hospital	Hwasun	Jun Eul Hwang
Dong-A University Hospital	Busan	Sung Yong Oh
Gachon University Gil Hospital	Incheon	Sun Jin Sym
Inha University Hospital	Incheon	Moon Hee Lee
Keimyung University, Dongsan hospital	Daegu	Jin Young Kim
Korea University Guro Hospital	Seoul	Sang Cheul Oh
National Cancer Center	Goyang	Woo Jin Lee
Samsung Medical Center	Seoul	Joon Oh Park
Seoul National University Bundang Hospital	Seongnam-si	Jin Won Kim
The Catholic University of Korea, Seoul St Mary's Hospital	Seoul	Myung Ah Lee
Severance Hospital	Seoul	Hye Jin Choi
Ajou University Hospital	Suwon	Seok Yun Kang
CHA Bundang Medical Center	Seongnam-si	Hong Jae Chon
Poland		
WARSAW: M.Sklodowska-Curie Institute of Oncology	Warsaw	Lucjan Wyrwicz
Klinika Onkologii Uniwersytetu Medyczneg	Poznan	Rodryg Ramlau
Mrukmed Medical Center	Rzeszow	Andrzej Mruk
Uniwersytecki Szpital Kliniczny we Wrocławiu	Wroclaw	Beata Freier
Oncology and Radiotherapy Clinic University Clinical Center Non-Invasive Medicine Center	Warsaw	Ewa Kosakowska
Hungary		
Bacs-Kiskun County Teaching Hospital	Kecskemet	Judit Kocsis
Jasz-Nagykun-Szolnok Megyei Hetenyi Geza	Szolnok	Tibor Csoszi
National Institute of Oncology	Budapest	Erika Hitre
Tolna County Balassa Janos Hospital	Szekszard	Yousuf Al-Farhat
Békés Megyei Pándy Kálmán Kórháza Megyei Onkológiai Központja	Gyula	Ali Bassam
China		
Beijing Cancer Hospital	Beijing	Chunyi Hao
Jilin Guowen Hospital	Gongzhuling City, Jilin Province	Bo Liang
Henan Provincial People's Hospital	Henan	Shundong Cang
Shanghai Changhai Hospital	Shanghai	Gang Jin
Xingtai People's Hospital	Xiangtai	Changzeng Zuo
The First Affiliated Hospital of Zhengzhou University	Zhengzhou	Lijie Song
First Affiliated Hospital of Xi'an Jiaotong University	Xi'an	Zheng Wu
Beijing University People's Hospital	Beijing	Jie Gao
Union Hospital affiliated to Tongji Medical College of Huazhong University of Science and Technology	Wuhan	Tao Zhang
Shanxi Province Cancer Hospital	Taiyuan	Yusheng Wang
Tongji Hospital affiliated to Tongji Medical College of Huazhong University of Science and Technology	Wuhan	Xinaglin Yuan

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TABLE A1. Study Sites and Principal Investigators (continued)

Site Name	Location	Principal Investigator
Sun Yat-Sen Memorial Hospital of Sun Yat-Sen University	Guangzhou	Zhihua Li
Guangdong Provincial People's Hospital	Guangzhou	Rufu Chen
Bethune First Hospital of Jilin University	Changchun	Wei Li
Sir Run Run Shaw Hospital affiliated to Zhejiang University School of Medicine	Hangzhou	Xiujun Cai
Linyi Cancer Hospital	Linyi	Zhizhen Zhu
Harbin Medical University Cancer Hospital	Harbin	Yuxian Bai
Beijing Union Medical College Hospital	Beijing	Chunmei Bai
Hong Kong		
Queen Mary Hospital	Hong Kong	Thomas Yau
Greenslopes Oncology	Woolloongabba	Warren Joubert
Australia		
Westmead Hospital	Westmead	Ka Yeung Mark Wong
Sydney Adventist Hospital	Wahroonga	Gavin Marx
St John of God Murdoch Hospital	Murdoch	Kynan Feeney
Monash Health	Clayton	Marion Harris
Croatia		
UHC Zagreb	Zagreb	Ana Misir (formerly Zoran Rakušić)
Brazil		
Instituto Ribeiraopretano de Combate ao Cancer	Ribeirão Preto	Adilson Faccio
Instituto Brasileiro de Controle do Cancer (IBCC)	São Paulo	Felipe Cruz
Hospital de Clínicas de Porto Alegre	Porto Alegre	Sergio De Azevedo
COI	Rio De Janeiro	Ana Paula De Souza Victorino
Ynova Pesquisa Clinica	Florianópolis	Tadeu Ferreira de Paiva Jr
Hospital de Caridade de Ijui (HCI)	Ijui	Fabio Andre Franke
Centro de Pesquisa Clínica Multidisciplinar da Santa Casa de Porto Alegre	Porto Alegre	Katsuki Arima Tiscoski
Hospital São Lucas da PUCRS	Porto Alegre	Gabriel Parolla
Oncoclinicas Rio de Janeiro S.A	Rio De Janeiro	Flora Lilno
Instituto D'Or de Pesquisa e Ensino—Matriz Rio de Janeiro	Rio De Janeiro	Mariana Bruno Siqueira
Instituto D'Or de Pesquisa e Ensino—Filial Salvador (Hospital São Rafael)	Rio De Janeiro	Marcos Lyra
Instituto D'Or de Pesquisa e Ensino	Rio De Janeiro	Paulo Hoff
Mexico		
Accelerium Clinical Research	Monterrey	Jose Luis Martinez Lira
Centro Potosino de Investigación Médica	San Luis Potosí	Dolores Mendoza Oliva
Mediadvance Clinical	Chihuahua	Arturo Vazquez
Centro de Investigación Médica Aguascalientes (CIMA)	Aguascalientes	Jesus Elvis Cabrera Luviano
FAICIC Clinical Research	Veracruz	Erika Castillo Gutierrez
Clinstile S.A de C.V	Monterrey	Vanessa Rosas Camargo
Centro de Estudios de Alta Especialidad de Sinaloa	Mazatlán	Cristian Chavez Guerra
Phylasis Clinicas Research	Izcalli	Osvaldo Hernandez Flores
Hospitales Star Medica	Izcalli	David Orta Cortez
PCR Toluca Corporativo Hospital Satelite	Toluca De Lerdo	Saul Campos
Clinica Integral Internacional de Oncologia	Puebla	Ivan Romarico González Espinoza
Hospital Angeles—Centro Medico del Potosi	Potosi	Jessica Reyes Contreras
Practice of Centro Hemato Oncologico Privado	Toluca De Lerdo	Angel Gomez Villanueva
Hospital Universitario "Dr Jose Eleuterio Gonzalez"	Monterrey	Omar Zayas Villanueva

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OPTUNE PAX® FOR LOCALLY ADVANCED PANCREATIC CANCER

Physician Instructions for Use

novocure®

This manual is intended for physicians prescribing the use of Optune Pax® for Locally Advanced Pancreatic Cancer

Caution: Federal law restricts this device to sale by or on the order of a physician

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1 INDICATION FOR USE

Optune Pax is intended for the treatment of adult patients with locally advanced pancreatic cancer, concomitant with gemcitabine and nab-paclitaxel.

2 CONTRAINDICATIONS, WARNINGS, PRECAUTIONS & NOTICES

Contraindications

Do not use Optune Pax if you have an electrical implant. Use of Optune Pax together with electrical implants has not been tested and may lead to malfunctioning of the implanted device.

Do not use Optune Pax if you are known to be sensitive to gels like the gel used on electrocardiogram (ECG) stickers or transcutaneous electrical nerve stimulation (TENS) electrodes. In this case, skin contact with the gel used with Optune Pax may commonly cause increased redness and itching and rarely may even lead to severe allergies such as a fall in blood pressure and breathing difficulty.

Warnings

Warning – Use Optune Pax only after receiving training from Novocure or other qualified personnel, such as your doctor, a nurse, or other medical personnel who have completed a training course given by Novocure (the device manufacturer).

Your training will include a detailed review of the patient user manual and practice in the use of the device. In addition, you will be trained in what to do if there are problems with treatment. Use of Optune Pax without receiving this training can result in breaks in treatment and may rarely cause increased skin irritation, open sores on your abdomen or back, or allergic reactions or even an electric shock.

Warning – In case of skin irritation, which appears as redness under the transducer arrays (a mild rash), contact your doctor who will prescribe you high potency topical steroids (hydrocortisone cream) to use when replacing the transducer arrays. Using this cream will help relieve your skin irritation. If you do not use this cream, the skin irritation can become more serious and may even lead to skin breakdown, infections, pain and blisters. If this happens, stop using the topical steroid cream and contact your doctor. Your doctor will supply you with an antibiotic cream to use when replacing transducer arrays. If you do not use this cream, your symptoms may continue and your doctor may ask you to take a break from treatment until your skin heals.

Warning – All device servicing must be performed by qualified and trained personnel. No modification of this equipment is allowed. If you attempt to open and service the device yourself, you may cause damage to the device. You could also get an electric shock by touching the inner parts of the device.

Warning – The transducer arrays are for single use and should not be taken off your body and then put back on again. If you put a used transducer array back on again, it may not stick well to your skin and the device could turn off. The transducer arrays should not be re-used. Re-use of transducer arrays can lead to poor contact with the skin and may cause the device to alarm and stop working. Re-use of transducer arrays can lead to worsening of the skin inflammation and rarely even to local infection. If you suffer from an infection on your skin (pus, swelling and warmth) consult with your doctor immediately.

Precautions

Caution – Do not use Optune Pax with any parts that did not come with the device, that were not sent to you by the device manufacturer, or that were not given to you by your doctor. Use of other parts, manufactured by other companies or for use with other devices, can damage the device. This may lead to a break in treatment.

Caution – Do not use Optune Pax if any parts look damaged (such as torn wires, loose connectors, loose sockets, cracks or breaks in the plastic case, opening in power supply). Use of damaged components can damage the device and cause a break in treatment.

Caution – Do not get the device, transducer arrays or other parts wet. Getting the device wet may damage it, preventing you from receiving treatment. Getting the transducer arrays very wet is likely to cause them to come loose from your skin. If this happens, the device will turn off and you will need to change the transducer arrays.

Caution – Before connecting or disconnecting the transducer arrays, make sure that Optune Pax power switch is in the OFF position. Disconnecting transducer arrays with the power switch in the ON position may cause a device alarm to go off and could damage the device.

Caution – If you have an underlying serious skin condition on the abdomen, discuss with your doctor whether this may prevent or temporarily interfere with Optune Pax treatment.

Caution – Do not use Optune Pax if you are pregnant, you think you might be pregnant or are trying to get pregnant. If you are a woman who is able to get pregnant, you must use birth control when using the device. Optune Pax was not tested in pregnant women. It is unknown what side effects the device may cause if you are pregnant, or if it will be effective.

Caution – There is a hazard of falling due to entanglement in the connection cable. You may consider clipping the cable to your belt.

Caution – The device dropping on the user may result in injury.

Notices

Notice – Optune Pax and transducer arrays will activate metal detectors.

Notice – If you plan to be away from home for more than 1 hour, carry an extra battery and/or the power supply with you in case the battery you are using runs out. If you do not take a spare battery and/or the power supply, you may have a break in your treatment.

Notice – Make sure you have at least 12 extra transducer arrays at all times. This will last until the next transducer array shipment arrives. Remember to order more transducer arrays when there are at least 12 extra transducer arrays left. If you do not order transducer arrays on time, you may have a break in your treatment.

Notice – Batteries may weaken over time and need to be replaced. You will know this has happened when the amount of time the device can run on a fully charged battery begins to shorten. For example, if the low battery indicator light flashes within only 1 hour from the start of treatment, replace the battery. If you do not have replacement batteries when your batteries run out, you may have a break in your treatment.

Notice – You should carry the Troubleshooting Guide from the Patient Information and Operation Manual at all times. This guide is necessary to ensure Optune Pax works properly. If you do not work the device correctly, you may have a break in your treatment.

Notice – Do not block the device vents located on the front and back of the device. Blocking the vents may cause the device to overheat and turn off, leading to a break in treatment. If this happens, unblock the vents, wait 5 minutes and restart the device. In case the vents are blocked with pet hair/dust, return the device to the manufacturer for service.

Notice – Do not block the battery charger vents located on the sides of the battery chargers. Blocking the vents may cause the charger to overheat. This could prevent your batteries from charging. In case the vents are blocked with pet hair/dust, return the battery charger to the manufacturer for service.

Notice – Before using a transducer array, make sure its package is sealed by gently rubbing the package between thumb and pointer finger on all four sides. The package should be closed on all sides. There should be no openings in the package seal. If the package is not sealed, the transducer array may be damaged. A damaged transducer array will not work properly and may cause the device to turn off.

Notice – Keep the device out of the reach of children and pets.

Notice – The device has a cord that may cause tripping when connected to an electric socket.

Notice – Do not cover the device or power supply. This can lead to overheating of the device and cause superficial thermal injury.

3 DEVICE DESCRIPTION

Optune Pax is a portable, battery-powered or mains-powered device that produces alternating electrical fields, called tumor treating fields ("TTFields") within the body. TTFields are applied to the patient by non-invasive, electrically-insulated surface transducer arrays that are placed on the patient's abdomen and connected to the Electric Field Generator. TTFields physically disrupt the rapid cell division exhibited by cancer cells.

Optune Pax is comprised of two main components: (1) an Electric Field Generator (the Optune Pax device) and (2) Insulated Transducer Arrays (the transducer arrays). In addition, the following components are also included: power supply, battery, battery charger, connection cable and carrying bag.

Optune Pax delivers TTFields at 150 kHz to the entire abdominal cavity. The device's treatment parameters are preset by Novocure. No adjustments can be made to the device by the physician or patient. Patients are initially trained on the use of the device by a Novocure device support specialist (DSS). The patient should learn to switch out and recharge depleted device batteries, connect to an external power supply and replace the transducer arrays every 3-4 days according to the array layout recommended by you, their physician.

The physician should follow the *Clinical Practice Guidelines: Optimizing the transducer array layout in TTFields-treated patients (pancreatic malignancies)* to select the optimized layout for their patient. However, at their discretion, the physician may select an alternative configuration tailored to the patient's needs or may include more than one recommended layout in the prescription (For example, substituting large arrays with smaller ones for patients who prefer them).

Optune Pax is designed to accompany the patient throughout their daily activities for continuous treatment, with short breaks for personal needs, such as to shower or replace the arrays. Patients can carry the device and battery in the specially designed bag to receive continuous treatment without changing their daily routine.

Optune Pax should be used for at least 12 hours per day, on average.

4 PRINCIPLES OF OPERATION

Optune Pax produces TTFields within the human body through transducer arrays placed on the abdomen. TTFields physically disrupt the rapid cell division exhibited by cancer cells.[1] TTFields harness electric fields to arrest the proliferation of tumor cells and to destroy them. TTFields technology takes advantage of the special characteristics and geometrical shape of dividing cells, which make them susceptible to the effects of the TTFields. These special fields alter the tumor cell polarity at an intermediate frequency (on the order of 100-300 kHz). The frequency used for a particular treatment is specific to the cell type being treated (e.g., 150 kHz for pancreatic cancer).

In contrast, TTFields have not been shown to have an effect on cells that are not undergoing division. Since most normal adult cells proliferate very slowly, if at all, they are hypothesized to be little affected by TTFields. Testing demonstrates no differences between treated and control animals in histology of the major internal organs (including the lungs), blood examination, cardiac rhythm, body temperature, or in animal behavior. In addition, because the fields alternate so rapidly, they have no effect on normal quiescent cells nor do they stimulate nerves and muscles. It is noted that, because TTFields are only applied to the abdomen, they have no effect on rapidly proliferating cells in the rest of the body. The intensities of the electric fields within the tissues are very small and do not result in any meaningful increase in tissue temperature.

The above mechanisms of action are consistent with the extensive research regarding the effects of TTFields. These results demonstrate both disruption of cell division up to complete cessation of the process, as well as complete destruction of the dividing cells. In addition, various in vitro experiments have demonstrated abnormal mitotic process outcomes following TTFields application, which can lead to different forms of cellular death. Specifically, the abnormal chromosome segregation induced by TTFields can lead to mitotic cell death, or to the formation of abnormal daughter cells experiencing endoplasmic reticulum (ER) stress and autophagy, leading them to downstream immunogenic cell death. It is important to note that all the described effects can be obtained by fields of low intensity such that they are not accompanied by any significant elevation of temperature (Kirson et al. 2004; Giladi et al 2015).

5 PRECLINICAL DATA

TTFields have been shown in vitro to inhibit cancer cell replication during mitosis without any systemic side effects. At intensities of approximately 1 V/cm, TTFields can be frequency-tuned to inhibit different cancer cell types, due to disruption of microtubule polymerization and physical disruption of cell integrity at the cleavage plane during telophase.[2]

Specifically, TTFields have been shown to inhibit pancreatic cancer cells in vitro at a frequency of 150 kHz and an intensity of 1 V/cm. Based on realistic finite element mesh simulations, Novocure has concluded that therapeutic TTFields intensities can be generated in the abdomen of large animals and humans.

Using a model developed to simulate the growth kinetics of a malignant tumor, the minimal treatment course duration for TTFields has been determined to be approximately 4 weeks to reach tumor stabilization. Stopping treatment prior to completion of a 4 week treatment course will most likely lead to continued tumor growth and appearance of symptoms within approximately 1-2 weeks.

6 CLINICAL DATA

Pilot Clinical Study in Locally Advanced Pancreatic Cancer

The PANOVA study was a multicenter, non-randomized, open-label pilot study designed to assess the safety and preliminary effectiveness of TTFields therapy when used together with gemcitabine or gemcitabine + nab-paclitaxel (GnP) in advanced pancreatic adenocarcinoma (a mix of locally-advanced and metastatic patients). The primary endpoint was safety. Secondary endpoints were progression free survival (PFS), overall survival (OS) and usage rates of TTFields therapy. Forty (40) patients with advanced pancreatic cancer were enrolled. All patients had unresectable tumors, an ECOG performance score of 0-1, and no prior therapy. Study subjects received continuous daily TTFields at 150 kHz (18 hours per day recommended) to the abdomen together with standard doses of either gemcitabine or GnP per their approved package inserts. TTFields treatment continued until radiological disease progression, death or unacceptable device-related adverse events. Chemotherapy continued until disease progression, death or unacceptable toxicity.

The results of the pilot PANOVA study demonstrated the safety and effectiveness of TTFields therapy in an advanced pancreatic cancer population.

- Safety: In the TTFields + gemcitabine cohort, fourteen patients (70%) had serious adverse events (AEs) during the study period. Ten patients (50%) had treatment-related skin toxicity, of which only 2 were grade 3, and both resolved with appropriate treatment. No TTFields-related serious AEs were reported. In the TTFields+GnP cohort, ten patients (50%) had serious AEs during the study period. Eleven patients (55%) had treatment-related skin toxicity, of which 5 had grade 3 toxicity. No TTFields-related serious AEs were reported.

- Preliminary Efficacy: In the TTFields+gemcitabine cohort, the median PFS was 8.3 months (95% CI 4.3, 10.3). In locally-advanced patients specifically, the median PFS was 10.3 months. The median OS was 14.9 months (95% CI 6.2, NA) in the TTFields+gemcitabine cohort; 1-year survival rate was 55% (95% CI 29, 75). In locally-advanced patients specifically, the 1-year survival rate was 86%. In the TTFields+GnP cohort, the median PFS was 12.7 months (95% CI 5.4, NA). In locally-advanced patients specifically, the median PFS was not reached (PFS6 was 87.5%). Median OS was not reached for the TTFields+GnP cohort; the 1-year survival rate was 72% (95% CI 44, 88). In locally-advanced patients specifically, the 1-year survival rate was 87.5%.

- Device Usage: In the TTFields+GnP group, the median TTFields usage rate was 12.2 hours per day. The median TTFields usage rate in the gemcitabine alone cohort was 14 hours per day. In patients experiencing a grade 3 skin toxicity, there was a median decrease in daily usage of the device of 12.5% (3 hours).

Pivotal Clinical Study in Locally Advanced Pancreatic Cancer – The PANOVA-3 Study

Study Design: The PANOVA-3 study was a pivotal, randomized, open-label, two-arm, multi-center study evaluating the effectiveness and safety of Optune Pax concomitant with gemcitabine and nab-paclitaxel (GnP) for front-line treatment of locally advanced pancreatic cancer. GnP is approved for the treatment of pancreatic cancer, and is one of only a few accepted treatments for patients with locally-advanced pancreatic cancer. Gemcitabine and nab-paclitaxel were administered according to their approved package inserts in both study arms. Subjects in the study were randomized in a 1:1 ratio to receive TTFields together with GnP (TTFields+GnP Arm) or GnP (GnP Alone Arm). A total of 138 sites enrolled 571 subjects globally (285 in the TTFields+GnP Arm; 286 in the GnP Alone Arm).

Eligibility Criteria: The inclusion and exclusion criteria were as follows:

Inclusion Criteria

1. *18 years of age and older*
2. *Life expectancy of ≥3 months*
3. *Histological/cytological diagnosis of de novo adenocarcinoma of the pancreas*
4. *Unresectable, locally advanced stage disease according to the following criteria (per Al-Hawary MM, et al., Radiology 201413; NCCN Clinical Practice Guidelines in Oncology)*
   a. *Head/uncinate process:*
      i. *Solid tumor contact with SMA>180°*
      ii. *Solid tumor contact with the CA>180°*
      iii. *Solid tumor contact with the first jejunal SMA branch*
      iv. *Unreconstructible SMV/PV due to tumor involvement or occlusion (can be d/t tumor or bland thrombus)*
      v. *Contact with most proximal draining jejunal branch into SMV*
   b. *Body and tail:*
      i. *Solid tumor contact of >180° with the SMA or CA*
      ii. *Solid tumor contact with the CA and aortic involvement*
      iii. *Unreconstructible SMV/PV due to tumor involvement or occlusion (can be d/t tumor or bland thrombus)*
   c. *No distant metastasis, including non-regional lymph node metastasis*
   d. *No borderline resectable (per Al-Hawary MM, et al., Radiology 201413)*
5. *ECOG score 0-2*
6. *Amenable and assigned by the investigator to receive therapy with gemcitabine and nab-paclitaxel*
7. *Able to operate the NovoTTF-200T independently or with the help of a caregiver*
8. *Signed informed consent form for the study protocol*

Exclusion Criteria

1. *Prior palliative treatment (e.g. surgery, radiation) to the tumor*
2. *Cancer requiring anti-tumor treatment within the 5 years before inclusion, excluding treated stage I prostate cancer, in situ cervical or uterus cancer, in situ breast cancer and nonmelanomatous skin cancer*
3. *Serious co-morbidities:*
   a. *Clinically significant (as determined by the investigator) hematological, hepatic and renal dysfunction, defined as: Neutrophil count <1.5 x 109/L and platelet count <100 x 109/L; bilirubin >1.5 x Upper Limit of Normal (ULN); AST and/or ALT >2.5 x ULN; and serum creatinine >1.5 x ULN*
   b. *History of significant cardiovascular disease unless the disease is well controlled. Significant cardiac disease includes second/third degree heart block; significant ischemic heart disease; poorly controlled hypertension; congestive heart failure of the New York Heart Association (NYHA) Class II or worse (slight limitation of physical activity; comfortable at rest, but ordinary activity results in fatigue, palpitation or dyspnea)*

   c. *History of arrhythmia that is symptomatic or requires treatment. Subjects with atrial fibrillation or flutter controlled by medication are not excluded from participation in the study*
   d. *History of cerebrovascular accident (CVA) within 6 months prior to randomization or that is not stable*
   e. *Active infection or serious underlying medical condition that would impair the ability of the subject to receive protocol therapy*
   f. *History of any psychiatric condition that might impair subject's ability to understand or comply with the requirements of the study or to provide consent*
4. *Concurrent anti-tumor therapy beyond gemcitabine and nab-paclitaxel*
5. *Implantable electronic medical devices in the torso, such as pacemakers*
6. *Known severe hypersensitivities to medical adhesives or hydrogel, or to one of the chemotherapies used in this study*
7. *Pregnancy or breast-feeding (female subjects with reproductive potential and their partners must accept to use effective contraception throughout the entire study period and for 3 months after the end of treatment). All subjects who are capable of becoming pregnant must take a pregnancy test which is negative within 72 hours before beginning study drug administration. The definition of effective contraception is left up to the decision of the investigator*
8. *Unable to follow the protocol for medical, psychological, familial, geographic or other reasons*
9. *Admitted to an institution by administrative or court order*

Study Procedures:

TTFields+GnP Arm: Participants received Optune Pax together with gemcitabine and nab-paclitaxel (GnP). TTFields therapy was initiated within 7 days of randomization, and ± 3 days of administering GnP. Participants received uninterrupted multiple single month courses of continuous TTFields therapy. Treatment was to be stopped in cases of intolerable toxicity or disease progression in the abdomen ("local disease progression"). The recommended transducer array layout was determined by the investigator for each participant using the *Clinical Practice Guidelines-Layout Optimization in Pancreatic Malignancies*, which was developed to maximize TTFields intensity in the area of maximal disease burden in the abdomen (based on the patient's baseline CT scan). After being trained on how to use the device and place the arrays, participants continued TTFields therapy at home. Participants were instructed to replace the arrays two to three times per week. At array replacement, the skin was re-shaved if needed, and treated using topical steroids or antibiotic creams, if recommended. The concomitant chemotherapy, GnP, was administered as described below.

GnP Alone Arm: Participants received gemcitabine and nab-paclitaxel according to their approved package inserts. Gemcitabine was administered as follows: 1000 mg/m^2 over 30-minute infusion administered immediately after nab-paclitaxel on Days 1, 8 and 15 of each 28-day cycle, until radiological progression per RECIST V1.1, or unacceptable toxicity based on investigator assessment. Nab-paclitaxel was administered as follows: 125 mg/m^2 administered as an intravenous infusion over 30-40 minutes on Days 1, 8 and 15 of each 28-day cycle, until radiological progression per RECIST V1.1, or unacceptable toxicity based on investigator assessment.

Follow-Up: During the treatment period, participants were seen every four weeks until local disease progression, with the following assessments performed: concomitant medication recording, ECOG performance status, physical examination (including vital signs), complete blood count including differential, serum chemistry including CA-19-9, AE and device deficiency collection and recording, documentation of ascitic fluid drainage (if applicable), pain assessment using VAS and device usage time assessment (only for subjects in the TTFields+GnP Arm). In addition, every eight weeks, the following assessments were performed until local disease progression: CT/MRI scan of the chest and abdomen, assessment of local and distant disease status per RECIST v1.1. Furthermore, EORTC QLQ C30 questionnaires with the PAN26 addendum were completed by the participating subjects. In addition, bone scan and/or CT/MRI of the brain were performed if clinically indicated. One month following treatment discontinuation, the following assessments were performed: concomitant medications recording, ECOG performance status, physical examination (including vital signs), complete blood count including differential, serum chemistry panel including CA-19-9, AE and device deficiency collection and recording and documentation of ascitic fluid drainage were performed during this visit. In addition, following local disease progression, telephone follow-up was conducted every four weeks for survival status until study completion or death.

Analyses: Primary and secondary effectiveness endpoints were analyzed in the ITT (Intent-to-Treat) and modified Per Protocol (mPP)[1] populations. The ITT population includes all 571 randomized participants (285 in the TTFields+GnP arm and 286 in the GnP Alone arm). The mPP population includes only those participants who received at least one cycle of GnP (as defined in the approved Package Inserts) (both arms), and for the TTFields+GnP Arm, also received at least 4 weeks (28 days) of TTFields therapy (198 in the TTFields+GnP arm and 207 in the GnP Alone arm). Safety endpoints were analyzed in the Safety population, which included all 547 randomized participants who received any amount of TTFields or GnP treatment (274 participants in the TTFields+GnP arm, and 273 participants in the GnP Alone arm).

Protocol Deviations: Protocol deviations were categorized per the definitions set forth in the ICH E3 Guideline. Of the deviations categorized as "Major and Important", eleven were identified as deviations with the potential to impact study outcomes and/or subject safety, and involved either enrollment of patients who did not meet the eligibility criteria or incorrect dose or administration timing of a study treatment. Following a careful evaluation, it was determined that these deviations did not impact study outcomes and/or subject safety. Overall, protocol deviations were generally balanced between the two arms. The majority of protocol deviations involved failure to report SAEs within 24 hours or missed/out of window assessments that in many cases were included at future visits, allowing for an appropriate clinical and safety evaluation during the study period.

Participant Demographics and Baseline Characteristics: Demographics and baseline characteristics were well balanced between treatment groups. Overall, participants' median age was 67 years (range: 31-90 years), with 3.9% ECOG performance score of 2, 57.6% with score of 1 and 38.5% with score of 0. The median time from diagnosis to study enrollment was 3.6 weeks (range: 0.1- 53.7).

[1] *Referred to as the Modified Intent-to-Treat (mITT) population in the PANOVA-3 protocol and SAP.*

Demographics and Baseline Characteristics – ITT Population

	TTFields + GnP (N=285)	GnP Alone (N=286)	Overall (N=571)
Age (Years) Median (range)	67 (31, 90)	67.5 (40, 88)	67 (31, 90)
Gender, n (%)			
Male	147 (51.6)	125 (43.7)	272 (47.6)
Female	138 (48.4)	161 (56.3)	299 (52.4)
Race, n (%)			
American Indian or Alaska Native	9 (3.2)	4 (1.4)	13 (2.3)
Asian	44 (15.4)	44 (15.4)	88 (15.4)
Black or African American	16 (5.6)	14 (4.9)	30 (5.3)
Native Hawaiian or Other Pacific Islander	0	0	0
White	202 (70.9)	204 (71.3)	406 (71.1)
Other	3 (11)	5 (1.7)	8 (1.4)
Not Reported	11 (3.9)	15 (5.2)	26 (4.6)
Ethnicity, n (%)			
Hispanic or Latino	32 (11.2)	22 (7.7)	54 (9.5)
Not Hispanic or Latino	238 (83.5)	247 (86.4)	485 (84.9)
Not Reported/Unknown	15 (5.3)	17 (5.9)	32 (5.6)
Region, n (%)			
North America	123 (43.2)	125 (43.7)	248 (43.4)
Eastern Europe	43 (15.1)	42 (14.7)	85 (14.9)
Western Europe and Israel	62 (21.8)	61 (21.3)	123 (21.5)
Rest of the World	57 (20.0)	58 (20.3)	115 (20.1)
ECOG Performance Status, n (%)			
0	109 (38.2)	111 (38.8)	220 (38.5)
1	166 (58.2)	163 (57.0)	329 (57.6)
2	10 (3.5)	12 (4.2)	22 (3.9)
BMI Group, n (%)			
< 25 kg/m^2	166 (58.2)	174 (60.8)	340 (59.5)
≥ 25 kg/m^2	117 (41.1)	108 (37.8)	225 (39.4)
CA-19.9, n (%)			
Low (≤37 U/mL)	48 (16.8)	44 (15.4)	92 (16.1)
Moderate (38-1,000 U/mL)	140 (49.1)	152 (53.1)	292 (51.1)
High (>1,000 U/mL)	88 (30.9)	79 (27.6)	167 (29.2)
Untested	9 (3.2)	11 (3.8)	20 (3.5)
Target Lesion Site, n (%)			
Head of Pancreas	164 (57.5)	160 (55.9)	324 (56.7)
Body of Pancreas	82 (28.8)	81 (28.3)	163 (28.5)
Tail of Pancreas	9 (3.2)	19 (6.6)	28 (4.9)
Other	55 (19.3)	49 (17.1)	104 (18.2)
Multiple regions in pancreas	26 (9.1)	22 (7.7)	48 (8.4)
Extra-pancreatic	29 (10.2)	27 (9.4)	56 (9.8)

Pancreatic Cancer History – ITT Population

	TTFields + GnP (N=285)	GnP Alone (N=286)	Overall (N=571)
Time Since Initial Pathological Diagnosis (weeks) Median (range)	3.7 (0.1, 53.7)	3.6 (0.1, 21.4)	3.6 (0.1, 53.7)

Histologic Subtype at Baseline – ITT Population

Histology at Baseline	TTFields + GnP (N=285)	GnP Alone (N=286)
	n (%)	
Pancreatic Adenocarcinoma, Not Otherwise Specified	251 (88)	258 (90)
Adenosquamous carcinoma	2 (1)	1 (0.3)
Ductal adenocarcinoma	27 (9)	24 (8)
Histology not further specified	5 (2)	3 (1)

Treatment exposure to GnP was similar between the two arms, both in terms of number of cycles received and duration of exposure. Median duration of TTFields exposure was similar, at 27.6 weeks, with average daily usage 59.3%, and median daily usage 62.1%. The most common reason for discontinuation of concomitant treatments in both arms was disease progression or clinical deterioration. The most common reason for TTFields discontinuation was local disease progression.

Exposure to GnP by Study Arm (Safety Population)

	TTFields + GnP (N=274)	GnP Alone (N=273)
Gemcitabine Number of Cycles Received Median (range) **Duration of Exposure (weeks)** Median (range)	6.0 (1.0, 57.0) 24.1 (0.1, 232.4)	6.0 (1.0, 30.0) 22.1 (0.1, 134.1)
Nab-paclitaxel Number of Cycles Received Median (range) **Duration of Exposure (weeks)** Median (range)	6.0 (1.0, 57.0) 23.0 (0.1, 232.4)	5.0 (1.0, 30.0) 21.4 (0.1, 134.1)

TTFields Therapy Usage Duration (Safety Population)

	TTFields + GnP (N=274)
Duration of Exposure (weeks)	
Median (range)	27.6 (0.1, 234.4)
Average Usage	
Mean (SD)	59.3 (21.2)
Median (range)	62.1 (0, 99)
Average Usage, (%)	
≤75%	200 (73.0)
>75%	74 (27.0)

Effectiveness Results:

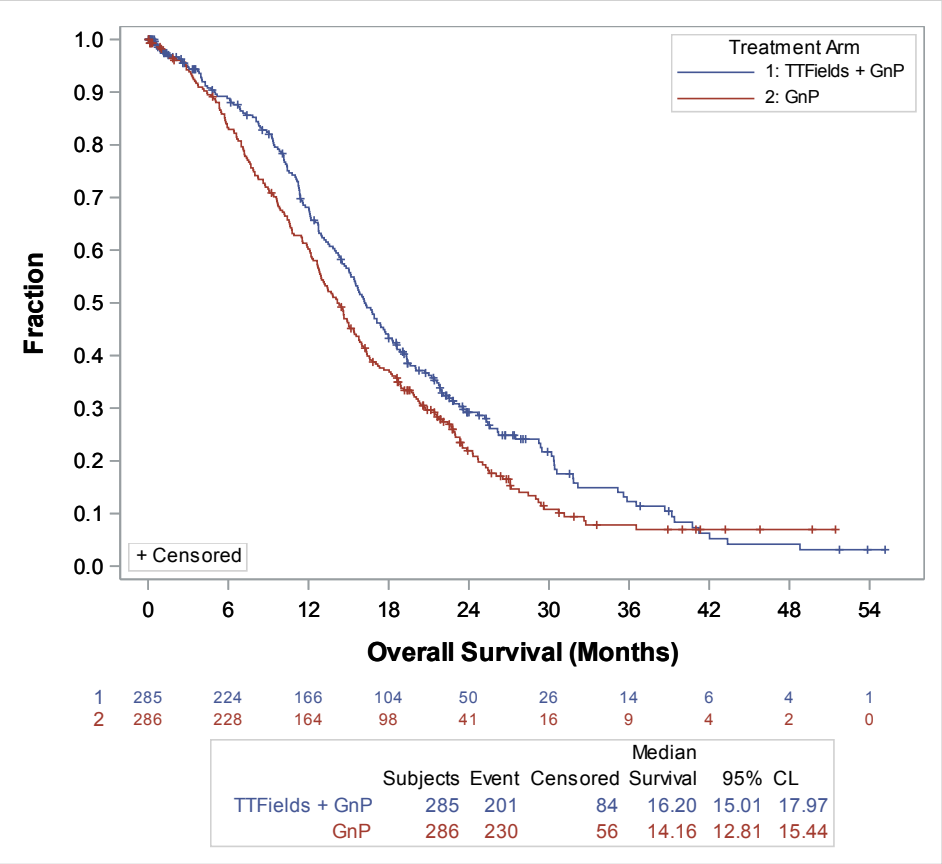
Analysis Populations

- Intent to Treat (ITT): All randomized patients, regardless of whether the treatment was received. The ITT population consists of 285 patients in the TTFields+GnP arm and 286 patients in the GnP Alone arm.
- Modified Per Protocol (mPP): All patients who received at least one cycle of GnP (as defined in the approved Package Inserts) (both arms) and at least 4 weeks (28 days) of TTFields therapy (in the TTFields+GnP arm). The mPP population consists of 198 patients in the TTFields+GnP arm and 207 patients in the GnP Alone arm.

Primary Endpoint – Overall Survival (OS)

Overall Survival (ITT): Overall survival was measured from the date of randomization to the date of death (in months). At the time of analysis, patients lost to follow-up or still on protocol follow-up were censored at the last date when they were known to be alive. The OS at the final analysis in the ITT population met the threshold for statistical significance which was pre-defined as p=0.04794. A statistically significant difference in the OS distribution between study arms was observed (log-rank P=0.039). The median OS in the TTFields+GnP arm was 16.2 months (95% CI 15.0-18.0) compared to 14.2 months (95% CI 12.8-15.4) in the GnP Alone arm. A 2-month improvement in median OS was observed in favor of the TTFields+GnP arm. The hazard ratio (HR) for OS was 0.82 (95% CI 0.68 – 0.99). A descriptive analysis of the Kaplan-Meier overall survival curves showed an early separation between the TTFields+GnP and GnP Alone arms, which was maintained at multiple time points.

Overall Survival (ITT)

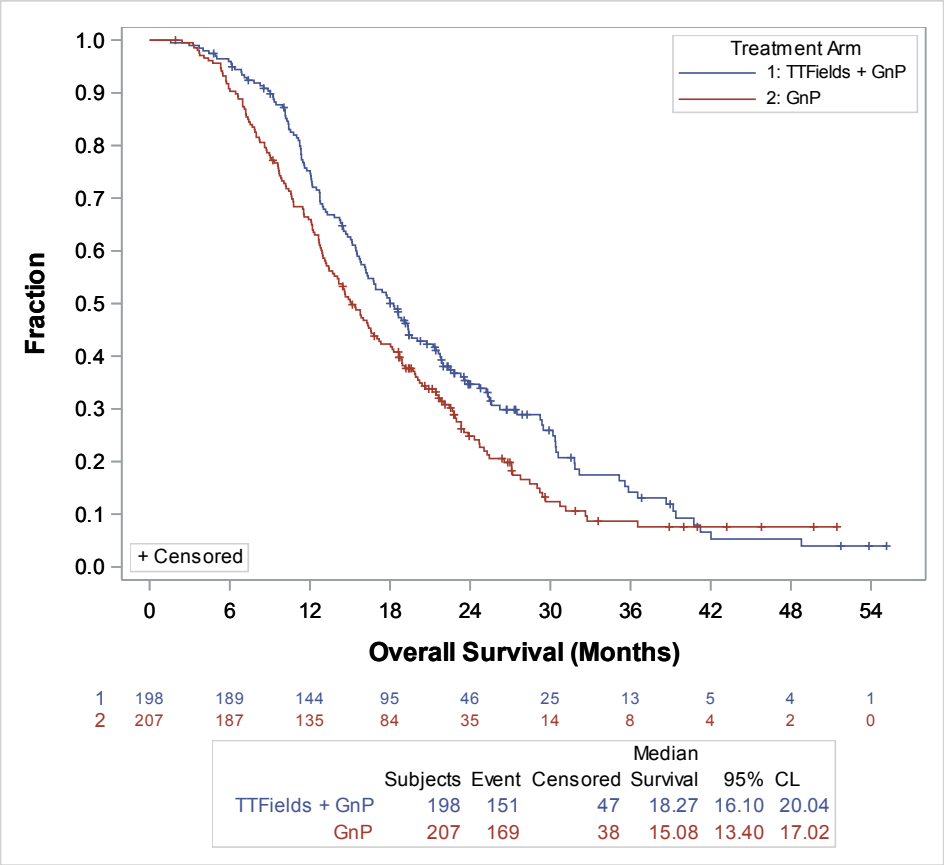


	TTFields + GnP (N=285)	GnP Alone (N=286)	% Improvement*
Overall Survival Rate % (95% CI)			
6 Months	88.8 (84.3, 92.1)	83.3 (78.3, 87.2)	6.6
9 Months	82.4 (77.1, 86.6)	71.6 (65.9, 76.5)	15.1
12 Months	68.1 (62.0, 73.5)	60.2 (54.2, 65.7)	13.1
24 Months	29.2 (23.4, 35.2)	21.9 (16.9, 27.3)	33.3
36 Months	12.3 (7.6, 18.2)	7.8 (4.4, 12.5)	NE
42 Months	6.3 (2.8, 11.7)	7.0 (3.7, 11.6)	NE
48 Months	4.2 (1.5, 9.2)	7.0 (3.7, 11.6)	NE
54 Months	3.1 (0.9, 7.8)		NE
Log Rank P-value	0.039		
Hazard Ratio (95% CI)	0.82 (0.68, 0.99)		

*Improvement not calculated for groups with N < 10; NE = Not Estimated

Overall Survival (mPP): OS was also analyzed in the mPP population. The median OS in the TTFields+GnP Arm was 18.3 months (95% CI 16.1-20.0) compared to 15.1 months (95% CI 13.4-17.0) in the GnP Alone Arm. A statistically significant difference in the overall survival distribution between treatment arms was observed (log-rank P=0.023). A 3.2 months improvement in median OS was observed in favor of the TTFields+GnP arm. The HR for OS was 0.77 (95% CI 0.62-0.97). A descriptive analysis of the Kaplan–Meier overall survival curves showed an early separation between the TTFields+GnP and GnP Alone arms, which was maintained at multiple time points.

Overall Survival (mPP)



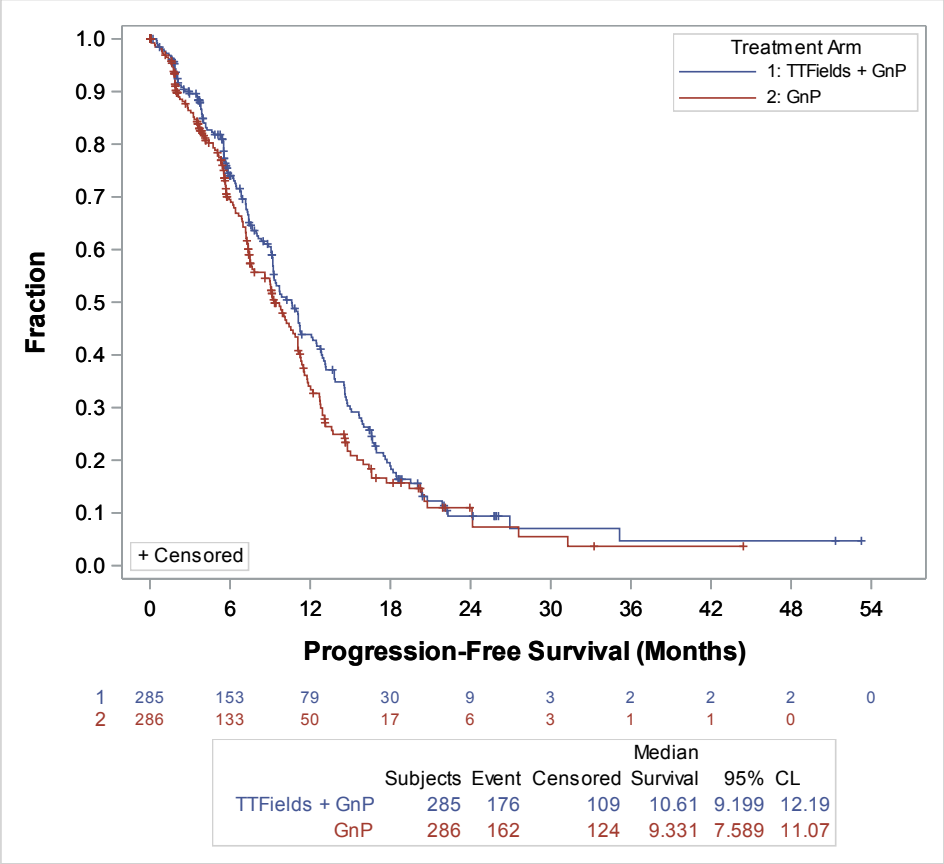
	TTFields + GnP (N=198)	GnP Alone (N=207)	% Improvement*
Overall Survival Rate % (95% CI)			
6 Months	96.0 (92.1, 98.0)	90.8 (85.9, 94.0)	5.7
9 Months	90.3 (85.3, 93.7)	78.2 (71.9, 83.2)	15.6
12 Months	75.2 (68.5, 80.7)	65.9 (59.0, 72.0)	14.0
24 Months	34.7 (27.8, 41.7)	24.8 (18.8, 31.3)	39.7
36 Months	14.2 (8.5, 21.3)	8.7 (4.6, 14.3)	NE
42 Months	6.6 (2.7, 13.0)	7.6 (3.8, 13.2)	NE
48 Months	5.3 (1.9, 11.4)	7.6 (3.8, 13.2)	NE
54 Months	4.0 (1.1, 9.8)		NE
Log Rank 2-sided P-value	0.023		
Hazard Ratio (95% CI)	0.77 (0.62, 0.97)		

*Improvement not calculated for groups with N < 10; NE = Not Estimated

Key Secondary Endpoint – Progression Free Survival (PFS)

Progression Free Survival (ITT): Treatment with TTFields+GnP showed no statistically significant improvement in PFS compared to GnP Alone (logrank test p = 0.137). The hazard ratio was 0.85 (95% CI 0.68 – 1.05). Median PFS was 10.6 months (95% CI: 9.2 – 12.2) with TTFields+GnP compared to 9.3 months (95% CI: 7.6 – 11.1) with GnP Alone.

Progression Free Survival (ITT)

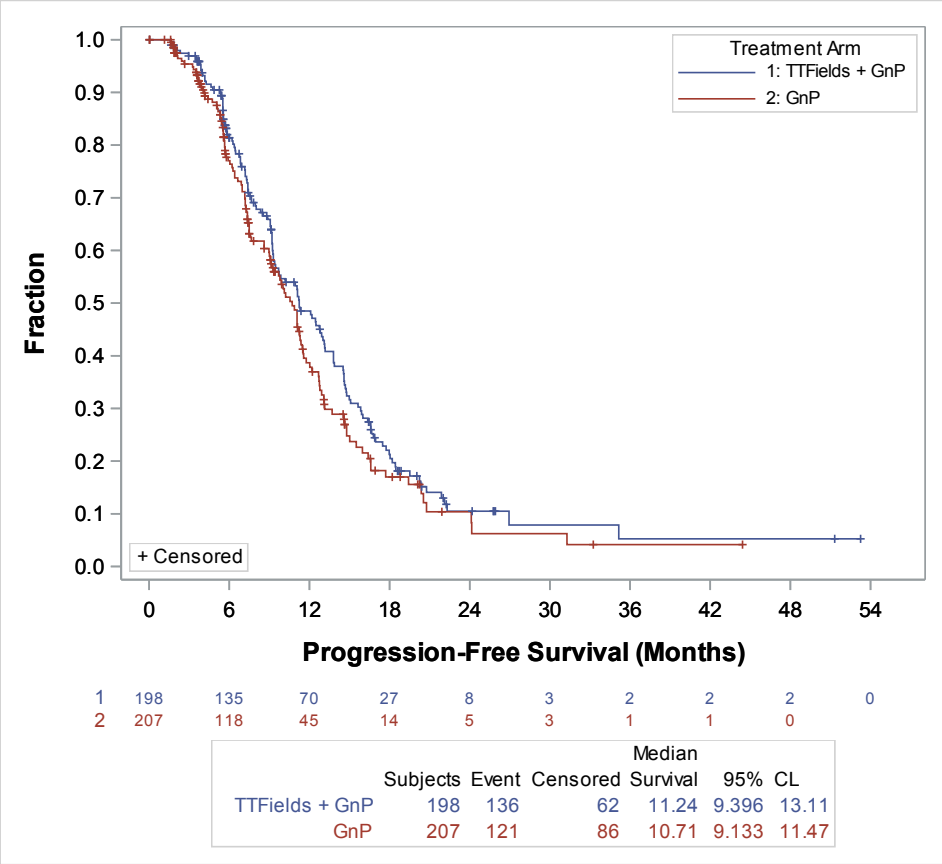


	TTFields + GnP (N=285)	GnP Alone (N=286)	% Improvement*
Progression-Free Rate % (95% CI)			
6 Months	74.0 (67.9, 79.2)	69.5 (63.0, 75.1)	6.5
9 Months	60.5 (53.7, 66.7)	54.0 (46.9, 60.5)	12.2
12 Months	43.9 (36.9, 50.6)	34.1 (27.1, 41.2)	28.8
24 Months	13.3 (7.6, 20.7)	16.4 (9.9, 24.3)	NE
36 Months	6.7 (1.7, 16.4)	5.7 (1.3, 15.2)	NE
42 Months	6.7 (1.7, 16.4)	5.7 (1.3, 15.2)	NE
48 Months	6.7 (1.7, 16.4)	0	NE
Log Rank 2-sided P-value	0.137		
Hazard Ratio (95% CI)	0.85 (0.68, 1.05)		

*Improvement not calculated for groups with N < 10; NE = Not Estimated

Progression-Free Survival (mPP): In the mPP population, the median progression-free survival (PFS) per RECIST v1.1 was 11.2 months (95% CI: 9.4–13.1) in participants treated with TTFields + GnP, compared to 10.7 months (95% CI: 9.1–11.5) with GnP Alone (HR: 0.84; 95% CI: 0.66–1.08; log-rank P = 0.183).

Progression Free Survival (mPP)



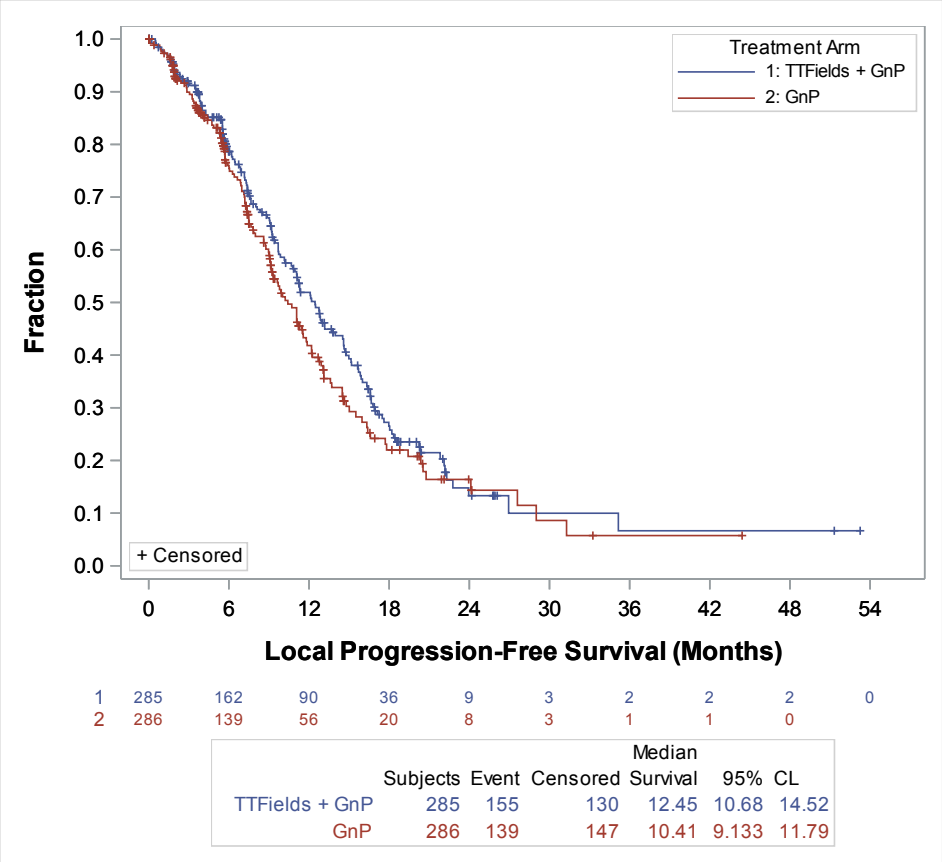
	TTFields + GnP (N=198)	GnP Alone (N=207)	% Improvement*
PFS Survival Rate % (95% CI)			
6 Months	81.4 (74.9, 86.3)	77.0 (70.0, 82.6)	5.7
9 Months	65.9 (58.2, 72.5)	59.6 (51.5, 66.8)	10.5
12 Months	48.5 (40.5, 56.0)	38.7 (30.5, 46.8)	25.4
24 Months	10.5 (5.6, 17.1)	10.4 (4.9, 18.2)	NE
36 Months	5.2 (1.3, 13.3)	4.2 (0.9, 11.7)	NE
42 Months	5.2 (1.3, 13.3)	4.2 (0.9, 11.7)	NE
48 Months	5.2 (1.3, 13.3)	0	NE
Log Rank 2-sided P-value	0.183		
Hazard Ratio (95% CI)	0.84 (0.66, 1.08)		

*Improvement not calculated for groups with N < 10; NE = Not Estimated

Additional Secondary Effectiveness Endpoints

Local Progression Free Survival (ITT): Median local PFS according to RECIST v1.1 was 12.5 months (95% CI: 10.7-14.5) in the TTFields+GnP alone arm compared to 10.4 months (95% CI: 9.1 – 11.8) in the GnP alone arm; HR 0.84 (95% CI: 0.67 – 1.06).

Local Progression-Free Survival (ITT)

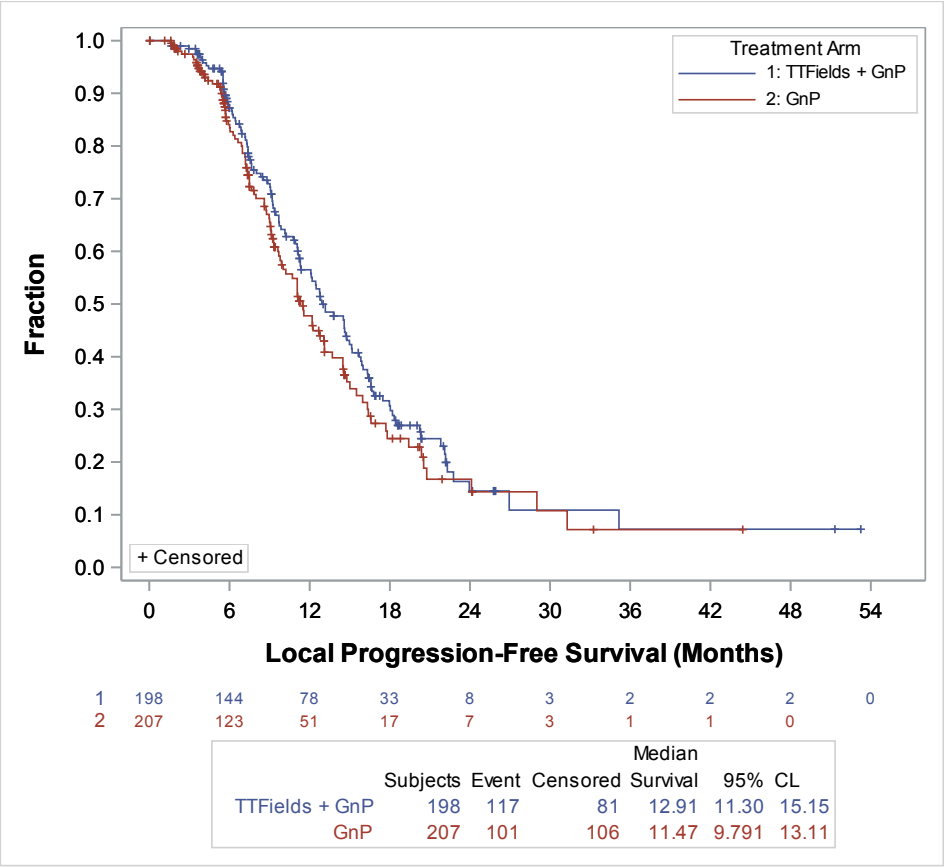


	TTFields + GnP (N=285)	GnP Alone (N=286)	% Improvement*
Local Progression-Free Rate % (95% CI)			
6 Months	78.7 (72.8, 83.4)	76.0 (69.8, 81.1)	3.5
9 Months	66.1 (59.3, 72.0)	59.5 (52.2, 66.1)	11.0
12 Months	51.9 (44.8, 58.6)	41.8 (34.2, 49.2)	24.2
24 Months	13.3 (7.6, 20.7)	16.4 (9.9, 24.3)	NE
36 Months	6.7 (1.7, 16.4)	5.7 (1.3, 15.2)	NE
42 Months	6.7 (1.7, 16.4)	5.7 (1.3, 15.2)	NE
48 Months	6.7 (1.7, 16.4)	0	NE
Hazard Ratio (95% CI)	0.84 (0.67, 1.06)		

*Improvement not calculated for groups with N < 10; NE = Not Estimated

Local Progression Free Survival (mPP): Treatment with TTFields + GnP resulted in a median local PFS of 12.9 months (95% CI: 11.3 – 15.1) compared to 11.5 months (95% CI: 9.8 – 13.1) with GnP Alone (HR 0.84 [95% CI 0.64 – 1.10]).

Local Progression-Free Survival (mPP)



	TTFields + GnP (N=198)	GnP Alone (N=207)	% Improvement*
Local Progression-Free Survival Rate % (95% CI)			
6 Months	87.2 (81.4, 91.3)	84.1 (77.6, 88.8)	3.7
9 Months	72.8 (65.4, 78.9)	66.2 (58.0, 73.2)	9.9
12 Months	56.5 (48.3, 63.9)	47.8 (39.0, 56.0)	18.3
24 Months	14.5 (7.8, 23.1)	16.7 (9.1, 26.3)	NE
36 Months	7.2 (1.8, 18.0)	7.2 (1.7, 18.2)	NE
42 Months	7.2 (1.8, 18.0)	7.2 (1.7, 18.2)	NE
48 Months	7.2 (1.8, 18.0)	0	NE
Hazard Ratio (95% CI)	0.845 (0.64, 1.10)		

*Improvement not calculated for groups with N < 10; NE = Not Estimated

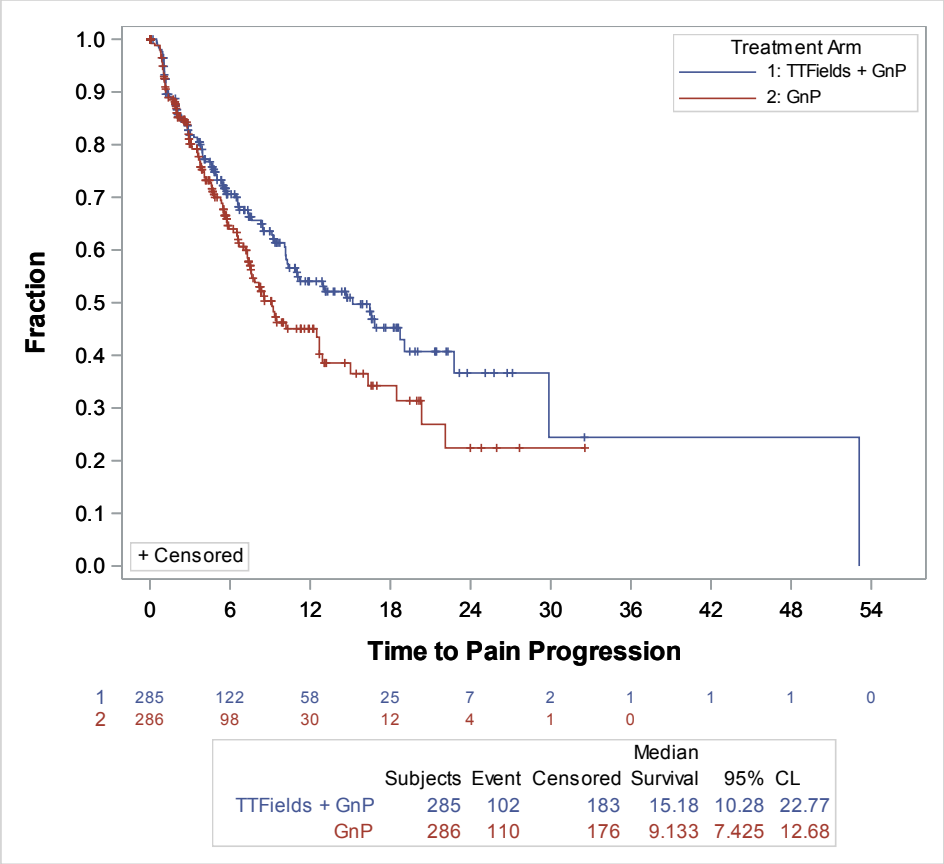
Objective Response Rate (ITT and mPP): Analysis of the ORR was performed based on disease evaluation by the investigator according to RECIST v1.1. In the ITT population, which included 244 participants in the TTFields+GnP Arm and 243 participants in the GnP Alone Arm who had at least one evaluable CT scan after baseline, complete and partial responses in the TTFields+GnP Arm were observed in 3 (1.2%) and 85 (34.8%) participants, respectively, compared to 0 (0%) and 73 (31%) participants, respectively in the GnP Alone Arm. The ORR was 36.1% in the TTFields+GnP Arm compared to 30.0% in the GnP Alone Arm.

In the mPP population, which included 196 participants in the TTFields+GnP Arm and 202 participants in the GnP Alone Arm who had at least one evaluable post-baseline CT scan, complete and partial responses in the TTFields+GnP arm were observed in 3 (1.5%) and 77 (39.8%) participants, respectively, and 0 (0%) and 68 (33.7%), respectively, in the GnP Alone Arm. The ORR was 41.3% in the TTFields+GnP Arm compared to 33.7% of the GnP Alone Arm.

Time to Pain Progression (ITT): Time to pain progression was defined as the duration between the time of randomization until a greater than or equal to twenty-point increase from baseline in a patient self-reported visual analogue scale (VAS) was recorded or death, whichever occurred first. In accordance with the study protocol, patients who experienced local disease progression were no longer followed for pain progression (67/285 patients in the TTFields + GnP arm and 56/286 patients in the GnP alone arm).

The following estimate treats missing evaluations due to discontinued assessment as censored (i.e., pain progression or death are considered as independent of local disease progression) in Kaplan Meier estimate. Median time to pain progression was 15.2 months [95% CI: 10.3-22.8] in the TTFields+GnP arm and 9.1 months [95% CI: 7.4-12.7] in the GnP alone arm. Because a large number of patients stopped pain assessments after local disease progression, this censoring approach can lead to an overestimation, as evidenced below at timepoints beyond 30 months, where the pain progression rates (estimated to be above 20%) are higher than the 10% overall survival observed in both arms at the same timepoint.

Time to Pain Progression (ITT)



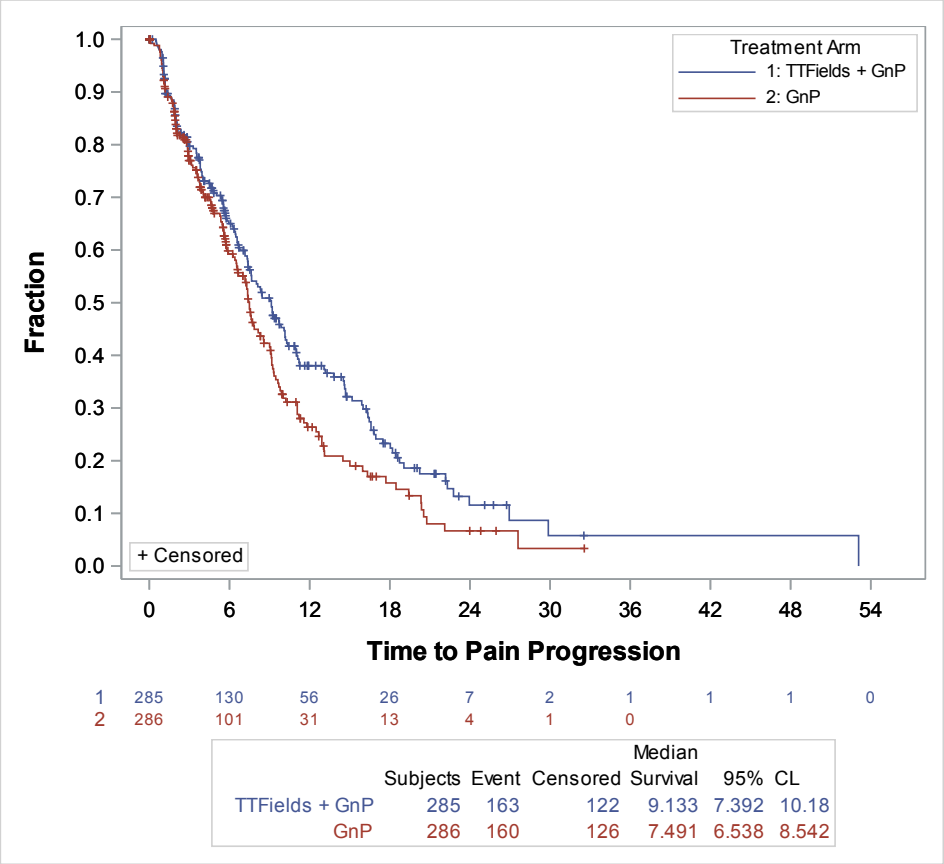
	Subjects	Event	Censored	Median Survival	95% CL	
TTFields + GnP	285	102	183	15.18	10.28	22.77
GnP	286	110	176	9.133	7.425	12.68

	TTFields + GnP (N=285)	GnP Alone (N=286)	% Improvement*
Time to Pain Progression Rate % (95% CI)			
6 Months	70.6 (64.1, 76.1)	64.0 (57.0, 70.2)	10.3
9 Months	63.6 (56.5, 69.8)	50.3 (42.4, 57.7)	26.4
12 Months	54.1 (46.2, 61.3)	45.1 (36.8, 53.0)	20.0
24 Months	36.6 (25.2, 48.2)	22.4 (11.1, 36.2)	NE
36 Months	24.4 (7.4, 46.5)	0	NE
42 Months	24.4 (7.4, 46.5)	0	NE
48 Months	24.4 (7.4, 46.5)	0	NE
Hazard Ratio (95% CI)	0.74 (0.56, 0.97)		

*Improvement not calculated for groups with N < 10; NE = Not Estimated

When local disease progression and death are treated as an event in the Kaplan Meier estimate, median time to pain progression before local progression or death was 9.1 months [95% CI: 7.4 – 10.2] in the TTFields+GnP arm and 7.5 months [95% CI: 6.5 – 8.5] in the GnP alone arm. Although the difference in median values was smaller, the overall pattern showed a delay in pain progression in patients treated with TTFields+GnP compared with GnP alone (HR=0.76, 95% CI: 0.61–0.95).

Time to Pain Progression (ITT) Including Local Disease Progression



	TTFields + GnP (N=285)	GnP Alone (N=286)	% Improvement*
Time to Pain Progression Rate % (95% CI)			
6 Months	65.0 (58.4, 70.8)	59.2 (52.3, 65.5)	9.7
9 Months	50.9 (43.9, 57.4)	42.3 (35.1, 49.3)	20.3
12 Months	38.0 (31.2, 44.8)	26.4 (19.7, 33.5)	44.2
24 Months	11.6 (6.1, 18.9)	6.7 (2.7, 13.1)	73.4
36 Months	5.8 (1.5, 14.7)	0	NE
42 Months	5.8 (1.5, 14.7)	0	NE
48 Months	5.8 (1.5, 14.7)	0	NE
Hazard Ratio (95% CI)	0.76 (0.61, 0.95)		

*Improvement not calculated for groups with N < 10; NE = Not Estimated

Puncture Free Survival (ITT):

Patients who experienced local disease progression were not evaluated for this endpoint post-progression (93/285 and 70/286 subjects in TTFields+GnP and GnP alone arms). In the puncture-free survival analysis, patients who discontinued assessments following local disease progression were censored at the time of discontinuation. Using this approach, median puncture-free survival was 22.8 months [95% CI: 15.5-NE] in the TTFields+GnP arm and 16.6 months [95% CI: 13.1-NE] in the GnP alone arm. However, because patients who discontinued the study due to local progression were no longer followed, resulting in reduced follow-up time and incomplete capture of subsequent puncture events, this analysis approach can lead to an overestimation, at timepoints beyond 30 months, where puncture-free survival rates are 40% and 30% in the TTFields+GnP and GnP alone arms, respectively, while the estimated median puncture free survival times (22.8 in TTFields + GnP arm and 16.6 in GnP arm) are much higher than median Overall Survival time (16.2 months in TTFields + GnP arm and 14.2 in GnP arm). When local disease progression is also treated as an event in the Kaplan-Meier estimate, the median puncture-free survival is 12.75 months [95% CI: 10.7-14.5] in the TTFields+GnP arm and 11.07 months [95% CI: 9.3-12.7] in the GnP alone arm.

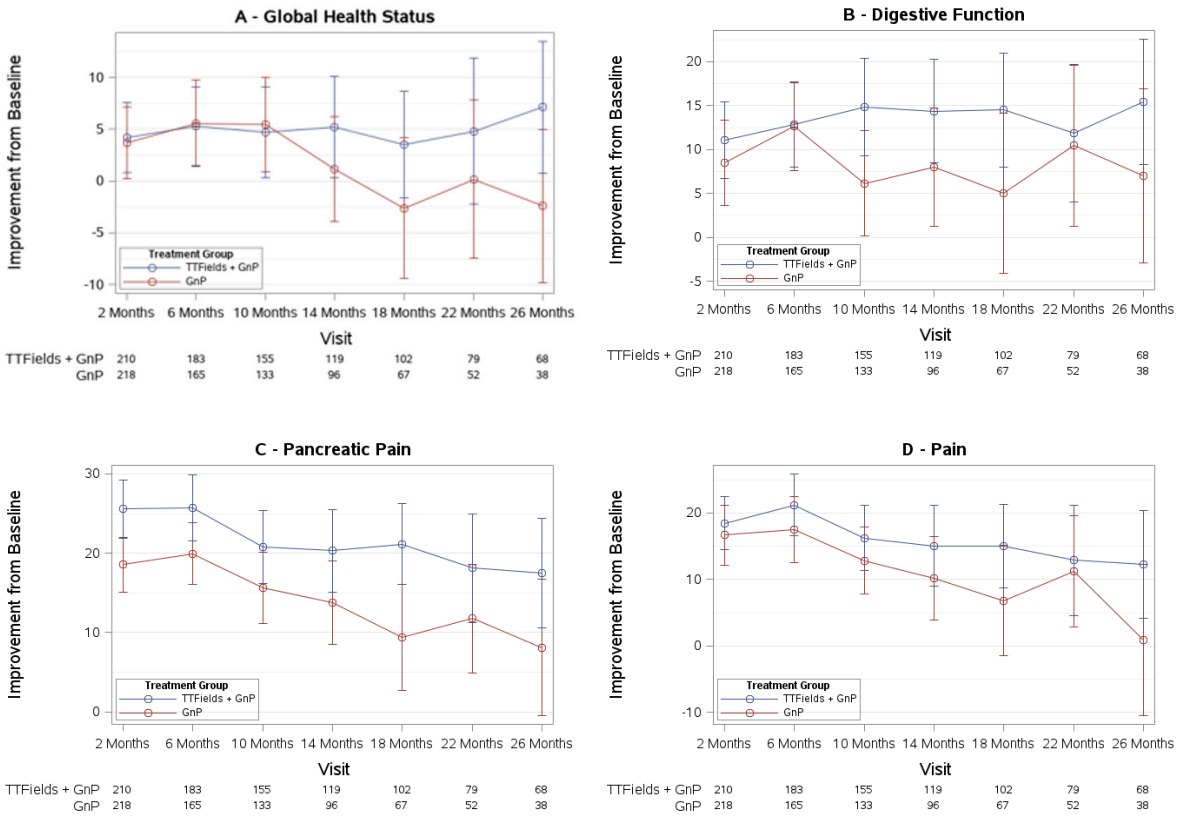
Resectability Rate (ITT): The resectability rates were 7.0% and 10.1% in the TTFields+GnP Arm and GnP Alone Arm, respectively.

Quality of Life (ITT): Quality of Life (QoL) was measured at baseline and every 8 weeks using the EORTC QLQ C-30 questionnaire and PAN26 module (Pancreatic Cancer), and compared between groups for each scale from the questionnaire.

Mean and median baseline QoL scores were comparable between the two arms for all scales/items. The deterioration free survival (DFS) in health-related quality of life or death (defined as the time between randomization and first deterioration in HRQoL score ≥ 10-point with no further improvement in HRQoL score ≥ 10 points), was estimated by Kaplan-Meier methodology using a two-sided stratified Cox Proportional Hazard model. The addition of TTFields to GnP resulted in longer DFS in global health status, pain, pancreatic pain and most of the digestive problems. Similar trends were observed for emotional function and fatigue/lack of energy.

Subjects who experienced local disease progression were not evaluated for Quality of Life endpoints following progression. Consequently, these results do not capture the quality of life status of patients with local disease progression. Notably, analyses that accounted for local disease progression showed consistent trends across the same QoL domains.

Improvement from Baseline Health-Related Quality of Life (ITT)

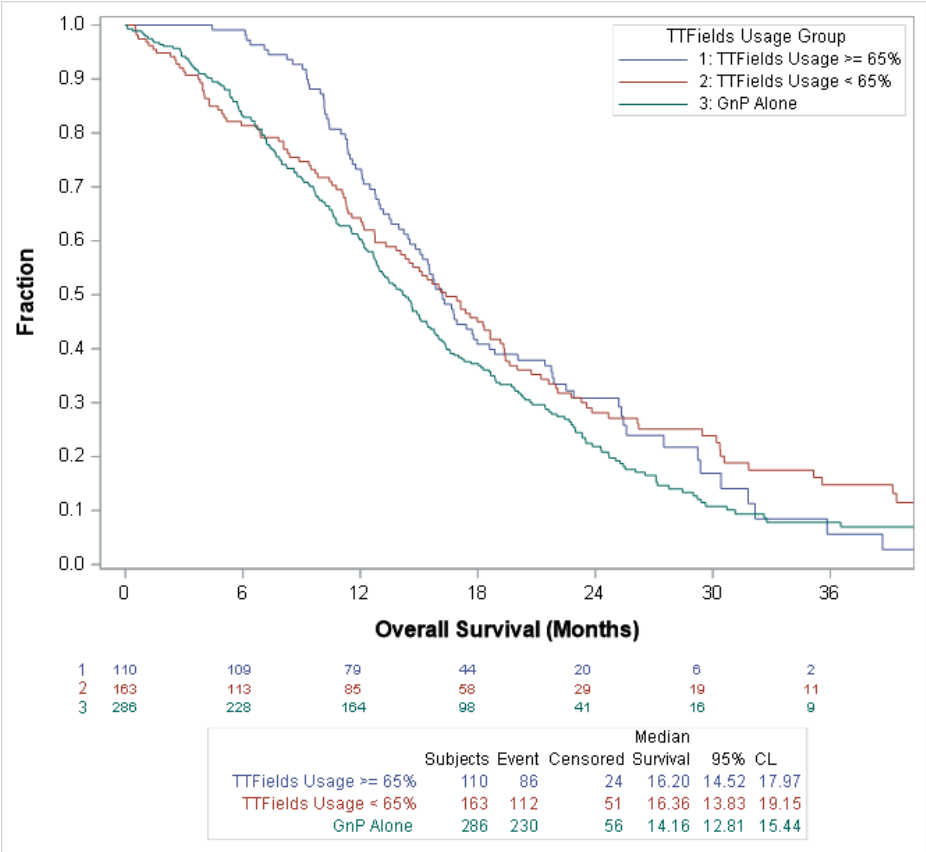


Pain Medication Use (ITT) (Post-Hoc): The pain medication consumption analysis found that overall pain medication use (in terms of type of medications and grade of impact on pain) was similar between study arms, with approximately half of all subjects receiving pain medications of meaningful grade. However, a longer time to first use of pain medication was observed in the TTFields+GnP arm, compared to the GnP Alone arm.

Opioid Medication Use (ITT) (Post Hoc): The opioid medication consumption analysis found that overall opioid medication exposure (in terms of opioid types and frequency of exposure) was similar between study arms, with approximately half of all subjects receiving at least one dose of an opioid throughout the study. However, a trend of longer time to first use of opioid pain medication was observed in the TTFields+GnP arm, compared to the GnP Alone arm.

TTFields Therapy Usage: The impact of TTFields usage on OS was explored for participants with TTFields usage of ≥65% vs <65% during the first 3 months of treatment. The HR for participants using TTFields therapy ≥65% compared to the GnP Alone was 0.79 (95% CI 0.6157-1.03).

OS by TTFields Usage in the First 3 Months (ITT)



	TTFields Usage ≥ 65% (N=110)	GnP Alone (N=286)	% Improvement*
Survival Rate % (95% CI)			
6 Months	99.1 (93.7, 99.9)	83.3 (78.3, 87.2)	19.0
9 Months	92.7 (86.0, 96.3)	71.6 (65.9, 76.5)	29.5
12 Months	73.3 (63.9, 80.6)	60.2 (54.2, 65.7)	21.7
24 Months	30.9 (22.1, 40.0)	21.9 (16.9, 27.3)	40.8
36 Months	5.6 (1.2, 15.7)	7.8 (4.4, 12.5)	NE
Hazard Ratio (95% CI)	0.79 (0.61; 1.03)		

*Improvement not calculated for groups with N < 10; NE = Not Estimated

Safety Results: Overall, TTFields therapy was well-tolerated, with no exacerbation of GnP-related systemic toxicity, no new safety signals, and comparable SAE between study arms. Most TTFields-treated patients experienced the expected device-related skin toxicity under the arrays (76.3% of the TTFields-treated participants). The majority of these events were low grade (Grade 1-2), with 21 (7.7%) experiencing a Grade ≥3 event. The most common device-related AE not related to skin toxicity was fatigue, reported in 14 participants (5.1%). There was one Grade 4 AEs suspected to be related to the device by the investigator, which was a non-serious event of neutrophil count decrease. There were no device-related AEs that led to death, and no unanticipated device-related safety issues during the course of the study.

AEs by Severity Per CTCAE Version 4.03 or Modified Grading for Skin AEs (Safety)

Severity	TTFields + GnP (N=274) n (%)	GnP Alone (N=273) n (%)	Overall (N=547) n (%)
Number of Subjects with at least one AE	268 (97.8)	270 (98.9)	538 (98.4)
Subjects with AE by Maximum CTCAE Grade			
Grade 1	4 (1.5)	4 (1.5)	8 (1.5)
Grade 2	21 (7.7)	36 (13.2)	57 (10.4)
Grade 3	164 (59.9)	151 (55.3)	315 (57.6)
Grade 4	62 (22.6)	63 (23.1)	125 (22.9)
Grade 5	17 (6.2)	16 (5.9)	33 (6.0)
Subjects with Study Device-related AE	222 (81.0)	NA	222 (40.6)
Subjects with Study Device-related AE by Maximum Severity			
Grade 1	79 (28.8)	NA	79 (14.4)
Grade 2	117 (42.7)	NA	117 (21.4)
Grade 3	25 (9.1)	NA	25 (4.6)
Grade 4	1 (0.4)	NA	1 (0.2)
Grade 5	0 (0)	NA	0 (0)
Subjects with Gemcitabine or Nab-paclitaxel related AE	258 (94.2)	263 (96.3)	521 (95.2)
Subjects with Gemcitabine or Nab-paclitaxel related AE by Maximum Severity			
Grade 1	4 (1.5)	11 (4.0)	15 (2.7)
Grade 2	50 (18.2)	61 (22.3)	111 (20.3)
Grade 3	155 (56.6)	142 (52.0)	297 (54.3)
Grade 4	46 (16.8)	48 (17.6)	94 (17.2)
Grade 5	3 (1.1)	1 (0.4)	4 (0.7)
Device-related AE Leading to Device Discontinuation	23 (8.4)	NA	23 (4.2)
Systemic Therapy related AE Leading to Systemic Therapy Discontinuation	47 (17.2)	43 (15.8)	90 (16.5)
Subjects with SAE	147 (53.6)	131 (48.0)	278 (50.8)
Subjects with SAE by Maximum CTCAE Grade			
Grade 1	0 (0)	0 (0)	0 (0)
Grade 2	4 (1.5)	1 (0.4)	5 (0.9)
Grade 3	104 (38.0)	92 (33.7)	196 (35.8)
Grade 4	22 (8.0)	22 (8.1)	44 (8.0)
Grade 5	17 (6.2)	16 (5.9)	33 (6.0)
Subjects with Device related SAE	1 (0.4)	NA	1 (0.2)
Subjects with SAE related to Gemcitabine or Nab-paclitaxel	59 (21.5)	56 (20.5)	115 (21.0)
Subjects with SAE Leading to Death	17 (6.2)	16 (5.9)	33 (6.0)
Device-related SAE Leading to Death	0 (0)	NA	0 (0)
Systemic Therapy related SAE Leading to Death	3 (1.1)	1 (0.4)	4 (0.7)
Device-related SAE Leading to Device Discontinuation	0 (0)	NA	0 (0)
Systemic Therapy Related SAE Leading to Systemic Therapy Discontinuation	10 (3.6)	8 (2.9)	18 (3.3)

Conclusions: The PANOVA-3 study met its primary endpoint, demonstrating that TTFields therapy added to GnP resulted in statistically significant improvement in overall survival in patients with locally advanced pancreatic cancer compared to GnP alone (log rank test p = 0.039). In the ITT population, median overall survival (OS) was 16.2 months (95% CI 0.68 – 0.99) with TTFields + GnP compared with 14.2 months (95% CI 12.8 – 15.4) for GnP alone (HR 0.82; p=0.039).

It cannot be concluded from the data that TTFields therapy added to GnP improves PFS compared with using GnP alone. Radiographic response rates were directionally aligned with the survival findings, increasing from 30.0% to 36.1% in ITT.

TTFields therapy was well-tolerated, with no exacerbation of GnP-related systemic toxicity, no new safety signals, and comparable SAE rates between study arms. Most TTFields-treated patients experienced the expected device-related skin toxicity under the arrays (76.3% of the TTFields-treated participants). The majority of these events were low grade (Grade 1-2), with only 21 (7.7%) experiencing a Grade ≥3 event. The most common device-related AE not related to skin toxicity was fatigue, reported in 14 participants (5.1%). There was one Grade 4 AEs suspected to be related to the device by the investigator, which was a non-serious event of neutrophil count decrease. There were no device-related AEs that led to death, and no unanticipated device-related safety issues during the course of the study.

7 PREVENTIVE SKIN CARE AND PROPHYLAXIS FOR TREATMENT-RELATED REACTIONS UNDER THE TRANSDUCER ARRAYS

To reduce the incidence and severity of device-related dermatologic AEs, advise your patient to adopt proactive skin care, emphasizing prevention and early identification.

General guidance

Effective monitoring and prompt management of device-related dermatologic AEs prevent the progression of minor irritations into more severe skin complications and support treatment continuity.

General skin care guidelines are provided to the patient in the "Patient Information and Operation Manual", aiming to preserve skin intactness and minimize irritation. The recommended routine measures include the following:

- Cleanse skin daily with lukewarm water and mild, fragrance-free soap or bodywash
- Avoid products containing alcohol, fragrances, solvents, petroleum-based products or harsh disinfectants
- Minimize sun exposure and apply appropriate sun protection when outdoors
- Avoid friction and abrasion. Do not rub skin with towels and avoid tight-fitting clothing
- Moisturize regularly
- Choose loose-fitting clothing when possible, to allow air circulation around the abdomen/arrays.
- Avoid clothing made of materials that can irritate the skin (e.g., coarse wool), as these materials may cause itching
- Avoid clothing made of materials that are not breathable (e.g., some synthetic fabrics), as these materials may cause excessive sweating around the abdomen and arrays.

Consider prescribing

- Routine prophylaxis using water- or silicone-based (e.g., dimethicone-based films or non-petroleum-based wipes)
- Skin barrier films
- Topical corticosteroids, or nonsteroidal immunomodulators

Monitoring and Evaluation

- Monitor the patient closely for skin issues, especially during the first 25 days of TTFields treatment, by scheduling periodic follow-up visits.
- Whenever feasible, patients should be asked to attend follow-up visits with the arrays temporarily removed, allowing direct skin inspection by the clinical team.

Recommended Treatment of Skin Adverse Events

Skin adverse events (AEs) related to TTFields therapy are consistent in nature with those observed in other dermatologic conditions.

The table below outlines standard severity grading, clinical descriptions, and recommended dermatologic management strategies, based on *Haanen et al., and* adapted from *Lacouture et al, 2020 and Anadkat et al. 2023.*

Where a referral to a dermatologist is indicated in the table, it is recommended to refer to a dermatologist with expertise in oncology.

Severity	Description	Recommended management	TTFields guidance	Dermatology referral
Grade 1	• Asymptomatic or mild skin changes (e.g. erythema, dryness, pruritic) • No functional impact	• Initiate or optimize use of water-based moisturizers • Add barrier film or dimethicone-based protectant, if needed • Low-potency topical corticosteroids, if needed (e.g. hydrocortisone 1%) • Preference for non-occlusive, alcohol-free, fragrance-free products	• Continue TTFields uninterrupted	Not required unless symptoms persist or diagnosis is unclear
Grade 2	• Symptomatic erythema, localized erosions, or pruritus interfering with daily activities	• Moderate-potency corticosteroids (e.g. triamcinolone 0.1%) • Topical antibiotics for suspected secondary infection • Antihistamines or anti-pruritic as needed	• Continue TTFields if tolerable • Consider brief treatment break (2-7 days) for recovery	Recommended if symptoms do not resolve or diagnosis is uncertain
Grade 3	• Skin ulceration, bleeding, or widespread erosions	• Wound care with hydrogels or hydrocolloid dressings • Topical and/or systemic antibiotics based on culture • Short-course systemic corticosteroids if topical therapy is inadequate	• Interrupt treatment with TTFields • Resume once lesion is re-epithelialized and resolves to Grade $\leq$1	Strongly recommended to seek dermatologist or wound care specialist
Grade 4	Full thickness ulceration, systemic infection, or necrosis	• Hospital-based wound care • IV antibiotics • Multidisciplinary care including dermatology and infectious disease	Discontinue TTFields temporarily or permanently based on clinical judgement. Reinitiate only after full resolution and multidisciplinary approval.	Mandatory multidisciplinary referral

8 ADDITIONAL INFORMATION

Information for physicians on determining the optimal array layout for patients

- Clinical Practice Guidelines: Optimizing the transducer array layout in TTFields-treated patients (pancreatic malignancies)

Detailed information for patients on the use of Optune Pax can be found in the following documents:

- Optune Pax® Patient Information and Operation Manual (ITE Transducer Arrays) – QSD-QR-916

9 GLOSSARY

AE – Adverse event

ITT – Intent-to-Treat. This analysis population includes all randomized subjects.

kHz – kilo hertz; number of cycles per second

Optune Pax – A portable, battery, or power supply, operated device for delivering 150 kHz TTFields to the abdomen of patients with pancreatic adenocarcinoma

OS – Overall survival

PFS – Progression free survival

Radiological Response Rate – sum of complete and partial radiological response rates

Disease Control Rate – sum of stable disease, complete and partial radiological response rates

TTFields – Tumor Treating Fields: Low intensity (1-3 V/cm), intermediate frequency (100-300 kHz), alternating electric fields, delivered using insulated transducer arrays to the region of the body inflicted with a solid tumor. The fields have been shown in vitro to arrest the replication of tumor cells by disrupting the proper formation of the microtubule spindle and by dielectrophoretic disruption of cell integrity during late telophase

V/cm – Volts per centimeter; the unit of intensity measurement of electric fields

10 CONTACT INFORMATION

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11 BIBLIOGRAPHY

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Manufacturer information:
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QSD-QR-917 US(EN)

Cardiac PET for Suspected Cardiac Ischemia

Plain Language Summary:

A cardiac PET scan is a heart scan that uses radioactive dye to take detailed pictures of the heart. Cardiac ischemia is a common condition where blockages in blood vessels can cause damage to the heart muscle.

Experts recommend this test for some people who have symptoms that might mean they have a condition causing heart muscle damage. HERC staff recommends adding coverage for cardiac PET scan in some circumstances.

Staff Analysis Summary:

Significant proposed changes or discussion items:

1. Add coverage for cardiac PET for evaluation of cardiac ischemia in some circumstances

No changes were made from the advance packet (no comments received)

Coverage Question:

Should cardiac PET be covered for the evaluation of suspected cardiac ischemia?

Question source:

Holly Jo Hodges, MD, MBA – CMO Eastern Oregon Coordinated Care Organization

Background:

Cardiac positron emission tomography (PET) is a type of non-invasive, nuclear imaging that can be used to evaluate the heart muscle, also known as the myocardium. It can be used to evaluate multiple possible types of cardiac disease, including suspected coronary artery disease (CAD). CAD can lead to reduced blood flow to the myocardium resulting in ischemia and damage to the heart. Multiple types of non-invasive cardiac imaging, such as

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an echocardiogram or another nuclear test known as SPECT (single photon emission computed tomography), can be done to evaluate the level of ischemia or impaired blood flow to the heart.

Cardiac PET creates 3-dimensional images of the heart by taking images of the heart after injection of a radioactive tracer. Scans can be performed both at rest and after the infusion of pharmaceutical stressors or vasodilators which are medicines that impact heart function to evaluate for changes under stress.

Previous HSC/HERC reviews:

Review of cardiac PET was included in a coverage guidance focused on advanced cardiac imaging in 2019. At that time, the coverage guidance conclusion was "PET is not recommended for coverage for screening or diagnosis of coronary artery disease (CAD) *(strong recommendation)."* This decision was based on insufficient evidence in all populations for effectiveness, as well as the potential risks of radiation exposure which was not present in alternatives and the higher cost versus alternatives. Based on this coverage guidance, the following entry was made in the PET guideline: "PET scans are NOT indicated for cardiac evaluation." Additionally, the CPT codes for cardiac PET (CPT 78459, 78492 and 78493) were placed on line 662/GN173 (now Excluded Services Guideline E2).

Cardiac PET was briefly reviewed in November 2019 as part of the 2020 CPT code review, but no new evidence was presented.

Cardiac PET was recently reviewed in March 2026 in the setting of cardiac sarcoidosis and coverage was added for evaluation and management of cardiac sarcoidosis.

Current Prioritized List/Coverage status:

DIAGNOSTIC GUIDELINE D22, PET SCANS

Diagnosis:

PET Scans are covered for diagnosis only when:

A) The PET scan is for evaluation of either:
   1) Solitary pulmonary nodules, small cell lung cancer and non-small cell lung cancer, OR

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2) Evaluation of cervical lymph node metastases when CT or MRI do not demonstrate an obvious primary tumor, AND

B) The PET scan will
1) Avoid an invasive diagnostic procedure, OR
2) Assist in determining the optimal anatomic location to perform an invasive diagnostic procedure.

Initial staging:

A) PET scans are covered for the initial staging when:
1) The staging is for one of the following cancers/situations:
2) Cervical cancer only when initial MRI or CT is negative for extra-pelvic metastasis
3) Head and neck cancer when initial MRI or CT is equivocal
4) Colon cancer
5) Esophageal cancer
6) Solitary pulmonary nodule
7) Non-small cell lung cancer
8) Lymphoma
9) Melanoma
10) Breast cancer ONLY when metastatic disease is suspected AND standard imaging results are equivocal or suspicious
11) Small cell lung cancer
12) Neuroendocrine tumors
13) Multiple myeloma
14) Thyroid cancers
15) PSMA PET for unfavorable intermediate, high-risk, or very-high-risk prostate cancer, AND

B) Clinical management of the patient will differ depending on the stage of the cancer identified and either:
1) the stage of the cancer remains in doubt after standard diagnostic work up, OR
2) PET replaces one or more conventional imaging studies when they are insufficient for clinical management of the patient.

Monitoring:

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For monitoring tumor response during active therapy for purposes of treatment planning, PET is covered for

A) classic Hodgkin's lymphoma treatment
B) metastatic breast cancer ONLY when a change in therapy is contemplated AND PET scan was the imaging modality initially used to find the neoplasm being monitored.

Restaging:

Restaging is covered only when:

A) the cancer has staging covered above, AND
B) initial therapy has been completed, AND
C) the PET scan is conducted for
    1) detecting residual disease, or
    2) detecting suspected recurrence, or
    3) determining the extent of a known recurrence.

Other indications:

PET scans are covered for preoperative evaluation of the brain in patients who have intractable seizures and are candidates for focal surgery. PET scans are covered for patients being considered for treatment with aducanumab or similar FDA approved medications for treatment of Alzheimer's disease.

Non-covered conditions/situations:

A) PET scans are NOT covered to monitor tumor response during the planned course of therapy for any cancer other than classic Hodgkin's lymphoma or the limited indication described above for metastatic breast cancer.
B) PET scans are NOT covered for routine follow up of cancer treatment or routine surveillance in asymptomatic patients.
C) PET scans are NOT covered for cardiac evaluation.

Evidence:

Washington State Health Care Authority, October 19, 2021 Noninvasive Cardiac Imaging for Coronary Artery Disease – A Re-review: Final Evidence Report

a. N=2 trials comparing SPECT and PET

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    a. Mullani 2000 trial (N=210) of PET vs SPECT for diagnosis of CAD in patients with suspected (70%) or known (30%) CAD
        i. Poor quality
        ii. Insufficient evidence to draw conclusions for any outcome
    b. Patel 2019 trial (N=322) of PET vs SPECT in patients with known CAD for diagnosis of worsening disease
        i. Good quality
        ii. Insufficient evidence to draw conclusions for any outcome
b. Diagnostic accuracy based on a 2016 AHRQ report and a 2016 NICE review in patients with suspected CAD and stable symptoms
    a. AHRQ 2016: 82-90% sensitivity, 86-88% specificity, 93-95% PPV, 53-84% NPV for diagnosis of CAD
    b. NICE 2016: 91% sensitivity, 86% specificity for diagnosis, 87% PPV, 90% NPV for diagnosis of CAD of CAD
c. Most of reviewed evidence in report compares nuclear imaging (SPECT and PET) with non-nuclear imaging. Section outlined below shows 2 studies comparing PET and SPECT with key questions.
d. PET versus SPECT evidence summary, 2 trials (n=540) evaluated effectiveness of PET compared with SPECT across different outpatient populations (suspected CAD and known CAD with worsening symptoms)
e. <u>Key question 1</u>: Primary outcomes (MI, all-cause mortality, cardiac death)
    a. "In the good-quality trial in patients with known CAD and new or worsening symptoms, the absolute risks of MI and all-cause mortality were 1 per 10 patients across both PET and SPECT arms over 12 months."
f. <u>Key question 2</u>: Clinical decision making
    a. "Over 12 months, risk of invasive coronary angiography (ICA) was 29 versus 28 per 100 patients; of any revascularization was 16 versus 15 per 100 patients; and of escalation in antianginal therapy was 26 versus 23 per 100 patients for PET versus SPECT, respectively, in the good-quality trial."
g. <u>Key question 3</u>: Safety
    a. Neither trial reported on adverse events related to diagnostic tests or radiation
h. <u>Key question 4</u>: Differential effectiveness and safety
    a. Neither trial reported differential effectiveness or safety

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Submitted literature:

None

Expert guidelines:

1. Guloti 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain
    a. For acute chest pain
        i. For intermediate-risk patients with acute chest pain and no known CAD who are eligible for cardiac testing, either exercise ECG, stress echocardiography, stress PET/SPECT MPI, or stress CMR is useful for the diagnosis of myocardial ischemia
            1. Level 1 recommendation (strong, benefit > risk), LOE B-NR (moderate quality evidence
        ii. For intermediate-risk patients with acute chest pain and no known CAD, with an inconclusive CCTA, stress imaging (with echocardiography, PET/SPECT MPI, or CMR) can be useful for the diagnosis of myocardial ischemia
            1. Level 2a recommendation (moderate), LOE C-EO (expert consensus)
    b. For stable chest pain and no known CAD
        i. For intermediate-high risk patients with stable chest pain and no known CAD, CCTA is effective for diagnosis of CAD, for risk stratification, and for guiding treatment decisions
            1. Level 1 recommendation (strong), LOE A (high quality evidence)
        ii. For intermediate-high risk patients with stable chest pain and no known CAD, stress imaging (stress echocardiography, PET/SPECT MPI or CMR) is effective for diagnosis of myocardial ischemia and for estimating risk of MACE.
            1. Level 1 recommendation (strong), LOE B-R (moderate quality evidence)
    c. For intermediate-high risk patients with stable chest pain and no known CAD for whom rest/stress nuclear MPI is selected, PET is reasonable in

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preference to SPECT, if available to improve diagnostic accuracy and decrease the rate of nondiagnostic test results

i. Level 2a recommendation (moderate), LOE B-R (moderate quality evidence)

d. For intermediate-high risk patients with stable chest pain and no known CAD with an interpretable ECG and ability to achieve maximal levels of exercise (≥5 METs), exercise electrocardiography is reasonable

i. Level 2a recommendation (moderate), LOE B-R (moderate quality evidence)

e. "After acute coronary syndrome has been ruled out, rest/stress positron emission tomography (PET) or single-photo emission computed tomography (SPECT) myocardial perfusion imaging (MPI) allows for detection of perfusion abnormalities, measures of left ventricular function, and high-risk findings such as transient ischemic dilation. For PET, calculation of myocardial blood flow reserve (MBFR) adds diagnostic and prognostic information over MPI data."

f. "For intermediate-high risk patients with stable chest pain and no known CAD for whom rest/stress is selected, PET is reasonable in preference to SPECT, if available to improve diagnostic accuracy and decrease the rate of nondiagnostic test results. Although PET and SPECT are grouped together, PET has improved diagnostic and prognostic performance."

i. Patients with moderate-severe ischemia on PET treated with PCI reported an improvement in angina when compared with those treated medically.

ii. With known CAD, PET is preferable over SPECT when both are available given PET findings

g. "For patients with persistent, stable chest pain and nonobstructive CAD, stress PET is reasonable to diagnose microvascular dysfunction and enhance risk stratification."

i. "PET improves risk stratification, including for patients with nonobstructive CAD, especially women, for whom coronary microvascular dysfunction is suspected."

2. Virani 2023 American College of Cardiology and the American Heart Association Guideline for the Management of Patients With Chronic Coronary Disease

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   a. "In patients with chronic coronary disease (CCD) and a change in symptoms or functional capacity that persists despite guideline-directed management and therapy (GDMT), when selected for rest/stress nuclear myocardial perfusion imaging (MPI), PET is reasonable in preference to SPECT, if available, to improve diagnostic accuracy and decrease the rate of nondiagnostic test results."
      i. Strength of recommendation: Moderate (benefit>risk)
      ii. Level (quality) of evidence: B - randomized
   b. "In patients with CCD undergoing stress PET MPI or stress (cardiovascular magnetic resonance (CMR) imaging, the addition of myocardial blood flow reserve (MBFR) can be useful to improve diagnostic accuracy and enhance risk stratification."
      i. Strength of recommendation: Moderate (benefit>risk)
      ii. Level (quality) of evidence: B - randomized
3. European Society of Cardiology 2024 Guidelines for the management of chronic coronary syndromes.
   a. "Recommendation for non-invasive functional myocardial imaging tests in the initial diagnostic management of individuals with suspected chronic contrary syndrome. PET myocardial perfusion imaging is recommended."
   b. In intermediate-high risk patients, PET MPI is preferred over SPECT MPI
   c. PET MPI is recommended to identify individuals at high risk of adverse events
   d. In patients with heart failure, preserved ejection fraction (HFpEF) with angina or equivalent symptoms and normal or non-obstructive epicardial coronary arteries, PET MPI should be considered to detect or rule out coronary microvascular dysfunction
4. American Society of Nuclear Cardiology, Bateman T, et al 2025: Clinical indications for positron emission tomography myocardial perfusion imaging and myocardial blood flow quantification: An American Society of Nuclear Cardiology position statement
   a. "Clinical advantages of PET MPI: diagnostic accuracy, risk stratification, robust and reproducible quantification of myocardial blood flow (MBF), equitable across diverse patient populations, rapid acquisitions, low radiation exposure, high image quality"

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Other payer policies:

1. Washington Medicaid 2021
    1) Adopted as part of the WHTA review above
    2) Stress echocardiography for:
        a) Symptomatic adult patients (≥18 years of age) at intermediate or high risk of Coronary Artery Disease (CAD), or
        b) Adult patients with known CAD who have new or worsening symptoms.
    3) Single Positron Emission Tomography (SPECT) for:
        a) Patients under the same conditions as stress echocardiography when stress echocardiography is not technically feasible or clinically appropriate
    4) Positron Emission Tomography (PET) for:
        a) Patients under the same conditions as SPECT, when SPECT is not technically feasible or clinically appropriate

2. Regence Blue Cross Blue Shield (Commercial) – Effective 3/1/26
   Cardiac PET scanning is established for the following indications:

    • Assessing myocardial perfusion for diagnosing coronary artery disease in individuals with indeterminate SPECT scan
    • For individuals for whom SPECT could be reasonably expected to be suboptimal in quality on the basis of body habitus. (e.g., BMI > 40, large breasts, breast implants, mastectomy, chest wall deformity, pleural or pericardial effusion)
    • For assessing the myocardial viability in individuals with severe left ventricular dysfunction as a technique to determine candidacy for a revascularization procedure
    • Suspected CAD in symptomatic patients who have not had evaluation for CAD within the preceding 60 days
    • Established flow-limiting CAD in asymptomatic patients
    • Established flow-limiting CAD in patients who have new or worsening symptoms
    • Established or suspected CAD

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- Preoperative cardiac evaluation of patients undergoing non-emergency non-cardiac surgery (includes surveillance for CAD in patients awaiting solid organ transplant)
- Miscellaneous indications for PET perfusion imaging

Exclusions:

- Quantification of myocardial blood flow in individuals diagnosed with CAD.

1. Aetna (Commercial) – 12/15/2025

Aetna considers positron emission tomography (PET) medically necessary for the following cardiac indications:

2. Evaluation of Coronary Artery Disease

PET scans using rubidium-82 (Rb-82) or N-13 ammonia done at rest or with pharmacological stress are considered medically necessary for non-invasive imaging of the perfusion of the heart for the diagnosis and management of members with known or suspected coronary artery disease, provided such scans meet *either* one of the two following criteria:

1. The PET scan is used in place of, but not in addition to, a single photon emission computed tomography (SPECT), in persons who meet medical necessity criteria for a cardiac SPECT (see CPB 0376 Single Photon Emission Computed Tomography (SPECT)); *or*
2. For use in assessment of coronary artery disease after cardiac transplant.

Aetna considers absolute quantitation of myocardial blood flow (AQMBF) a medically necessary adjunct to cardiac PET when criteria for rest/stress perfusion for coronary artery disease are met.

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3. Assessment of Myocardial Viability

Fluorodeoxy-D-glucose (FDG)-PET scans are considered medically necessary for the determination of myocardial viability prior to re-vascularization, either as a primary or initial diagnostic study or following an inconclusive SPECT. The greater specificity of PET makes a SPECT following an inconclusive PET not medically necessary.

The identification of members with partial loss of heart muscle movement or hibernating myocardium is important in selecting candidates with compromised ventricular function to determine appropriateness for re-vascularization. Diagnostic tests such as FDG-PET distinguish between dysfunctional but viable myocardial tissue and scar tissue in order to affect the management decisions in members with ischemic cardiomyopathy and left ventricular dysfunction.

3. Cigna (Commercial) – 3/1/25
    1. Cardiac PET Perfusion Indications
        1. Meets all of the criteria for an imaging stress test in Stress Testing with Imaging (CD-1.4) and additionally any one of the following:
        ◦ Individual is severely obese
        ◦ Individual has large breasts or implants
        ◦ Individual incapable of exercise due to physical (musculoskeletal or neurological) inability to achieve target heart rate. Target heart rate is calculated as 85% of the maximum age predicted heart rate (MPHR). MPHR is estimated as 220 minus the individual's age
        • Equivocal nuclear perfusion (SPECT MPI) stress test
        • Routine use in post heart transplant assessment of transplant CAD
    2. Cardiac PET – Absolute Quantitation of Myocardial Blood Flow (AQMBF)
        1. Absolute Quantitation of Myocardial Blood Flow (CPT® 78434) Quantitation of myocardial blood flow at rest and with stress in ml/g/min and the calculation of myocardial perfusion reserve (the ratio of stress to rest flow) can be used for diagnosis and prognosis of coronary artery disease and cardiac endothelial dysfunction that can be seen in diabetes, left ventricular hypertrophy, heart transplantation vasculopathy among other conditions.

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• AQMBF with PET (CPT® 78434) is an add-on procedure that is indicated when one of the following apply:

◦ Primary study Myocardial PET rest/stress perfusion (CPT® 78492 or 78431 only) has been approved

◦ Primary study Myocardial PET rest/stress perfusion (CPT® 78492 or 78431 only) has been ordered and is being approved at the same time (see- Cardiac PET - Perfusion - Indications (CD-6.2) or Stress Testing with Imaging - Indications (CD-1.4))

Expert input:

None

HERC staff summary:

In most evidence evaluating non-invasive diagnostic tests for cardiac ischemia, nuclear cardiac imaging modalities (SPECT and PET) are combined and compared with non-nuclear cardiac imaging. In this review, cardiac PET was reviewed separately from SPECT to evaluate for a coverage recommendation. There are 2 studies comparing SPECT and PET as cardiac nuclear imaging study modalities to evaluate for cardiac ischemia, however a 2021 Washington HTA review found insufficient evidence to draw outcome conclusions. This review evaluated for primary outcomes (myocardial infarction, all-cause mortality and cardiac death), clinical decision making, safety and differential effectiveness. Clinical guidelines published since 2021 cite that cardiac PET appears to provide additional benefits as compared to other non-invasive cardiac imaging, such as SPECT, in some clinical circumstances, however a review of the primary evidence does not indicate a benefit in cardiac outcomes. Some payer policies cover cardiac PET for the evaluation of ischemia when other non-invasive cardiac imaging modalities are insufficient or not feasible for reasons such as anatomy.

HERC staff recommendations:

1) Remove CPT 78429-78434, 78459, 78491-78492 (Myocardial imaging, positron emission tomography (PET)) from Excluded Services Guideline E2
    a. Advise Medicaid to add CPT 78429-78434, 78459, 78491-78492 to the Diagnostic Procedures file
2) Delete the entry for cardiac PET from Excluded Services Guideline E2 as shown below

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3) Modify Diagnostic Guideline D22 as shown below
    a. Wording in purple adopted at the March 2026 HERC meeting

EXCLUDED SERVICES GUIDELINE E2, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

The following Interventions are unproven, have no clinically important benefit or have harms that outweigh benefits and should be excluded from coverage

Procedure Code	Intervention Description	Rationale	Last Review
~~* 78429-78434, 78459, 78491-78492~~	~~Myocardial imaging, positron emission tomography (PET), metabolic evaluation and/or perfusion~~	~~Insufficient evidence of benefit, unclear harms of radiation exposure~~	~~November 2019~~ ~~Coverage Guidance~~

DIAGNOSTIC GUIDELINE D22, PET SCANS

Diagnosis:

PET Scans are covered for diagnosis only when:

C) The PET scan is for evaluation of either:
    1) Solitary pulmonary nodules, small cell lung cancer and non-small cell lung cancer, OR
    2) Evaluation of cervical lymph node metastases when CT or MRI do not demonstrate an obvious primary tumor, AND

D) The PET scan will
    1) Avoid an invasive diagnostic procedure, OR
    2) Assist in determining the optimal anatomic location to perform an invasive diagnostic procedure.

Initial staging:

C) PET scans are covered for the initial staging when:
    1) The staging is for one of the following cancers/situations:

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2) Cervical cancer only when initial MRI or CT is negative for extra-pelvic metastasis
3) Head and neck cancer when initial MRI or CT is equivocal
4) Colon cancer
5) Esophageal cancer
6) Solitary pulmonary nodule
7) Non-small cell lung cancer
8) Lymphoma
9) Melanoma
10) Breast cancer ONLY when metastatic disease is suspected AND standard imaging results are equivocal or suspicious
11) Small cell lung cancer
12) Neuroendocrine tumors
13) Multiple myeloma
14) Thyroid cancers
15) PSMA PET for unfavorable intermediate, high-risk, or very-high-risk prostate cancer, AND

D) Clinical management of the patient will differ depending on the stage of the cancer identified and either:
1) the stage of the cancer remains in doubt after standard diagnostic work up, OR
2) PET replaces one or more conventional imaging studies when they are insufficient for clinical management of the patient.

Monitoring:

For monitoring tumor response during active therapy for purposes of treatment planning, PET is covered for

A) classic Hodgkin's lymphoma treatment
B) metastatic breast cancer ONLY when a change in therapy is contemplated AND PET scan was the imaging modality initially used to find the neoplasm being monitored.

Restaging:

Restaging is covered only when:

A) the cancer has staging covered above, AND
B) initial therapy has been completed, AND
C) the PET scan is conducted for

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1) detecting residual disease, or
2) detecting suspected recurrence, or
3) determining the extent of a known recurrence.

Other indications:

PET scans are covered for preoperative evaluation of the brain in patients who have intractable seizures and are candidates for focal surgery. PET scans are covered for patients being considered for treatment with aducanumab or similar FDA approved medications for treatment of Alzheimer's disease.

Non-covered conditions/situations:

A) PET scans are NOT covered to monitor tumor response during the planned course of therapy for any cancer other than classic Hodgkin's lymphoma or the limited indication described above for metastatic breast cancer.
B) PET scans are NOT covered for routine follow up of cancer treatment or routine surveillance in asymptomatic patients.
C) ~~PET scans are NOT covered for cardiac evaluation.~~

Cardiac PET

1) Cardiac Sarcoidosis
    a. For evaluation of suspected cardiac sarcoidosis:
        i. Cardiac PET is covered if cardiac MRI is contraindicated, is normal but high clinical suspicion for cardiac sarcoidosis remains, or if cardiac MRI is inconclusive
    a. For monitoring of treatment of established cardiac sarcoidosis
        i. Cardiac PET is covered every 3-6 months while on active immunosuppression
        ii. Cardiac PET is covered every 6 months once there is minimal residual or resolved inflammation
    b. Routine cardiac surveillance of asymptomatic individuals with extracardiac sarcoidosis is not covered after the initial diagnostic work up
    c. NOTE: full body PET/CT (CPT *78815) is not indicated for the diagnosis or monitoring response to therapy of cardiac sarcoid
2) For evaluation of suspected cardiac ischemia

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a. Cardiac PET is covered if cardiac ischemia is suspected in the following population:
    i. Symptomatic patient at intermediate or high risk of coronary artery disease (CAD), or
    ii. Patients with known CAD who have new or worsening symptoms, AND
    iii. Evaluation with stress echocardiography or Single-Photon Emission Computed Tomography (SPECT) is not technically feasible or clinically appropriate.
b. NOTE: full body PET/CT (CPT *78815) is not indicated for the diagnosis of cardiac disease

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Circulation

CLINICAL PRACTICE GUIDELINE

2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines

Developed in Collaboration With and Endorsed by the American College of Clinical Pharmacy, American Society for Preventive Cardiology, National Lipid Association, and Preventive Cardiovascular Nurses Association

Endorsed by the Society for Cardiovascular Angiography and Interventions

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AIM: The "2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease" provides an update to and consolidates new evidence since the "2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease" and the corresponding "2014 ACC/AHA/AATS/PCNA/SCAI/STS Focused Update of the Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease."

METHODS: A comprehensive literature search was conducted from September 2021 to May 2022. Clinical studies, systematic reviews and meta-analyses, and other evidence conducted on human participants were identified that were published in English from MEDLINE (through PubMed), EMBASE, the Cochrane Library, Agency for Healthcare Research and Quality, and other selected databases relevant to this guideline.

*Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry may apply; see Appendix 1 for detailed information. †ACC/AHA representative. ‡National Lipid Association representative. §Preventive Cardiovascular Nurses Association representative. ||Former Joint Committee on Clinical Practice Guideline member; current member during the writing effort. ¶Society for Cardiovascular Angiography and Interventions representative. #Patient representative/lay stakeholder. **American Society for Preventive Cardiology representative. ††AHA/ACC Joint Committee on Clinical Data Standards. ‡‡American College of Clinical Pharmacy representative. §§AHA/ACC Joint Committee on Performance Measures.

Peer Review Committee Members and AHA/ACC Joint Committee on Clinical Practice Guidelines Members, see page e82.

The American Heart Association requests that this document be cited as follows: Virani SS, Newby LK, Arnold SV, Bittner V, Brewer LC, Demeter SH, Dixon DL, Fearon WF, Hess B, Johnson HM, Kazi DS, Kolte D, Kumbhani DJ, LoFaso J, Mahtta D, Mark DB, Minissian M, Navar AM, Patel AR, Piano MR, Rodriguez F, Talbot AW, Taqueti VR, Thomas RJ, van Diepen S, Wiggins B, Williams MS. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA guideline for the management of patients with chronic coronary disease: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *Circulation*. 2023;148:e9–e119. doi: 10.1161/CIR.0000000000001168

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STRUCTURE: This guideline provides an evidenced-based and patient-centered approach to management of patients with chronic coronary disease, considering social determinants of health and incorporating the principles of shared decision-making and team-based care. Relevant topics include general approaches to treatment decisions, guideline-directed management and therapy to reduce symptoms and future cardiovascular events, decision-making pertaining to revascularization in patients with chronic coronary disease, recommendations for management in special populations, patient follow-up and monitoring, evidence gaps, and areas in need of future research. Where applicable, and based on availability of cost-effectiveness data, cost–value recommendations are also provided for clinicians. Many recommendations from previously published guidelines have been updated with new evidence, and new recommendations have been created when supported by published data.

Key Words: AHA Scientific Statements ■ acute coronary syndrome ■ air pollution ■ angina ■ antiplatelet therapy ■ aspirin ■ atherosclerosis ■ autoimmune diseases ■ cardiac events ■ cardiac rehabilitation ■ cardiovascular diseases ■ colchicine ■ coronary artery disease ■ coronary disease ■ cost-benefit analysis ■ depression ■ diabetes ■ type 2 diabetes ■ diet ■ diet therapy ■ dietary supplements ■ drug therapy ■ dual antiplatelet therapy ■ environmental exposure ■ exercise tolerance ■ factor Xa inhibitors ■ fibrinolytic agents ■ glucagon-like peptide-1 receptor agonists ■ guideline-directed management and therapy ■ health equity ■ heart disease risk factors ■ heart failure ■ health care outcome assessments ■ hormone replacement therapy ■ hypercholesterolemia ■ hypertension ■ immunization ■ ischemic heart disease ■ mental health ■ multidisciplinary ■ myocardial ischemia ■ outcomes ■ outpatient ■ patient care team ■ pharmacology ■ pregnancy ■ proton pump inhibitors ■ quality of life ■ safety ■ secondary prevention ■ sexual behavior ■ sexual health ■ smoking cessation ■ shared decision-making ■ social determinants of health ■ sodium-glucose cotransporter 2 inhibitors ■ spontaneous coronary artery dissection ■ stress ■ therapeutic use ■ therapy ■ vaccination

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TOP 10 TAKE-HOME MESSAGES FOR CHRONIC CORONARY DISEASE

1. Emphasis is on team-based, patient-centered care that considers social determinants of health along with associated costs while incorporating shared decision-making in risk assessment, testing, and treatment.
2. Nonpharmacologic therapies, including healthy dietary habits and exercise, are recommended for all patients with chronic coronary disease (CCD).
3. Patients with CCD who are free from contraindications are encouraged to participate in habitual physical activity, including activities to reduce sitting time and to increase aerobic and resistance exercise. Cardiac rehabilitation for eligible patients provides significant cardiovascular benefits, including decreased morbidity and mortality outcomes.
4. Use of sodium glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists are recommended for select groups of patients with CCD, including groups without diabetes.
5. New recommendations for beta-blocker use in patients with CCD: (a) Long-term beta-blocker therapy is not recommended to improve outcomes in patients with CCD in the absence of myocardial infarction in the past year, left ventricular ejection fraction ≤50%, or another primary indication for beta-blocker therapy; and (b) Either a calcium channel blocker or beta blocker is recommended as first-line antianginal therapy.
6. Statins remain first line therapy for lipid lowering in patients with CCD. Several adjunctive therapies (eg, ezetimibe, PCSK9 [proprotein convertase subtilisin/kexin type 9] inhibitors, inclisiran, bempedoic acid) may be used in select populations, although clinical outcomes data are unavailable for novel agents such as inclisiran.
7. Shorter durations of dual antiplatelet therapy are safe and effective in many circumstances, particularly when the risk of bleeding is high and the ischemic risk is low to moderate.
8. The use of nonprescription or dietary supplements, including fish oil and omega-3 fatty acids or vitamins, is not recommended in patients with CCD given the lack of benefit in reducing cardiovascular events.
9. Routine periodic anatomic or ischemic testing without a change in clinical or functional status is not recommended for risk stratification or to guide therapeutic decision-making in patients with CCD.
10. Although e-cigarettes increase the likelihood of successful smoking cessation compared with nicotine replacement therapy, because of the lack of long-term safety data and risks of sustained use, e-cigarettes are not recommended as first-line therapy for smoking cessation.

PREAMBLE

Since 1980, the American College of Cardiology (ACC) and American Heart Association (AHA) have translated scientific evidence into clinical practice guidelines with recommendations to improve cardiovascular health. These guidelines, which are based on systematic methods to evaluate and classify evidence, provide a foundation for the delivery of quality cardiovascular care. The ACC and AHA sponsor the development and publication of clinical practice guidelines without commercial support, and members volunteer their time to the writing and review efforts. Guidelines are official policy of the ACC and AHA. For some guidelines, the ACC and AHA collaborate with other organizations.

Intended Use

Clinical practice guidelines provide recommendations applicable to patients with or at risk of developing cardiovascular disease (CVD). The focus is on medical practice in the United States, but these guidelines are relevant to patients throughout the world. Although guidelines may be used to inform regulatory or payer decisions, the intent is to improve quality of care and align with patients' interests. Guidelines are intended to define practices meeting the needs of patients in most, but not all, circumstances and should not replace clinical judgment.

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Clinical Implementation

Management, in accordance with guideline recommendations, is effective only when followed by both practitioners and patients. Adherence to recommendations can be enhanced by shared decision-making between clinicians and patients, with patient engagement in selecting interventions on the basis of individual values, preferences, and associated conditions and comorbidities.

Methodology and Modernization

The AHA/ACC Joint Committee on Clinical Practice Guidelines (Joint Committee) continuously reviews, updates, and modifies guideline methodology on the basis of published standards from organizations, including the National Academy of Medicine (formerly the Institute of Medicine),[1,2] and on the basis of internal reevaluation. Similarly, presentation and delivery of guidelines are reevaluated and modified in response to evolving technologies and other factors to optimally facilitate dissemination of information to health care professionals at the point of care.

Numerous modifications to the guidelines have been implemented to make them shorter and enhance "user friendliness." Guidelines are written and presented in a modular, "knowledge chunk" format in which each chunk includes a table of recommendations, a brief synopsis, recommendation-specific supportive text and, when appropriate, flow diagrams or additional tables. Hyperlinked references are provided for each modular knowledge chunk to facilitate quick access and review.

In recognition of the importance of cost–value considerations, in certain guidelines, when appropriate and feasible, an assessment of value for a drug, device, or intervention may be performed in accordance with the ACC/AHA methodology.[3]

To ensure that guideline recommendations remain current, new data will be reviewed on an ongoing basis by the writing committee and staff. When applicable, recommendations will be updated with new evidence or new recommendations will be created when supported by published evidence-based data. Going forward, targeted sections/knowledge chunks will be revised dynamically after publication and timely peer review of potentially practice-changing science. The previous designations of "full revision" and "focused update" will be phased out. For additional information and policies on guideline development, readers may consult the ACC/AHA guideline methodology manual[4] and other methodology articles.[5–7]

Selection of Writing Committee Members

The Joint Committee strives to ensure that the guideline writing committee contains requisite content expertise and is representative of the broader cardiovascular community by selection of experts across a spectrum of backgrounds, representing different geographic regions, sexes, races, ethnicities, intellectual perspectives/biases, and clinical practice settings. Organizations and professional societies with related interests and expertise are invited to participate as collaborators.

Relationships With Industry and Other Entities

The ACC and AHA have rigorous policies and methods to ensure that documents are developed without bias or improper influence. The complete policy on relationships with industry and other entities (RWI) can be found online. Appendix 1 of the guideline lists writing committee members' comprehensive and relevant RWI; for the purposes of full transparency, comprehensive and relevant disclosure information for the Joint Committee is also available online.

Evidence Review and Evidence Review Committees

In developing recommendations, the writing committee uses evidence-based methodologies that are based on all available data.[4,5] Literature searches focus on randomized controlled trials (RCTs) but also include registries, nonrandomized comparative and descriptive studies, case series, cohort studies, systematic reviews, and expert opinion. Only key references are cited.

An independent evidence review committee is commissioned when there are ≥1 questions deemed of utmost clinical importance and merit formal systematic review to determine which patients are most likely to benefit from a drug, device, or treatment strategy, and to what degree. Criteria for commissioning an evidence review committee and formal systematic review include absence of a current authoritative systematic review, feasibility of defining the benefit and risk in a time frame consistent with the writing of a guideline, relevance to a substantial number of patients, and likelihood that the findings can be translated into actionable recommendations. Evidence review committee members may include methodologists, epidemiologists, clinicians, and biostatisticians. Recommendations developed by the writing committee on the basis of the systematic review are marked "SR".

Guideline-Directed Management and Therapy

The term guideline-directed management and therapy (GDMT) encompasses clinical evaluation, diagnostic testing, and both pharmacological and procedural treatments. For these and all recommended drug treatment regimens, the reader should confirm dosage with product insert material and evaluate for contraindications and interactions. Recommendations are limited to drugs, devices, and treatments approved for clinical use in the United States.

Joshua A. Beckman, MD, MS, FACC, FAHA
Chair, AHA/ACC Joint Committee on Clinical Practice Guidelines

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1. INTRODUCTION

1.1. Methodology and Evidence Review

The recommendations listed in this guideline are, whenever possible, evidence based. An initial extensive evidence review—which included literature derived from research involving human subjects, published in English, and indexed in MEDLINE (through PubMed), EMBASE, the Cochrane Library, the Agency for Healthcare Research and Quality, and other selected databases relevant to this guideline—was conducted from September 24, 2021, to May 2022. Key search words included but were not limited to the following: *AHA/ACC Clinical Practice Guidelines; acute coronary syndrome; angina; cardiac rehabilitation; cardiovascular diseases; coronary artery disease; coronary disease; diabetes; type 2 diabetes; diet; diet therapy; dietary supplements; drug therapy; dual antiplatelet therapy; factor Xa inhibitors; hypertension; outcomes; quality of life; secondary prevention; therapy*.

Additional relevant studies, which were published through November 2022 during the guideline writing process, were also considered by the writing committee and added to the evidence tables when appropriate. The final evidence tables are included in the Online Data Supplement and summarize the evidence used by the writing committee to formulate recommendations. References selected and published in the present document are representative and not all-inclusive.

The ACC and AHA have acknowledged the importance of value in health care to include development of cost–value statements for clinical practice recommendations. Available cost-effectiveness data were determined to be sufficient to support 9 specific recommendations in this guideline (Section 4.2.6, "Lipid Management"; Section 4.2.8, "SGLT2 Inhibitors and GLP-1 Receptor Agonists"; Section 5.1, "Revascularization"; and Section 8.1, "Cost and Value Considerations"). As a result, a Level of Value was assigned to those recommendations on the basis of the "ACC/AHA Statement on Cost/Value Methodology in Clinical Practice Guidelines and Performance Measures,"[1] as shown in Table 1. Available quality-of-life (QOL) data were deemed to be insufficient to support specific recommendations in this guideline.

1.2. Organization of the Writing Committee

The writing committee consisted of general cardiologists, interventional cardiologists, cardiovascular surgeons, cardiac imaging experts, advance practice nurses, clinical pharmacists, health economists, and lay/patient representatives. The writing committee included representatives from the AHA, ACC, American College of Clinical Pharmacy (ACCP), American Society for Preventive Cardiology (ASPC), National Lipid Association (NLA), and Preventive Cardiovascular Nurses Association (PCNA). Appendix 1 of the current document lists writing committee members' comprehensive and relevant RWI.

Table 1. Level of Value for Clinical Guideline Recommendations*

Level of Value for Clinical Guideline Recommendations*
Level of Value
High value: Better outcomes at lower cost [redacted]
Intermediate value: [redacted]
Low value: [redacted]
Uncertain value: Value examined but data are insufficient to draw a conclusion because of no studies, low-quality studies, conflicting studies, or prior studies that are no longer relevant
Not assessed: Value not assessed by the writing committee
Proposed abbreviations for each value recommendation:
Level of Value: H indicates high value; I, intermediate value; L, low value; U, uncertain value; and NA, value not assessed.

*Figures used in this table are based on US GDP data from 2012 and were obtained from WHO-CHOICE Cost-Effectiveness Thresholds.[2]

GDP indicates gross domestic product; [redacted] and WHO-CHOICE, World Health Organization Choosing Interventions that are Cost-Effective.

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1.3. Document Review and Approval

This document was reviewed by 2 official reviewers each nominated by the ACC and AHA; 1 reviewer each from the ACCP, ASPC, NLA, PCNA, and 6 individual content reviewers. Reviewers' RWI information was distributed to the writing committee and is published in this document (Appendix 2).

This document was approved for publication by the governing bodies of the ACC and the AHA and was endorsed by the ACCP, ASPC, NLA, PCNA, and Society for Cardiovascular Angiography and Interventions.

1.4. Scope of the Guideline

The scope of the "2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease" (referred to hereafter as the "2023 CCD guideline") is to provide an update to and consolidate new evidence since the publication of the "2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease"[3] and the "2014 ACC/AHA/AATS/PCNA/SCAI/STS Focused Update of the Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease" and will replace these prior guidelines.[4] This current document provides a patient-centered approach to management of chronic coronary disease (CCD) incorporating the principles of shared decision-making, social determinants of health (SDOH), and team-based care. Where applicable and based on availability of cost-effectiveness data, value recommendations are also provided for clinicians.

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The writing committee acknowledges that care of patients with CCD is a continuum from postacute care in patients presenting with chest pain, acute coronary syndromes (ACS), or both to outpatient CCD-related management. The primary intended audience for this guideline is clinicians in primary care and cardiology specialty who care for patients with CCD in the outpatient setting. It aims to provide succinct recommendations in the domains of diagnostic evaluation, symptom relief, improvement in QOL, and reduction of future atherosclerotic cardiovascular disease (ASCVD)–related events and heart failure (HF) in patients with CCD. The recommendations provided in this guideline pertain to the chronic outpatient care of patients with CCD. Clinicians are referred to the relevant guidelines when evaluating patients with acute chest pain, ACS, or both.[5–9] See Table 2 for other relevant guidelines.

1.4.1. CCD Definition

This guideline is intended to apply to the following categories of patients in the outpatient setting:

- Patients discharged after admission for an ACS event or after coronary revascularization procedure and after stabilization of all acute cardiovascular issues.
- Patients with left ventricular (LV) systolic dysfunction and known or suspected coronary artery disease (CAD) or those with established cardiomyopathy deemed to be of ischemic origin.
- Patients with stable angina symptoms (or ischemic equivalents such as dyspnea or arm pain with exertion) medically managed with or without positive results of an imaging test.
- Patients with angina symptoms and evidence of coronary vasospasm or microvascular angina.
- Patients diagnosed with CCD based solely on the results of a screening study (stress test, coronary computed tomography angiography [CTA]), and the treating clinician concludes that the patient has coronary disease.

This guideline is structured to address epidemiology and general principles in the management and transition of care in patients with CCD (Section 2, "Epidemiology/General Principles"). This is followed by evaluation of patients with CCD presenting with angina symptoms and risk stratification for future CVD events in patients with CCD (Section 3, "Evaluation, Diagnosis, and Risk Stratification"). Section 4, "Treatment" focuses on guiding principles in the management of patients with CCD (Section 4.1, "General Approach to Treatment Decisions"), overview of lifestyle and medical therapy (Section 4.2, "Guideline-Directed Management and Therapy"), and medical therapies to reduce cardiovascular events and manage symptoms (Section 4.3, "Medical Therapy to Prevent Cardiovascular Events and Manage Symptoms") in patients with CCD. This is followed by key considerations in decision-making related to revascularization in patients with CCD (Section 5, "Revascularization"). Special populations with key considerations are discussed next (Section 6, "Special Populations"), followed by recommendations related to follow-up and monitoring of patients with CCD (Section 7, "Patient Follow-up: Monitoring and Managing Symptoms"). Cost and value considerations while treating patients with CCD and future research needs in patients with CCD are covered in Section 8 ("Other Important Considerations"). Where applicable, key recommendations from ACC/AHA guidelines and other scientific statements (Table 2) pertinent to outpatient management of patients with CCD are referenced and discussed. Readers should refer to these ACC/AHA guidelines and scientific statements for further details.

The writing committee acknowledges several principles while managing patients with CCD. First, the population of patients with CCD is heterogenous, and the risk of future cardiovascular events is not uniform across this patient population. Therefore, clinicians should prioritize therapies based on a patient's future risk of CVD-related events. Second, symptom relief and improvement in QOL are extremely important considerations in patients with CCD. In several circumstances and after shared decision-making, clinicians may, as a first step, recommend therapies that improve symptom relief without necessarily improving cardiovascular outcomes. Third, several domains in the management of patients with CCD (eg, lifestyle, medical therapy, management of symptoms, and initial work-up) can be effectively performed by primary care clinicians. Therefore, this guideline acknowledges the principle of collaboration between clinicians in primary care and cardiology specialties. Lastly, the writing committee acknowledges that asymptomatic patients with significant coronary artery calcium noted on cardiac computed tomography (CT) or chest CT performed for noncardiac indications showing extensive coronary artery calcifications without history of a previous ASCVD event, have a high risk of future ASCVD events. Although this guideline does not address those patients, aggressive lifestyle management and the use of evidence-based medical therapies to prevent further progression of atherosclerosis and to reduce the risk of future cardiovascular events remain important considerations in such patients. Readers are referred to the appropriate ACC/AHA guidelines that address ASCVD risk reduction in this patient phenotype.[7,10]

In developing the 2023 CCD guideline, the writing committee reviewed previously published guidelines and related scientific statements. Table 2 contains a

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Table 2. Associated AHA/ACC Guidelines

Title	Organization	Publication Year (Reference)
Guidelines		
Secondary prevention and risk reduction therapy in coronary and other atherosclerotic disease	AHA/ACCF	2011[11]
Stable ischemic heart disease	ACC/AHA/AATS/PCNA/SCAI/STS	2012[3]
Overweight and obesity in adults	AHA/ACC/TOS	2013[12]
Focused update on stable ischemic heart disease	ACC/AHA	2014[4]
Focused update on DAPT with coronary artery disease	ACC/AHA	2016[13]
Ventricular arrhythmias and the prevention of sudden cardiac death	AHA/ACC/HRS	2017[14]
Management of blood cholesterol	AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA	2018[10]
Prevention, detection, evaluation, and management of high blood pressure in adults	ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA	2018[15]
Focused update on patients with atrial fibrillation	AHA/ACC/HRS	2019[16]
Primary prevention of CVD	ACC/AHA	2019[7]
Valvular heart disease	ACC/AHA	2021[17]
Coronary artery revascularization	ACC/AHA/AATS/STS/SCAI	2021[8]
Evaluation and diagnosis of chest pain	AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR	2021[6]
Management of heart failure	AHA/ACC/HFSA	2022[18]
Scientific Statements		
Core components of cardiac rehabilitation and secondary prevention programs	AHA	2007[19]
Sexual activity and CVD	AHA	2012[20]
Depression and poor prognosis among patients with CHD	AHA	2014[21]
Hypertension in patients with CAD	AHA	2015[22]
Management of clinically significant drug-drug interactions with statins and select agents used in patients with CVD	AHA	2016[23]
Dietary pattern to achieve adherence to AHA/ACC guidelines	AHA/ACC	2016[24]
Spontaneous coronary artery dissection	AHA	2018[25]
CVD in people living with HIV	AHA	2019[26]
Cardiovascular considerations and pregnant patients	AHA	2020[27]
Clinical management of stable CAD and type 2 diabetes	AHA	2020[28]
Psychological health, well-being, and the mind-heart-body connection	AHA	2021[29]
Air pollution and the impact on CVD	ACC/AHA/ESC	2021[30]
Cardio-oncology drug interactions	AHA	2022[31]
Consensus Document/Reports/Presidential Advisory		
Hypertension in elderly	ACCF/AHA	2011[32]
Diagnostic catheterization	ACCF/SCAI/AATS/AHA/ASE/ASNC/HFSA/HRS/SCCM/SCCT/SCMR/STS	2012[33]
Tobacco cessation treatment	ACC	2018[34]
Novel therapies for cardiovascular risk reduction in patients with type 2 diabetes	ACC	2020[35]
ASCVD risk reduction in patients with persistent hypertriglyceridemia	ACC	2021[36]
Anticoagulant and antiplatelet therapy in patients with AF or VT undergoing PCI or with ASCVD	ACC	2021[37]
Life's Essential 8 and cardiovascular health	AHA	2022[38]

AACVPR indicates American Association of Cardiovascular and Pulmonary Rehabilitation; AAPA, American Academy of Physician Associates (formerly American Academy of Physician Assistants); AATS, American Association for Thoracic Surgery; ABC, Association of Black Cardiologists; ACC, American College of Cardiology; ACCF, American College of Cardiology Foundation; ACP, American College of Chest Physicians; ACPM, American College of Preventive Medicine; ADA, American Diabetes Association; AF, atrial fibrillation; AGS, American Geriatrics Society; AHA, American Heart Association; APhA, American Pharmacists Association; ASCVD, atherosclerotic cardiovascular disease; ASE, American Society of Echocardiography; ASH, American Society of Hypertension; ASNC, American Society of Nuclear Cardiology; ASPC, American Society for Preventive Cardiology; CAD, coronary artery disease; CHD, coronary heart disease; CHEST, American College of Chest Physicians; CVD, cardiovascular disease; DAPT, dual antiplatelet therapy; ESC, European Society of Cardiology; HFSA, Heart Failure Society of America; HRS, Heart Rhythm Society; NLA, National Lipid Association; NMA, National Medical Association; PCI, percutaneous coronary intervention; PCNA, Preventive Cardiovascular Nurses Association; SAEM, Society for Academic Emergency Medicine; SCAI, Society for Coronary Angiography and Interventions; SCCM, Society of Critical Care Medicine; SCCT, Society of Cardiovascular Computed Tomography; SCAI, Society for Cardiovascular Angiography and Interventions; SCMR, Society for Cardiovascular Magnetic Resonance; STS, Society of Thoracic Surgery; TOS, The Obesity Society; and VT, venous thromboembolism.

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Table 3. Applying the American College of Cardiology/American Heart Association Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care* (Updated May 2019)

CLASS (STRENGTH) OF RECOMMENDATION	
CLASS 1 (STRONG)	**Benefit >>> Risk**
Suggested phrases for writing recommendations: • Is recommended • Is indicated/useful/effective/beneficial • Should be performed/administered/other • Comparative-Effectiveness Phrases†: – Treatment/strategy A is recommended/indicated in preference to treatment B – Treatment A should be chosen over treatment B	
CLASS 2a (MODERATE)	**Benefit >> Risk**
Suggested phrases for writing recommendations: • Is reasonable • Can be useful/effective/beneficial • Comparative-Effectiveness Phrases†: – Treatment/strategy A is probably recommended/indicated in preference to treatment B – It is reasonable to choose treatment A over treatment B	
CLASS 2b (WEAK)	**Benefit ≥ Risk**
Suggested phrases for writing recommendations: • May/might be reasonable • May/might be considered • Usefulness/effectiveness is unknown/unclear/uncertain or not well-established	
CLASS 3: No Benefit (MODERATE) **(Generally, LOE A or B use only)**	**Benefit = Risk**
Suggested phrases for writing recommendations: • Is not recommended • Is not indicated/useful/effective/beneficial • Should not be performed/administered/other	
Class 3: Harm (STRONG)	**Risk > Benefit**
Suggested phrases for writing recommendations: • Potentially harmful • Causes harm • Associated with excess morbidity/mortality • Should not be performed/administered/other	

LEVEL (QUALITY) OF EVIDENCE‡	
LEVEL A	
• High-quality evidence‡ from more than 1 RCT • Meta-analyses of high-quality RCTs • One or more RCTs corroborated by high-quality registry studies	
LEVEL B-R	**(Randomized)**
• Moderate-quality evidence‡ from 1 or more RCTs • Meta-analyses of moderate-quality RCTs	
LEVEL B-NR	**(Nonrandomized)**
• Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies • Meta-analyses of such studies	
LEVEL C-LD	**(Limited Data)**
• Randomized or nonrandomized observational or registry studies with limitations of design or execution • Meta-analyses of such studies • Physiological or mechanistic studies in human subjects	
LEVEL C-EO	**(Expert Opinion)**
• Consensus of expert opinion based on clinical experience	

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR 1 and 2a; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely-used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

list of these publications deemed pertinent to this writing effort. It is intended for use as a resource, obviating the need to repeat existing guideline recommendations. Some recommendations have been carried forward from previously published guidelines. If unchanged, those recommendations remain current. Any changes to the formatting or content of these recommendations are defined as:

- Modified: formatting changes (eg, minor modifications such as PICO[TS] structure)
- Adapted: substantive changes (eg, major adaptations, such as a change in COR, LOE, drug or device classification).

Changes are depicted in a footnote below the recommendation tables.

1.5. Class of Recommendations and Level of Evidence

The Class of Recommendation (COR) indicates the strength of recommendation, encompassing the estimated magnitude and certainty of benefit in proportion to risk. The Level of Evidence (LOE) rates the quality of scientific evidence supporting the intervention on the basis of the type, quantity, and consistency of data from clinical trials and other sources (Table 3).[1]

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1.6. Abbreviations

Abbreviation	Meaning/Phrase
ACE	angiotensin-converting enzyme
ACS	acute coronary syndrome
AF	atrial fibrillation
ARB	angiotensin-receptor blocker
ASCVD	atherosclerotic cardiovascular disease
BMI	body mass index
BP	blood pressure
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CCB	calcium channel blocker
CCD	chronic coronary disease
CHD	coronary heart disease
CKD	chronic kidney disease
CMR	cardiovascular magnetic resonance
COVID-19	coronavirus disease 2019
CR	cardiac rehabilitation
CVD	cardiovascular disease
CTA	computed tomography angiography
CCTA	coronary CT angiography
DAPT	dual antiplatelet therapy
DOAC	direct oral anticoagulant
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
FDA	US Food and Drug Administration
FH	familial hypercholesterolemia
FFR	fractional flow reserve
GDMT	guideline-directed management and therapy
GLP-1	glucagon-like peptide-1
HDL	high-density lipoprotein
HF	heart failure
HIV	human immunodeficiency virus
iFR	instantaneous wave-free ratio
INOCA	ischemia with nonobstructive coronary artery
LDL	low-density lipoprotein
LV	left ventricular
LVEF	left ventricular ejection fraction
MACE	major adverse cardiovascular event
MBFR	myocardial blood flow reserve
MPI	myocardial perfusion imaging
MI	myocardial infarction
NRT	nicotine replacement therapy
P2Y12	platelet adenosine diphosphate receptor
PET	positron emission tomography
PCI	percutaneous coronary intervention
PCSK9	proprotein convertase subtilisin/kexin type 9
PPI	proton pump inhibitor
QOL	quality of life
RAASi	renin-angiotensin-aldosterone system inhibitor
RCT	randomized controlled trial
SAPT	single antiplatelet therapy
SCAD	spontaneous coronary artery dissection
SDOH	social determinants of health
SGLT2	sodium glucose cotransporter 2
SPECT	single-photon emission computed tomography
TIA	transient ischemic attack

2. EPIDEMIOLOGY AND GENERAL PRINCIPLES

CCD is a heterogeneous group of conditions that includes obstructive and nonobstructive CAD with or without previous myocardial infarction (MI) or revascularization, ischemic heart disease diagnosed only by noninvasive testing, and chronic angina syndromes with varying underlying causes. Approximately 20.1 million persons in the United States live with CCD, 11.1 million Americans have chronic stable angina pectoris, and approximately one-quarter (n=200 000) of all MIs in the United States occur among the 8.8 million persons with CCD who have had a previous MI (Table 4).[1] Despite an approximate 25% overall relative decline in death from coronary heart disease (CHD) over the past decade, it remains the leading cause of death in the United States and worldwide and is associated with substantial individual, economic, and societal burdens.[1] Within the United States (Figures 1 and 2, Table 4) and worldwide (Figure 3), the prevalence of CCD and chronic stable angina vary by age, sex, race, ethnicity, and geographic region, and the role of SDOH in both risk for and outcomes from CCD is increasingly recognized.[1]

Since the publication of the "2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease,"[2] not only have health care expenditures for CCD remained high, but also the number and complexity of comorbid conditions and concurrent treatments for those conditions among patients with CCD have increased. For example, older age and chronic kidney disease (CKD) commonly coexist with CCD and independently and together raise unique considerations for diagnosis, risk stratification, and treatment. At the intersection between CCD and atrial fibrillation (AF), new information informs the use of antiplatelet therapy and anticoagulation in patients with CCD and atrial fibrillation. Additionally, as the population ages and both CCD and cancer survival improve, concurrent CCD and cancer more often coexist, and the field of cardio-oncology has emerged to address the challenges of these intersecting chronic conditions. Further, the fields of diabetes and lipid management have evolved rapidly with multiple new therapies (eg, sodium

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Table 4. US Heart Disease Prevalence, by Age, Race, Ethnicity, and Sex, 2015 to 2018

Population Group	Prevalence, CHD, 2015–2018, Age ≥20 y	Prevalence, MI, 2015–2018, Age ≥20 y	Prevalence, AP,* 2015–2018, Age ≥20 y
Both sexes	20.1 million (7.2% [95% CI, 6.5–7.9])	8.8 million (3.1% [95% CI, 2.7–3.6])	11 million (4.1%)
Men	11 million (8.3%)	5.8 million (4.3%)	5.3 million (4.2%)
Women	9.1 million (6.2%)	3 million (2.1%)	5.7 million (4.0%)
NH White men	8.7%	4.4%	4.5%
NH White women	6.0%	2.0%	4.0%
NH Black men	6.7%	3.9%	3.3%
NH Black women	7.2%	2.3%	4.7%
Hispanic men	6.8%	3.7%	3.5%
Hispanic women	6.4%	2.1%	4.3%
NH Asian men	5.0%	2.7%	2.1%
NH Asian women	3.2%	0.7%	2.2%
NH Native American/Alaska Native	---	---	---

CHD includes people who responded "yes" to at least 1 of the questions in "Has a doctor or other health professional ever told you that you had CHD, angina or angina pectoris, heart attack, or MI?" Those who answered "no" but were diagnosed with Rose angina are also included (the Rose questionnaire is administered only to survey participants >40 y of age). CIs have been added for overall prevalence estimates in key chapters. CIs have not been included in this table for all subcategories of prevalence for ease of reading. Source: Prevalence of CHD: unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using National Health and Nutrition Examination Survey and Behavioral Risk Factor Surveillance System data.[3,4] Percentages for racial and ethnic groups are age adjusted for Americans ≥20 y of age. Age-specific percentages are extrapolated to the 2018 US population estimates. These data, based on self-reports, include people who either answered "yes" to the question of ever having angina or angina pectoris or were diagnosed with Rose angina (the Rose questionnaire is administered only to survey participants >40 y of age). Percentages for racial and ethnic groups are age adjusted for US adults ≥20 y of age. Estimates from NHANES 2015 to 2018 were applied to 2018 population estimates (≥20 y of age).

*AP is chest pain or discomfort that results from insufficient blood flow to the heart muscle. Stable AP is predictable chest pain on exertion or under mental or emotional stress. The incidence estimate is for AP without MI.

AP indicates angina pectoris; CHD, coronary heart disease; CI, confidence interval; MI, myocardial infarction; and NH, non-Hispanic.

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glucose cotransporter 2 [SGLT2] inhibitors, glucagon-like peptide-1 [GLP-1] receptor agonists, proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors, bempedoic acid, and inclisiran) emerging in these areas, and the range of diagnostic and interventional procedures available for use in patients with CCD has expanded. Thus,

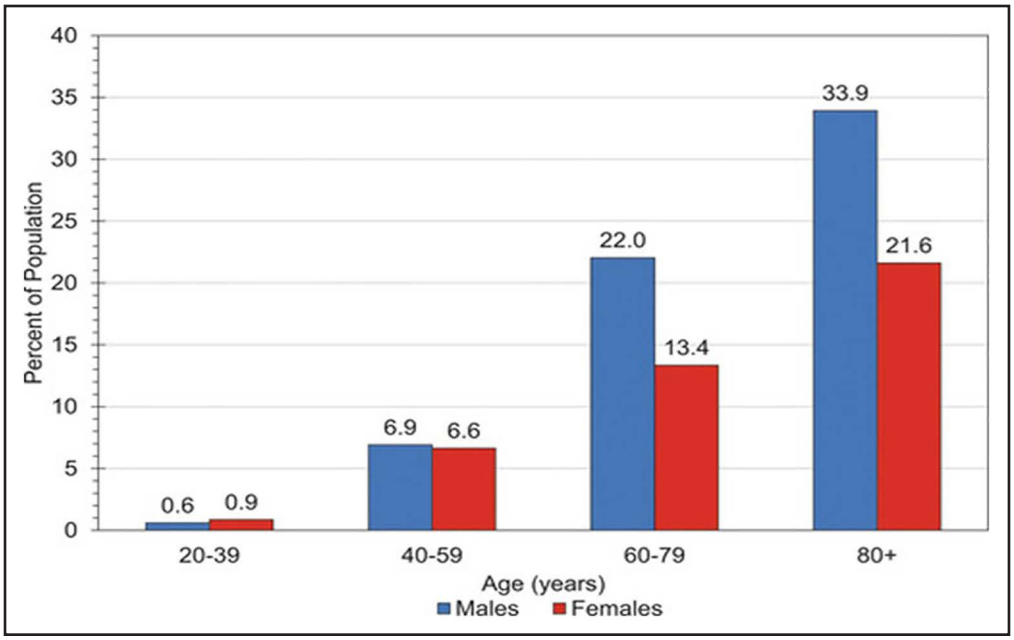

Figure 1. US Prevalence of CHD per 100 000, by Age and Sex (NHANES 2015 to 2018).
CHD indicates coronary heart disease. Source: Centers for Disease Control and Prevention, National Center for Health Statistics. National Health and Nutrition Examination Survey (NHANES) public use data files. Accessed April 15, 2021. https://www.cdc.gov/nchs/nhanes/. Reprinted with permission from Tsao CW et al.[1] Copyright 2022 American Heart Association, Inc.

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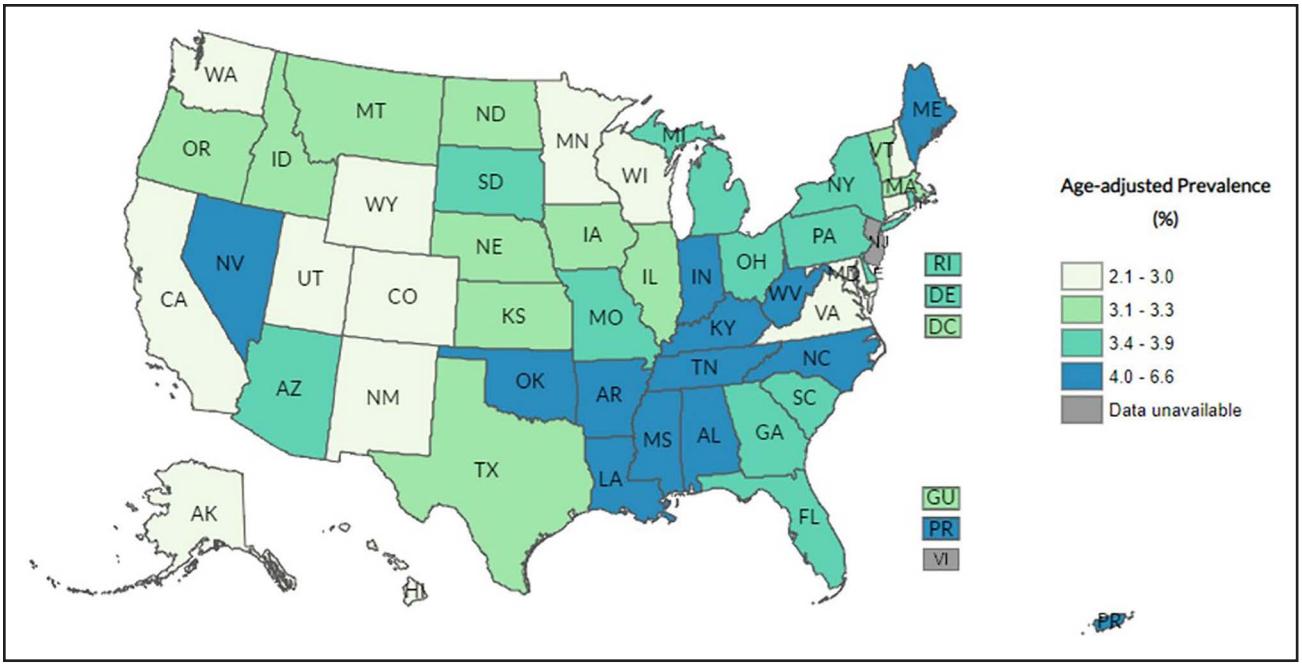

Figure 2. "Ever Told You Had Angina or CHD?" Age-Adjusted US Prevalence, by State (BRFSS Prevalence and Trends Data, 2019).
BRFSS indicates Behavioral Risk Factor Surveillance System; and CHD, coronary heart disease. Source: BRFSS prevalence and trends data. Reprinted with permission from Tsao CW et al.[1] Copyright 2022 American Heart Association, Inc. Original figure has been modified to remove white space between map and legend.

this guideline will address established diagnostic, risk stratification, and treatment approaches in a contemporary context, new therapies, and the intersection between CCD and other comorbid diseases in a framework that recognizes the importance of shared decision-making, team-based care, and cost and value.

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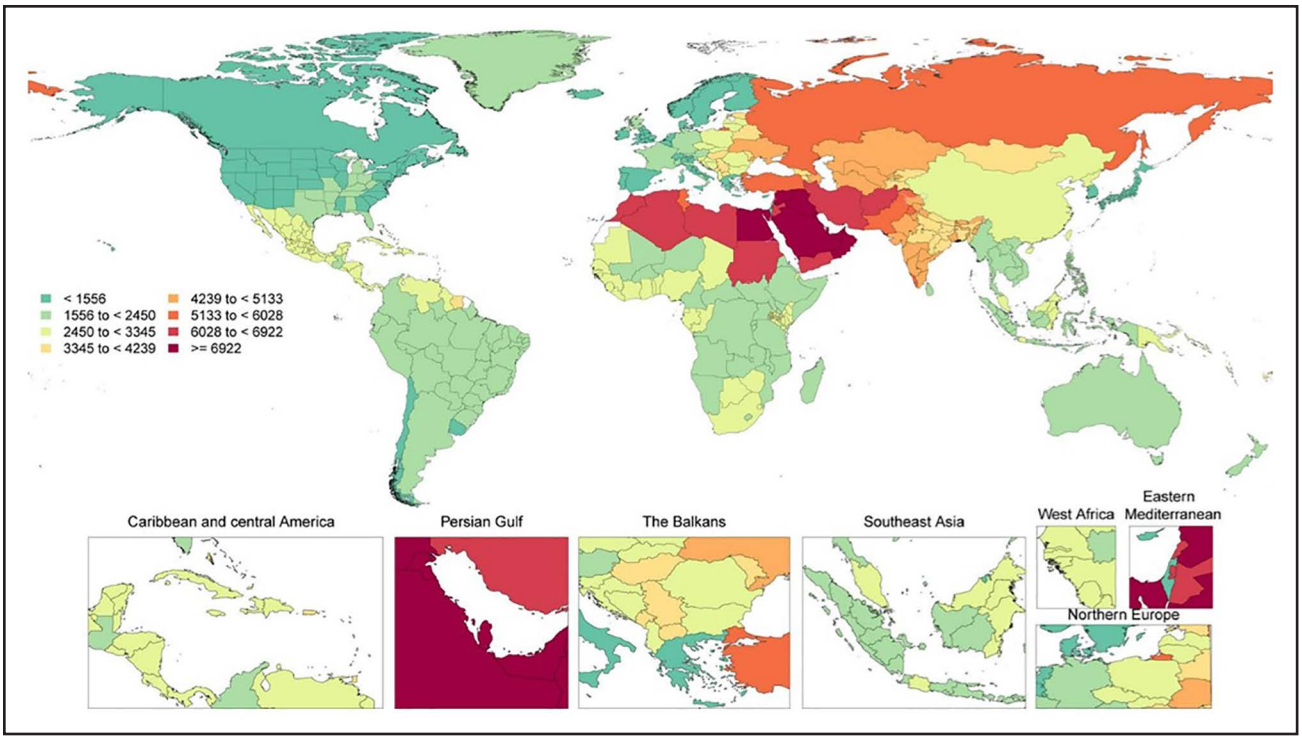

Figure 3. Global Age-Adjusted Prevalence of CCD per 100 000, by Sex, 2020.
CCD indicates chronic coronary disease. Modified with permission from Tsao CW et al.[1] Copyright 2022 American Heart Association, Inc. Source: Data courtesy of the Global Burden of Disease Study 2020, Institute for Health Metrics and Evaluation. Used with permission. All rights reserved. Copyright © 2021 University of Washington. More information is available on the Global Burden of Disease Study website.[5]

3. EVALUATION, DIAGNOSIS, AND RISK STRATIFICATION

3.1. Diagnostic Evaluation

Recommendations for Diagnostic Evaluation
Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	Recommendations
1	B-NR	1. In patients with CCD and a change in symptoms or functional capacity that persists despite GDMT, stress positron emission tomography/single photon emission CT myocardial perfusion imaging (PET/SPECT MPI), cardiovascular magnetic resonance (CMR) imaging, or stress echocardiography is recommended to detect the presence and extent of myocardial ischemia, estimate risk of major adverse cardiovascular events (MACE), and guide therapeutic decision-making.*[1–23]
1	B-R	2. In patients with CCD and a change in symptoms or functional capacity that persists despite GDMT, invasive coronary angiography (ICA) is recommended for guiding therapeutic decision-making with the goal of improving anginal symptoms.*[24–28]
2a	B-R	3. In patients with CCD and a change in symptoms or functional capacity that persists despite GDMT, when selected for rest/stress nuclear MPI, PET is reasonable in preference to SPECT, if available, to improve diagnostic accuracy and decrease the rate of nondiagnostic test results.*[29]
2a	B-NR	4. In patients with CCD and a change in symptoms or functional capacity that persists despite GDMT, exercise treadmill testing can be useful to determine whether the symptoms are consistent with angina pectoris, assess the severity of symptoms, evaluate functional capacity, and guide management.*[26,30–32]
2a	B-NR	5. In patients with CCD undergoing stress PET MPI or stress CMR imaging, the addition of myocardial blood flow reserve (MBFR) can be useful to improve diagnostic accuracy and enhance risk stratification.*[18–23]
2a	B-NR	6. In patients with CCD and a change in symptoms or functional capacity that persists despite GDMT, and who have had previous coronary revascularization, coronary CT angiography (CCTA) is reasonable to evaluate bypass graft or stent patency (for stents ≥3 mm).*[33–37]

*Modified from the 2021 AHA/ACC/Multisociety Guideline for the Evaluation and Diagnosis of Chest Pain.[38]

Synopsis

In patients with CCD, if there is an opportunity to do so, clinicians should first intensify GDMT and defer testing. In patients with CCD, assessing the severity of ischemia may be useful to guide clinical decision-making regarding the use of ICA and for intensification of preventive and anti-ischemic therapy. Imaging should be considered in those with new-onset or persistent stable chest pain. In patients with CCD and frequent angina or severe stress-induced ischemia, referral to ICA or CCTA is an option.[26] For additional recommendations about known obstructive and nonobstructive CAD, suspected ischemia, ischemia with nonobstructive coronary arteries (INOCA), role of invasive testing, and revascularization, refer to the 2021 AHA/ACC chest pain guideline,[38] the 2021 ACC/AHA/SCAI revascularization guideline,[39] as well as Section 6.1.2 ("Ischemia With Nonobstructive Coronary Arteries") of this guideline. Additionally, cost–value considerations for diagnostic testing contained within the 2021 AHA/ACC chest pain guideline, Section 5.3, should be considered.[38]

Recommendation-Specific Supportive Text

1. Observational studies reveal that patients with moderate to severe ischemia on PET and SPECT MPI have an improved outcome with early coronary revascularization.[7,21,40–43] Clinical trials of CMR imaging that included subgroups of patients with obstructive CAD, showed comparable diagnostic accuracy to stress SPECT MPI.[10,11] Several large, multicenter registries revealed that stress CMR imaging effectively risk stratifies patients with known CAD.[14–17] In a multicenter registry of 2496 patients with a history of CAD, an abnormal stress CMR image was associated with a nearly 2-fold increased mortality hazard.[14] Registry data also reported that patients with chest pain syndrome with ischemia by MPI and scarring by late gadolinium enhancement had a relative hazard of 1.5 to 2.1 for cardiovascular death or nonfatal MI.[17] Prognosis worsens for patients by the extent and severity of inducible wall motion abnormalities on stress echocardiography.[44,45] Recent randomized trial evidence supports the role of stress echocardiography to guide clinical decision-making. From the ORBITA (Objective Randomized Blinded Investigation With Optimal Medical Therapy of Angioplasty in Stable Angina) trial, a secondary outcome was a greater reduction in the stress echocardiographic wall motion score among patients with single-vessel CAD treated with percutaneous coronary intervention (PCI) compared with placebo ($P<0.0001$).[46] Patients with PCI and who have a wall motion score ≥1 were more often angina-free compared with those in the placebo arm.
2. Randomized trials of patients with CCD reveal a pattern that ischemia-guided PCI results in an improvement in angina when compared with medical therapy alone.[24-26,47,48] In the ISCHEMIA (International Study of Comparative Health Effectiveness with Medical & Invasive Approaches) trial, 5179 patients with stable CAD and site-determined moderate-severe ischemia on stress testing (patients with ≥50% left main stenosis on CCTA, left ventricular ejection fraction [LVEF] <35%, and unacceptable angina on medical therapy were excluded) were randomized to invasive versus conservative care strategies.[26] No difference

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in the composite primary MACE (cardiovascular death, MI, hospitalization for unstable angina, HF, or resuscitated cardiac arrest) endpoint was observed at ~3.3 years of follow-up. Angina symptoms improved in both the conservative and invasive treatment arms, although improvements were larger in the invasive arm, particularly with more frequent angina at baseline.[48] Therefore, in patients with CCD with known anatomy and ongoing angina despite GDMT, early invasive angiography and revascularization should be considered to improve symptoms. Notably, secondary analyses of RCTs have reported no differences in major adverse cardiovascular outcomes in medical versus invasive medical treatment strategies in patient with CCD[49] when stratified by ischemia severity on noninvasive testing.

3. The improved diagnostic accuracy of PET MPI is helpful in patients with known CAD. In a randomized trial of 322 symptomatic patients with known CAD, the presence of low- and high-risk stress PET findings was associated with lower and higher rates of ICA when compared with SPECT MPI (P=0.001).[29]
4. Observational studies of patients with CAD and stable chest pain have shown that exercise treadmill testing can be useful by evaluating the relation of symptoms to graded stress testing, thereby helping to confirm the diagnosis of angina pectoris; assessing symptom severity; and selecting appropriate management (eg, medical therapy, revascularization, cardiac rehabilitation [CR]).[26,30–32]
5. Reduced MBFR reflects abnormalities of flow within the epicardial coronary arteries, microvasculature, or both, and independently predicts risk of major CAD events. Measurement of MBFR can be effectively accomplished using PET[18,50,51] or CMR.[15] Normal MBFR may be helpful in excluding high-risk anatomy, although global reduced levels (<2) may provide a better estimate of disease extent and severity. Nonobstructive CAD with reduced MBFR is more frequently observed in women.[50]
6. CCTA is accurate for the assessment of native vessel CAD and bypass graft patency with high accuracy (~96%) and concordance (82% to >93%) to ICA. It may also be useful to assess patency of proximal large stents (≥3 mm) if such information is known at the time of presentation.[33–37] Other modalities may be considered in patients with CCD with smaller or more distal stents. Several controlled clinical trials have evaluated the concordance of fractional flow reserve (FFR)-CT with invasive FFR.[52–55] Diagnostic sensitivity of FFR-CT compared with invasive FFR is high.

3.2. Risk Stratification and Relationship to Treatment Selection

Recommendations for Risk Stratification and Relationship to Treatment Selection
Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	Recommendations
Risk Stratification and Prognosis		
1	B-NR	1. In patients with CCD, it is recommended that risk stratification incorporate all available information, including noninvasive, invasive, or both cardiovascular diagnostic testing results or use validated risk scores to classify patients as low (<1%), intermediate (1%-3%), or high (>3%) yearly risk for cardiovascular death or nonfatal MI.[1–4]
Relationship to Treatment		
1	A	2. In patients with CCD, optimization of GDMT is recommended to reduce MACE.*[5–7]
1	A	3. In patients with CCD with newly reduced LV systolic function, clinical heart failure, or both, ICA is recommended to assess coronary anatomy and guide potential revascularization.[8,9]
3: No benefit	A	4. In patients with CCD, ICA for risk stratification is not routinely recommended in patients without LV systolic dysfunction, heart failure, stable chest pain refractory to GDMT, and/or noninvasive testing suggestive of significant (>50%) left main disease.[5–7,10,11]

*Modified from the 2021 AHA/ACC/Multisociety Guideline for the Evaluation and Diagnosis of Chest Pain.[12]

Synopsis

In patients with CCD, the results of noninvasive or invasive testing alone are insufficient to accurately risk stratify an individual's annual future risk of future cardiovascular death or nonfatal MI.[13] Clinicians should integrate cardiovascular test results with demographic, social, and medical variables (Table 5) and use validated risk prediction models (where available) to estimate the annual cardiovascular risk. Although multiple randomized trials have shown that routine revascularization does not lead to a reduction in MACE, a symptom and integrated risk assessment may help identify subsets of patients, such as those with persistent angina, reduced LV function or HF, who may benefit from routine revascularization.[5-8,14]

Recommendation-Specific Supportive Test

1. Noninvasive test results alone are insufficient to adequately risk stratify patients with CCD, and the additional information improves risk prediction.[4] In an externally validated study of patients who underwent an exercise stress testing, the Duke Treadmill Score alone had a c-index of 0.62 for all-cause death, but the addition of clinical variables into an integrated risk score improved discrimination (c-index=0.83) and reclassified 64% of low-risk Duke Treadmill Score scores to intermediate or high risk.[1] Externally validated risk scores lack

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Table 5. Potential Features Associated With a Higher Risk of MACE Among Patients With Established CCD

Demographics and Socioeconomic Status (also see Section 4.1.4, "Social Determinants of Health")
Age
Male sex
Poor social support
Poverty or lack of health care access
Past or Concurrent Medical, Mental Health Conditions
Elevated body mass index
Previous MI, PCI, or CABG
HF
Atrial fibrillation or flutter
Diabetes
Dyslipidemia
Chronic kidney disease
Current or former smoker
Peripheral artery disease
Depression
Poor adherence with goal-directed pharmacotherapy
Ancillary Cardiac Testing or Imaging
Inability to exercise
Angina with stress
ECG: left bundle branch block, left ventricular hypertrophy, higher resting heart rate
Echocardiography: reduced left ventricular ejection fraction, left ventricular hypertrophy
EST: higher DTS, higher resting heart rate, achieved heart rate <85% predicted
Exercise or dobutamine stress echocardiography: higher DTS, lower exercise workload, peak rate-pressure product <15 000, coronary flow reserve <2, no change or increase in left ventricular end-systolic volume, reduced ejection fraction, ischemic electrocardiographic changes with stress
SPECT or PET: Percentage fixed myocardium on SPECT, transient ischemic dilation with stress, reduced coronary flow reserve, ischemic electrocardiographic changes with stress
Higher calcium score: alone and in addition to functional imaging
CCTA: total plaque burden, high-risk plaque (positive remodeling [remodeling index >1.1], low attenuation [mean CT number <30 HU], or napkin-ring sign), reduced CT-fractional flow reserve
CMR: reduced left and/or right ventricular ejection fraction, left ventricular hypertrophy, scar or infarct, reduced myocardial perfusion reserve, myocardial blood flow at stress
Biomarkers
High-sensitivity troponin, B-type natriuretic peptide

CABG indicates coronary artery bypass graft; CCD, chronic coronary disease; CCTA, coronary computed tomography angiography; CMR, cardiovascular magnetic resonance imaging; CT, computed tomography; DTS, Duke Treadmill Score; ECG, electrocardiogram; EST, exercise stress test; HF, heart failure; HU, Hounsfield units; MACE, major adverse cardiovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention; PET, positron emission tomography; and SPECT, single-photon emission computed tomography.

some functional and anatomic testing modalities, but observational studies and secondary analyses from randomized trials consistently report that the addition of clinical and ancillary imaging variables are associated with improved risk prediction (Table 5).[3,4,15–44] A meta-analysis of 165 studies reported that in patients with a normal functional test for CCD, a negative study did not uniformly predict a <1% annual risk of cardiovascular death or nonfatal MI, suggesting that population and patient differences may be associated with prognosis.[13] The lone exception is a normal CCTA.[45,46] Previous AHA/ACC guidelines have recommended stratifying patients with CCD as low (<1% annual risk), intermediate (1%-3% annual risk), or high (>3% annual risk) risk for MACE.[47,48] Although these cutoffs are somewhat arbitrary and may be grounded in historical Bethesda Conference recommendations based on Duke Treadmill Score risk tertiles, we suggest maintaining these categorizations for annual cardiovascular death or nonfatal MI.[47,49,50]

2. The 2021 AHA/ACC chest pain guideline recommends the optimization of anti-ischemic and preventive therapies with the goal to reduce the patient's angina burden and improve clinical outcomes.[12] Three major RCTs including COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation), ISCHEMIA, and BARI-2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) have shown that there is no reduction in MACE with routine cardiovascular revascularization.[5–7] The COURAGE trial, which included patients with stabilized Canadian Cardiovascular Society class IV angina and at least a 70% stenosis in at least 1 coronary artery with evidence of ischemia, reported no difference in all-cause death or nonfatal MI between revascularization with PCI and optimal medical therapy. The BARI-2D trial randomized patients with type 2 diabetes and CCD (≥70% stenosis of a major coronary artery and angina *or* ≥50% stenosis of a major coronary artery with a positive stress test) to revascularization or medical therapy and reported no difference in survival.
3. The STICH (Surgical Treatment for Ischemic Heart Failure) trial randomized 1212 patients with an ejection fraction ≤35% with coronary disease amenable to coronary artery bypass grafting (CABG) to either medical therapy alone or medical therapy and CABG. After a median follow-up of 56 months, no significant difference was observed in the primary outcomes of all-cause death (41% versus 36%; P=0.12), but cardiovascular death (33% versus 28%; P=0.05) and all-cause death or cardiovascular hospitalization (68% versus 58%; P<0.001) were lower in the CABG arm.[9] In a secondary analysis of the ISCHEMIA trial, 398 participants had HF or an LVEF <45%. Both the 4-year primary composite endpoint (17.2% versus 29.3%; event rate difference, −12.1% [95% CI, −22.6 to −1.6]) and cardiovascular death or MI (14.6% versus 25.9%; event rate difference

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−11.4% [95% CI, −21.4 to −1.4]) were lower in the invasive treatment arm.[8] The REVIVED-BCIS2 trial randomized 700 patients with and LVEF ≤35% with CCD amenable to PCI to either medical therapy or PCI plus medical therapy and reported no difference all-cause death or health failure hospitalization (38.0% versus 37.2%).[51] In addition to revascularization, ICA can also help diagnose the cause of HF and help direct medical therapies (eg, lipid lowering). We acknowledge the data are less robust for patient with HF with preserved ejection fraction.[9] Noninvasive modalities may be appropriate to evaluate for coronary ischemia in some circumstances. Alternatively, CCTA may be considered as an initial diagnostic strategy in selected patients with suspected nonischemic cardiomyopathy.[52]

4. Three multicenter trials (COURAGE, BARI 2D, ISCHEMIA) showed no improvement in clinical endpoints in patients with CCD randomized to routine revascularization plus GDMT or initial GDMT; although 21% to 42% of patients randomized to GDMT eventually underwent revascularization.[5–7] In a secondary analysis of the ISCHEMIA trial, although ischemia severity on noninvasive testing was associated with all-cause death, no treatment interaction was observed when participants were stratified by mild, moderate, or severe ischemia.[10] Similarly, in a secondary analysis of the COURAGE trial limited to the 60% of patients with stress perfusion imaging and coronary angiography information available, there was no interaction between therapeutic strategy and either severity of ischemia or coronary anatomy.[11]

4. TREATMENT

4.1. General Approach to Treatment Decisions

Recommendations for General Approach to Treatment Decisions Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	Recommendations
1	C-LD	1. In patients with CCD, clinical follow-up at least annually is recommended to assess for symptoms,[1–12] change in functional status, adherence to and adequacy of lifestyle and medical interventions,[13–15] and monitoring for complications of CCD and its treatments.[16–18]
2b	B-NR	2. In patients with CCD, use of a validated CCD-specific patient-reported health status measure may be reasonable to assess symptoms, functional status, and QOL.[19–23]

Synopsis

The ultimate goals for treatment of CCD are to prolong survival and improve QOL. To do this, treatments should target a reduction in (1) cardiac death, (2) nonfatal ischemic events, (3) progression of atherosclerosis, and (4) symptoms and functional limitations of CCD while considering patient preferences, potential complications of procedures/medications, and costs to the health care system. When engaging patients in shared decision-making (Section 4.1.3), clinicians should clearly identify that some therapies may improve patient's symptoms whereas other therapies may reduce the risk of ischemic events. To optimize treatment for each patient, several factors should be considered (Figure 4).[24,25]

First, a global assessment of the risk of the patient is needed (Section 3), including both the risk of ischemic events and complications of potential treatment options. Second, obtaining a careful assessment of symptoms of CCD, functional limitations, and QOL is important. Third, SDOH (Section 4.1.4) must be considered. Fourth, the patient must be educated (Section 4.1.2) so they can actively participate in shared decision-making (Section 4.1.3). Finally, a team-based approach (Section 4.1.1) can help patients and clinicians navigate this process.

Recommendation-Specific Supportive Text

1. Patients with CCD comprise a heterogeneous group that includes those with or without angina, a history of coronary revascularization, and previous ACS. The goals of routine clinical follow-up in these patients include: (a) to assess for new or worsened symptoms, change in functional status, or decline in QOL; (b) to assess for adherence to and adequacy of recommended lifestyle and medical interventions, including physical activity, nutrition, weight management, stress reduction, smoking cessation, immunization status, blood pressure (BP) and glycemic control, and antianginal, antithrombotic, and lipid-lowering therapies[13–15]; and (c) to monitor for complications of disease or adverse effects related to therapy.[16,17] Although there are insufficient data on which to base a definitive recommendation regarding frequency, clinical follow-up evaluation at least annually is recommended and may be sufficient if the patient is stable on optimized GDMT and reliable enough to seek care with a change in symptoms or functional capacity. For select individuals, an annual in-person evaluation may be supplemented with telehealth visits when clinically appropriate.[26] Implementation of remote, algorithmically driven-disease management programs may provide a useful adjunctive strategy to achieve GDMT optimization in eligible patients.[27]
2. Revascularization[1-3,12] and antianginal medications[4–7] primarily reduce the symptoms of CCD. The factor most strongly associated with improvement in symptoms and QOL after revascularization is the burden of ischemic symptoms before intervention.[8-12,28–30] Thus, assessment of symptoms at each clinic visit is important to identify times when additional interventions could be useful, as well as to quantify the symptomatic response to

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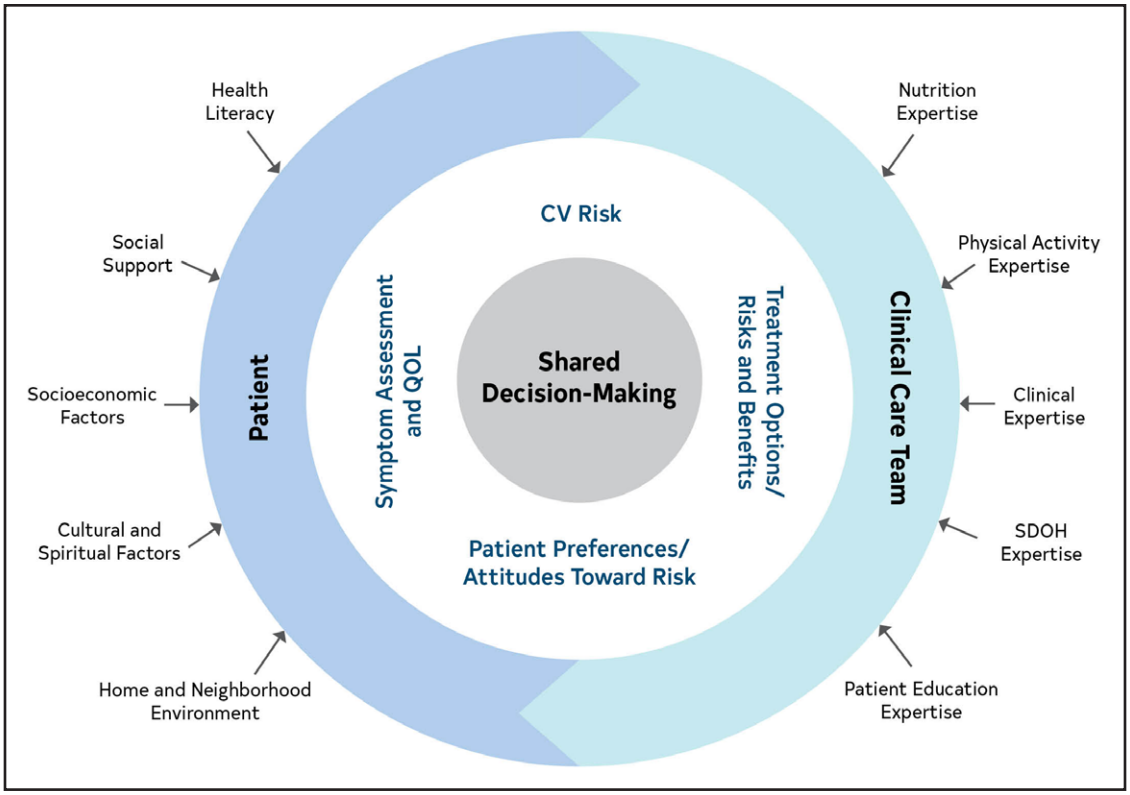

Figure 4. Domains to Consider When Seeing a Patient With CCD.
CCD indicates chronic coronary disease; CV, cardiovascular; QOL, quality of life; and SDOH, social determinants of health.

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interventions. Observational studies suggest that clinicians may inaccurately estimate the burden of ischemic symptoms,[19–21] which can lead to under-[22] or overtreatment.[21] Validated patient-reported disease-specific health status measures (eg, 7-item Seattle Angina Questionnaire[31]) may help to reliably quantify the burden of CCD symptoms and reduce variation in assessment among clinicians.[23] Furthermore, patient-reported disease-specific health status instruments also measure how the patient's angina affects their QOL, which should be an important component of the treatment decision process. Although several studies showed deficiencies with clinician estimation of patient's symptoms, no studies show an improvement in quality of care or outcomes with routine use of patient-reported measures in clinical care.

4.1.1. Team-Based Approach

Recommendation for Team-Based Approach Referenced studies that support the recommendation are summarized in the Online Data Supplement.		
COR	**LOE**	**Recommendation**
1	A	1. In patients with CCD, a multidisciplinary team-based approach is recommended to improve health outcomes, facilitate modification of ASCVD risk factors, and improve health service utilization.*[1–13]

*Modified from the 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease.[14]

Synopsis

A patient-centered, team-based approach that focuses on shared decision-making is essential to monitoring and managing patients' CCD symptoms throughout their disease course. These recommendations apply to all aspects of clinical practice for long-term management of CCD. A team-based approach can effectively be applied to nearly all aspects of CCD management and care. Continuous communication among the care team, the patient, and any caregivers is essential to optimize outcomes and meet patient needs. Figure 5 reflects the interconnectedness of the patient and caregiver to the care team and the care team members to each other. Components of the health care team include but are not limited to: physicians; nurse practitioners; physician assistants; nurses and nursing assistants; pharmacists; dietitians; exercise physiologists; physical, occupational, and speech therapists; psychologists; and social workers.

Recommendation-Specific Supportive Text

1. RCTs and systematic reviews with meta-analysis show that a patient-centered, multidisciplinary, team-based approach can improve patient self-efficacy, health-related QOL, and ASCVD risk factor management compared with usual care in patients with CCD who also

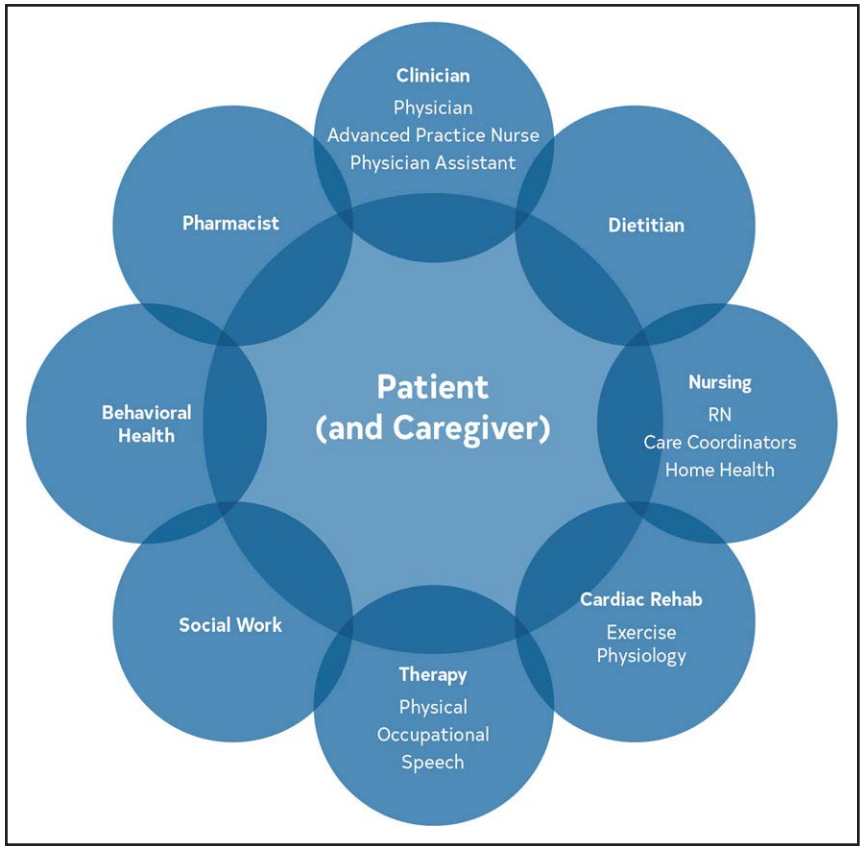

Figure 5. Team-Based Approach Reflective of Interconnectedness and Communication.
RN indicates registered nurse.

may have hypertension, diabetes, or hyperlipidemia.[1-8,11-13,15–34] Patients actively involved in their care with the medical team tend to have greater knowledge and confidence in self-management, which improves health-related QOL.[1,21,32] Team-based care also facilitates behavior change and promotes weight loss, tobacco cessation, and reduces depression.[8,12,16,31,33,35] A team-based approach may be more cost-effective and cost-efficient compared with usual care and reduces emergency department visits, unplanned health service utilization, cardiovascular complications in patients with diabetes, and readmission costs.[6,7,9,10,20-22,27,28,31,32,34] A large cohort study comparing health care resource utilization of >1 million patients with either diabetes or ASCVD found that, overall, health care resource utilization was comparable among patients receiving care from physicians compared with advanced practice providers, although physicians work with larger patient panels.[9] Communication through telehealth, patient education sessions, specialty clinics, medication therapy management, and patient decision support aids are appropriate and useful methods for providing patient care.[36] Refer to Sections 4.1, 4.2, 4.3, and 7 for management.

4.1.2. Patient Education

Recommendations for Patient Education Referenced studies that support the recommendations are summarized in Online Data Supplement.		
COR	**LOE**	**Recommendations**
1	C-LD	1. Patients with CCD should receive ongoing individualized education on symptom management, lifestyle changes, and SDOH risk factors to improve knowledge and facilitate behavior change.[1]
1	C-LD	2. Patients with CCD should receive ongoing individualized education on medication adherence to improve knowledge and facilitate behavior change.[2–4]

Synopsis

Patient education is defined as "the process by which health professionals and others impart information to patients that will alter their health behaviors or improve their health status."[1,5] Systematic reviews of studies using educational interventions suggest they improve patient knowledge and facilitate behavior change,[1] although impact on sustained lifestyle change, cholesterol and BP levels, and morbidity and mortality rates are less clear.[5–7] A meta-analysis of secondary prevention programs suggested education and counseling after MI reduced mortality but not recurrent MI.[6] In contrast, a review of RCTs on educational interventions among patients with various

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manifestations of coronary disease concluded that education had no effect on total mortality, recurrent MI, or hospitalizations.[5] Yet, Swedish registry data suggest that the education component of CR is strongly linked to cardiovascular and total mortality.[7] Published studies of educational interventions for patients with CCD, whether provided in person or by Internet, are heterogeneous, often incompletely described, many are short-term, and outcomes assessment varies. At this time, there are insufficient comparative data to provide clinicians and their care teams assistance when choosing among interventions, a gap that should be addressed in future research studies.

Recommendation-Specific Supportive Text

1. A systematic review of the effect of patient education reported improvement in knowledge about medications and appropriate responses to symptoms,[1] as well as improvements in physical activity, dietary habits, and smoking cessation rates, but no convincing evidence of improvement in response to cardiac symptoms or psychosocial well-being was observed.[1] A review of 7 RCTs of Internet-based education and support found there was some supportive evidence for these interventions, but the overall effectiveness could not be determined.[8] Education should be tailored to individual patients and their caregivers, reinforced at regular intervals, and modified as the patient's circumstances change. Health literacy is defined as "the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions."[9] Verbal and written communications should be designed at the appropriate reading level, preferably in a patient's native language, and culturally and contextually appropriate. The Agency for Healthcare Research and Quality has created a toolkit with detailed guidance on improving written and spoken communication, self-management and empowerment, and improving supportive systems.[10] Internet-based self-management programs to improve access to ongoing support have been developed, but data on their efficacy are limited.[8]
2. Of the 68 trials and 20 intervention approaches in an Agency for Healthcare Research and Quality comparative effectiveness analysis, only 1 trial enrolled patients with CCD (those with recent MI).[4] In that trial, patients in the treatment arm had 1.3 extra days of medication coverage per month over 9 months of follow-up and were 17% more likely to have >80% adherence compared with patients in the control arm. No significant difference in persistence of medication use was observed.[11] Another systematic review found no convincing evidence of improved medication adherence with educational interventions.[1] A 2020 systematic review of pharmacist-based patient education for patients on cardiovascular medications (only some with CCD) concluded that the interventions improved medication adherence but not necessarily clinical outcomes.[2] Another systematic review with the goal of comparing outcomes of different types of educational interventions targeting medication adherence found interventions delivered by pharmacists and nurses had the most favorable outcomes, although results were very heterogeneous.[12] A recent RCT of a pharmacist-administered intervention that used motivational interviewing to improve medication adherence among CCD patients improved medication adherence but had no effect on low-density lipoprotein cholesterol (LDL-C) levels, systolic BP, unplanned health care contact, or physical or emotional scores of the Heart Quality of Life Instrument.[3]

4.1.3. Shared Decision-Making

Recommendations for Shared Decision-Making
Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	Recommendations
1	C-LD	1. Patients with CCD and their clinicians should engage in shared decision-making particularly when evidence is unclear on the optimal diagnostic or treatment strategy, or when a significant risk or benefit tradeoff exists.[1–3]
2b	B-R	2. For patients with CCD and angina on GDMT who are engaged in shared decision-making regarding revascularization, a validated decision aid may be considered to improve patient understanding and knowledge about treatment options.[4]

Synopsis

Shared decision-making is a collaborative decision-making process that includes patient education about risks, benefits, alternatives to treatment and testing options, and clinician ascertainment of patient values and goals. Shared decision-making helps to maximize patient engagement in medical decision-making, increase patient knowledge about their care, and align treatment decisions with patient preferences. Even when evidence suggests one treatment or testing modality compared with another may lead to improved cardiovascular outcomes at a population level, the optimal treatment or testing choice for an individual patient may vary based on patient values and preferences, as well as the financial implications of the choice to the patient. Decision aids can improve knowledge and reduce decisional conflict in shared decision-making, but few validated decision aids are available for patients with CCD. Clinician-patient conversations, as well as corresponding educational materials, should be tailored to the patient's preferred language, reading level, health literacy, and visual acuity.

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Recommendation-Specific Supportive Text

1. Most patients prefer to have an active role in their treatment decisions.[1-3,5] The right to information includes patients without decision-making capacity or who have chosen to defer treatment decisions to a designated caregiver. In shared decision-making, clinicians inform patients of the availability, risks, benefits, and alternatives of all medically appropriate testing or treatment options (which may include no testing or treatment), confirm patient understanding, assess patient values and treatment goals, and collaborate with patients to decide about their care. Patients may choose to include others in the shared decision-making process. Patient choices can include a treatment or therapeutic decision, an active choice to defer the decision, or a delegation of that decision to their care team or other designated individual. Patients and clinicians should engage in shared decision-making particularly when multiple medically appropriate options are available, when treatments or testing options confer increased risks, or when evidence is unclear on the optimal treatment strategy or when a risk:benefit tradeoff exists between different options. In patients with CCD, example areas for shared decision-making include duration, dose, and choice of antithrombotic therapy for secondary prevention and revascularization or medical therapy for stable angina.
2. Decision aids can increase patient knowledge, accuracy of risk perception, and agreement between patient values and care choices made, and may reduce decisional conflict for patients, but aids have not been developed and validated for many decisions made by patients with CCD.[6] Before implementation of any decision aid, the decision aid should be developed according to best practice and validated in the target population.[7–9] Decision aids should augment, not replace, conversations between clinicians and patients. The decision aid PCI Choice was shown to increase knowledge about therapy options among patients with CCD choosing between optimal medical therapy alone or with PCI.[4]

4.1.4. Social Determinants of Health

Recommendation for SDOH
Referenced studies that support the recommendation are summarized in the Online Data Supplement.

COR	LOE	Recommendation
1	B-R	1. In patients with CCD, routine assessment by clinicians and the care team for SDOH is recommended to inform patient-centered treatment decisions and lifestyle change recommendations.*[1–8]

*Modified from the 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease.[9]

Synopsis

SDOH, such as health care access, economic stability, and social context are key drivers of persistent health disparities and health inequities.[1,10–13] SDOH have profound influences on the health and well-being of patients with CCD and have become increasingly recognized in cardiovascular medicine.[2,9,10,14–18] There is an intersection of SDOH with sex, socioeconomic class, race, ethnicity, sexual orientation, and social vulnerabilities.[12,19–21] SDOH impact all stages of CCD management, including secondary prevention, treatment, access to care, and patient follow-up (Section 7.1, "Follow-Up Plan and Testing") and self-management.[14] Clinicians should ensure health equity in cardiovascular care by viewing each patient through an SDOH lens with cultural humility to formulate comprehensive care plans (Figure 6). Brief, evidence-based screening tools are available to support clinicians in identifying SDOH that may negatively affect health outcomes and health care utilization.[4,13,22–24] Routine SDOH screening in patients with CCD by clinicians or front-line staff should encompass assessment of mental health (Section 4.2.2), psychosocial stressors, health literacy, sociocultural influences (language, religious affiliation, body image), financial strain, transportation, insurance status, barriers to adherence to a heart healthy diet (food security) (Section 4.2.1, "Nutrition, Including Supplements"), neighborhood or environmental exposures (Section 4.2.11), and viable options for regular physical activity (Section 4.2.10, "Cardiac Rehabilitation") and social support.[1,2,25] Based on identified barriers or needs, collaborative cardiovascular care teams can provide tangible and practical community-based resources and services to patients.[2,26–28] Operationalization of guidelines on addressing SDOH requires embedding health equity into clinical practice, team-based care, patient education, and shared decision-making tools (Sections 4.1.1, 4.1.2, and 4.1.3).[13,14,17,19,29–33]

Recommendation-Specific Supportive Text

1. Integration of SDOH is based on evidence showing the effect of SDOH on long-term cardiovascular outcomes.[9,10] Patients experiencing an MI at a young age had higher neighborhood disadvantage that was associated with 57% higher cardiovascular mortality after an 11-year period.[34] Women in the lower-income bracket were more likely to be under- or uninsured and had higher medication costs and higher 5-year rehospitalization rates compared with higher-income women.[35] Lower education and income levels were associated with lower prescribing of GDMT, as well as outcomes post-MI.[2,36–39] Further, there are disparities in CR (Section 4.2.10) referral and completion among racial and ethnic minorities, women, according to socioeconomic status, and across those living in rural and dense urban

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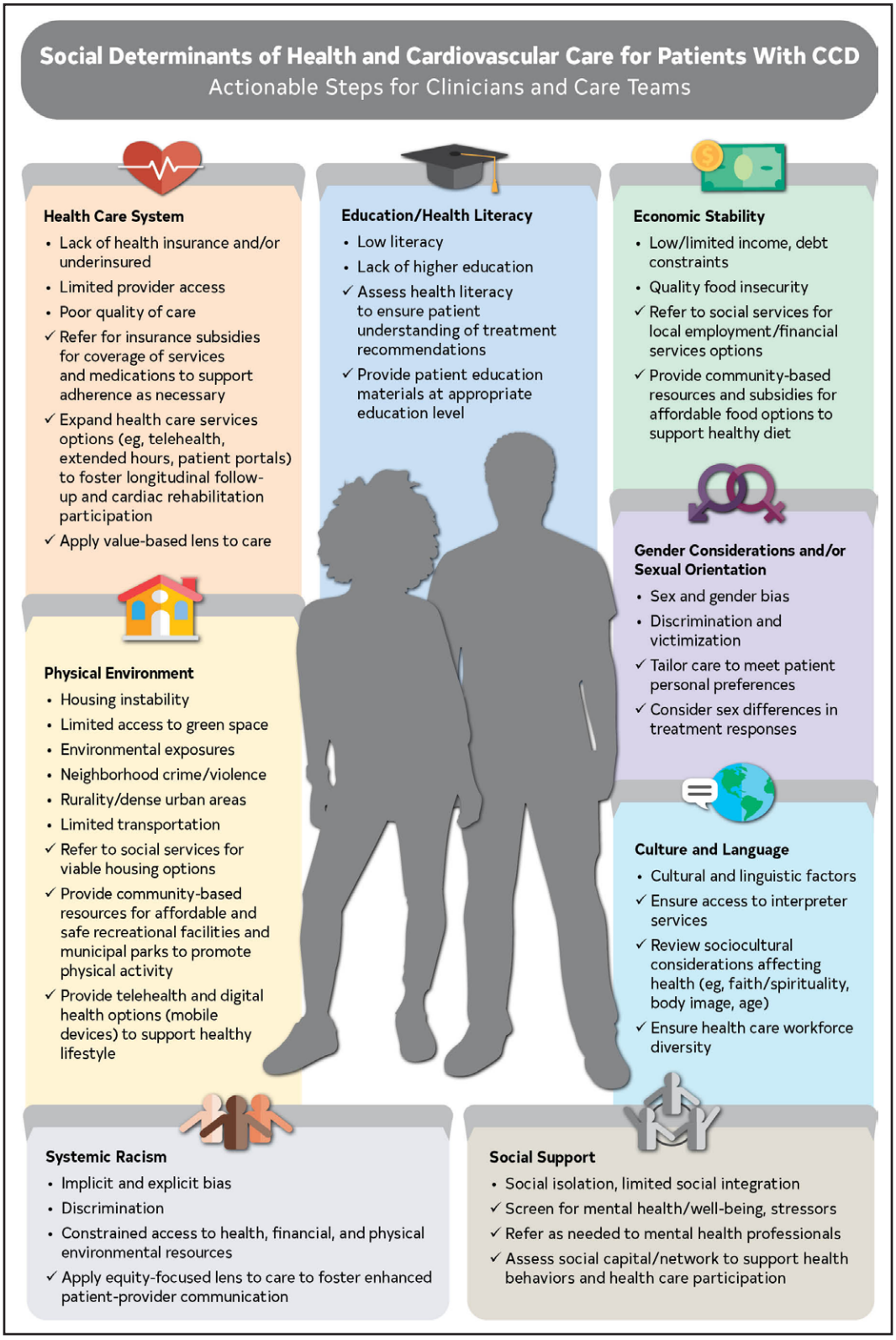

Figure 6. Social Determinants of Health and Cardiovascular Care for Patients With CCD.
• Identifies SDOH issue. ✓ Considerations for clinicians and care teams. CCD indicates chronic coronary disease, and SDOH, social determinants of health. Adapted with permission from Lindley KJ et al.[3] Copyright 2021 American College of Cardiology Foundation.

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areas.[2,40–42] Neighborhood environment influences healthy lifestyle promotion and maintenance, management of traditional and nontraditional cardiovascular risk factors, and outcomes.[43–48] Telehealth and digital interventions are promising strategies to improve access to health care, management and health behaviors; however, consideration of SDOH influences is warranted.[3,29,49–51] Empirical evidence supports the use of screening tools in patients with multiple chronic diseases to efficiently assess SDOH in the clinical setting, facilitate tailoring of individualized care plans, and improve quality of care and outcomes.[4,22,30,31,52–54] Collaborative partnerships between health care systems and community-based organizations can assist clinicians, patients, and their families in meeting unmet social needs as an extension of standard cardiovascular care for health equity.[3,55]

4.2. Guideline-Directed Management and Therapy

4.2.1. Nutrition, Including Supplements

Recommendations for Nutrition, Including Supplements
Referenced studies that support the recommendations are summarized in Online Data Supplement.

Recommendations		
COR	**LOE**	**Nutrition**
1	**B-R**	1. In patients with CCD, a diet emphasizing vegetables, fruits, legumes, nuts, whole grains, and lean protein is recommended to reduce the risk of CVD events.*[1–4]
2a	**B-NR**	2. In patients with CCD, reducing the percentage of calories from saturated fat (<6% of total calories) and replacing with dietary monounsaturated and polyunsaturated fat, complex carbohydrates, and dietary fiber can be beneficial to reduce the risk of CVD events.*[1–6]
2a	**B-NR**	3. In patients with CCD, minimization of sodium (<2300 mg/d; optimally 1500 mg/d) and minimization of processed meats (eg, cured bacon, hot dogs) can be beneficial to reduce the risk of CVD events.*[2,3,6,7]
2a	**B-NR**	4. In patients with CCD, limiting refined carbohydrates (eg, containing <25% whole grain by weight, including refined cold ready-to-eat breakfast cereal, white bread, white rice), and sugar-sweetened beverages (eg, soft drinks, energy drinks, fruit drinks with added sugars) can be beneficial to reduce the risk of CVD events.*[2–4,6,8]
3: Harm	**B-NR**	5. In patients with CCD, the intake of *trans* fat should be avoided because *trans* fat is associated with increased morbidity and mortality rates.*[9,10]
Nutrition Supplements		
3: No Benefit	**B-NR**	6. In patients with CCD, the use of nonprescription or dietary supplements, including omega-3 fatty acid, vitamins C, D, E, beta-carotene, and calcium, is not beneficial to reduce the risk of acute CVD events.[11–22]

*Modified from the 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease.[23]

Synopsis

Among patients with CCD, dietary behavior changes along with GDMT are important to reduce the risk of acute CVD events including ASCVD, and outcomes related to HF, stroke, and CVD-related deaths.[1,2,24] Among patients with CCD, it is well established that healthy dietary choices improve management of CVD risk factors and target pathophysiologic mechanisms contributing to acute CVD events.[25,26] Studies across diverse populations support the health benefits of a higher intake of whole grains and fiber, with lower intake of saturated fat, sodium, refined carbohydrates, and sweetened beverages[23,27,28] (Figure 7). Healthy dietary choices combined with caloric reduction will support weight loss goals and improve cardiometabolic health for overweight and obese patients.[29,30] In contrast, nonprescription nutrition or dietary supplements[28] have insufficient evidence to support their use to reduce the risk of acute CVD events in patients with CCD.[18,31] For this guideline, nutrition supplements is defined by the National Institutes of Health – Office of Dietary Supplements as nonprescription, dietary supplements that contain minerals (eg, calcium), herbs, amino acids, and vitamins across all dosage forms (eg, tablets, gummies).[32]

Recommendation-Specific Supportive Text

1. Mediterranean-type dietary plans with higher intake of healthy plant-based foods and lean protein (eg, fish), with lower quantities of saturated fat (eg, red meat) help reduce cardiovascular risk factors, including insulin resistance, diabetes, dyslipidemia, hypertension, and obesity.[1,2,30,33–35] Multiple secondary CVD prevention studies showed lower risk of subsequent CVD events and total mortality rate with higher intake of healthy plant-based diets, including Mediterranean diets.[1-3,33] The Lyon Diet Heart Study randomized participants hospitalized with their first MI to a Mediterranean diet intervention or usual care.[2] After a mean intervention follow-up of 44.9 months, the Mediterranean diet showed up to a 65% reduction in composite CVD outcomes (cardiac death and nonfatal MI).[2] Additionally, multiple prospective cohorts showed an inverse relationship between lower all-cause death, greater adherence across multiple components of the Mediterranean diet (including fish),[36] and higher intake of healthier plant-based options.[37] Specific dietary components and serving sizes have varied across studies[1]; the AHA has previously published recommendations according to energy needs and weight loss goals.[30] However, additional research is needed on mechanisms associated with Mediterranean-diet patterns, CVD death, and all-cause death.[1]

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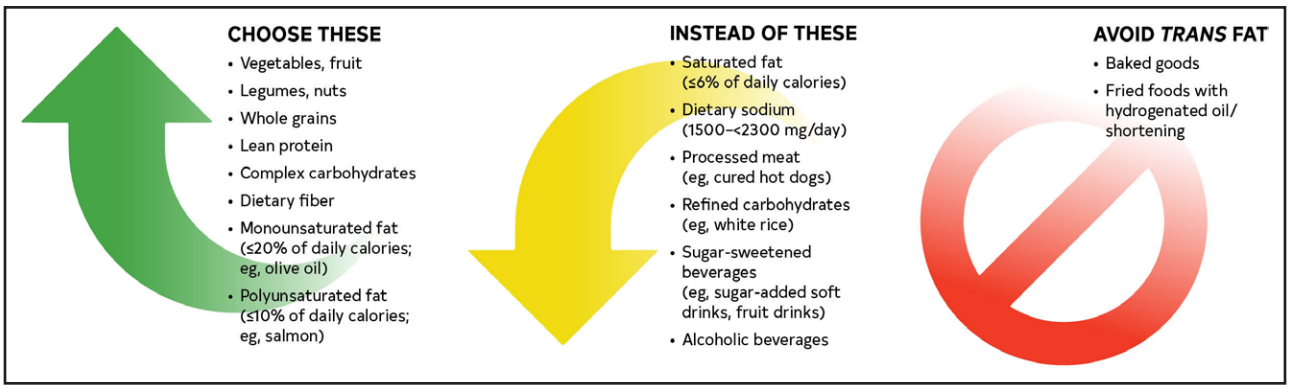

Figure 7. Recommended Nutrition.

2. Implementation of healthy plant-based and Mediterranean-based diets includes reducing saturated fat and optimizing caloric intake to include higher intake of monounsaturated fats, polyunsaturated fats, and complex carbohydrates.[2,34,35,38] Higher dietary fiber intake is associated with improvement in CVD risk factors, including lower BP, improved insulin sensitivity, and support of weight loss goals,[3,5] in addition to a lower risk of CVD events and all-cause death in patients with CCD.[3] A meta-analysis of prospective cohorts and randomized clinical trials supports a dose-response relationship of higher quality carbohydrate intake and lower CVD-related morbidity and mortality rates.[5,39] For patients at higher CVD risk, the AHA recommends lowering saturated fatty acids to <6% of total caloric intake.[30] Reduction in saturated fatty acids, with healthier fat and carbohydrate intake, lowers LDL-C, which is associated with lower CVD morbidity and mortality rates.[3,30,38–40] A recent Cochrane review of randomized trials that reduced saturated fat intake, altered dietary fats, or both highlighted a 17% reduction of CVD events in patients with CCD.[6] Among secondary prevention trials, the number needed to treat for an additional benefit was 53, by lowering saturated fat >4 years.[6,29]
3. Dietary sodium reduction to <2300 mg/d (optimal target of 1500 mg/d) is important to lower BP.[8,41] Sodium reduction with a healthy diet reduces the risk of future CVD events, even in patients with CCD.[3,7] Recent analysis of the DASH (Dietary Approaches to Stop Hypertension)-Sodium study showed that sodium reduction may improve biomarkers of cardiac injury, inflammation, and cardiac strain.[42] Dietary education should highlight potential sources of dietary sodium, including processed meat, which is a significant contributor to dietary sodium in the United States.[43,44] According to the AHA, processed meats include smoked, cured, salted meats, and/or meats with chemical preservatives.[23] Although the DASH diet supports higher potassium intake,[8] insufficient data are available in populations with CCD to provide specific potassium recommendations.
4. The consumption of simple carbohydrates (eg, high-fructose corn syrup) and refined grains (eg, containing <25% whole grain by weight, including some refined cold ready-to-eat breakfast cereal, white bread, white rice)[4] has adverse effects on lipoproteins, including LDL-C, apolipoprotein B, and plasma triglycerides.[6,38] Minimizing intake of simple carbohydrates and refined grains supports a healthier cardiometabolic profile.[4,6,39] Sugar-sweetened beverages are defined by the AHA as "manufactured carbonated and noncarbonated beverages containing caloric sweeteners or syrups and include caloric soft drinks (ie, not sugar-free), fruit drinks, sports and energy drinks, sweetened waters, and tea and coffee beverages with added sugars."[45] Sugar-sweetened beverage consumption is associated with an increased risk of CVD events, including in patients with CCD,[3] and associated with chronic conditions including diabetes, CKD, and obesity.[23,46] Overall, multiple healthy dietary components, including reduction in dietary sodium, sugar-sweetened beverages, and saturated fat reduces all-cause death among secondary prevention cohorts.[3] Recommendations are unavailable for artificial sweeteners because of limited data in populations with CCD.
5. Consumption of *trans* fat has been associated with an increased risk of CVD events, including CVD mortality rate, and all-cause death in primary prevention populations and among individuals with CCD.[9,10,23,47] This association has been primarily attributed to industrially processed hydrogenated vegetable oils (eg, baked goods, fried foods), and less from ruminant *trans* fats (eg, meat and milk from ruminant animals, including cattle and sheep),[40,47] resulting in a higher risk of CHD.[9,10,23,47]

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Table 6. Suggested Screening Tool to Assess Psychological Distress: Patient Health Questionnaire-2 Depression Screen

Over the past 2 weeks, how often have you been bothered by the following problems?	Not at all	Several days	More than half the days	Nearly every day
Little interest or pleasure in doing things	0	1	2	3
Feeling down, depressed, or hopeless	0	1	2	3
Total score of ≥3 warrants further assessment for depression.				

Data derived from Kroenke et al.[31] and Levine et al.[7,46] Reprinted with permission from Levine GN et al. Copyright 2021 American Heart Association, Inc.

6. In patients at high risk for CCD, nonprescription dietary omega-3 fatty acid supplements (eg, capsules, oil, soft gels) do not reduce CVD events or all-cause death[12,13]; a Cochrane meta-analysis including 86 RCTs showed "little or no effect."[11] See Section 4.2.6 ("Lipid Management") on the role of prescription icosapent ethyl (highly purified eicosapentaenoic acid ethyl ester).[48] Despite observational studies,[49,50] insufficient evidence is available that shows vitamin D supplementation reduces CVD events.[14,15,51] In a meta-analysis of 21 RCTs (vitamin D [n=41 669] versus placebo [n=41 662]), vitamin D supplementation did not lower the risk of MACE.[15] Additionally, antioxidant therapy is not associated with a decreased risk of CVD events.[17,19,22,31] Vitamin C, beta-carotene, multivitamins, or all of them do not decrease CVD event risk[19] or CVD mortality rate.[52] Insufficient data are available to support calcium supplementation (elemental calcium supplement ≥500 mg/d; carbonate, citrate, or gluconate formulation) in patients with CCD for CVD event reduction.[21] A meta-analysis of double-blind RCTs (n=14 692 [calcium supplement intervention] versus n=14 243 [placebo-controlled]) showed an increased risk of CVD and CHD events with calcium supplementation.[21] Mixed results on dietary calcium supplementation and CVD events suggests a U-shaped dose-response pattern.[20,21]

4.2.2. Mental Health Conditions

Recommendations for Mental Health Conditions
Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	Recommendations
2a	B-R	1. In patients with CCD, targeted discussions and screening for mental health is reasonable for clinicians to assess and to refer for additional mental health evaluation and management.[1–4]
2a	B-R	2. In patients with CCD, treatment for mental health conditions with either pharmacologic or nonpharmacologic therapies, or both, is reasonable to improve cardiovascular outcomes.[2,4–6]

Synopsis

Mental health has a major role in overall cardiovascular health and well-being in patients with CCD.[7] Mental health is defined as "a state of well-being in which an individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and is able to make a contribution to his or her community."[8] Mental health can have positive or negative effects on cardiovascular risk factors and outcomes.[7,9] It is estimated that 20% to 40% of patients with CCD have concomitant mental health conditions such as depression and anxiety.[10,11] Meta-analyses have shown that negative psychological states (eg, general distress) are associated with MACE in men and women with CCD.[12] Despite being a modifiable prognostic risk factor for CCD outcomes, screening for mental health disorders is seldom addressed in the clinical setting.[4,13] Potentially underpinning the bidirectional relationship between mental health and CCD is the resulting influence on health behaviors (eg, medication and CR adherence, diet, physical activity, sleep, smoking) and risk factors (eg, BP, lipids, body mass index [BMI], inflammation, thrombosis).[4,7] Pharmacologic and psychotherapeutic treatments may reduce recurrent cardiovascular events and mortality rate in patients with CCD.[5,14–17] See Section 4.1.4 for discussion of the interplay between mental health and SDOH.

Recommendation-Specific Supportive Text

1. Mental health factors, including depression, anxiety, anger or hostility, general distress and type D personality (where D stands for "distressed"), are common in diverse populations with CCD.[12] Psychological stress from environmental sources (eg, financial hardships, social isolation, discrimination) can have deleterious effects.[7,18–22] Studies consistently show that comorbid depression, anxiety, or emotional distress in patients with CCD is associated with diminished QOL,[23] atherosclerotic disease progression,[24] and negative effects on cardiovascular risk factors, leading to poorer cardiovascular outcomes.[6,7,25–30] An assessment of the use of depression screening found that among patients with recent ACS, screening positive for depression was associated with a 2-fold increase in MACE (adjusted hazard ratio, 2.15 [95% CI, 1.63-2.83]).[2] Patients randomized to antidepressants had significantly lower all-cause death than those not receiving treatment.[2] However, the CODIACS-QoL (Comparison of Depression Interventions After Acute Coronary Syndrome: Quality of Life) trial of patients after ACS showed no benefit of systematic depression screening (with or without subsequent treatment) on QOL or mortality.[2,3] Short, well-validated screening tools for depression or anxiety

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Table 7. Suggested Screening Questions to Assess Psychological Health

Well-being parameter	Question
Health-related optimism	How do you think things will go with your health moving forward?
Positive affect	How often do you experience pleasure or happiness in your life?
Gratitude	Do you ever feel grateful about your health? Do you ever feel grateful about other things in your life?

Data derived from Levine GN et al.[7,46] Reprinted with permission from Levine GN et al. Copyright 2021 American Heart Association, Inc.

(eg, Patient Health Questionnaire-2, Generalized Anxiety Disorder Questionnaire-2) or brief questions on psychological health (eg, positive affect) are available for use in clinical settings (Tables 7 and 8).[7,31,32] It is reasonable to refer patients with positive screening for in-depth assessment by qualified mental health professionals or to accessible resources to promote mental health care.[33]

2. Despite the preponderance of data showing the association of depression with adverse cardiovascular outcomes, treatment with antidepressants (14%) and psychotherapies (<10%) is low in patients after MI.[34] Studies including patients after ACS with depression found no definitive benefit of antidepressants on long-term cardiovascular outcomes.[15,17,35–37] However, the EsDEPACS (Escitalopram in Depressive Patients with Acute Coronary Artery Syndrome) study showed lower MACE after a median 8.1 years follow-up in patients with recent ACS treated with escitalopram compared with placebo (40.9% versus 53.6%; hazard ratio, 0.69 [95% CI, 0.49-0.96]).[5] The TRIUMPH (Lifestyle Interventions in Treatment-Resistant Hypertension) trial found a higher 1-year mortality rate among patients with untreated depression compared with patients with treated depression (rates similar to those without depression).[6] In a recent systematic review and meta-analysis, combination pharmacologic and psychotherapy, exercise, and antidepressants improved depressive symptoms among patients with CCD but had no mortality benefit.[38] CR (Section 4.2.10) improves depression, cardiovascular outcomes, and mortality

Table 8. Behavioral Resources for Smoking Cessation

Resource	Description
Telephone-based: Quitline English: 1-800-QUIT-NOW (1-800-784-8669) Spanish: 1-855-DÉJELO-YA (1-855-335-3569) Mandarin and Cantonese: 1-800-838-8917 Korean: 1-800-556-5564 Vietnamese: 1-800-778-8440	Counseling by telephone from a trained tobacco coach who offers support via a series of scheduled telephone calls before and after a smoker's quit date. Patients can self-refer to the Quitline, or clinicians can refer patients, with their consent, proactively. Quitline services vary by state, can include text messaging and web coaching support, and may provide free samples of nicotine replacement therapy. State-by-state information about Quitline services is available at https://www.cdc.gov/tobacco/patient-care/quitlines-other/index.html
Web-based: American Lung Association Freedom From Smoking https://www.lung.org/quit-smoking/join-freedom-from-smoking	Created by the American Lung Association to support smoking cessation in persons who want to quit. The program also provides information about nicotine replacement therapy and pharmacotherapy. Multiple modes of support available to patients, including group clinics, a telephone-based "Lung HelpLine," a self-help guide, and a web-based interactive customized program. Interactive program available for computer, tablet, or smartphone interface.
Web-based: National Cancer Institute English: Smokefree.gov Spanish: https://espanol.smokefree.gov/Spanish	Supported by the US Department of Health and Human Services and National Institutes of Health, created by the National Cancer Institute. Website contains information about quitting and resources for quitting and allows users to create a personalized quit plan. Specific websites are also available for women, teens, Veterans, and those >60 y of age. Programs available through the website include: SmokefreeTXT (text messaging program), QuitGuide, and quitSTART (mobile phone apps).
Web-based: Asian Smokers' Quitline Mandarin, Cantonese, Korean, and Vietnamese Speakers https://www.asiansmokersquitline.org/	Operated by the Moores Cancer Center at the University of California, San Diego, funded by a grant from the US Centers for Disease Control and Prevention. Created to support tobacco cessation for persons who speak Mandarin, Cantonese, Korean, and Vietnamese across the United States. Some participants may be eligible for a 2-wk starter kit of nicotine patches. Telephone counseling developed to deliver a quit plan and support quitting, and printed self-help materials sent to participants.
Web-based: BecomeAnEX Available in English and Spanish https://www.becomeanex.org	Created by the Truth Initiative, a nonprofit public education in partnership with the Mayo Clinic Nicotine Dependence Center. Website with information about cessation of smoking, vaping, or use of smokeless tobacco, with resources to build an individualized quit plan. Includes support from experts and an online community, and a text message–based program for quitting vaping focused on teens and young adults, "This is Quitting." An employer-based program, the EX Program, is also available through the Truth Initiative.

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in patients with CCD.[39,40] Mindfulness-based and psychotherapy interventions (eg, meditation, yoga, cognitive-behavioral therapy) improve depression, anxiety, stress, social support, and cardiovascular risk factors in patients with CCD but not all-cause or cardiovascular mortality, QOL, recurrent MI, or revascularization.[41–44] Pharmacological treatment of depression in patients with CCD is reasonable with consideration of adverse effects.[4,45]

4.2.3. Tobacco Products

Recommendations for Tobacco Products
Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	Recommendations
1	A	1. In patients with CCD, tobacco use should be assessed at every health care visit to facilitate identification of those who may benefit from behavioral or pharmacologic interventions.*[1–3]
1	A	2. Patients with CCD who regularly smoke tobacco should be advised to quit at every visit.*[4]
1	A	3. In patients with CCD who regularly smoke tobacco, behavioral interventions are recommended to maximize cessation rates in combination with pharmacotherapy, including bupropion, varenicline, or combination long- and short-acting nicotine replacement therapy (NRT).*[5–7]
2b	B-R	4. In patients with CCD who regularly smoke tobacco, varenicline may be considered versus bupropion or NRT to increase cessation rates.[6]
2b	B-R	5. In patients with CCD who regularly smoke tobacco, the short-term use of nicotine-containing e-cigarettes may be considered to aid smoking cessation, although the risk of sustained use and unknown long-term safety may outweigh the benefits.[8–10]
3: Harm	B-NR	6. Patients with CCD should avoid secondhand smoke exposure to reduce risk of cardiovascular events.*[11,12]

*Modified from the 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease.[13]

Synopsis

Tobacco smoke exposure, in particular cigarette smoking, is a leading cause of CVD and cardiovascular events in persons with CCD.[14–18] Cigarette smoke adversely affects endothelial function, promotes atherosclerosis, and is prothrombotic.[19] Beneficial short-term effects of smoking cessation include a decrease in heart rate and BP and improved endothelial function.[20,21] Prospective cohort studies of patients with CCD show that smoking cessation is associated with a 36% reduction in death and a 32% reduction in MI.[22] Pharmacotherapy and behavioral therapy in combination can increase the success of smoking cessation. Observational studies on smokeless tobacco (including snuff, snus, and chewing tobacco) and cardiovascular risk have found mixed results, but an increased risk of coronary heart disease events may be observed, albeit to a lesser degree than cigarette smoking.[23–26]

Recommendation-Specific Supportive Text

1. Most persons who smoke report they want to quit smoking, although annual quit rates among those who smoke are <10%.[2] Systematic assessment of tobacco and e-cigarette use is the first step to facilitating smoking cessation, but clinicians often do not screen for tobacco use.[3] Routine screening for smoking status by clinicians has been shown to increase the rate of clinician intervention to promote smoking cessation. Screening for smoking can also allow clinicians to reinforce continued abstinence among those who have successfully quit and identify patients who may have relapsed. Electronic health record-based interventions that include a means to document smoking status and other tools such as clinician prompts or decision support, can improve process outcomes, such as referral to smoking cessation programs or documentation of smoking cessation counseling, although electronic health record-based documentation of smoking status alone has not improved quit rates.[27,28] Data are unavailable on the effect of screening and most other tobacco cessation interventions on quit rates for persons who use smokeless tobacco and e-cigarettes. Nicotine-containing e-cigarette use is increasing, including among never-smokers, and many cigarette smokers have become "dual users," using both e-cigarettes and cigarettes.[29] Meta-analyses suggest that smokeless tobacco use is associated with increased risk of CHD events, albeit to a lesser degree than cigarette smoking.[23–25] E-cigarettes may increase the risk of CHD and cardiovascular events, and long-term risks of e-cigarettes are unknown.[8,30–37] Given these risks, screening for use as part of comprehensive risk assessment may be reasonable.
2. Even brief advice to quit tobacco smoking provided by a clinician increases the rate of quitting in persons who smoke (relative risk, 1.66 [95% CI, 1.42-1.94]).[4] Other members of the care team, including nurses, community pharmacists, and oral health professionals, can also effectively provide behavioral support for smoking cessation.[7] Messages to patients should be clear, personalized, nonjudgmental, and focus on the benefits of smoking cessation, such as: "Quitting smoking is the most important thing you can do for your heart health."[38]
3. Behavioral therapy is also effective for smoking cessation including group and individual in-person counseling, telephone-based support, interactive internet-based interventions, and text message–based interventions.[7] A meta-analysis of 37 RCTs of behavioral interventions for smoking cessation in persons with CCD found a 22% increase

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in abstinence rates at 6 to 12 months.[7,39] Table 8 describes behavioral support programs available throughout the United States. NRT and varenicline have been shown to increase the success of smoking cessation in the overall population who smoke daily, including persons with CCD.[6,40–46] The effectiveness of NRT is highest when used as a combination of long- and short-acting NRT.[45] Adding behavioral therapy to pharmacotherapy increases quit rates.[47] In 2011, the FDA issued a warning for possible increased risk of cardiovascular events in persons with CVD who use varenicline. One meta-analysis of trials through 2016 found no increased cardiovascular risk in persons receiving varenicline.[48] Subsequently, a trial randomized 8058 persons to bupropion, varenicline, or NRT and found no difference in cardiovascular events among the 3 groups.[44] Trials of pharmacotherapy and behavioral therapy for smoking cessation typically enroll persons who smoke cigarettes daily; more research is needed on the efficacy and optimal strategy for smoking cessation among those who smoke intermittently, those who use smokeless tobacco, and those who use e-cigarettes.

4. Varenicline is more effective than bupropion or NRT in achieving abstinence from cigarette smoking in meta-analyses of randomized trials, with a pooled estimate from 5 trials (n=5877 persons) showing a relative risk versus bupropion of 1.39 (95% CI, 1.25-1.54), and a pooled estimate of 8 trials (N=6264 persons) showing a relative risk versus NRT of 1.25 (95% CI, 1.14-1.37) for abstinence favoring varenicline.[49] One network meta-analysis evaluated the efficacy of RCTs of smoking cessation specifically among those with CVD and concluded that varenicline was more effective than bupropion or NRT, although no trials have compared various agents with each other in patients with CCD.[6] The ultimate choice of pharmacotherapy for smoking cessation should incorporate patients' previous experiences, preferences, and comorbidities (see "2018 ACC Expert Consensus Decision Pathway on Tobacco Cessation Treatment" for dosing information and information about pharmacotherapy for smoking cessation).[38] No data are available on the efficacy of pharmacologic therapy to support cessation of either e-cigarettes or smokeless tobacco. More research is needed on how to optimize both pharmacologic and behavioral therapy to support cessation of smokeless tobacco and e-cigarettes.
5. Twenty-nine RCTs evaluated the efficacy of e-cigarettes on smoking cessation, including 5 at low risk of bias.[9] In meta-analyses, nicotine e-cigarettes appeared to be more effective than NRT for smoking cessation (relative risk, 1.69 [95% CI, 1.25-2.27]), corresponding to a 4% absolute increase in the success rates of smoking cessation compared with NRT.[9] Persons using e-cigarettes for smoking cessation are at risk of long-term dependence. In 1 trial, 80% of those assigned to the e-cigarette group who successfully quit smoking were still using the device at 1 year (versus only 9% still using NRT in the NRT arm).[10] Nicotine e-cigarettes appear to affect endothelial function, vascular stiffness, and BP less than combustible cigarettes.[33,34,36] No data are available on the long-term risks of e-cigarettes on overall health and cardiovascular risk, but physiologic and toxicology studies suggest that e-cigarettes may increase cardiovascular risk.[8,30–37] Substantial variability exists in e-cigarette additives, flavorings, and nicotine dose in e-cigarette liquid; the effect on cardiovascular risk is unknown. Because of the lack of long-term safety data and high rates of ongoing use, nicotine e-cigarettes should not be recommended as first-line therapy for smoking cessation. Patients with CCD who use e-cigarettes to support smoking cessation should be warned about the risks of developing long-term dependence and encouraged to quit use of e-cigarettes promptly to avoid potential long-term risks.
6. Secondhand smoke exposure has similar deleterious physiologic effects as active cigarette smoking.[50,51] Even low doses of exposure to secondhand smoke exposure are associated with a marked increase in the risk of ischemic heart disease events, including recurrent events in patients with previous MI.[11,12,50–52] Many persons are exposed to secondhand smoke exposure via their workplaces and may not individually be able to avoid exposure. For this reason, policy-level interventions are necessary to decrease occupational secondhand smoke exposure. Policies designed to reduce secondhand smoke exposure, such as smoke-free workplaces and restaurant policies, are associated with lower population-level risk of CVD.

4.2.4. Alcohol and Substance Use

Recommendations for Alcohol and Substance Use
Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	Recommendations
1	C-LD	1. Patients with CCD should be routinely asked and counseled about substance use to reduce ASCVD events.[1–5]
2a	B-NR	2. In patients with CCD who consume alcohol, it is reasonable to limit alcohol intake (≤1 drink/d for women, ≤2 drinks/d for men) to reduce cardiovascular and all-cause death.[6–8]
3: No Benefit	B-NR	3. Patients with CCD should not be advised to consume alcohol for the purpose of cardiovascular protection.[9,10]

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Synopsis

Various substances can have adverse effects on the cardiovascular system, including cocaine, amphetamines, opioids, alcohol, and marijuana (Table 9). These substances also have the potential for abuse and drug-drug interactions with cardiovascular therapies. Because some of these substances are illicit (eg, cocaine, heroin), studies examining the link between substances and patients with CCD are limited, observational, and with imprecise measures of exposure risk. Although observational data show a J-shaped relationship between alcohol consumption and cardiovascular risk, no RCTs support moderate alcohol consumption to reduce cardiovascular risk.[6,11] In fact, recent studies suggest that no safe level of alcohol use is acceptable and that previously observed cardioprotective effects of light-to-moderate alcohol use are likely confounded by other lifestyle and sociodemographic factors.[8] With the recent legalization of marijuana and its derivatives in some states, its use in patients with CCD is expected to grow.[1] A scientific statement from the AHA highlights the cardiac-specific effects of cannabis, including stimulation of the sympathetic nervous system, platelet activation, endothelial dysfunction, and carbon monoxide toxicity from smoking and inhalation.[12] Observational studies of the association between marijuana and cardiovascular events are limited by selection bias with rigorous data about the long-term effect of marijuana and cardiovascular risk lacking.[12,13] The AHA released a scientific statement discussing the importance of distinguishing and managing out-of-hospital cardiac arrests from opioids and in engaging patients with opioid use disorders in secondary prevention programs.[14] Because of potential cardiac toxicity, drug-drug interactions, and high risk for misuse, long-term opioid use for patients with CCD and chronic pain should be avoided. For recommendations regarding tobacco products, please see Section 4.2.3.

Table 9. Substances With Abuse Potential and Adverse Cardiovascular Effects for Patients With CCD*

Substance	Potential Adverse Cardiovascular Effects
Alcohol	J-shaped relationship between alcohol intake and cardiovascular risk in observational studies but limited by confounding.[18] Heavy alcohol use and binge drinking associated with increased morbidity and mortality rates.[9,10,19] May increase serum triglycerides. Potential drug-drug interactions with cardiovascular therapies.
Cocaine, methamphetamine	Stimulation of the sympathetic nervous system.[5,20] Platelet activation and aggregation.[20] Increased myocardial oxygen demand.[5] Can present with cocaine-associated chest pain. MI risk independent of route of administration.[21]
Opioids	Possible association with risk of MI in chronic use.[22] High potential for dependence and abuse with chronic use. Potential for drug-drug interactions with cardiovascular therapies.
Marijuana	Stimulation of the sympathetic nervous system. Platelet activation. Endothelial dysfunction. Carbon monoxide toxicity from smoking and inhalatation.[12] Route of administration may impact toxicity, with edible products associated with fewer acute cardiovascular symptoms.[23]

*List is not all inclusive.
CCD indicates chronic coronary disease; and MI, myocardial infarction.

Recommendation-Specific Supportive Text

1. Substance use is underrecognized and can be a significant contributor to CVD risk and outcomes.[1,3,5] Alcohol and other substances, such as cocaine, amphetamines, opioids, and marijuana can have particular adverse cardiovascular effects among patients with CCD (Table 9) and lead to premature or recurrent CVD events. A study across 2 large tertiary care centers found that drug use was observed in 10% of patients <50 years of age presenting with an MI from 2000 to 2016.[2] Similarly, recreational substance use of alcohol, cannabis, and amphetamines was independently associated with premature CVD in the nationwide Veterans Affairs Healthcare database and the VITAL (Veterans with Premature Atherosclerosis) registry.[15] Single-question screening for unhealthy alcohol and drug use has been validated in primary care settings.[4] These simple screening questions can also be self-administered.
2. There is a J-shaped relationship between alcohol consumption and death, although data on alcohol consumption is of variable quality. Proposed mechanisms supporting beneficial effects of moderate alcohol consumption include favorable effects on lipids, platelet aggregation, insulin resistance, and endothelial function.[16] In the United States, 1 "standard" drink contains about 14 g of pure alcohol, which is typically found in 12 oz of regular beer (usually about 5% alcohol), 5 oz of wine (usually about 12% alcohol), and 1.5 oz of distilled spirits (usually about 40% alcohol).[17] Observational studies have consistently found an inverse association between light-to-moderate alcohol consumption and vascular risk.[18] In patients with CVD, a similar observation has been documented with light-to-moderate alcohol consumption (5–25 g/d) associated with lower incidence of cardiovascular and all-cause death.[6,8,7] Conversely, heavy, episodic drinking (binge drinking) is consistently associated with higher cardiovascular risk including acute myocardial infarction.
3. All available data on the benefit of alcohol on cardiovascular risk are observational and subject to confounding. In the absence of a randomized

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clinical trial, data are insufficient to recommend alcohol for cardioprotection.[11] In fact, a recent genetic analysis found that the causal association between light-to-moderate levels of alcohol intake and lower CVD risk are likely mediated by confounding lifestyle factors.[8] In patients with CCD, excessive alcohol is linked to hypertension, increased mortality rate, and recurrent cardiovascular events. PRIME (Prospective Epidemiological Study of Myocardial Infarction) found that binge drinking (>50 g at least once a week) was associated with a higher risk of coronary events (hazard ratio, 2.03 [95% CI, 1.41-2.94]) compared with regular drinking.[10] In the Determinants of Myocardial Infarction Onset Study across 45 community and tertiary-care medical centers, binge drinking was associated with a 2-fold higher mortality rate after an acute MI.[9] The Global Burden of Disease 2016 analysis confirmed a J-shaped relationship with alcohol and outcomes, but the benefit appeared to be offset by increasing cancer risks, concluding that the level of alcohol consumption that minimized harm was zero.[19] Therefore, patients who do not drink alcohol or who have a medical reason to avoid alcohol (eg, liver dysfunction, drug-drug interactions) should not be encouraged to drink alcohol for the purposes of cardiovascular protection. Clinicians should further counsel their patients against binge drinking.

4.2.5. Sexual Health and Activity

Recommendations for Sexual Health and Activity
Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	Recommendations
2a	B-NR	1. In patients with CCD, it is reasonable to individualize resumption of sexual activity based on type of sexual activity, exercise capacity, and postprocedural healing.*[1,2]
2a	B-NR	2. In patients with CCD, cardiac rehabilitation and regular exercise can be useful to reduce the risk of cardiovascular complications with sexual activity.*[3]
3: Harm	B-NR	3. In patients with CCD, phosphodiesterase type 5 inhibitors should not be used concomitantly with nitrate medications because of risk for severe hypotension.*[4]

*Modified from the 2012 AHA Scientific Statement on Sexual Activity and Cardiovascular Disease.[5]

Synopsis

Sexual health is important to QOL. Sexual activity represents moderate physical activity at around 3 to 5 metabolic equivalents.[5] If a patient with CCD can reach this level during exercise testing without ischemia or symptoms, then the risk for ischemia during sexual activity is low, especially considering the short exposure period.[2] It is rare for a patient to die from cardiac disease during sexual intercourse; in this regard, men appear more at risk than women,[6] with the absolute rate being very small. Sexual activity is associated with 1% of all MIs.[3] Men and women with CCD and its risk factors have a high prevalence of sexual dysfunction.[7] Recent MI and coronary artery bypass surgery may additionally compromise sexual function[5]; in this regard, sexual counselling may be helpful, and resuming sexual activity does not appear to be associated with an increased risk of death. Of particular relevance to patients with CCD is the need to avoid the combined use of nitrates with phosphodiesterase type 5 inhibitors.[4]

Recommendation-Specific Supportive Text

1. Recommendations after PCI and CABG may depend on whether femoral or radial access was performed, and whether surgery was performed in a sternal-sparing manner.[5,8] The patient should be well compensated, euvolemic, and without significant angina. Patients with CCD who are functionally well compensated or patients with no or mild angina, given the low risk of MI or sudden death, should be considered safe for sexual activity. Sexual activity represents an exercise level of approximately 3 to 5 metabolic equivalents, compared with a typical exercise treadmill test that involves approximately 4 metabolic equivalents. The risk of MI or sudden death resulting from sexual activity is very low. [3] Patients with CCD who want to engage in sexual activity should undergo a medical evaluation, similar to other forms of exercise in the presence of CCD.[5] Because sexual activity is associated with increased metabolic requirements, patients with unstable or decompensated CCD should refrain from sexual activity.[5]
2. In addition to a recommendation for CR incorporating sexual counseling, in men with CCD, conservative measures such as sexual rehabilitation, consisting of 12 weeks of sexual rehabilitation with physical exercise training, pelvic floor exercise and psychoeducation, was associated with better sexual function by the International Index of Erectile Function.[9,10]
3. Phosphodiesterase type 5 inhibitors should not be used concomitantly with nitrate medications, often used to treat CCD, because of the potential for severe hypotension.[4] Sildenafil and vardenafil have half-lives of ~4 hours. Tadalafil is long-acting and has a half-life of 17.5 hours. Patients on sildenafil or vardenafil should avoid taking nitroglycerine for ≥24 hours (≥48 hours for tadalafil).[5] In patients on long-acting nitrate therapy who want to use a phosphodiesterase type 5 inhibitor, decision on the use of phosphodiesterase type 5 inhibitor should

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be guided by the need for continued nitrate therapy versus other alternative options available to the treating clinician.

4.2.6. Lipid Management

Recommendations for Lipid Management
Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	Recommendations
1	A	1. In patients with CCD, high-intensity statin therapy is recommended with the aim of achieving a ≥50% reduction in LDL-C levels to reduce the risk of MACE.*[1–3]
1	A	2. In patients in whom high-intensity statin therapy is contraindicated or not tolerated, moderate-intensity statin therapy is recommended with the aim of achieving a 30% to 49% reduction in LDL-C levels to reduce the risk of MACE.*[2,4–8]
1	A	3. In patients with CCD, adherence to changes in lifestyle and effects of lipid-lowering medication should be assessed by measurement of fasting lipids in 4 to 12 weeks after statin initiation or dose adjustment and then every 3 to 12 months thereafter based on need to assess response or adherence to therapy.*[2,9–11]
Cost Value Statement: High Value	B-NR	4. In patients with CCD, the use of generic formulations of maximally tolerated statin therapy is projected to be cost saving.[12,13]
2a	B-R	5. In patients with CCD who are judged to be at very high risk (Table 10) and on maximally tolerated statin therapy with an LDL-C level ≥70 mg/dL (≥1.8 mmol/L), ezetimibe can be beneficial to further reduce the risk of MACE.*[14–19]
Cost Value Statement: High Value	B-NR	6. In patients with CCD, addition of generic ezetimibe to maximally tolerated statin therapy in appropriately selected patients is projected to be of high economic value at US prices.[12,20,21]
2a	A	7. In patients with CCD who are judged to be at very high risk (Table 10) and who have an LDL-C level ≥70 mg/dL (≥1.8 mmol/L), or a non–high-density lipoprotein cholesterol (HDL-C) level ≥100 mg/dL (≥2.6 mmol/L), on maximally tolerated statin and ezetimibe, a PCSK9 monoclonal antibody can be beneficial to further reduce the risk of MACE.*[22–29]
Cost Value Statement: Uncertain	B-NR	8. In patients with CCD who are very high risk, the use of PCSK9 monoclonal antibodies is projected to be of uncertain economic value at US prices[12,20,21,30,31]
2b	B-R	9. In patients with CCD on maximally tolerated statin therapy with an LDL-C level <100 mg/dL (<2.6 mmol/L) and a persistent fasting triglyceride level of 150 to 499 mg/dL (1.7–5.6 mmol/L) after addressing secondary causes, icosapent ethyl may be considered to further reduce the risk of MACE and cardiovascular death.[32]
2b	B-R	10. In patients with CCD who are not at very high risk and on maximally tolerated statin therapy with an LDL-C level ≥70 mg/dL (≥1.8 mmol/L), it may be reasonable to add ezetimibe to further reduce the risk of MACE.*[14,15,18,19]

Recommendations for Lipid Management (Continued)

COR	LOE	Recommendations
2b	B-R	11. In patients with CCD on maximally tolerated statin therapy who have an LDL-C level ≥70 mg/dL (≥1.8 mmol/L), and in whom ezetimibe and PCSK9 monoclonal antibody are deemed insufficient or not tolerated, it may be reasonable to add bempedoic acid[33,34] or inclisiran[35] (in place of PCSK9 monoclonal antibody) to further reduce LDL-C levels.
3: No Benefit	B-R	12. In patients with CCD receiving statin therapy, adding niacin,[36,37] or fenofibrate[38] or dietary supplements containing omega-3 fatty acids, are not beneficial in reducing cardiovascular risk.[39–41]

*Modified from the 2018 AHA/ACC/Multisociety Guideline on the Management of Blood Cholesterol.[42]

Synopsis

LDL-C is a primary cause of atherosclerotic disease and target of lipid management.[38] RCTs established the efficacy and safety of high-intensity statin therapy as the preferred initial approach to reduce LDL-C levels by ≥50% and reduce cardiovascular morbidity and mortality rates (Figure 8).[1–3] Despite maximally tolerated statin therapy, residual cardiovascular risk persists, especially among patients with CCD and additional high-risk clinical factors (Table 10).[14–17] Several nonstatins[36–38] did not provide benefit when added to background statin therapy; however, ezetimibe, PCSK9 monoclonal antibodies, and icosapent ethyl further reduce cardiovascular risk when added to background statin therapy.[15,22,23,32] Bempedoic acid and inclisiran have only recently become available and, although they effectively reduce LDL-C levels,[34,35] RCTs are ongoing to determine their effect on MACE. Clinicians should prioritize use of ezetimibe and PCSK9 monoclonal antibodies when additional LDL-C lowering is necessary in patients on maximally tolerated statin therapy unless not tolerated or effective in achieving desired LDL-C levels. Regardless of the lipid-lowering regimen, lipid monitoring is essential to assess individual response to lipid-lowering therapy and monitor adherence and persistence with therapy over time.[9–11]

Recommendation-Specific Supportive Text

1. The CTT (Cholesterol Treatment Trialists) meta-analysis of 5 RCTs showed that LDL-C lowering with high-intensity statins compared with moderate-intensity statins reduces major vascular events by 15% (Table 11).[2] This benefit occurred irrespective of age, even among patients >75 years of age with established ASCVD.[2,3] Greater absolute reductions in LDL-C were associated with a greater proportional reduction in MACE. The greatest absolute benefit from statin therapy

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Table 10. Very High-Risk* of Future ASCVD Events

Definition of Very High-Risk*
History of multiple major ASCVD events
OR
One major ASCVD event **AND** ≥2 high-risk conditions
Major ASCVD Events
Recent ACS (within the past 12 mo)
History of MI (other than recent ACS events listed above)
History of ischemic stroke
Symptomatic peripheral artery disease (history of claudication with ABI <0.85, or previous revascularization or amputation)[51]
High-Risk Conditions
Age ≥65 y
Familial hypercholesterolemia†
History of previous coronary artery bypass graft surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
Diabetes
Hypertension
Chronic kidney disease (eGFR, 15–59 mL/min/1.73 m^2)[15,29]
Current tobacco smoking
Persistently elevated LDL-C ≥100 mg/dL despite maximally tolerated statin therapy and ezetimibe
History of congestive heart failure

*Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.

†Management of patients with familial hypercholesterolemia often requires combination lipid lowering therapy and referral to a lipid specialist, and possibly lipoprotein apheresis.[58,59]

ABI indicates ankle brachial index; ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; and MI, myocardial infarction.

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is observed in those with the highest baseline LDL-C levels and at similar risk of events. Furthermore, percent reduction in LDL-C appears to provide additional prognostic value over-achieved LDL-C levels.[43] The expected percent reduction in LDL-C levels with high-intensity statin therapy is ≥50% and should be used to assess clinical efficacy. However, baseline LDL-C levels in patients before statin initiation are not always available in clinical practice. The threshold of LDL-C ≥70 mg/dL is then useful to determine whether to intensify lipid management.

2. Although high-intensity statin therapy is preferred, high-intensity statin therapy may not be tolerated by some patients or may be contraindicated because of clinically significant drug-drug interactions.[44] Statin intolerance is defined as adverse effects associated with statin therapy that improve or resolve with dose modification or discontinuation of statin therapy; and requires a trial of at least 2 statins with one at the lowest approved daily dose.[45] Statin intolerance may also be complete or partial (tolerating less than the recommended statin intensity). Clinicians should also consider the possibility of a "nocebo effect"—patient expectation of harm resulting in perceived adverse effects.[46] Multiple RCTs showed that moderate-intensity statin therapy also reduces cardiovascular events and death among patients with established ASCVD, including those >75 years of age; therefore, a moderate-intensity statin should be used in patients unable to tolerate a high-intensity statin.[2,4–8] Additional strategies may also be used to identify a tolerable statin regimen (eg, low-intensity statin, alternative daily dosing) to reduce LDL-C but it is unclear if these strategies also reduce the risk of ASCVD events.[47]
3. The goal for LDL-C lowering is defined as percentage responses in LDL-C relative to baseline levels. Although reductions in LDL-C are expected with moderate- and high-intensity statins (Table 11), individual response can vary substantially.[11] The maximum percentage change in LDL-C occurs within 4 to 12 weeks after initiation of or change in lipid-lowering therapy. The Friedewald equation is known to underestimate LDL-C in the setting of elevated TG levels, thus other approaches to LDL-C measurement (eg, Martin/Hopkins method) may be desirable.[48,49] Obtaining lipid profile measurements every 3 to 12 months is associated with increased adherence to therapy and identification of patients requiring further intensification of treatment.[9,10] See Sections 4.4.3 and 5 of the 2018 AHA/ACC multisociety cholesterol guideline[50] for additional information regarding efficacy and safety monitoring.
4. The economic value of a lipid-lowering therapy depends on the absolute benefit [redacted] that patients derive from receiving the treatment relative to the comparator as well as the cost of the therapy being evaluated.[13] Because of the very low annual cost of generic formulations of statins in the United States, the use of maximally tolerated statin therapy in patients with CCD is projected to be cost-saving (ie, the lifetime savings from averted cardiovascular events more than offset the lifetime cost of statin therapy and resulting adverse effects).[12] Note that this value statement should not be extrapolated to higher-cost branded formulations of statins.
5. In IMPROVE-IT (Improved Reduction of Outcomes; Vytorin Efficacy International Trial), the addition of ezetimibe to moderate-intensity statin therapy among patients with ACS resulted in a significant ASCVD risk reduction (7% relative

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Table 11. High-, Moderate-, and Low-Intensity Statin Therapy*

	High Intensity	Moderate Intensity	Low Intensity
LDL-C Lowering†	≥50%	30%-49%	<30%
Statins	**Atorvastatin (40 mg‡), 80 mg** **Rosuvastatin 20 mg (40 mg)**	**Atorvastatin 10 mg** (20 mg) **Rosuvastatin** (5 mg) **10 mg** **Simvastatin 20-40 mg§**	Simvastatin 10 mg
		Pravastatin 40 mg (80 mg) **Lovastatin 40 mg** (80 mg) Fluvastatin XL 80 mg **Fluvastatin 40 mg BID** Pitavastatin 1-4 mg	**Pravastatin 10-20 mg** **Lovastatin 20 mg** Fluvastatin 20-40 mg

Percent LDL-C reductions with the primary statin medications used in clinical practice (atorvastatin, rosuvastatin, simvastatin) were estimated using the median reduction in LDL-C from the VOYAGER database.[11] Reductions in LDL-C for other statin medications (fluvastatin, lovastatin, pitavastatin, pravastatin) were identified according to FDA-approved product labeling in adults with hyperlipidemia, primary hypercholesterolemia, and mixed dyslipidemia.[60] **Boldface type** indicates specific statins and doses that were evaluated in RCTs and the Cholesterol Treatment Trialists' 2010 meta-analysis.[2,3] These RCTs demonstrated a reduction in major cardiovascular events.

*Percent reductions are estimates from data across large populations. Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice.[11]

†LDL-C lowering that should occur with the dosage listed below each intensity.

‡Evidence from 1 RCT only: down titration if unable to tolerate atorvastatin 80 mg in the IDEAL (Incremental Decrease through Aggressive Lipid Lowering) study.[61]

§Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA because of the increased risk of myopathy, including rhabdomyolysis.

FDA indicates US Food and Drug Administration; LDL-C, low-density lipoprotein cholesterol; RCT, randomized controlled trial; VOYAGER, an indiVidual patient data meta-analysis Of statin therapY in At risk Groups: Effects of Rosuvastatin, atorvastatin and simvastatin; and XL, extended release.

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risk reduction; 2% absolute risk reduction) at a median follow-up of 6 years.[15] An analysis using the TIMI (Thrombolysis in Myocardial Infarction) Risk Score for Secondary Prevention (TRS 2 P) found the addition of ezetimibe was associated with significantly greater risk reduction (19% relative risk reduction; 6.3% absolute risk reduction) among patients with ≥3 high-risk features, with more modest benefit among those with 2 high-risk features and no benefit among those with 0 or 1 additional features.[14] Ezetimibe was allowed at study entry in both PCSK9 monoclonal antibody trials,[23,24] but only 3% and 5%, respectively, were on ezetimibe. No RCT has evaluated whether an ezetimibe-first strategy is preferred before adding a PCSK9 monoclonal antibody; however, clinicians should generally add ezetimibe first, then a PCSK9 monoclonal antibody, if necessary, to achieve desired LDL-C levels, given the generic availability of ezetimibe, its once-daily oral administration, and proven long-term safety and tolerability. This is supported by 2 well-designed simulation studies showing that a high proportion of patients will achieve an LDL-C level of <70 mg/dL with the addition of ezetimibe to high-intensity statin therapy.[18,19]

6. Generic ezetimibe is an inexpensive drug, with net price of <$10 for a 1-month supply. To the extent that LDL-C lowering with ezetimibe translates to fewer lifetime MACE, the use of generic ezetimibe is likely to be improve health outcomes at modest increase in cost, especially in very high-risk patients, resulting in high value [redacted][12,20,21] However, the cost-effectiveness of adding generic ezetimibe to maximally tolerated statin therapy is sensitive to the assumption regarding the effect of ezetimibe on cardiovascular and all-cause death.
7. Very high risk ASCVD is defined in Table 10. The efficacy of alirocumab and evolocumab was shown in 2 RCTs.[22,23] The FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition Subjects with Elevated Risk) trial evaluated evolocumab among those with established ASCVD with an LDL-C level of ≥70 mg/dL or non–HDL-C level of ≥100 mg/dL on maximal statin with or without ezetimibe. Cardiovascular events were significantly reduced by 15% with evolocumab, with greater benefit observed among those with additional high-risk clinical factors. No increased risk of neurocognitive adverse effects was observed, even among those achieving the very low levels of LDL-C.[29] The ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab) trial evaluated alirocumab use in patients with an ACS event 1 to 12 months earlier on maximal statin with or without ezetimibe. Cardiovascular events were significantly reduced by 15% with alirocumab, especially in those with additional high-risk clinical factors.[25–27] The absolute risk reduction was relatively modest (1.5% and 0.6%, respectively) in both trials, given the ~60% reduction in LDL-C levels. However, analyses from both FOURIER and ODYSSEY Outcomes trials subsequently showed that among several groups of patients noted in the very high-risk ASCVD category (Table 10), the

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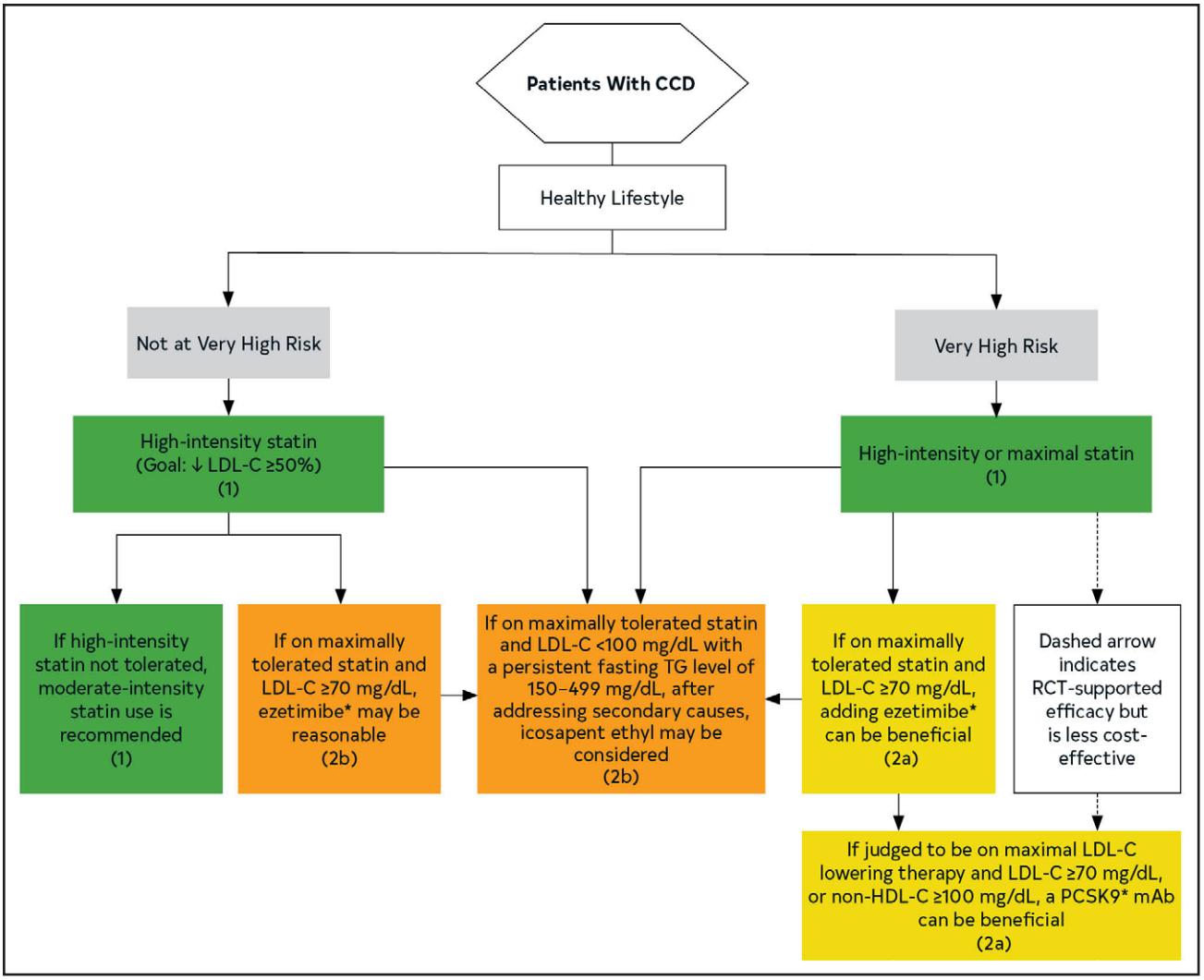

Figure 8. Lipid Management in Patients With CCD.
Colors correspond to Class of Recommendation in Table 3. Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions (Table 10). *Only when ezetimibe and PCSK9 mAb are deemed insufficient or not tolerated should bempedoic acid or inclisiran (in place of PCSK9 mAb) be considered to further reduce LDL-C levels. The effect of bempedoic acid and inclisiran on MACE is being evaluated. LDL-C indicates low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; PCSK9 mAb, PCSK9 monoclonal antibody; RCT, randomized controlled trial; and TG, triglycerides. Adapted with permission from Grundy SM, et al.[42] Copyright 2019 American Heart Association, Inc., and American College of Cardiology Foundation.

absolute risk of future ASCVD events was significantly higher; therefore, the absolute risk reduction from the use of a PCSK9 monoclonal antibody was also much higher than the overall absolute risk reductions seen in the original trials.[23,26,28,51,52] Although generally well tolerated, injection site reactions can occur, and long-term safety data are limited. Maximal LDL-C-lowering therapy should include maximally tolerated statin plus ezetimibe; however, ezetimibe may be insufficient when a ≥25% reduction in the LDL-C level is desired. Clinicians bypassing the addition of ezetimibe before adding a PCSK9 monoclonal antibody should recognize this may not be cost effective (Figure 8).

8. The US cost of PCSK9 monoclonal antibodies has declined by 60% since their initial market entry (from approximately $14 000 per year to $5850 per year), which, all things being equal, has improved the cost-effectiveness of these drugs.[12,20,21] At this price point, the cost-effectiveness of the agents in very high risk patients with CCD is uncertain, with some studies projecting low economic value[12,20] and others suggesting intermediate to high economic value.[30,31] This value statement should not be extrapolated to patients with CCD who are at low to moderate risk of adverse cardiovascular events, in whom PCSK9 inhibitor monoclonal antibodies are of low economic value. The cost-effectiveness

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of a therapy is a function of the incremental cost of the therapy relative to the comparator, its effectiveness relative to the comparator, as well as baseline risk of cardiovascular events in the target population. Patients who have higher baseline risk are likely to derive a larger absolute health benefit from an effective drug. It follows that CVD prevention is more cost-effective in a population at higher risk of CVD events. Thus, PCSK9 inhibitors may be intermediate value in patients at higher-than-average risk of recurrent events, such as those with a recent ACS, symptomatic peripheral artery disease, or familial hypercholesteremia (FH).[12,20,21] The cost-effectiveness of PCSK9 monoclonal antibody is also likely improved in patients who are unable to tolerate statins because of severe statin-associated side effects.[12]

9. REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial) randomized patients with established ASCVD or diabetes plus additional risk factors, triglyceride levels between 150 mg/dL and 499 mg/dL, and an LDL-C level of <100 mg/dL on background statin therapy, to either 4 g/day of icosapent ethyl (purified EPA only) or mineral oil placebo. Icosapent ethyl significantly reduced the relative risk of MACE by 25% and cardiovascular death by 20%.[32] The benefit appeared driven by the increase in EPA levels and not the modest 17% reduction in triglyceride levels. RESPECT-EPA (Randomized Trial for Evaluation in Secondary Prevention Efficacy of Combination Therapy-Statin and Eicosapentaenoic Acid) was another secondary prevention trial that showed a borderline significant reduction in MACE with icosapent ethyl 1800 mg/day (10.9% versus 14.9%; P=0.055) in 2506 participants enrolled in Japan on background statin therapy. Limitations of this trial were the lack of placebo control, and it was underpowered. Contrarily, the STRENGTH (Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia) trial found no benefit with a 4 g/day carboxylic acid formulation of omega-3 fatty acids (EPA and DHA) compared with a corn oil placebo, and no association with harm or benefit in those at the highest achieved tertiles for EPA and DHA levels. Incident AF was more common with both icosapent ethyl and the carboxylic acid formulation of omega-3 fatty acids and has been observed in other studies of omega-3 fatty acid formulations. Several factors could explain the discrepant outcomes observed in these trials; however, the use of a mineral oil placebo in REDUCE-IT is of concern given its adverse effects on lipid and inflammatory biomarkers, suggesting mineral oil may not be an inert placebo.[53] For patients with LDL-C levels between 70 mg/dL and <100 mg/dL, it is unclear whether further LDL-C lowering or adding icosapent ethyl is more effective. Patient preference and shared decision-making are recommended, and secondary causes of elevated triglyceride levels (eg, medications, diabetes, lifestyle) should be addressed before considering icosapent ethyl. Dietary supplements containing omega-3 fatty acids are not acceptable substitutes for icosapent ethyl.
10. In patients not at very high risk, there may be instances where high-intensity statin therapy is insufficient to achieve desired LDL-C levels or not tolerated. Although moderate-intensity statin therapy effectively reduces cardiovascular risk, it is inferior to high-intensity statin therapy.[2] Additional LDL-C lowering may also be necessary in patients on moderate-intensity statin therapy with LDL-C levels ≥70 mg/dL. Adding ezetimibe to moderate-intensity statin therapy may compensate for the reduced LDL-C lowering observed with moderate-intensity statin therapy alone. Although the net benefit of ezetimibe may be less robust among patients not at very high risk, it is preferred before a PCSK9 monoclonal antibody for reasons provided in Recommendation 5.
11. Bempedoic acid is a first-in class therapy adenosine triphosphate-citrate lyase[54] inhibitor that reduces LDL-C levels by 15% to 25% depending on the type and dose of background statin therapy and is associated with fewer muscle-related adverse effects.[33,34] It is also available in a combination product with ezetimibe that reduces LDL-C levels by ~35%. Although it can be combined with statins, bempedoic acid should be avoided when using doses of simvastatin >20 mg daily or pravastatin 40 mg daily because of an ~2-fold increase in serum levels of both statins. Elevation in uric acid levels may occur with bempedoic acid use, and rare cases of tendon rupture have been reported. Inclisiran is a first-in-class small interfering RNA directed to break down PCSK9 mRNA, resulting in reduced synthesis of PCSK9.[35] Inclisiran reduces LDL-C levels by approximately 50% and is administered as a single subcutaneous dose, with a second dose at 3 months, then every 6 months. Inclisiran administration must be performed by a health care professional, which may limit accessibility. It is generally well tolerated, but injection site reactions can occur. The effect of bempedoic acid and inclisiran on MACE is currently under investigation; therefore, nonstatin therapies with proven efficacy (ie, ezetimibe, PCSK9 monoclonal antibody) should be prioritized over these 2 therapies. Preliminary modeling studies project that the use of bempedoic acid or inclisiran in patients unable

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to tolerate statin therapy because of severe statin-associated side effects is of intermediate value [redacted] as is the use of inclisiran in patients with CCD and heterozygous FH.[55] However, the cost-effectiveness of these novel therapies is sensitive to assumptions regarding the effect of each drug on cardiovascular and all-cause death and should be updated when long-term outcomes data become available.

12. Dietary supplements containing omega-3 fatty acids (ie, fish oil) are widely used for presumed cardioprotective benefits. However, low-dose omega-3 fatty acid supplementation does not reduce MACE in patients with CCD.[39–41] The only omega-3 fatty acid formulation that can be recommended in patients with CCD is icosapent ethyl (EPA only) as described in Recommendation 9. The AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health) trial found no benefit with the addition of extended-release niacin to background statin therapy.[36] Another niacin trial in secondary prevention, HPS2-THRIVE (Treatment of HDL to Reduce the Incidence of Vascular Events), also found no benefit with a combination product of niacin and laropiprant, a prostaglandin receptor antagonist; however, this product is no longer available.[37] ACCORD-LIPID (Action to Control Cardiovascular Risk in Diabetes-Lipid Trial)[56] found no benefit with the addition of fenofibrate to background statin therapy. Although this trial was conducted in patients with type 2 diabetes, more than half of the trial participants had established CVD at baseline, and no benefit was observed in this subgroup of patients. A selective PPARα modulator, pemafibrate, was investigated in the PROMINENT (Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Diabetic Patients) trial in high-risk patients with diabetes, but this trial was stopped early for futility.[57] Fenofibrate should only be considered for severe hypertriglyceridemia (triglycerides, ≥500 mg/dL) to reduce the risk of acute pancreatitis.

4.2.7. Blood Pressure Management

Recommendations for Blood Pressure Management
Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	Recommendations
1	A	1. In adults with CCD, nonpharmacologic strategies are recommended as first-line therapy to lower BP in those with elevated BP (120-129/<80 mm Hg) (see Table 12).*[1–9]
1	B-R	2. In adults with CCD who have hypertension, a BP target of <130/<80 mm Hg is recommended to reduce CVD events and all-cause death.*[10–14]

Recommendations for Blood Pressure Management (Continued)

COR	LOE	Recommendations
1	B-R	3. In adults with CCD and hypertension (systolic BP ≥130 and/or diastolic BP ≥80 mm Hg), in addition to nonpharmacological strategies, GDMT angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARB), or beta blockers[15–17] are recommended as first-line therapy for compelling indications (eg, recent MI or angina), with additional antihypertensive medications (eg, dihydropyridine calcium channel blockers [CCB], long-acting thiazide diuretics, and/or mineralocorticoid receptor antagonists) added as needed to optimize BP control.*[13,18]

*Modified from the 2017 ACC/AHA Multisociety Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults.[19]

Synopsis

Hypertension is a well-established risk factor for CVD[20] and is a highly prevalent comorbid condition among individuals with CCD, affecting >60% of such individuals.[21] Individuals with CCD who also have hypertension are at increased risk of death and morbidity compared with individuals with CCD who are normotensive.[22] Treatment of hypertension with lifestyle[1-6,22] and medication therapies[13,16,17,23–28] helps control hypertension and reduce subsequent risk of MACE. The recommendations apply to individuals with CCD who have hypertension. See Section 4.2.1 for additional recommendations regarding nutritional therapies and Sections 4.2.10 to 4.2.11 for additional recommendations about physical activity and CR. For additional information, see the 2017 ACC/AHA/multisociety guideline for the prevention, detection, evaluation, and management of high blood pressure in adults.[19]

Recommendation-Specific Supportive Text

1. Lifestyle-related factors influence BP levels, and lifestyle modifications are effective strategies to help lower elevated BP. These factors include weight loss,[1,5] a heart-healthy diet that is rich in fruits and vegetables,[2,3] reduced dietary sodium,[29,30] physical activity,[4,8] and reduction or elimination of alcohol intake.[6]
2. Among patients with increased cardiovascular risk, reduction of systolic BP to <130 mm Hg has been shown to reduce CVD complications by 25% and all-cause death by 27%.[13] Optimal diastolic BP for clinical outcomes appears to be in the range of 70 to 80 mm Hg.[10,14]
3. In the HOPE (Heart Outcomes Prevention Evaluation) trial, ramipril therapy in patients with CVD or at high risk for CVD reduced the risk of MI, stroke, or CVD by 22% compared with placebo.[16] In patients with CAD and hypertension who were randomized into the INVEST (International

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Table 12. Nonpharmacologic Strategies for Blood Pressure Management*

Approximate Impact on SBP					
Nonpharmacologic Intervention	Dose		Hypertension	Normotension	Reference
Weight loss	Weight/body fat	Best goal is ideal body weight but aim for at least a 1-kg reduction in body weight for most adults who are overweight. Expect about 1 mm Hg for every 1-kg reduction in body weight.	−5 mm Hg	−2/3 mm Hg	5
Healthy diet	DASH dietary pattern	Consume a diet rich in fruits, vegetables, whole grains, and low-fat dairy products, with reduced content of saturated and total fat.	−11 mm Hg	−3 mm Hg	2,3
Reduced intake of dietary sodium	Dietary sodium	Optimal goal is <1500 mg/d but aim for at least a 1000-mg/d reduction in most adults.	−5/6 mm Hg	−2/3 mm Hg	29,30
Enhanced intake of dietary potassium	Dietary potassium	Aim for 3500–5000 mg/d, preferably by consumption of a diet rich in potassium.	−4/5 mm Hg	−2 mm Hg	35
Physical activity	Aerobic	90–150 min/wk 65%–75% heart rate reserve	−5/8 mm Hg	−2/4 mm Hg	4,8
	Dynamic resistance	90–150 min/wk 50%–80% of 1 repetition maximum 6 exercises, 3 sets/exercise, 10 repetitions/set	−4 mm Hg	−2 mm Hg	4
	Isometric resistance	4×2 min (hand grip), 1 min rest between exercises, 30%–40% maximum voluntary contraction, 3 sessions/wk 8–10 wk	−5 mm Hg	−4 mm Hg	36,37
Moderation in alcohol intake	Alcohol consumption	In individuals who drink alcohol, limit alcohol† to: Men: ≤2 drinks daily Women: ≤1 drink daily	−4 mm Hg	−3 mm Hg	6

Resources: Your Guide to Lowering Your Blood Pressure With DASH—How Do I Make the DASH?[38] Available at: https://www.nhlbi.nih.gov/files/docs/public/heart/new_dash.pdf.

*Type, dose, and expected impact on BP in adults with a normal BP and with hypertension.

†In the United States, 1 "standard" drink contains roughly 14 g of pure alcohol, which is typically found in 12 oz of regular beer (usually about 5% alcohol), 5 oz of wine (usually about 12% alcohol), and 1.5 oz of distilled spirits (usually about 40% alcohol).

DASH indicates Dietary Approaches to Stop Hypertension; and SBP, systolic blood pressure.

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Verapamil SR/Trandolapril Study) trial, CCB and ACE inhibitors and beta-blocker/thiazide diuretic therapy had similar cardiovascular morbidity and death outcomes.[31] In the EUROPA (Exclusive Endocrine Therapy or Partial Breast Irradiation for Women ≥70 Years Early Stage Breast Cancer) study involving patients with CCD, ACE inhibitor therapy produced a 20% reduction in risk of CVD death, MI, or cardiac arrest compared with placebo.[15] Beta blockers are particularly effective in patients with CCD, especially those with recent MI and those with ongoing angina, given their ability to reduce angina, improve angina-free exercise tolerance, reduce exertion-related myocardial ischemia, and reduce risk of CVD events.[17,23,27,32,33] Because of the significant benefits from beta blockers and ACE inhibitors and ARB agents in patients with CCD, these medications are recommended as a first-line therapy in the treatment of hypertension in such individuals. GDMT beta blockers for CCD and for lowering BP include carvedilol, metoprolol tartrate, metoprolol succinate, nadolol, bisoprolol, propranolol, and timolol.[19] Outcomes with atenolol appear to be inferior compared with other antihypertensive drugs in the treatment of hypertension.[34] When beta blockers, ACE inhibitors, and ARB therapies do not sufficiently control BP, additional GDMT BP-lowering therapies can be added, including thiazide diuretics, CCB, and mineralocorticoid receptor antagonists.[19]

4.2.8. SGLT2 Inhibitors and GLP-1 Receptor Agonists

Recommendations for Use of SGLT2 Inhibitors and GLP-1 Receptor Agonists
Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	Recommendations
1	A	1. In patients with CCD who have type 2 diabetes, the use of either an SGLT2 inhibitor[1–8] or a GLP-1 receptor agonist[9–17] with proven cardiovascular benefit is recommended to reduce the risk of MACE.
Cost Value Statement: High Value	B-NR	2. In patients with CCD and type 2 diabetes, addition of a GLP-1 receptor agonist at US prices is projected to be of high value compared with standard of care.[18]

Recommendations for Use of SGLT2 Inhibitors and GLP-1 Receptor Agonists (Continued)

COR	LOE	Recommendations
Cost Value Statement: Intermediate Value	B-NR	3. In patients with CCD and type 2 diabetes, addition of an SGLT2 inhibitor at US prices is projected to be of intermediate value compared with standard of care.[18]
1	A	4. In patients with CCD and heart failure with LVEF ≤40%, use of an SGLT2 inhibitor is recommended to reduce the risk of cardiovascular death and heart failure hospitalization[19–22] and to improve QOL,[23,24] irrespective of diabetes status.*
Cost Value Statement: Intermediate Value	B-NR	5. In patients with CCD and heart failure with LVEF ≤40%, addition of an SGLT2 inhibitor to GDMT, irrespective of diabetes status, is projected to be of intermediate value at US prices.[25,26]
2a	B-R	6. In patients with CCD and heart failure with LVEF >40%, use of an SGLT2 inhibitor can be beneficial in decreasing heart failure hospitalizations[27,28] and to improve QOL,[4,29] irrespective of diabetes status.
Cost Value Statement: Intermediate Value	B-NR	7. In patients with CCD and heart failure with LVEF >40%, addition of an SGLT2 inhibitor to GDMT, irrespective of diabetes status, is projected to be of uncertain value at US prices.[30]

*Modified from the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure.[31]

Synopsis

Comprehensive cardiovascular risk reduction strategies are effective in patients with CCD and type 2 diabetes.[32] Despite these efforts, cardiovascular event rates remain high among patients with type 2 diabetes, even among well-managed patients,[1,10,33] and CAD remains the leading cause of morbidity and death.[34] Two classes of glucose-lowering medications (SGLT2 inhibitors and GLP-1 receptor agonists) have potent cardiovascular benefits, independent of their effects on glycemic control.[1,3,4,9,10,13] Both medications improve glycemic control, facilitate weight loss, reduce progression of kidney disease, and reduce the risk of cardiovascular events through distinct pathways. Yet their adoption in clinical practice has been slow,[35,36] highlighting an opportunity for cardiovascular specialists to have a greater collaborative role in the care of patients with CCD and type 2 diabetes.[37]

Comprehensive risk factor control should include lifestyle modifications[38] and GDMT to optimize dyslipidemia (Section 4.2.6, "Lipid Management"), hypertension (Section 4.2.7, "Blood Pressure Management"), weight management (Section 4.2.9), nutrition (Section 4.2.1), physical activity (Section 4.2.11), and hyperglycemia.[39] Regarding glucose control, the American Diabetes Association recommends a hemoglobin A1C goal of <7%[40] and a more conservative glycemic target (eg, hemoglobin A1c <8% or 8.5%) for those older (>65 years of age) with CCD and type 2 diabetes or comorbidities,[41] to limit the risk of hypoglycemia.[40–48] Among patients with CCD and type 2 diabetes, a patient-centered approach (Section 4.1.1, "Team-Based Approach") should guide shared decision-making (Section 4.1.3) about glycemic targets and the decision to initiate an SGLT-2 inhibitor, GLP-1 receptor agonist, or both.[39]

Recommendation-Specific Supportive Text

1. In patients with CCD and type 2 diabetes, both SGLT2 inhibitors and GLP-1 receptor agonists significantly reduce the risk of MACE, with additional benefits in terms of weight loss[49] and progression of kidney disease.[7,16,17] SGLT2 inhibitors do not appear to primarily reduce atherosclerosis as much as they reduce incident and worsening HF (for which patients with CCD and type 2 diabetes who are at risk).[1–8] In contrast, GLP-1 receptor agonists appear to primarily reduce the risk of atherosclerotic events, such as MI and stroke. Although there has been some inconsistency across the cardiovascular outcomes trials,[9–15] meta-analyses have shown no statistically significant heterogeneity in cardiovascular risk reduction across different GLP-1 receptor agonists.[16,17] Currently, no compelling evidence is available that either medication reduces cardiovascular risk in patients with CCD but without type 2 diabetes,[50,51] or in the case of SGLT2 inhibitors, without concomitant HF. Given their distinct mechanisms, the cardiovascular risk reduction may be greater using both classes of medications compared with either medication alone. Data on concurrent use are mostly limited to safety and metabolic endpoints,[52] but available studies showed benefit in BP and weight reduction with dual therapy.[53,54] Whether the effects on cardiovascular outcomes are additive, or even synergistic, is not yet known.
2. In a systematic review of cost-effectiveness analyses examining the addition of GLP-1 agonists compared with alternative therapies (including insulin or other classes of diabetes medications) among patients with diabetes, the use of a GLP-1 agonist is projected to be of high value [redacted][18] Although these analyses were performed in all patients with type 2 diabetes rather than specifically in patients with CCD, these results appear to be robust to a range of assumptions regarding underlying risk and are likely applicable to patients with CCD.
3. In a systematic review of cost-effectiveness analyses examining the addition of SGLT2 inhibitors to standard of care among patients with diabetes, the use of an SGLT2 inhibitor is projected to be of intermediate value [redacted] compared with standard of care.[18] As

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noted previously, these analyses were performed in all patients with type 2 diabetes rather than specifically in patients with CCD, but these results appear to be robust to a range of assumptions regarding underlying risk and are likely applicable to patients with CCD.

4. Among patients with HF with reduced ejection fraction (with or without type 2 diabetes), SGLT2 inhibitors reduce the risk of cardiovascular death and HF hospitalization[19–22] and improve functional capacity and QOL.[23,24] These effects were independent of cause of cardiomyopathy, because approximately half of enrolled patients across the trials had CCD. SGLT2 inhibitors should be avoided or used with caution in patients with type 1 diabetes or with advanced CKD (eg, eGFR <30 mL/min/1.73 m^2).
5. Among patients with HF with reduced ejection fraction (with or without type 2 diabetes), the use of SGLT2 inhibitors is projected to be of intermediate value [redacted] from a US health care sector perspective and a lifetime horizon. One modeling-based study compared dapagliflozin and GDMT with GDMT alone in a hypothetical cohort of adults in the United States with similar clinical characteristics as participants of the DAPA-HF (Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction) trial.[25] Assuming the cost of dapagliflozin to be $4192 annually, dapagliflozin was projected to add 0.63 (95% uncertainty interval, 0.25-1.15) [redacted] Findings were similar among individuals with or without diabetes but were sensitive to drug cost. Similar findings were independently reported by another group of investigators.[26]
6. Among patients with HF with preserved ejection fraction (with or without type 2 diabetes), SGLT2 inhibitors reduced the risk of HF hospitalization or cardiovascular death in the EMPEROR-PRESERVED (Evaluation of the effects of sodium-glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality in patients with chronic heart failure and a preserved ejection fraction) trial[27] and the risk of worsening HF or cardiovascular death in the DELIVER trial (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure), with the primary endpoints driven by significant reductions in HF hospitalization in both trials. SGLT2 inhibitors also improved functional capacity and QOL in the PRESERVED-HF and DELIVER trials.[28,29] CCD was diagnosed in 35% of enrolled patients in EMPORER-PRESERVED and 20% of enrolled patients in PRESERVED-HF (Effects of Dapagliflozin on Symptoms and Functional Status in Patients with Heart Failure and Preserved Ejection Fraction), with no significant difference in risk of HF hospitalization (subgroup was not tested in the QOL study); the CCD rate was not reported in DELIVER.
7. Among patients with HF with preserved ejection fraction (with or without type 2 diabetes), the economic value of SGLT2 inhibitors is sensitive to the effect of SGLT2 inhibitors on cardiovascular mortality. The reduction in cardiovascular mortality was not statistically significant in the EMPEROR-PRESERVED or DELIVER trials, or in a pooled analysis of the 2 trials. If one were to assume no reduction in cardiovascular mortality and minimal improvement in QOL among patients with HF with preserved ejection fraction, the use of empagliflozin is of low value (incremental cost-effectiveness ratio $437 000).[30] However, if one were to assume a 9% reduction in cardiovascular mortality (as consistent with the point-estimate of EMPEROR-PRESERVED), the incremental cost-effectiveness ratio is lowered to $174 000 (which the authors defined as intermediate value after adjusting the ACC/AHA thresholds for interval change in per capita GDP). Although the trials included patients with and without CCD, it is likely that patients with CCD have a higher risk of events (including cardiovascular mortality) and therefore derive a larger-than-average benefit from SGLT2 inhibitors. Additional clinical studies that examine the effect of SGLT2 inhibitors on cardiovascular and noncardiovascular mortality, and additional economic evaluations that synthesize the available clinical evidence and consider a range of costs and risks, are needed to ascertain the value of SGLT2 inhibitors in patients with CCD and HF with preserved ejection fraction.

4.2.9. Weight Management

Recommendations for Weight Management
Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	Recommendations
1	C-EO	1. In patients with CCD, assessment of BMI with or without waist circumference is recommended during routine clinical follow-up.[1–6]
1	B-NR	2. Patients with CCD and overweight or obesity should receive counseling on diet, lifestyle, and goals for weight loss.[7–10]
2a	B-R	3. For patients with CCD and overweight or obesity in whom pharmacologic therapy is warranted for further weight reduction, a GLP-1 receptor agonist can be beneficial in addition to counseling for diet and physical activity,[11,12] and it is reasonable to choose semaglutide over liraglutide.[13,14]

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Recommendations for Weight Management (Continued)		
COR	LOE	Recommendations
2a	B-NR	4. In patients with CCD and severe obesity who have not met weight loss goals with lifestyle and pharmacologic intervention, and who have acceptable surgical risk, referral for consideration of a bariatric procedure is reasonable for weight loss and cardiovascular risk factor reduction.[15–18]
3: Harm	B-R	5. In patients with CCD, use of sympathomimetic weight loss drugs is potentially harmful.[19]

Synopsis

Compared with individuals with normal weight, patients with obesity experience CCD events at an earlier age, live with CCD for a greater proportion of their lifetime, and have a shorter average life span.[6,20] Excess adiposity accelerates atherosclerosis and promotes adverse changes in cardiac function through deleterious effects on the myocardium as well as the vasculature and through obesity-related comorbidities, including hypertension, dyslipidemia and type 2 diabetes.[21–23] Although BMI can be a heterogeneous marker of individual risk, increasing BMI is associated with increasing risk of morbidity and death across populations, and BMI thresholds continue to guide clinical diagnosis and management of overweight and obesity ("2013 AHA/ACC Guideline for the Management of Overweight and Obesity in Adults").[24] The general goals of weight loss and management are to: (1) prevent further weight gain, (2) reduce body weight, and (3) maintain a lower body weight over the long term. Weight loss in association with lifestyle modification (see Section 4.2.1, "Nutrition," Section 4.2.11, "Physical Activity," and Section 4.1.4 "Social Determinants of Health") and select pharmacologic interventions (see Section 4.2.8, "SGLT2 Inhibitors and GLP-1 Receptor Agonists") and surgical interventions for eligible patients with CCD improves metabolic and hemodynamic risk profiles, with potential for improved cardiovascular outcomes.

Table 13. Core Components of CR[18]

Patient assessment
Nutritional counseling
Weight management
Blood pressure management
Lipid management
Diabetes management
Tobacco cessation
Psychosocial management
Physical activity counseling
Exercise training

CR indicates cardiac rehabilitation.

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Recommendation-Specific Supportive Text

1. Patients with CCD should undergo routine measurement of BMI with or without waist circumference for initial evaluation and as a guide to efficacy of weight loss intervention.[1–6] Although not a measure of body composition, BMI remains the most practical way to evaluate for overweight and obesity, defined as a BMI 25 to 29.9 kg/m^2 and ≥30 kg/m^2, respectively.[24] Waist circumference, a surrogate estimate of visceral adiposity, may be a better indicator of risk than BMI in some patients and populations,[25,26] with central obesity defined as a waist circumference >102 cm (40 in) in men and >88 cm (35 in) in women.[24] As with BMI, racial and ethnic differences in waist circumference thresholds associated with cardiometabolic risk have been reported.[27] Recognizing that weight assessment in some individuals may represent a deterrent to seeking care, gender- and culturally sensitive approaches to assessing weight are recommended in all patients, with an option for patients to self-report values where appropriate.
2. Lifestyle modification (see Section 4.2.1, "Nutrition" and Section 4.2.11, "Physical Activity") with associated weight loss improves obesity-related CCD comorbidities. With lifestyle measures alone, a weight loss of 5% to 7% of body weight is typical but often difficult to sustain. Multicomponent interventions including dietary modification, exercise, and behavioral counseling are more effective than interventions targeting single components.[7,8] A meta-analysis of 122 RCTs and 2 observational studies compared an intensive, multicomponent behavior-based weight loss intervention with a comparison group receiving usual care. At 12 to 18 months, patients receiving multicomponent behavior-based interventions were more likely to achieve a ≥5% weight loss (relative risk, 1.94 [95% CI, 1.70-2.22]).[7] In patients with CCD, regular physical activity with increased lean mass may be more important for improving survival than achieving a normal BMI.[10] Patients with CCD and overweight or obesity should be counseled to lose weight, especially if accomplished with increases in physical activity and improvements in cardiorespiratory fitness.[9]
3. Candidates for weight-loss drug therapy include individuals with a BMI ≥30 kg/m^2 or a BMI of 27 to 29.9 kg/m^2 with weight-related comorbidities who have not met weight-loss goals (eg, loss of ≥5% of total body weight at 3–6 months) with a comprehensive lifestyle intervention alone. The decision to initiate drug therapy in patients with CCD should be individualized, considering associated

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risks and benefits. The cardiovascular safety of certain weight-loss drugs, such as naltrexone/bupropion, has not been established and remains controversial.[28] Use of a GLP-1 receptor agonist (Section 4.2.8) is beneficial when pharmacologic therapy is warranted for further weight reduction.[11,12,14] Among eligible adults without diabetes, the STEP 8 (Semaglutide Treatment Effect in Patients with Obesity) randomized controlled trial (N=338, 3.3% with known CCD) found that once-weekly subcutaneous semaglutide 2.4 mg added to counseling for diet and physical activity resulted in significantly greater weight loss at week 68 compared with once-daily subcutaneous liraglutide 3.0 mg or placebo (mean weight change, −15.8% [95% CI, −17.6 to −13.9] versus −6.4% [95% CI, −8.2 to −4.6] versus −1.9% [95% CI, −4.0 to 0.2] for semaglutide versus liraglutide versus placebo, respectively).[13] Both semaglutide (0.5–1.0 mg weekly) and liraglutide (1.2–1.8 mg daily) were associated with reduced MACE in patients with type 2 diabetes and CCD.[29,30] Recently, the double-blind randomized controlled trial SURMOUNT-1 (A Study of Tirzepatide [LY3298176] in Participants with Obesity or Overweight) also showed a dose-dependent weight loss benefit (mean weight change up to −20.9% [95% CI, −21.8 to −19.9]) with once-weekly subcutaneous tirzepatide (at 5 mg, 10 mg, or 15 mg) relative to placebo in eligible obese adults without diabetes (N=2539, 3.1% with ASCVD) over 72 weeks.[31]

4. Patients with CCD and severe obesity (BMI ≥40 kg/m^2 or BMI 35-39.9 kg/m^2 with a weight-related comorbidity) who have not met weight loss goals with lifestyle and pharmacologic intervention may benefit from a bariatric procedure such as gastric bypass surgery. Bariatric procedures appear to be relatively safe and effective among patients with CCD, at least in those <65 years of age.[15,17,18] In the nonrandomized prospective SOS (Swedish Obese Subjects) study, bariatric surgery was associated with prevention of type 2 diabetes and fewer cardiovascular deaths and lower incidence of MI or stroke compared with matched obese controls (hazard ratio, 0.47 [95% CI, 0.29-0.76] for death, and hazard ratio, 0.67 [95% CI, 0.54-0.83] for MI or stroke).[16,32] These benefits do not appear to occur with liposuction, suggesting that the negative energy balance associated with bariatric intervention may be necessary for achieving the metabolic benefits of weight loss.[33] Specifically among patients with obesity and type 2 diabetes, bariatric surgery is an effective strategy for achieving weight loss, glycemic control, and reducing cardiovascular risk factors.[34] More recently, 2 retrospective observational studies of patients with CCD showed significant reductions in MACE among those undergoing bariatric surgery compared with matched controls.[17,18]
5. Sympathomimetic drugs (eg, phentermine, diethylproprion, benzphetamine, phendimetrazine) can increase heart rate and BP and are not recommended in patients with CCD. In a trial of sibutramine versus placebo in >10 000 patients with or at high risk for CCD, sibutramine was associated with a higher risk of nonfatal MI (4.1% versus 3.2%; hazard ratio, 1.28 [95% CI, 1.04-1.57]) and nonfatal stroke (2.6% versus 1.9%; hazard ratio, 1.36 [95% CI, 1.04-1.77]).[19] As a result, the FDA removed sibutramine from the US market in 2010, but it can still be found illicitly in dietary supplements marketed for weight loss and in other parts of the world.[35] Clinicians are encouraged to ask patients about potential use of dietary supplements for weight management.

4.2.10. Cardiac Rehabilitation

Recommendation for Cardiac Rehabilitation
Referenced studies that support the recommendation are summarized in the Online Data Supplement.

COR	LOE	Recommendation
1	A*	1. All patients with CCD and appropriate indications*†‡ should be referred to a cardiac rehabilitation program to improve outcomes.[1–3]
	B-R†	
	C-LD‡	

*After recent MI, PCI, or CABG.[1–5]
†With stable angina[2,3,6,7] or after heart transplant.[8–13]
‡After recent spontaneous coronary artery dissection event.[14–17]

Synopsis

CR is a comprehensive, team-based, and evidence-based approach to delivering lifestyle, behavioral, and medical therapies of known benefit to individuals with CVD.[18–23] Because of underutilization of CR,[24] novel delivery models have been and continue to be developed, tested, and implemented, including home-based, remote CR services.[25] Home-based CR have similar shorter-term safety and clinical outcomes as facility-based CR and can be considered as an alternative option for patients who cannot attend facility-based CR.[26–29] This is of particular importance for patients with limited option for center-based CR, such as those living in rural settings and other areas with limited number of CR centers. In whatever delivery model CR is provided, the multidisciplinary CR team develops and applies patient-centered care based on specific core components (Table 13), including recovery and recuperation strategies, quality improvement, and adherence to lifestyle and medication therapies.[18,30,31] Key benefits from CR have been noted to be dose-related.[32,33]

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Published evidence suggests favorable cost-effectiveness of CR.[34–36] One multicenter, randomized trial of longer-term "maintenance" CR of up to 3 years was associated with moderate but significant improvements in cardiovascular outcomes compared with those who participated in the traditional 12-week course of CR.[37] For related information, refer to these Sections: 3.2, "Risk Stratification and Relationship to Treatment Selection"; 4.1.1, "Team-Based Approach"; 4.1.2, "Patient Education," 4.1.3, "Shared Decision-Making"; 4.2.1, "Nutrition, Including Supplements"; 4.2.2, "Mental Health"; 4.2.6, "Lipid Management"; 4.2.7, "Blood Pressure Management"; 4.2.8, "Sodium Glucose Cotransporter 2 Inhibitors and Glucagon-Like Peptide-1 Receptor Agonists"; 4.2.9, "Weight Management"; 6.1, "Existing Heart Diseases and Conditions"; 6.9, "Post-Heart Transplant Cardiac Allograft Vasculopathy"; and 2022 ACC/AHA/HFSA heart failure guideline.[38]

Recommendation-Specific Supportive Text

1. Patients with CCD with a recent MI, PCI, or CABG procedure who participate in CR have significantly better outcomes compared with those who do not participate,[39–41] including lower all-cause and cardiovascular mortality rates,[27,41,42] lower rehospitalization rates (total, cardiovascular, and noncardiovascular),[43–45] and superior QOL.[27,41,42,44,45] Participation in CR appears to improve symptom control, functional capacity, and QOL in patients with stable angina.[2,40]

   CR is also associated with improved outcomes in special populations with CCD. CR improves exercise capacity in heart transplant recipients,[8] including those in maintenance (1–8 years after heart transplant) as well as de novo (7–16 weeks after heart transplant).[9,10] In maintenance of patients with heart transplant with or without cardiac allograft vasculopathy, high-intensity interval training versus usual care resulted in significantly lower rates of cardiac allograft vasculopathy progression at 1 year,[11] but these effects were no longer present on long-term (3–5 years) follow-up, suggesting that continued intermittent periods of high-intensity interval training may be necessary to maintain the initial benefits.[12,46,47] One observational study showed an association between the dose of CR sessions and survival in patients with heart transplant.[48]

   Similarly, patients with spontaneous coronary artery dissection (SCAD) who participated in CR, compared with those who did not, had lower MACE and lower rates of recurrent MI with favorable trends in physical, emotional, and mental domains.[14–17] For patients with CCD and concomitant HF, CR is also recommended as a Class 2a recommendation, LOE B-NR (see 2022 ACC/AHA/HFSA heart failure guideline).[38]

4.2.11. Physical Activity

Recommendations for Physical Activity
Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	Recommendations
1	A	1. For patients with CCD who do not have contraindications, an exercise regimen is recommended, including ≥150 minutes/wk of moderate-intensity aerobic activities or ≥75 minutes/wk of higher-intensity aerobic activities to improve functional capacity and QOL, and to reduce hospital admission and mortality rates.[1–3]
1	B-R	2. For patients with CCD who do not have contraindications, resistance (strength) training exercises are recommended on ≥2 days/wk to improve muscle strength, functional capacity, and cardiovascular risk factor control.[4–6]
2a	B-NR	3. For patients with CCD who do not have contraindications, lower-intensity lifestyle activities (eg, walking breaks at work) to reduce sedentary behavior (ie, sitting time) are reasonable to improve functional capacity and reduce cardiovascular risk, especially in individuals with low levels of habitual leisure time physical activity.[7–9]

Synopsis

Habitual physical activities—including nonexercise lifestyle activities, aerobic (cardiovascular) exercise training, and resistance (strength) training—are associated with improved outcomes in individuals with CVD, including functional capacity, QOL, and mortality and morbidity rates.[1–9] Moving individuals from sedentary lifestyle habits to at least lower-intensity physical activities can improve metabolic and cardiovascular health.[9–11] Health benefits occur even with lower doses (eg, frequency, duration, and intensity) of physical activity and increase with increasing doses of physical activity.[7] Mechanisms of the benefits from physical activity and exercise training include antiatherosclerotic, antiarrhythmic, antithrombotic, anti-ischemic, and antidepressant effects.[12]

Exercise is contraindicated in patients with severe, life-threatening, and unstable conditions. Contraindications include unstable angina, other high risk cardiovascular conditions (eg, high-grade arrhythmias, decompensated heart failure, active thromboembolic disease), or other unstable or life-threatening noncardiovascular conditions such as active infection, uncontrolled diabetes, end-stage cancer, or unstable psychological issues.

Recommendation-Specific Supportive Text

1. Moderate-to-higher intensity exercise training in individuals with CCD, which is done in CR programs, improves functional capacity, health-related QOL, cardiovascular risk factor control, and mortality rates.[2,3,13,14] In addition to continuous, moderate-intensity exercise training, high-intensity interval training also appears to be an effective and safe

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approach to aerobic exercise training in individuals with CCD.[15,16] US guidelines recommend that adults who do not have contraindications to exercise should do at least 150 to 300 minutes per week of moderate-intensity aerobic physical activity, or at least 75 to 150 minutes per week of vigorous (higher)-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic activity.

2. Muscle-strengthening (resistance training) activities are recommended on ≥2 days a week.[17] Resistance training to safely improve muscular strength improves functional capacity and QOL.[5,6,18] Resistance training may also reduce mortality rates in individuals with CCD.[19]
3. Compared with a sedentary lifestyle, lower-intensity lifestyle activities (eg, gardening), office-based physical activities, and climbing stairs improve energy expenditure, functional capacity, and cardiometabolic risk, especially in previously sedentary individuals who are not exercising on a regular basis.[20–25] Interventions, such as the use of step counters and walking prompts, may be helpful in decreasing sedentary time and increasing lifestyle activities in individuals with CCD.[9-11,20-23,26]

4.2.12. Environmental Exposures

Recommendations for Environmental Exposures
Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	Recommendations
2a	B-NR	1. In patients with CCD, minimization of exposure to ambient air pollution is reasonable to reduce the risk of cardiovascular events.[1–7]
2b	B-NR	2. In patients with CCD, minimization of climate-related exposures (eg, extreme temperatures, wildfire smoke) may be reasonable to reduce the risk of cardiovascular events.[8–10]

Synopsis

Adverse environmental exposures such as air pollution, extremes of ambient temperature, and excess noise should be systematically assessed in patients with CCD. Numerous ecological studies have examined the adverse effect on cardiovascular health of ambient air pollution such as that produced by transportation exhaust or wildfire smoke.[1-7,11,12] Exposure to extreme heat or extreme cold ambient temperatures has been associated with increased cardiovascular events among patients with CCD.[8-10,13,14] As extreme temperatures have become increasingly frequent, clinicians should identify at-risk individuals, provide guidance regarding medication titration (eg, loop diuretics) during extreme temperature events, and encourage the use of publicly available controlled-temperature environments during extreme weather events. Numerous observational studies document a connection between excess environmental noise and the progression of CCD,[15,16] but data are limited regarding the benefit of noise reduction devices. Adverse environmental exposures disproportionately affect racial and ethnic minority populations and individuals of low socioeconomic status; therefore, they contribute to inequitable health outcomes.[17,18] Policy interventions that reduce the burden of these exposures or provide resources to mitigate their adverse effects may reduce health disparities.[18]

Recommendation-Specific Supportive Text

1. Ambient air pollution, especially small particulate matter with an aerodynamic diameter ≤2.5 microns (also referred to as "PM2.5"), is associated with worse cardiovascular outcomes.[1–7] Most outdoor and indoor PM2.5 pollutants are produced by combustion (eg, car engines, coal- or natural gas-fired power plants, woodstoves, or wildfires). Proximity to automobile traffic or fossil fuel-dependent industries and use of poorly ventilated stoves are key predictors of exposure to increased PM2.5 levels. Long-term exposure to PM2.5 levels >10 micrograms per cubic meter (μg/m^3) is associated with a >10% increase in the odds of having CCD, progression of CCD, and suffering an acute MI or cardiovascular mortality.[1–5] Even short-term exposure (<7 days) to elevated levels is associated with increased hospitalization and cardiovascular death.[6,7] There are insufficient data to support regular use of in-home high-efficiency air purifiers or N95 filters to improve cardiovascular outcomes.[19] Other pollutants, such as ground-level ozone, are associated with a small increase in risk of cardiovascular death, but additional studies are needed to quantify the magnitude of risk.[20] Information regarding air pollutants and their relation to air quality in a specific geography can be found via the US Environmental Protection Agency at AirNow.gov.[21]
2. Exposure to extreme ambient heat or several consecutive days of extreme heat ("heat wave") is associated with increased death from ischemic heart disease.[8] Older adults, individuals with outdoor jobs, and patients receiving certain medications such as loop diuretics are at increased risk.[8,9] The effects of extreme heat are exacerbated in urban areas because of the "urban heat island effect," wherein dense concentrations of pavement and buildings absorb and retain heat.[13] Individualized assessment should include risk of exposure (ie, regional temperature and occupational exposure), clinical susceptibility (ie, age, comorbidities, and medications used), and capacity for adaptation (ie, cognitive skills, housing quality, and community resources).[14] Similarly, exposure to wildfire smoke has been associated with increased hospitalizations for acute

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MI, ischemic heart disease, and cardiac arrest.[12] Wildfire smoke can be carried long distances, exposing individuals thousands of miles from the source.[11] The population health impact of wildfires is projected to increase in the coming years because of climate change–related increases in temperature and changes in precipitation patterns, as well as increased human habitation in wildland-urban interfaces.[22] Minimizing exposure to these environmental extremes may improve outcomes for individuals with CCD.

4.3. Medical Therapy to Prevent Cardiovascular Events and Manage Symptoms

4.3.1. Antiplatelet Therapy and Oral Anticoagulants

Recommendations for Antiplatelet Therapy and Oral Anticoagulants
Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	Recommendations
Antiplatelet Therapy Without Oral Anticoagulants		
1	A	1. In patients with CCD and no indication for oral anticoagulant therapy, low-dose aspirin 81 mg (75-100 mg) is recommended to reduce atherosclerotic events.*[1–3]
1	A	2. In patients with CCD treated with PCI, dual antiplatelet therapy (DAPT) consisting of aspirin and clopidogrel for 6 months post PCI followed by single antiplatelet therapy (SAPT) is indicated to reduce MACE and bleeding events.*[4–7]
2a	A	3. In select patients with CCD treated with PCI and a drug-eluting stent (DES) who have completed a 1- to 3-month course of DAPT, P2Y12 inhibitor monotherapy for at least 12 months is reasonable to reduce bleeding risk.[8–12]
2b	A	4. In patients with CCD who have had a previous MI and are at low bleeding risk, extended DAPT beyond 12 months for a period of up to 3 years may be reasonable to reduce MACE.*[13,14]
2b	B-R	5. In patients with CCD and a previous history of MI without a history of stroke, transient ischemic attack (TIA), or ICH, vorapaxar may be added to aspirin therapy to reduce MACE.[15–17]
2b	B-R	6. In patients with CCD, the use of DAPT after CABG may be useful to reduce the incidence of saphenous vein graft occlusion.[18]
3: No benefit	A	7. In patients with CCD without recent ACS or a PCI-related indication for DAPT, the addition of clopidogrel to aspirin therapy is not useful to reduce MACE.*[19]
3: Harm	A	8. In patients with CCD and previous stroke, TIA, or ICH, vorapaxar should not be added to DAPT because of increased risk of major bleeding and ICH.[15,20]
3: Harm	B-R	9. In patients with CCD and previous stroke, TIA, or ICH, prasugrel should not be used because of risk of significant or fatal bleeding.[21]
3: Harm	B-R	10. In patients with CCD, chronic nonsteroidal anti-inflammatory drugs should not be used because of increased cardiovascular and bleeding complications.*[22]

Recommendations for Antiplatelet Therapy and Oral Anticoagulants (Continued)

COR	LOE	Recommendations
Antiplatelet Therapy With Direct Oral Anticoagulant (DOAC)		
1	B-R	11. In patients with CCD who have undergone elective PCI and who require oral anticoagulant therapy, DAPT for 1 to 4 weeks followed by clopidogrel alone for 6 months should be administered in addition to DOAC.†[23]
2a	B-R	12. In patients with CCD who have undergone PCI and who require oral anticoagulant therapy, continuing aspirin in addition to clopidogrel for up to 1 month is reasonable if the patient has a high thrombotic risk and low bleeding risk.*[23–25]
2b	B-R	13. In patients with CCD who require oral anticoagulation and have a low atherothrombotic risk, discontinuation of aspirin therapy with continuation of DOAC alone may be considered 1 year after PCI to reduce bleeding risk.*[26]
2b	C-LD	14. In patients with CCD who require oral anticoagulation, DOAC monotherapy may be considered if there is no acute indication for concomitant antiplatelet therapy.[27–29]
Antiplatelet Therapy and Low-Dose DOAC		
2a	B-R	15. In patients with CCD without an indication for therapeutic DOAC or DAPT and who are at high risk of recurrent ischemic events but low-to-moderate bleeding risk, the addition of low-dose rivaroxaban 2.5 mg twice daily to aspirin 81 mg daily is reasonable for long-term reduction of risk for MACE.[30–32]
DAPT and Proton Pump Inhibitor (PPI)		
2a	B-R	16. In patients with CCD on DAPT, the use of a PPI can be effective in reducing gastrointestinal bleeding risk.*[33]

*Modified from the 2016 ACC/AHA Guideline Focused Update on DAPT.[34]
†Modified from the 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization.[35]

Synopsis

These recommendations on the use of antiplatelet therapy in patients with CCD update and supplement the 2016 AHA/ACC guideline for DAPT.[34] Significant benefits remain for aspirin use in secondary prevention.[2,36,37] The use of DAPT can be considered in those who have high thrombotic risk and low bleeding risk. Figure 9 summarizes recommendations for antiplatelet therapy in CCD. The use of validated risk scores to address bleeding risk can be useful in choice and duration of antiplatelet therapy. The more frequently used risk calculators are PRECISE DAPT (Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy), DAPT, and PARIS (Patterns of Non-Adherence to Antiplatelet Regimen in Stented Patients) risk scores.[18–20] Several clinical trials have evaluated strategies for concurrent use of antiplatelet agents and DOACs in patients with atherosclerotic disease. The breadth and consistency of trials evaluating the efficacy and safety of DOAC use with or without antiplatelet therapy among patients with CCD and with or without AF is modest.[27,28,30-32,38–44] The combination of antiplatelet

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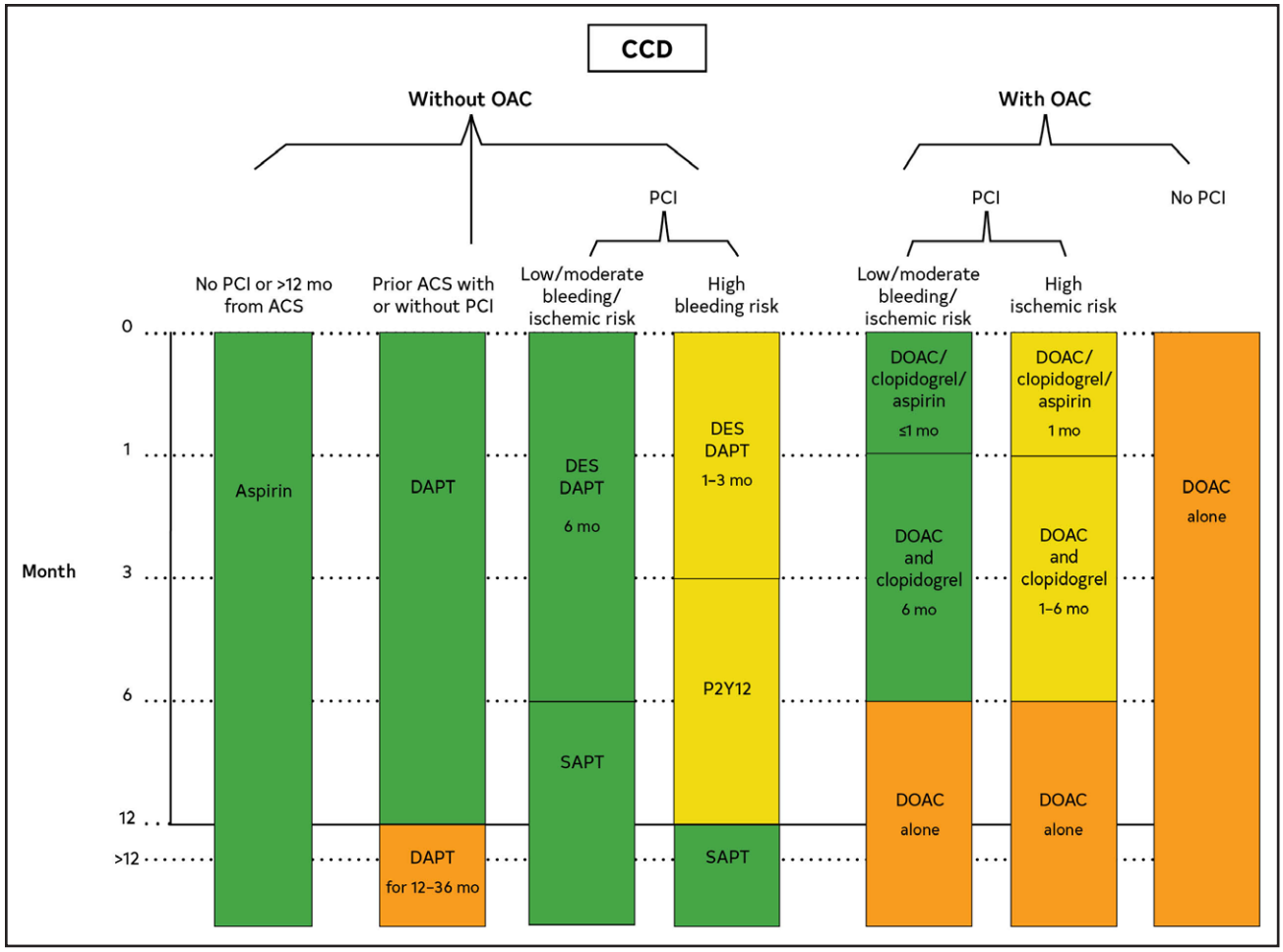

Figure 9. Recommended Duration of Antiplatelet Therapy.*†
ACS indicates acute coronary syndrome; ASA, aspirin; CCD, chronic coronary disease; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; DOAC, direct oral anticoagulant; MI, myocardial infarction; OAC, oral anticoagulants; PCI, percutaneous coronary intervention; SAPT, single antiplatelet therapy. *Colors correspond to Class of Recommendation in Table 3. †This figure does not encompass all recommendations within this section.

therapy and standard dose DOACs for reducing stroke risk among patients with atrial fibrillation (dabigatran 150 mg twice daily, apixaban 5 mg twice daily, rivaroxaban 20 mg daily, edoxaban 60 mg daily) is not without added bleeding risk. The variability in treatment duration, as well as various platelet adenosine diphosphate receptor (P2Y12) agents and DOAC regimens tested in these trials highlights the need for an individualized approach to achieve the optimal balance between ischemic and bleeding risks. Although DES are the predominant stent used in the United States, bare metal stents are still used in a small proportion of patients. The reader is referred to the 2016 AHA/ACC guideline for DAPT[34] for specific treatment details for bare metal stents.

Recommendation-Specific Supportive Text

1. The use of aspirin for secondary ASCVD prevention is well established for reduction in MACE.[2,45] More recently, the ADAPTABLE (Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-Term) trial used a large (N=15 076), open-label design to assign patients with established ASCVD to either 81 mg or 325 mg of aspirin.[3] No significant differences were observed in the primary composite of death from any cause, hospitalization for MI, or hospitalization for stroke by aspirin dose. No differences in major bleeding were observed. However, substantial dose switching was observed (41.6% of patients assigned to take 325 mg daily switched to 81 mg daily and 7.1% assigned to take 81 mg daily switched to 325 mg daily). As an alternative to low-dose aspirin, clopidogrel may be used in individuals who cannot tolerate aspirin therapy, and many of the contemporary trials have used clopidogrel monotherapy after a short course of DAPT.[46,47]
2. To assess optimal duration of antiplatelet therapy, a meta-analysis of RCTs (n=31 666 patients) comparing shorter DAPT with longer DAPT

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showed that shorter DAPT was associated with lower all-cause mortality.[4] Patients treated with DAPT for ≤6 months had similar mortality rates, MI, and stent thrombosis, but lower rates of major bleeding than patients treated with 1-year DAPT.[4] Data supporting the use of DAPT for 6 months with continued use of aspirin after 6 months come from several trials. The largest trial was ISAR-SAFE (Randomized, Double Blind Trial of 6 Versus 12 Months of DAPT After DES-Implantation; N=4005 patients, of which 60% had stable CAD).[7] In these trials, aspirin use continued for the duration of the 12-month trial design.[5,12] Data are limited on which antiplatelet agent—aspirin or clopidogrel—is best for indefinite therapy after a 12-month period after PCI. The HOST-Exam (Harmonizing Optimal Strategy for Treatment of coronary artery diseases-Extended Antiplatelet Monotherapy) trial enrolled 5530 East Asian participants if they tolerated DAPT for 6 to 18 months without any ischemic or major bleeding complication and randomized them to receive clopidogrel 75 mg daily or aspirin 100 mg daily for 24 months.[46] The benefit of clopidogrel over aspirin was observed in both thrombotic and bleeding complications. This study used an open-label design in a homogenous East Asian population known to have lower rates of thrombotic complications, and the observed event rate was lower than expected. Therefore, further clinical trials would be useful to guide recommendations regarding the long-term use of clopidogrel versus aspirin as SAPT in CCD.[46,48,49]

3. Multiple clinical trials (SMART CHOICE [Comparison Between P2Y12 Antagonist Monotherapy and Dual Antiplatelet Therapy after DES], STOP-DAPT2 [Short and Optimal Duration of Dual Antiplatelet Therapy after Everolimus-Eluting Cobalt-Chromium Stent-2 Acute Coronary Syndrome], TWILIGHT [Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention], and GLOBAL LEADERS [A Clinical Study Comparing Two Forms of Antiplatelet Therapy After Stent Implantation]) found reduced bleeding complications without increased ischemic complications when DAPT was used for 1 to 3 months followed by P2Y12 monotherapy.[8,9,47,50–52] These trial populations comprised 35% to 62% in stable patients with stable CAD. In a network meta-analysis that included 29 089 patients randomized to short-term DAPT followed by P2Y12 inhibitor monotherapy versus standard duration DAPT, a net clinical benefit was seen that favored short-term DAPT followed by P2Y12 inhibitor monotherapy with less MI and bleeding.[8] A meta-analysis showed discontinuation of aspirin after 1 to 3 months with continuation of a P2Y12 agent (mostly prasugrel or ticagrelor) reduced the risk of major bleeding by 40% without an increased risk of MACE.[10] These trials were not powered to assess ischemic events, particularly stent thrombosis. Therefore, longer duration DAPT may be needed for patients with higher thrombotic risk (eg, several lesions, long stent length, bifurcation location, atherectomy use, lesion location [left main], bypass graft, or chronic occlusion).
4. A systematic review and meta-analysis of prospective RCTs of secondary prevention examined data from 33 435 participants. Of these, 20 203 were treated with DAPT and 13 232 were given only aspirin. Patients were considered high risk and almost half had previous MI. Comorbidities also included diabetes, previous PCI, and CKD. Extended DAPT for >1 year reduced MACE (relative risk, 0.78 [95% CI, 0.67-0.90]; P=0.001) and absolute risk difference of 1.09%, or a number needed to treat for benefit of 91 to prevent 1 MACE over 31-month follow up. This came with an increased absolute 0.8% risk of major bleeding without significant intracranial or fatal bleeding.[13] Similarly, a systematic review conducted for the 2016 ACC/AHA guidelines on DAPT[34] examined the incidence of death, major hemorrhage, MI, stent thrombosis, and major adverse cardiac events in 33 051 patients in 11 RCTs of prolonged versus short-course DAPT after stenting with DES and in secondary prevention after MI. Among those treated with DES, prolonged DAPT reduced stent thrombosis and MI but increased major hemorrhage. Patients with previous MI had evidence of reduced cardiovascular events at the expense of increased bleeding.[53–55] The PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54) trial enrolled 21162 patients who had MI 1 to 3 years before being given ticagrelor 90 mg or 60 mg twice daily compared with placebo on a background of low-dose aspirin.[56] Treatment with ticagrelor 60 mg reduced the risk of cardiovascular death, MI, or stroke by 16% and increased the risk of major bleeding at 33-month follow up.[14]
5. Given multiple pathways of platelet activation, options for additional suppression of platelet activity have been studied. PAR-1 is a key receptor for thrombin activation. Vorapaxar selectively inhibits PAR-1 on platelets, thereby potently inhibiting thrombin-induced platelet aggregation. The TRAP 2P TIMI 50 (Trial to Assess the Effects of SCH 530348 in Preventing Heart Attack and Stroke in Patients with Atherosclerosis) trial

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randomized 26 449 patients with history of MI, ischemic stroke, or peripheral artery disease to either 2.5 mg of vorapaxar daily or placebo on a background of aspirin therapy. At a mean follow up of 3 years, patients who received vorapaxar experienced an ischemic event less often or died from cardiovascular causes; however, they had more major and intracranial bleeding.[15] In a prespecified subgroup analysis of 17 779 patients who had previous MI, there was a reduced incidence of cardiovascular death, MI, or stroke in the vorapaxar group compared with placebo; however, moderate or severe bleeding was increased.[16] In a prespecified analysis of 16 897 patients with previous MI without a history of stroke or TIA and on thienopyridine therapy, vorapaxar reduced the composite of cardiovascular death, MI, or stroke compared with thienopyridine use; however, GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) moderate or severe bleeding was increased. Three-year rates of fatal bleeding were 0.2% versus 0.1% in patients receiving vorapaxar versus thienopyridine. Intracranial hemorrhage rates were 0.5% versus 0.4% in that cohort. Vorapaxar had net clinical benefit with a combined risk of all-cause death, MI, stroke, or GUSTO severe bleeding decreased by 13% compared with placebo. Of note, thienopyridine use was not randomized in this study; therefore, formal comparison is limited. The thienopyridine used was clopidogrel therefore extrapolation to more potent P2Y12 agents is not possible.[17]

6. In a systematic review and meta-analysis of observational and RCTs (N=20 315 patients) comparing DAPT with SAPT after urgent or elective CABG,[18] investigators performed a pooled sensitivity analysis of studies with stable ischemic heart disease–predominant patients (>50% of study population), and found no difference between SAPT and DAPT after CABG in overall mortality (odds ratio, 0.83 [95% CI, 0.63–1.10]; *P*=0.20), cardiovascular mortality (odds ratio, 0.66 [95% CI, 0.34–1.29]; *P*=0.23), MI (odds ratio, 1.15 [95% CI, 0.66–1.99]; *P*=0.63), stroke (odds ratio, 0.58 [95% CI, 0.32–1.06]; *P*=0.08), combined incidence of cardiovascular death, MI, and stroke (odds ratio, 0.81 [95% CI, 0.57–1.16]; *P*=0.25), and arterial graft occlusions (odds ratio, 1.13 [95% CI, 0.73–1.73]; *P*=0.59). In the studies that had predominantly stable patients with CAD, the rate of saphenous vein graft occlusion was lower among those receiving DAPT (odds ratio, 0.74 [95% CI, 0.60–0.90]; *P*<0.01).
7. Clopidogrel plus aspirin is not more effective than aspirin alone in reducing the rate of MI, stroke, or death from cardiovascular causes in patients at high risk for atherothrombotic events.[19]
8. In the TRAP 2P–TIMI 50 trial, after 2 years the data and safety monitoring board recommended discontinuation of study treatment in patients with a history of stroke because of the risk of intracranial hemorrhage. Significant reduction in cardiovascular death, MI, stroke, or recurrent ischemia leading to revascularization was observed; however, the primary driver of benefit was in lower risk of MI, at a cost of increased moderate to severe bleeding along with increased intracranial bleeding.[15,57] Vorapaxar is FDA approved for use in patients with previous MI for the reduction in cardiovascular death, MI, stroke, or recurrent ischemia leading to revascularization; however, it carries a 55% increase in moderate or severe bleeding and is contraindicated with a history of stroke, TIA, or intracranial hemorrhage.
9. In the TRITON-TIMI 38 (Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis In Myocardial Infarction 38) trial, patients with previous TIA or stroke had increased risk of intracranial hemorrhage leading to an FDA warning: Prasugrel can cause significant, sometimes fatal, bleeding and should not be used in patients with active pathological bleeding or with a history of TIA or stroke. Patients ≥75 years of age and weighing <60 kg had less clinical efficacy with prasugrel use.[21,58]
10. Investigators have assessed the vascular and gastrointestinal side effects in patients with vascular disease and have found major vascular events were increased by about a third by a coxib (relative risk, 1.37 [95% CI, 1.14–1.66]; *P*=0.0009) or diclofenac (relative risk, 1.41 [95% CI, 1.12–1.78]; *P*=0.0036), because of an increase in major coronary events (coxibs relative risk, 1.76 [95% CI, 1.31–2.37]; *P*=0.0001; diclofenac relative risk, 1.70 [95% CI, 1.19–2.41]; *P*=0.0032). Ibuprofen also significantly increased major coronary events (relative risk, 2.22 [95% CI, 1.10–4.48]; *P*=0.0253). Vascular death was increased significantly by coxibs (relative risk, 1.58 [99% CI, 1.00–2.49]; *P*=0.0103) and diclofenac (relative risk, 1.65 [95% CI, 0.95–2.85], *P*=0.0187). HF risk was doubled by all nonsteroidal anti-inflammatory drugs.[22] However, at moderate doses, celecoxib was found to be noninferior to naproxen or ibuprofen regarding increased cardiovascular risk in patients with arthritis who were considered high cardiovascular risk (stable angina, history of MI, unstable angina, status post CABG or PCI, TIA, or cerebrovascular accident within 3 months, >50% stenosis, carotid disease, peripheral artery disease, diabetes, age

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>55 years in men, age >65 years in women, hyperlipidemia, hypertension, early family history of CAD, smoking). These trials involved celecoxib, rofecoxib, etoricoxib, and lumiracoxib and 3 high-dose nonsteroidal anti-inflammatory regimens: diclofenac 150 mg, ibuprofen 2400 mg, and naproxen 1000 mg daily.

11. A systematic review and network meta-analysis of 4 RCTs, including 10 026 patients (39%–72% with stable CAD)[23,59] showed that the combination of a DOAC with a P2Y12 inhibitor was associated with less bleeding compared with vitamin K agonists and DAPT. The omission of aspirin led to less bleeding, including intracranial bleeding, without differences in MACE, compared with strategies including aspirin.[59] In an updated network meta-analysis including these trials and a fifth trial (ENTRUST-AF PCI [Edoxaban Treatment Versus Vitamin K Antagonist in Patients with Atrial Fibrillation Undergoing Percutaneous Coronary Intervention]; N=11 542), fewer bleeding complications were observed with preserved antithrombotic efficacy when aspirin was discontinued within a few days (3–14 days) after PCI. The authors concluded that an antithrombotic regimen of vitamin K agonists plus DAPT should generally be avoided. The use of a DOAC (apixaban 5 mg twice daily or 2.5 mg twice daily in those with 2 of 3 criteria for high bleeding risk; rivaroxaban 15 mg daily; edoxaban 60 mg daily or 30 mg if creatinine clearance 15-50 mL/min, weight <60 kg, or concurrent use of specific potent P-glycoprotein inhibitors; and dabigatran 110 mg or 150 mg twice daily) plus a P2Y12 inhibitor without aspirin may be the most favorable treatment option and the preferred antithrombotic regimen for most patients with AF undergoing PCI. The AUGUSTUS trial (A Study of Apixaban in Patients with AF, not Caused by a Heart Valve Problem, who are at Risk for Thrombosis due to having had a Recent Coronary Event, such as a Heart Attack or a Procedure to Open the Vessels of the Heart) examined randomized treatment effects of low-dose aspirin (compared with placebo) and apixaban (compared with vitamin K antagonist [VKA]) on the risk of stent thrombosis and found a 2-fold increase in bleeding with aspirin while the incidence of stent thrombosis was low, occurring in <1% over 6 months. However, the study had limited power to detect a difference in stent thrombosis. Rates of stent thrombosis were lower with aspirin compared with placebo and with apixaban compared with VKA. Among patients with a high risk of stent thrombosis and an acceptable bleeding risk, the use of aspirin up to 30 days after PCI should be considered.[25]
12. Triple therapy after PCI in patients with AF increases bleeding risk without significant reduction in ischemic risk.[59] A recent expert consensus document recommends triple therapy with aspirin, a P2Y12 inhibitor, and an oral anticoagulant for up to 30 days after PCI for patients at particularly high risk for coronary thrombosis such as previous MI, complex lesions, presence of select traditional cardiovascular risk factors, or extensive CVD but with bleeding risk that is judged to be low.[29] A subgroup analysis of the REDUAL PCI trial (Dual Therapy with Dabigatran/Ticagrelor Versus Dual Therapy with Dabigatran/Clopidogrel in ACS Patients with Indication for NOAC Undergoing PCI) examined effect of lesion complexity and clinical risk factors. This trial found that dabigatran dual therapy after PCI was associated with reduced bleeding risk compared with warfarin triple therapy, independent of the presence of procedural or clinical complexity factors. However, patients in the highest lesion complexity and clinical risk factor group had the highest hazard ratio (1.43 [95% CI, 0.74-2.77]) for death, thromboembolic event, or unplanned revascularization in the dabigatran 110 mg dual therapy compared with dabigatran 150 mg dual therapy (hazard ratio, 0.88 [95% CI, 0.33-2.36]) both compared with warfarin triple therapy.[60–63]
13. The AFIRE (Atrial Fibrillation and Ischemic Events With Rivaroxaban) trial was a multicenter, open-label trial that randomized 2236 patients with AF who had previous PCI or CABG >1 year earlier or who had CCD to rivaroxaban versus rivaroxaban plus a single antiplatelet agent (70.2% received aspirin, and 26.8% received a P2Y12 inhibitor). The primary endpoint was a composite of stroke, systemic embolism, MI, unstable angina requiring revascularization, or death from any cause, with a safety endpoint of major bleeding. Rivaroxaban monotherapy was noninferior to combination therapy for efficacy and superior for safety among patients with AF and stable CAD. In patients with stable CCD and AF, the addition of antiplatelet therapy to a VKA does not reduce the risk of recurrent coronary events or thrombosis; furthermore, this combination leads to significantly increased bleeding risk.[26,64,65]
14. Several studies have evaluated triple therapy with a DOAC and DAPT as well as a DOAC and SAPT in patients with AF and recent ACS.[27,28,38–44] Although these trials showed a lower risk of bleeding with a DOAC combined with a single antiplatelet agent compared with triple therapy, none of the studies were powered to clearly show differences in reducing ischemic events. Additionally, data are limited comparing either of these therapies for secondary prevention in patients with AF. This recommendation

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is based on historical data with warfarin as well as data extrapolated from more recent studies evaluating various combination therapies versus monotherapy in patients with a recent ACS.[38-44,66–70]

15. The COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial evaluated the efficacy and safety of low-dose rivaroxaban 2.5 mg twice daily, with or without low-dose aspirin therapy, in reducing CVD events in patients with stable ASCVD.[30] The primary outcome of cardiovascular death, stroke, or MI occurred in 4.1% of the aspirin plus rivaroxaban group, 4.9% of the rivaroxaban alone group, and 5.4% for aspirin monotherapy. The study was terminated early because of the observed benefit of rivaroxaban plus aspirin compared with aspirin alone. Evaluation of high-risk patients (multivessel CAD and at least one of the following: diabetes requiring medication, recurrent MI, peripheral artery disease, HF, or CKD with an eGFR of 15-59 mL/min/m^2 [69]) showed an absolute net clinical benefit with combination therapy, with substantial reductions in ischemic events and all-cause death.[31] The high-risk population also derived a larger absolute risk reduction, resulting in an even lower number needed to treat.[30–32] The combination of rivaroxaban plus aspirin resulted in a higher risk of major bleeding compared with aspirin monotherapy (3.1% versus 1.9%; hazard ratio, 1.70 [95% CI, 1.40–2.05]; $P<0.001$]). The use of DAPT was an exclusion criteria.
16. Increased bleeding including gastrointestinal bleeding is a common side effect of DAPT; the mitigation of this risk has been an area of clinical investigation. SAPT (aspirin or clopidogrel) compared with DAPT leads to lower gastric or small intestinal mucosal injury.[71] Aspirin increases gastroduodenal ulcer formation. When combined with aspirin therapy, P2Y12 inhibitors can promote gastric ulcer bleeding. Clopidogrel is a prodrug that requires cytochrome CYP P450 2C19 for metabolism to its active form. PPIs are also metabolized by the P450 system, thereby leading to concern for inadequate clopidogrel therapy in those on both PPIs and DAPT. The FDA has added a boxed warning to avoid use of omeprazole with clopidogrel as well as other potent CYP 2C19 inhibitors, including esomeprazole. Several studies assessed the safety and efficacy of PPI in the context of DAPT. A meta-analysis of 6 RCTs (6930 patients) showed that the use of PPIs is associated with a reduced risk of gastrointestinal bleeding in patients treated with DAPT after PCI. No significant differences were observed in the incidence of MACE, MI, and all-cause death in patients with CAD on DAPT and PPIs.[33]

4.3.2. Beta Blockers

Recommendations for Beta Blockers
Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	Recommendations
1	A	1. In patients with CCD and LVEF ≤40% with or without previous MI, the use of beta-blocker therapy is recommended to reduce the risk of future MACE, including cardiovascular death.[1–3]
1	A	2. In patients with CCD and LVEF <50%, the use of sustained release metoprolol succinate, carvedilol, or bisoprolol with titration to target doses is recommended in preference to other beta blockers.*[1,3–8]
2b	B-NR	3. In patients with CCD who were initiated on beta-blocker therapy for previous MI without a history of or current LVEF ≤50%, angina, arrhythmias, or uncontrolled hypertension, it may be reasonable to reassess the indication for long-term (>1 year) use of beta-blocker therapy for reducing MACE.[9–15]
3: No Benefit	B-NR	4. In patients with CCD without previous MI or LVEF ≤50%, the use of beta-blocker therapy is not beneficial in reducing MACE, in the absence of another primary indication for beta-blocker therapy.†[16–19]

*Modified from the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure.[20]

†Adapted from the 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization.[21]

Synopsis

Beta blockers exhibit their clinical effects by decreasing myocardial oxygen demand, improving ischemic threshold, and impeding maladaptive LV remodeling.[1,22–24] Patients with CCD comprise patients with or without previous MI, LV systolic dysfunction, or both. These distinctions should be considered in determining the indications for use of beta-blocker therapy in patients with CCD. The strongest data for the benefit of beta-blocker therapy in CCD is for patients with LV systolic dysfunction but is less clear for patients without LV dysfunction.[1,3-8,13-15,25–27] Several ongoing RCTs hope to better elucidate the need for and duration of beta-blocker therapy for MACE reduction among post-MI patients with preserved LV systolic function in the contemporary era. Other primary indications for beta blockers may include their use for angina, uncontrolled hypertension, or arrhythmias. A comprehensive screening as well as assessment of their symptoms and comorbid conditions is recommended given that beta-blocker therapy may still be indicated for its antianginal properties (see Section 4.3.6), antihypertensive properties (see Section 4.2.7, "Blood Pressure Management"), or for its negative chronotropic effects among patients with rhythm disturbance disorders.[28,29]

Recommendation-Specific Supportive Text

1. Multiple well-conducted RCTs from the precontemporary as well as modern era showed the efficacy of beta-blocker therapy in reducing cardiovascular

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death and MACE among patients with LV systolic dysfunction.[1-4,7,25] This benefit was found among patients with previous MI and those without history of MI.[1,2,4,5,25] Furthermore, data from the KAMIR-NIH (Korea Acute Myocardial Infarction Registry-National Institute of Health) registry suggest that the clinical benefits of beta-blocker therapy may extend beyond patients with reduced LVEF (≤40%) and even toward patients with mid-range LVEF (40%–49%).[2] Given unequivocal benefit of beta-blocker therapy, widespread use of these agents in this subset of patients has been recommended. For detailed discussion of beta-blocker use in heart failure patients, see the "2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure."[20]

2. Different beta blockers have been at the center of multiple clinical investigations evaluating their effectiveness among patients with HF with LV systolic dysfunction.[3,4,8,30–32] CIBIS-II (Cardiac Insufficiency Bisoprolol Trial II), COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival Study), and MERIT-HF (Metoprolol Randomized Intervention Trial in Congestive Heart Failure) RCTs have shown clinical efficacy of bisoprolol, carvedilol, and metoprolol succinate among patients with LV systolic dysfunction in reducing cardiovascular death and MACE.[3,4,30] Continued dose titration was performed within these trials to target doses of 10 mg per day for bisoprolol, 200 mg per day for metoprolol succinate, and 25 mg twice daily for carvedilol (or 50 mg twice daily for patients weighing >84 kg).
3. Although previous iterations of the ACC/AHA guidelines on patients with stable ischemic heart disease recommended the use of beta-blocker therapy in patients with previous MI and preserved LV systolic function, this recommendation was based on data gathered from the noncontemporary era.[33] In the contemporary era of timely reperfusion/revascularization and progressive pharmacotherapy (including antithrombotic and lipid-lowering therapy) among patients with MI, the recommendation for long-term use (>1 year) of beta-blocker therapy in the absence of LV systolic dysfunction has been challenged.[13,14] Observational studies from the current era evaluating post-MI patients with preserved LV systolic function showed discrepant results with some studies suggesting clinical benefit while others showed lack of clinical benefit with long-term use of beta-blocker therapy.[9-15,34] Long-term use of beta-blocker therapy may also confer potential clinical risks including fatigue, depression, and drug-drug interactions, thereby necessitating future high-quality data to ascertain the need for and duration of beta-blocker use among this population. Several ongoing large randomized controlled clinical trials including REBOOT-CNIC (Treatment with Beta-blockers after MI without Reduced Ejection Fraction), REDUCE-SWEDEHEART (Evaluation of Decreased Usage of Beta-blockers After MI in the Swedeheart Registry), BETAMI (Beta-blocker Treatment after Acute MI in Revascularized Patients without Reduced LVEF), and DANBLOCK (Danish Trial of Beta-blocker Treatment after MI Without Reduced LVEF) aim to provide more clarity on the efficacy, safety, and QOL associated with beta-blocker therapy in patients with CCD, including post-MI patients with preserved LV systolic function.
4. Protective clinical benefits of beta-blocker therapy in reducing cardiovascular death have not been shown among CCD patients without previous MI or LV systolic dysfunction. The REACH (Reduction of Atherothrombosis for Continued Health) registry evaluated patients with CAD without history of MI and studied the effect of beta-blocker therapy on the primary endpoint of cardiovascular death, nonfatal MI, or nonfatal stroke.[18] Among patients with CAD without a history of MI, the use of beta-blocker therapy was not associated with a significant reduction in event rates for the primary endpoint. Similarly, a recent analysis from the National Cardiovascular Data Registry CathPCI registry evaluated the clinical benefit of beta blockers among patients with stable angina without a history of MI, LV systolic dysfunction, or systolic HF who were undergoing PCI.[19] The authors showed that the use of beta blockers was not associated with improvement in cardiovascular morbidity or mortality rates at 30 days or at 3-year follow-up. Similar results were seen in a post-hoc analysis from the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance) trial in which no reduction in cardiovascular events was observed with the use of beta blockers among patients without previous MI or HF.[17]

4.3.3. Renin-Angiotensin-Aldosterone Inhibitors

Recommendations for Renin-Angiotensin-Aldosterone Inhibitors Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	Recommendations
1	A	1. In patients with CCD who also have hypertension, diabetes, LVEF ≤40%, or CKD, the use of ACE inhibitors, or ARBs if ACE inhibitor–intolerant, is recommended to reduce cardiovascular events.[1–5]
2b	B-R	2. In patients with CCD without hypertension, diabetes, or CKD and LVEF >40%, the use of ACE inhibitors or ARBs may be considered to reduce cardiovascular events.[6–10]

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Synopsis

Patients at high risk for CCD who have structural abnormalities (LVEF ≤40%), comorbid conditions (eg, diabetes, CKD, hypertension), or both are at significantly elevated risk of developing symptomatic HF and recurrent cardiovascular events. In addition to lowering BP (see Section 4.2.6, "Lipid Management"), renin-angiotensin-aldosterone system inhibitors (RAASi) decrease MACE in high-risk patients with CCD.[1,3,5,8] In contrast, the efficacy of RAASi is less certain among populations with CCD with LVEF >40% and without comorbid hypertension, diabetes, or CKD.[6,8,9,11,12] RAASi trials (PEACE [Prevention of Events with Angiotensin Converting Enzyme Inhibition], QUIET [Quinapril Ischemic Event Trial], CAMELOT [Comparison of Amlodipine versus Enalapril to Limit Occurrences of Thrombosis], and IMAGINE [Clazakizumab for the Treatment of Chronic Active Antibody Mediated Rejection in Kidney Transplant Recipients]) in lower-risk populations with CCD showed no consistent CVD event reduction.[8,11,13] Patients on RAASi therapy require close follow-up after medication initiation and titration, including assessment of adherence, BP control, laboratory testing, evaluation for potential adverse effects (eg, orthostatic hypotension), intolerance (eg, cough, angioedema), or both. ARBs should be used as an alternative for patients who are ACE intolerant.[14,15]

Recommendation-Specific Supportive Text

1. In RCTs,[1–5] RAASi improved symptoms, reduced hospitalizations, prolonged survival, or all 3 among high-risk patients with CCD. In patients with hypertension and diabetes, RAASi reduce the incidence of moderate albuminuria and end-stage renal disease.[16–18] For patients with CCD and LVEF ≤40% who are clinically symptomatic beyond stage B, refer to the 2022 AHA/ACC/HFSA heart failure guideline.[19]
2. In the HOPE trial,[10] high-risk patients with CCD and preserved LVEF assigned to ramipril 10 mg daily had significant reductions in the composite of death, cardiovascular events, and stroke, although the concurrent use of other risk reduction medications was low compared with other trials.[10] The EUROPA trial compared perindopril 8 mg daily to placebo in a lower risk population.[9] In the PEACE trial,[20] which compared trandolapril versus placebo in populations with CCD and normal LVEF, RAASi were not associated with reduced total mortality rate; however, there was a benefit in a subset of patients with reduced renal function (eGFR, <60 mL/min/m^2).[11] In QUIET,[13] quinapril had no effect on progression of atherosclerosis in patients with CCD and preserved LVEF, except in those with CKD. The CAMELOT study[8] found no reduction in MACE among patients with CCD and normal BP. The lack of overall benefit of RAASi in lower risk populations likely reflects both baseline comorbidities and levels of concurrent pharmacotherapies with other evidence-based therapies for CCD.[20,21]

4.3.4. Colchicine

Recommendation for Colchicine
Referenced studies that support the recommendation are summarized in the Online Data Supplement.

COR	LOE	Recommendation
2b	B-R	1. In patients with CCD, the addition of colchicine for secondary prevention may be considered to reduce recurrent ASCVD events.[1,2]

Synopsis

Inflammation is a key component in the development of atherosclerosis.[3] As a result, using select anti-inflammatory agents may have a role in improving cardiovascular outcomes. However, studies evaluating agents thus far have showed mixed results.[4,5] Colchicine exhibits anti-inflammatory properties by altering inflammatory cell-medicated chemotaxis and phagocytosis by inhibiting microtubule polymerization.[6] Colchicine also reduces the expression of adhesion molecules and has an effect on cytokine production.[7] Given its broad cellular effects and its established role in the management of pericarditis, there has been renewed interest in its potential benefits in patients with CCD. Colchicine is considered a drug with narrow therapeutic index, meaning there is a small difference in the dose that is effective and what can lead to serious or toxic adverse effects. Additionally, colchicine is metabolized by cytochrome P450 3A4 and p-glycoprotein, making it prone to drug-drug interactions. Therefore, monitoring for adverse effects is of paramount importance. Given this, there is a need for a highly individualized approach, limiting the use of colchicine to those patients who remain at very high risk despite maximum tolerated GDMT until further data become available. [redacted] Based on the dose tested in clinical trials, the recommended dose of colchicine for use in secondary prevention in patients with CCD is 0.5 mg daily.

Recommendation-Specific Supportive Text

1. The LoDoCo2 (Colchicine Reduces Risk of Major Cardiovascular Events in CCD) trial aimed to validate the LoDoCo (Low Dose Colchicine for Secondary

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Prevention of Cardiovascular Disease) results among patients with clinically stable ASCVD who had shown a reduced risk of recurrent cardiovascular events in patients taking colchicine 0.5 mg daily compared with placebo.[2,5] The primary endpoint was a composite of cardiovascular death, spontaneous MI, ischemic stroke, or ischemic-driven revascularization, which occurred in 6.8% of patients in the colchicine group compared with 9.6% in the placebo group ($P<0.001$). Despite the positive results, the study showed a trend toward increased risk of death from noncardiovascular causes in the colchicine group. The first trial to evaluate the efficacy of colchicine in secondary prevention in patients with ACS was the COLCOT trial.[8,9] Of patients treated with colchicine, the primary endpoint of death from cardiovascular causes, MI, resuscitated cardiac arrest, stroke, or urgent hospitalization for angina leading to coronary revascularization occurred in 5.5% of patients compared with 7.1% in the placebo group ($P=0.02$). These results were driven primarily by reductions in the incidence of strokes and urgent hospitalizations for angina leading to coronary revascularization. Although studies evaluating colchicine in secondary prevention excluded patients with creatinine clearance of <50 mL/min, these studies were also limited to a duration of just over 2 years.[1,2] Given its long half-life, narrow therapeutic window, and degree of dependence on renal function for clearance, use should be avoided in patients with advanced renal disease (eGFR, <30 mL/min/m^2). Additionally, colchicine is metabolized by CYP3A4 and is a substrate for P-glycoprotein, which necessitates careful evaluation for drug-drug interactions.[10]

4.3.5. Immunizations

Recommendations for Immunizations
Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	Recommendations
1	A	1. In patients with CCD, an annual influenza vaccination is recommended to reduce cardiovascular morbidity, cardiovascular death, and all-cause death.[1–7]
1	C-EO	2. In patients with CCD, coronavirus disease 2019 (COVID-19) vaccination is recommended per public health guidelines to reduce COVID-19 complications.[8–10]
2a	B-NR	3. In patients with CCD, a pneumococcal vaccine is reasonable to reduce cardiovascular morbidity and mortality and all-cause death.[11–13]

Synopsis

Infections such as influenza, pneumococcal pneumonia, and COVID-19 are a contributing factor to MACE and all-cause death, especially in patients with CCD.[1,2,8,12] The mechanisms by which infections such as these increase cardiovascular events may be related to proinflammatory mediators, stimulation of the sympathetic system, and coagulation cascade activation, which may cause rupture of vulnerable atherosclerotic plaques.[14] Vaccination against these respiratory infections may not only improve clinical outcomes but also potentially reduce hospitalization and health care costs. RCTs and nonrandomized clinical trials have concluded that vaccination for these infections offer the greatest benefit in the highest risk populations, which includes those with advanced age, CCD, or both. Vaccination promotion is the best defense in protecting those with CCD who may be exposed to these infections in the community and face potential adverse clinical outcomes as a result.

Recommendation-Specific Supportive Text

1. Studies show a significant association between recent respiratory infection and acute MI.[1] Meta-analyses and systematic reviews showed that influenza vaccination was associated with a lower risk of acute MI, cardiovascular death, MACE, and all-cause death in patients with CAD or HF.[1-5,7] However, 1 study found no significant reduction in MI among those who received the influenza vaccine compared with control.[7] In patients with previous stroke, there was a nonsignificant trend for reduction of recurrent stroke risk.[3] No reduction was seen in all-cause death or cardiopulmonary hospitalization in high-risk patients with CCD who received high-dose trivalent influenza vaccine versus standard-dose quadrivalent influenza vaccine, although more vaccine-related adverse reactions occurred in the high-dose trivalent influenza vaccine group.[6]
2. Although outcome data about the benefit of the COVID-19 vaccination in patients with CCD are unavailable at the time of writing this guideline, the targeted population for whom this guideline is intended is among the highest risk for developing COVID-19–related complications and death.[8] Therefore, the writing committee supports COVID-19 vaccination for patients with CCD and that the benefits of the COVID-19 vaccination outweigh the potential adverse events related to the vaccine itself.[8–10] For reference, US Centers for Disease Control and Prevention (CDC) guidance may be accessed at https://www.cdc.gov/coronavirus/2019-ncov/communication/guidance.html.[15]
3. Limited data are available that evaluate pneumococcal polysaccharide vaccination in patients with CCD and its effect on cardiovascular outcomes and all-cause death. A population-based cohort study of 6171 patients (18% with ischemic heart disease) who were hospitalized for pneumonia within 90 days and received previous pneumococcal polysaccharide vaccination found a 58% reduction in ACS

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events (12 versus 16 events per 100 patient-years [adjusted hazard ratio, 0.42 (95% CI, 0.27-0.66)]).[11] A systematic review and meta-analysis of observational studies with >163 000 participants found that the PPSV23, PCV13, or both was associated with a 22% decrease in all-cause death in patients with CCD or those with very high cardiovascular risk, although the study design of some included studies led to a decreased level of design confidence.[12] A retrospective observational study using the 2012–2015 US National Inpatient Sample database evaluated the combined use of pneumococcal polysaccharide vaccine (PPV) and influenza vaccine and found lower mortality rate (2.21% versus 1.03%; P=0.001) and lower cardiac arrest (0.61% versus 0.51%; P<0.001). The relative risk was 0.46 (95% CI, 0.43–0.49) in the adjusted analysis for this combined vaccination group. This group also had significantly reduced risk of mortality among those admitted with MI (relative risk, 0.46), TIAs (relative risk, 0.58), and stroke (relative risk, 0.42) compared with the nonvaccinated group.[13]

4.3.6. Medical Therapy for Relief of Angina

Recommendations for Medical Therapy for Relief of Angina Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	Recommendations
1	B-R	1. In patients with CCD and angina, antianginal therapy with either a beta blocker, CCB, or long-acting nitrate is recommended for relief of angina or equivalent symptoms.*[1–3]
1	B-R	2. In patients with CCD and angina who remain symptomatic after initial treatment, addition of a second antianginal agent from a different therapeutic class (beta blockers, CCB, long-acting nitrates) is recommended for relief of angina or equivalent symptoms.*[3–6]
1	B-R	3. In patients with CCD, ranolazine is recommended in patients who remain symptomatic despite treatment with beta blockers, CCB, or long-acting nitrate therapies.*[7,8]
1	B-NR	4. In patients with CCD, sublingual nitroglycerin or nitroglycerin spray is recommended for immediate short-term relief of angina or equivalent symptoms.*[9,10]
3: Harm	B-R	5. In patients with CCD and normal LV function, the addition of ivabradine to standard anti-anginal therapy is potentially harmful.*[11]

*Modified from the 2012 ACC/AHA Multisociety Guideline for the Diagnosis and Management of Patients With SIHD.[12]

Synopsis

Medical antianginal therapies for patients with CCD are understood to act via 2 general mechanisms: by decreasing myocardial oxygen demand or by increasing myocardial arterial blood supply.[9] Beta blockers, non-dihydropyridine CCBs, and ivabradine decrease myocardial oxygen demand (via decreasing contractility, heart rate, or both) while nitrates and dihydropyridine CCBs increase arterial oxygenated blood supply via vasodilatory actions. Ranolazine has a less well-defined mechanism of action, potentially by decreasing calcium overload through inhibition of the late sodium current. The overriding goal is to maximize relief of symptoms while choosing therapy that will not exacerbate comorbidities, will not have important interactions with concomitant medications and will be well tolerated. In the context of CCD antianginal therapy, the justification for their use rests fully on their effectiveness in relieving symptoms. Specific circumstances may justify choosing 1 agent over another (eg, a beta blocker in a patient with concomitant LV dysfunction). Control of symptoms may be achieved by most patients, but full freedom from angina is only achieved in 40% to 50%, depending on anginal frequency at the onset of treatment.[13]

Recommendation-Specific Supportive Text

1. Beta blockers have been considered the first anti-anginal to use in patients with symptomatic CCD, although the evidence basis for this prioritization is not strong. Early randomized, placebo-controlled studies found that beta blockers increased the percentage of patients free of exertional angina, reduced anginal attacks and reduced nitroglycerin consumption.[1,2] A meta-analysis of 72 studies comparing beta blockers with CCBs found fewer episodes of angina per week with beta blockers and lower rates of drug discontinuation.[3] No difference was observed in the rate of death or MI between the 2 drug classes. A more recent meta-analysis including only larger studies comparing beta blockers with calcium channel blockers found no difference in the primary endpoint of exercise duration.[4] In randomized, placebo-controlled trials, CCBs effectively relieve angina, decrease nitroglycerin consumption, and increase exercise duration.[14,15] Long-acting nitrates decrease angina and improve exercise duration.[16] Non-dihydropyridine CCBs (verapamil and diltiazem) can further depress LV function and should not be used in patients with CCD and significant LV dysfunction.[17]
2. In patients with CCD and angina refractory to 1 agent, a combination with another antianginal agent improves symptom control.[5] Non-dihydropyridine CCBs should be used with caution in patients on beta blockers because of the potential for synergistic induction or exacerbation of bradycardia and LV dysfunction. The addition of a long-acting nitrate to a beta blocker or a CCB improves exercise tolerance, reduces angina frequency and short-acting nitrate use.[5]
3. Two randomized, placebo-controlled studies showed that the addition of ranolazine on the background of standard anti-anginal therapy

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improved anginal outcomes.[7,8] In the CARISA (Combination Assessment of Ranolazine in Stable Angina) trial, 823 patients with CCD were randomized to placebo or 1 of 2 doses of ranolazine.[7] After 12 weeks of therapy, ranolazine improved exercise capacity and more effectively relieved angina compared with placebo. In the ERICA (Efficacy of Ranolazine in Chronic Angina) trial, 565 patients with CCD and persistent symptoms despite a maximally tolerated dose of amlodipine were randomized to ranolazine or placebo.[8] After 6 weeks, patients randomized to ranolazine had significantly fewer anginal episodes and less nitroglycerin consumption.

4. Short-acting nitrates help to relieve acute episodes of angina.[9] One can decrease symptoms by administering a short-acting nitrate prior to activity that typically triggers symptoms. In randomized studies, nitroglycerin spray in comparison with a sublingual formulation is more effective and efficient at relieving angina, but with less headache.[10]
5. The role of ivabradine in patients with CCD has not been studied as extensively as other antianginal therapies. One study comparing ivabradine with atenolol and another comparing it with amlodipine in a double-blind, randomized manner both found similar improvements in exercise time and angina relief with ivabradine.[18,19] Another study found that the addition of ivabradine to atenolol in patients with CCD resulted in improved exercise capacity compared with placebo.[18] However, a more recent study randomized 19 102 patients with CCD, no evidence of HF, and a resting heart rate of at least 70 beats per minute to ivabradine or placebo in addition to GDMT, including standard anti-anginal treatment.[11] At approximately 28-month follow-up, the rate of the primary endpoint of cardiovascular death or MI was similar between both groups. In patients with activity-limiting angina, although ivabradine led to improvement in angina class in 24% compared with 18.8% receiving placebo (P=0.01), the primary endpoint of death or MI was significantly higher in the patients randomized to ivabradine (7.6% versus 6.5%; P=0.02), suggesting possible harm when ivabradine is used in this setting.

4.3.7. Management of Refractory Angina

Recommendation for Management of Refractory Angina
Referenced studies that support the recommendation are summarized in the Online Data Supplement.

COR	LOE	Recommendation
2b	B-R	1. In patients with CCD, refractory angina, and no other treatment options, enhanced external counterpulsation may be considered for relief of symptoms.*[1]

*Modified from the 2012 ACC/AHA Multisociety Guideline for the Diagnosis and Management of Patients With SIHD.[2]

Synopsis

Refractory angina represents a small but important segment of the CCD population.[3] Patients are identified by 3 major features: (1) anginal chest pain (or equivalent symptoms) that is uncontrolled despite intensive medical therapy; (2) objective evidence the anginal symptoms have an ischemic cause; and (3) no further options for coronary revascularization.[4] Typically, symptoms produce major lifestyle limitations, functional status limitations, and disabilities. Some definitions also specify Canadian Cardiovascular Society Class III/IV symptoms. Some sources include patients with microvascular angina in this category. No AHA/ACC class 1 recommendations are possible given the limited evidence currently available in this area. Enhanced external counterpulsation has the weak support of a single randomized trial reported in 2005, is FDA approved, but is very infrequently used.[1,5] Direct transmyocardial laser revascularization was studied in several RCTs and is FDA approved, but the largest trial of percutaneous transmyocardial laser revascularization with a placebo/sham control did not show any benefit and a possible signal of harm.[6] Earlier unblinded trials examining surgical transmyocardial laser revascularization reported a benefit in angina relief, but the operative mortality rate was in the range of 3% to 9%. The 2012 ACC/AHA stable ischemic heart disease guideline assigned a Class 2b recommendation to transmyocardial laser revascularization. Based on a thorough review of this evidence, the writing committee feels a recommendation is no longer warranted.[7]

Recommendation-Specific Supportive Text

1. MUST-EECP (Multicenter Study of Enhanced External Counterpulsation) did not study refractory angina.[1] This therapy has evolved for use in patients with no other options, but the evidence base supporting this shift is inadequate, consisting of observational studies and small RCTs. Enhanced external counterpulsation was a Class 2b recommendation in the 2012 ACC/AHA stable ischemic heart disease guideline, and this was reaffirmed in the 2014 focused update.[2,8] No interval data are available that warrant a change in this recommendation. Enhanced external counterpulsation has limited availability and appears to be used primarily in patients who remain symptomatic and without other therapeutic options.

4.3.8. Chelation Therapy

Synopsis

Chelation therapy refers to the therapeutic use of intravenous infusions of disodium EDTA.[1] Chelation has been used since the 1950s as a treatment for CCD, based until recently on anecdotal reports of benefit. EDTA avidly

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combines with biologically active heavy metal polyvalent cations, such as lead and cadmium, to form soluble complexes that can then be excreted.[1] Very small trials conducted in patients with intermittent claudication and with CCD failed to show clinically relevant benefits.[2–5] The first adequately powered trial of this intervention, TACT (Trial to Assess Chelation Therapy), randomized 1708 patients with previous MI to 40 infusions of chelation or placebo.[6] The primary composite endpoint of total mortality, recurrent MI, stroke, coronary revascularization, or hospitalization for angina occurred in 222 (26%) patients in the chelation group and 261 (30%) patients in the placebo group (hazard ratio, 0.82 [95% CI, 0.69–0.99]; *P*=0.035). Among the 633 TACT patients with diabetes, chelation reduced the primary composite endpoint by 41% reduction (hazard ratio, 0.59 [95% CI, 0.44–0.79]; *P*=0.02 for interaction).[6,7] EDTA is currently not approved by the FDA for preventing or treating cardiovascular disease. TACT2 (Trial to Assess Chelation Therapy 2) has randomized 1000 patients with diabetes and previous MI using the same treatment regimen as TACT and will report results in 2024.[8]

5. REVASCULARIZATION

The topic of revascularization is evolving. We highlight certain management decisions in the next section. Recommendations are typically based on results of the major trials, meta-analyses, or both, covering varying amounts of the same material. We acknowledge that the trials do not cover the area consistently or address all questions comprehensively. Some trials begin with angiographically proven CAD (and a decision already made to proceed with revascularization), while others begin earlier in the clinical presentation. With this in mind, we have made a concerted effort to stay within the strongest evidence in shaping these recommendations for revascularization in patients with CCD.

5.1. Revascularization

Recommendations for Revascularization
Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	Recommendations
Goals of Revascularization		
1	A	1. In patients with CCD and lifestyle-limiting angina despite GDMT and with significant coronary artery stenoses amenable to revascularization, revascularization is recommended to improve symptoms.*[1–7]
1	B-R	2. In patients with CCD who have significant left main disease or multivessel disease with severe LV dysfunction (LVEF ≤ 35%), CABG in addition to medical therapy is recommended over medical therapy alone to improve survival.*[8–11]

Recommendations for Revascularization (Continued)

COR	LOE	Recommendations
Cost Value Statement: Intermediate Value	B-NR	3. In patients with CCD and multivessel disease with severe LV dysfunction, CABG added to optimal medical therapy is of intermediate economic value compared with medical therapy alone.[12]
2a	B-R	4. In patients with CCD and multivessel CAD appropriate for either CABG or PCI, revascularization in addition to GDMT is reasonable to lower the risk of cardiovascular events such as spontaneous MI, unplanned urgent revascularizations, or cardiac death.*[13–20]
2a	B-NR	5. In selected patients with CCD and significant left main stenosis for whom PCI can provide equivalent revascularization to that possible with CABG, PCI is reasonable to improve survival.*[21]
Decision-Making for Revascularization		
1	A	6. In patients with CCD who have angina or an anginal equivalent, no previous evaluation for ischemia, and angiographically intermediate stenoses, the use of FFR or other proven nonhyperemic pressure ratios (eg, iFR) is recommended before proceeding with PCI.*[2,22,23]
Cost Value Statement: High Value	B-NR	7. In patients with CCD undergoing coronary angiography without previous stress testing, the use of invasive FFR to evaluate angiographically intermediate coronary stenoses before proceeding with PCI is a high economic value intervention.[24,25]
1	B-NR	8. In patients with CCD with complex 3-vessel disease or for whom the optimal treatment strategy is unclear, a Heart Team approach that includes representatives from interventional cardiology and cardiac surgery is recommended to improve patient outcomes.*[26–29]

*Modified from the 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization.[30]

Synopsis

The management of patients with CCD and stable angina is 3-fold: relief of symptoms, prevention of nonfatal events such as MI, and improving long-term survival. Medical therapy is often an effective option for these patients. However, revascularization results in a greater improvement in angina and QOL than does medical therapy alone. Similarly, revascularization among appropriate patients with CCD lowers the risk of cardiovascular death, MI and urgent revascularization, particularly among patients with multivessel disease.[2,13,15,31] However, the effect of revascularization on improving survival in patients with CCD is more nuanced.[32] Overall, multiple studies and subsequent meta-analyses have confirmed an overall null effect of revascularization on all-cause death for CCD, with few exceptions.[15,19,33] Of note, patients in those studies tended to have a low atherosclerotic burden. Predictors of survival include anatomic and functional severity of the disease, LV function, and comorbidities such as diabetes and renal dysfunction.[33] For

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patients with CCD and LV dysfunction (particularly when LVEF is ≤35%) and for patients with left main disease, CABG has been shown to be superior to medical therapy alone for improving survival.[8,10,11]

Recommendation-Specific Supportive Text

1. In the COURAGE trial, patients initially randomized to GDMT who crossed over to early revascularization had worse baseline Seattle Angina Questionnaire scores. When compared with patients who were randomized to PCI, these patients experienced worse health status over the initial year of treatment and more unstable angina admissions.[6] In the ISCHEMIA trial, the Seattle Angina Questionnaire summary scores were higher with an invasive strategy compared with a conservative strategy and sustained over 36 months of follow-up. Seattle Angina Questionnaire improvements were more pronounced among patients with greater frequency of baseline angina (daily/weekly > monthly > none). Similarly, the probability of being angina-free was greater among participants who had angina at baseline but was minimal among those who were asymptomatic before randomization.[1] In the ORBITA trial, PCI objectively reduced ischemia (assessed by dobutamine stress echocardiography), and although Seattle Angina Questionnaire scores did not differ among participants, PCI resulted in more patient-reported freedom from angina than placebo. Patients with greater ischemia burdens were more likely to have lower angina frequency score and freedom from angina with PCI than with the sham procedure.[7] In a pooled analysis of FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) and FAME-2 (Fractional Flow Reserve Guided Percutaneous Coronary Intervention Plus Optimal Medical Treatment [OMT] Versus OMT), patients with lower FFR, greater improvement in FFR post-PCI and higher angina class at baseline were associated with the greatest magnitude of QOL improvement at 1 month and 1 year.[34]
2. Although older studies suggested a mortality benefit with surgical revascularization, many recent studies and meta-analyses point to an overall null effect of revascularization on all-cause death for CCD.[15,19,33,35] Important reasons include advances in medical management and a lower mortality rate with CCD in the contemporary era. For example, the annualized mortality rate in the medical therapy arm of ACME-2 (Angioplasty Compared to Medicine: Two-Vessel Disease) was 4.0%, but 1.0% in FAME-2 and 1.6% in ISCHEMIA.[33] However, many of these trials also had high rates of crossover, and many patients had low angiographic complexity. Numerous technical advances in the field of revascularization also have occurred for CABG and PCI since some of these earlier trials were conducted.[8,36,37] Two subgroups with mortality benefit of CABG over GDMT alone are patients with multivessel disease and moderate to severe LV dysfunction (ejection fraction ≤35%), and those with left main disease, both of which may occur concurrently.[38] In the STICH trial, patients with ischemic cardiomyopathy and reduced LVEF (≤35%) who received CABG in addition to optimal medical therapy had improved survival at 10 years compared with patients who received medical therapy alone.[11] In the REVIVED-BCIS 2 trial (Revascularization for Ischemic Ventricular Dysfunction: a Randomized Comparison of PCI [with Optimal Medical Therapy] Versus Optimal Medical Therapy Alone for Treatment of HF Secondary to Coronary Disease), PCI among patients with ejection fraction ≤35% did not improve MACE including survival at a median follow-up of 3.4 years.[39] For patients with left main disease, the focus has been on comparing CABG and PCI in recent years; no recent trials are available that compare revascularization to GDMT alone for this indication. Further, most of the contemporary CCD trials have excluded patients with left main disease. Accordingly, the evidence to support revascularization is derived mainly from older RCTs, and no new data refute this evidence.[8]
3. Using data from the STICH trial, a decision-analytic patient-level simulation model was developed to estimate the lifetime costs (in 2019 US dollars) and benefits ([redacted] of CABG for ischemic cardiomyopathy from the US healthcare sector perspective and the lifetime analytic horizon. [redacted].[12]
4. Clinical events such as nonfatal MI, unstable angina, and urgent revascularization are important for patients from a prognostic and a QOL perspective. Nonfatal MI rates appear to correlate with ischemia severity.[40] Some ambiguity has

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been observed about the impact of revascularization on these clinical events. In MASS II (Medicine, Angioplasty, or Surgery Study), the 10-year rates of cardiac death were lower after CABG or PCI than after medical therapy alone.[14] In ISCHEMIA, revascularization had a null effect on cardiovascular death and MI at 4 years overall, with a benefit noted among patients with most severe CAD (3-vessel severe stenosis [≥70%] or 2-vessel severe stenosis with proximal left anterior descending artery).[40,41] At 7-year follow-up, a reduction in cardiovascular mortality with revascularization was observed.[35] Moreover, in the ISCHEMIA trial, the incidence of procedural type 4a or type 5 MIs was increased with revascularization (20.1% of all MIs in the trial), but the incidence of late MI (spontaneous MI [type 1]), demand-induced MI (type 2), or MIs associated with stent thrombosis (type 4b) or with restenosis (4c) was reduced. A spontaneous MI was associated with a 2.4-fold increased hazard for all-cause death and a 3.4-fold increased hazard for cardiovascular mortality compared with no MI, whereas a procedural MI was not associated with all-cause or cardiovascular death.[16] A contemporary meta-analysis of patients with CCD noted a reduction in cardiac death and spontaneous MI with revascularization compared with medical therapy alone. On meta-regression, cardiac death risk reduction was linearly associated with reductions in spontaneous MI and percentage of multivessel disease at baseline.[15] Another contemporary meta-analysis confirmed a reduction in spontaneous MI with revascularization, but also noted an increase in procedural MI, with no improvement for MI overall with revascularization.[33] However, revascularization reduced unstable angina (particularly among contemporary stent era trials) and unplanned revascularization in this and other meta-analyses.[19]

5. There are no RCTs directly comparing PCI to medical therapy for the treatment of left main disease. Most of the recent trials have focused on CABG versus PCI.[42–45] Data from these trials and from subsequent meta-analyses suggest that patients with low-to-medium anatomic complexity left main disease that is equally suitable for surgical or percutaneous revascularization and predominantly with normal ejection fraction have similar survival with PCI and CABG [42,46–51] In addition, several registry studies have reported a survival advantage of PCI over medical therapy in patients with left main CAD,[52] particularly using contemporary DES and PCI techniques.[53–55] A network meta-analysis of 19 studies found that the survival advantage for PCI over medical therapy in patients with left main CAD was similar to the survival advantage for CABG over medical therapy.[21]
6. In FAME-2, among patients with CCD, FFR-guided PCI (FFR, ≤0.8) of lesions ≥50% angiographic severity was superior to medical therapy alone in reducing the primary MACE endpoint, primarily driven by a reduction in the need for urgent revascularization.[31] This benefit appeared to be sustained over 5 years of follow-up.[2] FFR-guided PCI is also superior to angiography-guided PCI for reducing MACE rates among patients with multivessel CAD.[23] More recently, iFR-guided PCI has been shown to be noninferior to FFR-guided PCI.[22,56] iFR can be accomplished with shorter procedure times compared with FFR. Patients with FFR >0.8 or iFR >0.89 appear to have low event rates with medical therapy alone.[57,58] Several other nonhyperemic pressure ratios, both wire-and angiography-based, have been developed and are undergoing further evaluation.[59]
7. In an economic evaluation of the FAME-2 trial (888 patients with stable single-vessel or multivessel coronary artery disease with reduced fractional flow reserve, randomly assigned to PCI plus medical therapy or medical therapy alone), mean initial costs were higher in the PCI group ($9944 versus $4440; $P<0.001$) but by 3 years were similar between the 2 groups ($16792 versus $16737; $P=0.94$).[60] [redacted]. These findings were robust in sensitivity analyses. This suggested that FFR-guided PCI of lesions is economically attractive compared with medical therapy alone in patients with stable coronary artery disease. Further, iFR has been shown to be noninferior to FFR, with economic evaluations suggesting that it has lower procedural costs.[61] Thus, the use of iFR-guided PCI is also likely to be a high value intervention [redacted] in this context.
8. A multidisciplinary Heart Team, involving an interventional cardiologist, cardiac surgeon, and other cardiovascular specialists, has become a critical component of the revascularization decision. Ideal situations for Heart Team consideration include patients with complex coronary disease/multivessel disease, comorbid conditions that could impact the success of the revascularization strategy, and other clinical or social situations that may impact outcomes. Treatment decisions should be patient-centered, incorporate patient preferences and goals, and include shared decision-making between the clinicians and the patients. For example, there may be patients who may prefer revascularization even if not on GDMT.

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5.2. Revascularization: PCI Versus CABG

Recommendations for Revascularization: PCI Versus CABG
Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	Recommendations
Patients With CCD		
1	B-R	1. In patients with CCD who require revascularization for significant left main involvement associated with high-complexity CAD, CABG is recommended in preference to PCI to improve survival.*[1,2]
2a	B-R	2. In patients with CCD who require revascularization for multivessel CAD with complex and diffuse CAD (eg, SYNTAX score >33), it is reasonable to choose CABG over PCI to improve survival.*[1,3–6]
Patients With CCD at High Surgical Risk		
2a	B-NR	3. In patients with CCD who are appropriate for revascularization but poor candidates for surgery, it is reasonable to choose PCI over CABG to improve symptoms and reduce MACE.[7–9]
Patients With CCD and Diabetes		
1	A	4. In patients with CCD, diabetes, and multivessel CAD with involvement of the left anterior descending artery who are appropriate candidates for CABG, CABG (with a left internal mammary artery to the left anterior descending artery) is recommended in preference to PCI to reduce mortality and repeat revascularizations.*[5,10–17]
2b	B-R	5. In patients with CCD and diabetes who have left main stenosis and low- or intermediate-complexity CAD (eg, SYNTAX score ≤33), PCI may be considered as an alternative to CABG to reduce MACE.*[10,18]

*Modified from the 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization.[19]

Synopsis

There are fundamental differences between how CABG and PCI restore blood flow to ischemic myocardium.[20] In CABG, bypass grafts deliver blood beyond the proximal coronary segments that are usually diseased and are at risk for development of de novo lesions. Thus, in addition to the immediate benefit of CABG in treating existing lesions, CABG could offer future protection against ischemic insults by furnishing an alternative route for blood that is unhindered by upstream native CAD. The field protection is unique to CABG because PCI only treats the coronary segment where the stent is implanted with no prophylactic potential. Improved outcomes associated with CABG are largely driven by a reduction in spontaneous MI and repeat revascularization compared with PCI.[3,15,21–24] However, certain subgroups of patients derive a survival benefit from CABG compared with PCI,[1,2,4,25] including patients with complex or diffuse coronary disease and those with diabetes. Although the evidence for the recommendations is based on studies that included predominantly patients with CCD, some studies incorporated patients with unstable or acute coronary ischemia. The choice of revascularization therapy should be guided by Heart Team deliberations and shared decision-making (Section 4.1.3) in the context of available evidence and the patient's specific risk profile and life expectancy.

Recommendation-Specific Supportive Text

1. The SYNTAX (Synergy Between PCI With TAXUS and Cardiac Surgery) trial showed a significantly higher MACE and cardiac mortality rate at 5 years for the subgroup of patients with left main and high-complexity disease (defined as a SYNTAX score >33) who were treated with PCI.[1] Other RCTs that compared revascularization strategies in patients with left main disease excluded patients with complex disease.[20-22,26]
2. The 10-year follow-up of the SYNTAX trial found a 40% higher mortality rate with PCI compared with CABG in the group of patients with triple-vessel disease.[4] In a pooled analysis of individual data of 11 518 patients from 11 RCTs, Head et al showed a mortality benefit with CABG over PCI in patients with multivessel disease.[5] The SYNTAX score was a significant modifier of treatment effect, with higher scores (≥33) favoring CABG.[5]
3. In a subgroup analysis of the 10-year follow-up of the SYNTAX trial comparing PCI with CABG in patients with left main CAD, triple-vessel disease, or both, preprocedural physical and mental health status was an important modifier of the relative treatment effects of the 2 different revascularization approaches. Among patients with low Physical Component Summary (PCS) scores, low Mental Component Summary (MCS) scores, or both, no significant difference was seen in the 10-year mortality rate between PCI and CABG.[7] Of the 3075 patients who were treated in the SYNTAX trial, 198 (6.4%) and 1077 (35.0%) patients were included in PCI and CABG registries, respectively. The main reason for inclusion in the CABG registry was too complex coronary anatomy, while the main reason for inclusion in the PCI registry was too high risk for surgery (70.7%).[8] In the OPTIMUM (Outcomes of Percutaneous RevascularizaTIon for Management of SUrgically Ineligible Patients with Multivessel or Left Main Coronary Artery Disease) registry, patients undergoing PCI (n=726) had complex clinical profiles that were incompletely represented by surgical prediction models. Poor distal targets or conduits (18.9%), severe LV dysfunction and nonviable myocardium (16.8%), severe lung disease (10.1%), and frailty or immobility (9.7%) were among the top reasons for

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surgical ineligibility. PCI was associated with significant improvements in patients' symptom burden, physical function, and QOL. [9]

4. The FREEDOM (Revascularization in Diabetics with Multivessel Disease) trial (n=1900) compared CABG with PCI in patients with diabetes and multivessel CAD.[10,11] The trial excluded patients with significant left main stenosis. Of the enrolled patients, 82% in the PCI group and 85% in the CABG group had triple-vessel disease, and 91% of patients had left anterior descending artery involvement. At 5-year follow-up, all-cause death rate was higher in the PCI group than in the CABG group. In the FREEDOM follow-up study, all-cause death rate up to 8 years continued to be significantly higher with PCI (hazard ratio, 1.36 [95% CI, 1.07-1.74]).[11] The Head et al meta-analysis showed consistent results, with a nearly 50% increase in 5-year mortality risk among patients with diabetes who were treated with PCI than among those treated with CABG.[5] A patient-level pooled analysis of 3 trials associated CABG with a reduction in the composite primary endpoint of death, MI, or stroke and the individual components of the endpoint except for stroke.[17]
5. To date, no RCTs have compared revascularization strategies that focus exclusively on patients with diabetes with stable left main CAD. In a prespecified subgroup analysis of the EXCEL (Evaluation of XIENCE versus CABG Surgery for Effectiveness of Left Main Revascularization) trial, which included patients with left main CAD, predominantly normal ejection fraction, and low- or intermediate-complexity CAD,[27] no difference was observed in the primary endpoint composite of death, stroke, or MI for PCI and CABG among patients with or without diabetes.[18] However, all-cause death at 3 years occurred in 13.6% of patients with diabetes treated with PCI and 8.0% of patients treated with CABG (P=0.046). No difference in the mortality rate was seen among patients without diabetes (5.5% versus 5.0% among patients treated with PCI and CABG, respectively; P=0.71).

6. SPECIAL POPULATIONS

In these sections, recommendations are highlighted for populations that are unique, either based on comorbidities, life stage, or mechanism of coronary pathology or pathophysiology. Unless modified or otherwise specified, the preceding recommendations for patients with CCD generally apply to these "special" populations. In some sections, additional recommendations that are unique to the populations being discussed are provided.

6.1. Existing Heart Diseases and Conditions

6.1.1. Chronic Management After SCAD

Recommendations for Chronic Management After SCAD
Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	Recommendations
1	C-LD	1. In patients with CCD who have experienced SCAD, counseling should be provided regarding potential triggers and risk of SCAD recurrence.[1–12]
2a	C-LD	2. In patients with CCD who have experienced SCAD, evaluation for underlying vasculopathies is reasonable to identify abnormalities in other vascular beds.[1–4,7,10,13–15]
2b	C-LD	3. In patients with CCD who have experienced SCAD, beta-blocker therapy may be reasonable to reduce the incidence of recurrent SCAD.[1]

Synopsis

SCAD is an underrecognized cause of MI.[16,17] SCAD is more common among women than men and occurs predominantly in younger women with low burden of classic risk factors for ASCVD. Triggers include pregnancy, vigorous physical exertion, and severe emotional distress.[16,17] SCAD may be a manifestation of an underlying arteriopathy.[1,13,16,17] Pregnancy-associated SCAD has a worse prognosis than SCAD in the absence of pregnancy.[1,12,16,17] Conservative medical management of the acute event is favored, but selected unstable patients may require percutaneous or surgical revascularization.[16,17] Medical care after SCAD is focused on managing sequelae of the acute event, evaluation and treatment of recurrent symptoms, and prevention of recurrent SCAD. In the absence of specific data among patients with SCAD, DAPT among those who have undergone stenting should follow current guidelines for DAPT (Section 4.3.1, "Antiplatelet Therapy and Oral Anticoagulants"), while being aware that excess uterine bleeding in premenopausal women may require treatment.[1,2] Management of LV dysfunction after the ischemic insult is addressed in Section 4.3.2, "Beta Blockers," Section 4.3.3, "Renin-Angiotensin-Aldosterone Inhibitors," and Section 6.1.2 "INOCA." Observational data suggest benefits of CR[18–21] and beta blockade.[1] CR is addressed in Section 4.2.10.

Recommendation-Specific Supportive Text

1. SCAD recurrence can be attributable to extension of the initial dissection or attributable to a new dissection. Recurrence rates are highest early after the initial dissection but can occur years later.[2,22] Reported recurrence rates of SCAD vary widely depending on participant characteristics, definition of recurrent SCAD, and length of follow-up,

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ranging from 0% to 26.9% at 1 year and estimated 5-year Kaplan-Meier rates up to 27%.[1-3,5–9] Similar to incident SCAD, recurrent SCAD may be triggered by intense physical exertion or psychosocial distress. Recurrent SCAD may be more common among patients with highly tortuous coronary arteries, underlying fibromuscular dysplasia, history of migraine headaches, and hypertension.[1,4,10,11] Pregnancy in women with previous SCAD was not associated with recurrent SCAD in multivariable modeling that controlled for age at first SCAD, year of first SCAD, and history of fibromuscular dysplasia.[12]

2. Multiple studies have reported a high prevalence of extracoronary vascular abnormalities (eg, cerebral aneurysms, pseudoaneurysms) and concomitant fibromuscular dysplasia among patients with SCAD. The true prevalence of these disorders is unclear because reports are based on screening rates between 30% and 80%.[1-4,7,10,13–15] Table 14 lists screening questions that may point toward an underlying vasculopathy and, together with a detailed vascular physical examination, may facilitate a patient-clinician discussion about benefits and risks of imaging extracoronary vascular beds.[16] Although some cerebral aneurysms detected by screening have been large enough to warrant intervention, no studies to date show that screening for underlying arteriopathies changes patient treatment or patient outcomes.
3. No randomized trials exist of pharmacological management after SCAD. Using multivariable modeling, a Canadian prospective follow-up study of 327 patients with SCAD found that use of beta blockade was associated with a 64% reduction in recurrent SCAD.[1] Given the pathophysiology of SCAD, statin therapy is not indicated for SCAD but should be continued for patients who qualify for statin therapy based on global cardiovascular risk or inherited disorders like FH.[17] Patients who received a stent during their acute hospitalization for SCAD should continue DAPT (see Section 4.3.1, "Antiplatelet Therapy and Oral Anticoagulants") in the outpatient setting.[17] Several prospective registries and a randomized trial are underway to improve understanding of the natural history of SCAD and potential treatments.[23,24]

Table 14. Screening Questions for SCAD-Associated Arteriopathies and Connective Tissue Disorders

Personal history (Have you ever been diagnosed with or experienced any of the following?)
Early-onset hypertension
Stroke or transient ischemic attack
Pulsatile tinnitus
Migraine headaches
Renal infarction
Subarachnoid hemorrhage
Aneurysm (aortic, peripheral, brain)
Dissection (aortic, peripheral)
Rupture of hollow organs (intestinal, bladder, uterine)
Pneumothorax
Tendon or muscle rupture
Joint dislocation
Talipes equinovarus (clubfoot)
Umbilical or inguinal hernia
Scoliosis or pectus deformity
Pregnancy complications (cervical incompetence, hemorrhage, uterine prolapse, hypertension)
Poor wound healing
Ectopia lentis
Myopia
Detached retina, early glaucoma, or early cataracts
Tall stature
Abnormality of cardiac valve
Systemic inflammatory disease
Family history (Does anyone in your family have the following?)
Dissection (coronary, aortic, peripheral)
Inherited arteriopathy or connective tissue disorder (eg, vascular Ehlers-Danlos syndrome, Marfan syndrome, Loeys-Dietz syndrome)
Early stroke, early myocardial infarction, sudden cardiac death
Review of systems (Are you currently experiencing any of the following?)
Headaches
Pulsatile tinnitus
Postprandial abdominal pain
Flank pain
Claudication
Easy bruising
Joint hypermobility or laxity

SCAD indicates spontaneous coronary artery dissection.

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6.1.2. Ischemia With Nonobstructive Coronary Arteries

Recommendation for INOCA
Referenced studies that support the recommendation are summarized in the Online Data Supplement.

COR	LOE	Recommendation
2a	B-R	1. In symptomatic patients with nonobstructive CAD, a strategy of stratified medical therapy* guided by invasive coronary physiologic testing can be useful for improving angina severity and QOL.[1,2]

*See recommendation-specific supportive text for details.

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Table 15. Clinical Criteria for Suspecting Microvascular Angina*

Criteria	Evidence	Diagnostic Parameters
1	Symptoms of myocardial ischemia	Effort or rest angina; exertional dyspnea
2	Absence of obstructive CAD (<50% diameter reduction or FFR >0.80)	Coronary CTA; invasive coronary angiography
3	Objective evidence of myocardial ischemia	Ischemic changes on ECG during an episode of chest pain; stress-induced chest pain and/or ischemic changes on ECG in the presence or absence of transient/reversible abnormal myocardial perfusion and/or wall motion abnormality
4	Evidence of impaired coronary microvascular function	Impaired coronary flow reserve (cut-off value depending on methodology between ≤0.20 and ≤0.25); coronary microvascular spasm, defined as reproduction of symptoms, ischemic shifts on ECG but no epicardial spasm during acetylcholine testing; abnormal coronary microvascular resistance indices (eg, IMR >25); coronary slow flow phenomenon, defined as TIMI frame count >25

Suspected microvascular angina is diagnosed if symptoms of ischemia are present (criteria 1) with no obstructive CAD (criteria 2) but only (a) objective evidence of myocardial ischemia (criteria 3) or (b) evidence of impaired coronary microvascular function (criteria 4) alone.

*Definitive microvascular angina is only diagnosed if all 4 criteria are present for a diagnosis of microvascular angina.

CAD indicates coronary artery disease; CFR, coronary flow reserve; CTA, computed tomographic angiography; ECG, electrocardiogram; FFR, fractional flow reserve; and IMR, index of microcirculatory resistance.

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Synopsis

Nonobstructive CAD is present in >50% of patients undergoing elective coronary angiography and is associated with an increased risk of all-cause death and MI.[3–5] INOCA refers to myocardial ischemia caused by coronary vasomotor dysfunction without obstructive CAD.[6] In INOCA, the myocardial oxygen supply-demand mismatch may be caused by coronary microvascular dysfunction, coronary vasospasm, or both. Microvascular angina is the clinical manifestation of coronary microvascular dysfunction, and vasospastic angina is the clinical manifestation of myocardial ischemia caused by dynamic epicardial coronary obstruction caused by a vasomotor disorder. Table 15 outlines the diagnostic criteria for microvascular angina proposed by COVADIS (Coronary Vasomotion Disorders International Study Group).[7] The criteria used to diagnose vasospastic angina are outlined in Table 16.[8] For nonobstructive CAD imaging recommendations, see Section 3.1. ("Diagnostic Evaluation") of this guideline and the 2021 AHA/ACC chest pain guideline.[9] The CorMicA (Coronary Microvascular Angina) trial showed that in patients with persistent stable chest pain and nonobstructive CAD, invasive coronary physiology testing is feasible and safe, with clear diagnostic use in identifying specific INOCA endotypes.[1]

Recommendation-Specific Supportive Text

1. In the CorMicA trial, a stratified medical therapy approach guided by invasive coronary physiology testing (guidewire-based assessment of coronary flow reserve index of microvascular resistance [IMR], and FFR), followed by vasoreactivity testing with acetylcholine improved angina severity and QOL in patients with INOCA (<50% diameter reduction or FFR >0.80).[1,2] Based on the results of testing in the intervention arm (vasospastic angina versus microvascular angina), patients were stratified to medical therapy, as shown in Table 17.[1] Patients with noncardiac chest pain were discharged from the cardiology clinic and antianginal medications were discontinued. At 6 months, the intervention resulted in improvement of 11.7 units in the Seattle Angina Questionnaire summary score, as well as improvement in QOL, as assessed by the EuroQoL (EQ-5D-5L).[1] No differences were observed in MACE between the intervention and control arms at 6-month follow-up. The improvements in angina severity and QOL were sustained at 1-year follow-up.[2]

Table 16. Diagnostic Criteria for Vasospastic Angina

Nitrate-responsive angina: during spontaneous episode, *with at least 1* of the following: Rest angina, especially between night and early morning Marked diurnal variation in exercise tolerance, reduced in morning Hyperventilation can precipitate an episode Calcium channel blockers (not beta blockers) suppress episodes
Transient ischemic electrocardiographic changes: during spontaneous episode, including any of the following *in at least 2* contiguous leads: ST segment elevation ≥0.1 mV ST segment depression ≥0.1 mV New negative U waves
Coronary artery spasm: defined as transient total or subtotal coronary artery occlusion (>90% constriction) with angina and ischemic electrocardiographic changes either spontaneously or in response to a provocative stimulus (typically acetylcholine, ergot, or hyperventilation)

"Definitive" vasospastic angina is diagnosed if nitrate-responsive angina is evident during spontaneous episodes and either the transient ischemic ECG changed during the spontaneous episodes or coronary artery spasm criteria are fulfilled. "Suspected" vasospastic angina is diagnosed if nitrate-responsive angina is evident during spontaneous episodes but transient ischemic electrocardiographic changes are equivocal or unavailable and coronary artery spasm criteria are equivocal.

ECG indicates electrocardiogram.

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Table 17. Invasive Coronary Function Testing Definition and Linked Pharmacotherapy for INOCA Endotypes

Endotype	Disorder of Coronary Artery Function		Linked Pharmacotherapy
Microvascular angina (nonobstructive CAD and proven CMD)	↑ **Microvascular resistance**	IMR ≥25. IMR is a quantitative method for specifically assessing microvascular function independent resting hemodynamics. IMR is distal coronary pressure* transmit time (average time for 3 saline bolus runs at hyperemia).	**Baseline therapy:** Consider aspirin, statin, and ACEi therapy in all patients. Sublingual nitroglycerin as needed. Smoking cessation and lifestyle changes. **Antianginal Rx** **First line: Beta blocker** (eg, carvedilol 6.25 mg BID uptitrated) **Second line: CCB** substituted (non DHP [eg, verapamil 40 mg BID titrated]) where beta blockers are not tolerated or ineffective. **Third line: Add-in therapy** **CCB-DHP** (eg, amlodipine)-only for those on beta blockers **Nicorandil*** (5 mg BID, uptitrated) **Ranolazine** (375 mg BID, uptitrated)
	↓ **Coronary vasorelaxation**	CFR by thermodilution <2.0. This reflects the inability to increase coronary flow above 2 times the resting flow.	
	↓ **Microvasodilator capacity**	Resistive reserve ratio <2.0. This reflects the vasodilator capacity of the microcirculation to change from baseline to hyperemia (resistance at rest divided by resistance at hyperemia).	
	Microvascular spasm	Angina during acetylcholine infusion or bolus with typical ischemic ST-segment changes and epicardial coronary constriction <90% reduction in epicardial coronary artery diameter. Represents inappropriate susceptibility microvascular constriction.	
Vasospastic angina	**Epicardial spasm**	Epicardial coronary artery spasm is defined as reduction in coronary diameter >90% after intracoronary acetylcholine in comparison with baseline resting condition after intracoronary glyceryl trinitrate (nitroglycerin) administration in any epicardial coronary artery segment together with symptoms and ST-segment deviation on the ECG.	**Baseline therapy**: If atherosclerosis or endothelial impairment, aspirin and statin should be considered. Sublingual nitroglycerin as needed. Smoking cessation and lifestyle changes. **Antianginal Rx** **First line: CCB** (eg, verapamil 40 mg BID uptitrated) **Second line: Add long-acting nitrate** (eg, isosorbide monotitrate 10 mg BID) **Third line: Change nitrate to nicorandil*** (eg, nicorandil 5 mg BID)
Mixed MVA/VSA	**CMD and epicardial vasospasm**	Epicardial spasm plus any abnormality of: Microvascular resistance Coronary vasorelaxation Microvasodilator capacity	**Baseline therapy:** Consider aspirin, statin and ACEi therapy in all patients. Sublingual nitroglycerin as needed.
Obstructive CAD		>50% lesion by diameter stenosis in epicardial artery >2.5 mm or a FFR ≤0.80	**Baseline therapy**: If atherosclerosis or endothelial impairment, patients should be considered for aspirin, statin, and ACEi. Consideration of revascularization, antianginal therapy as per guidelines
Noncardiac	**None**	Exclusion of diffuse or obstructive epicardial coronary disease (FFR >0.8) without any of the after abnormalities of coronary function: CFR <2.0, IMR ≥25 or functional angina/spasm during acetylcholine.	Cessation of antianginal therapy. Stop antiplatelet and statins unless other indication. Consider noncardiac investigation or referral where appropriate (eg, psychology, gastroenterology)

*Currently unavailable in the United States.

ACEi indicates angiotensin converting enzyme inhibitor; CAD, coronary artery disease; CCB, calcium channel blocker; CFR, coronary flow reserve; CMD, coronary microvascular disease; DHP, dihydropyridine; ECG, electrocardiogram; FFR, fractional flow reserve; IMR, index of microvascular resistance; MVA, microvascular angina; and VSA, vasospastic angina.

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6.1.3. HF With Preserved or Reduced Ejection Fraction

Synopsis

CAD is the most common cause of HF in the United States and has a pivotal role in the development and progression of both HF with preserved ejection fraction and HF with reduced ejection fraction.[1,2] Management of patients with CCD and HF with preserved ejection fraction and HF with reduced ejection fraction should follow associated guideline recommendations for revascularization[3] and HF,[4,5] as well as sections in this guideline: Section 4.2, "Guideline-Directed Management and Therapy," Section 4.3, "Medical Therapy to Prevent Cardiovascular Events and Manage Symptoms," and Section 5, "Revascularization."

6.2. CCD With Valvular Heart Disease

Synopsis

Concurrent CCD is common in patients with valvular heart disease.[1,2] The evaluation and management of CCD at the time of valve intervention is discussed in the "2021 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease."[3] After valve intervention, patients

with valvular heart disease and concomitant CCD should be managed according to current recommendations for secondary prevention as outlined in this guideline. Patients with severe aortic stenosis and concomitant CCD who undergo PCI and transcatheter aortic valve implantation should be treated with DAPT according to the 2021 ACC/AHA/SCAI revascularization guidelines.[4]

6.3. Young Adults

Recommendation for Young Adults Referenced studies that support the recommendation are summarized in the Online Data Supplement.		
COR	**LOE**	**Recommendation**
2a	**C-LD**	1. In young adults with CCD, after optimization of traditional cardiovascular risk factors, a comprehensive evaluation and treatment of nontraditional cardiovascular risk factors can be beneficial in reducing the risk of cardiovascular events.[1–3]

Synopsis

Young adults with CAD represent a unique subset of patients who remain at risk for prolonged cardiovascular morbidity, recurrent MACE[redacted].[1,4] Most have ≥1 traditional cardiovascular risk factors (Table 18).[5,6] Suboptimal control of traditional risk factors has been associated with a higher incidence of recurrent MACE among young adults, thereby warranting optimization similar to older adults, including similar secondary prevention strategies.[1,4,7,8] Given a substantial prevalence of FH,[3] screening for FH can be beneficial (with genotypic screening performing less well than phenotypic screening in non-White population). Safety and efficacy of statin therapy in reduction of cardiovascular events was shown in a 20-year follow-up analysis of young patients with FH.[9] Among those diagnosed with FH or with increased lipoprotein(a) levels, appropriate lipid screening of family members can be considered. Evaluation and treatment of nontraditional risk factors should be considered to decrease risk of future cardiovascular events. Furthermore, implementing strategies such as optimizing health care access, educating patients, motivational interviewing, using health information technology tools, and reducing barriers in obtaining medications may be beneficial in optimizing medication adherence[10,11] (see Section 4.1.2, "Patient Education" and Section 4.1.4, "Social Determinants of Health"). Evaluation and management of nonatherosclerotic causes such as coronary anomalies, Kawasaki disease, or myocardial bridging may be beneficial (Table 19).[12–14] Longitudinal follow-up of these patients with CVD specialists should be encouraged (see Section 7.1, "Follow-Up Plan and Testing").

Recommendation-Specific Supportive Text

1. AFIJI (Appraisal of Risk Factors in Young Ischemic Patients Justifying Aggressive Intervention) was a prospective multicenter cohort study evaluating young patients diagnosed with CAD at age ≤45 years.[1] During their long-term follow-up, the investigators observed diabetes and current smoking to be associated with higher risk of recurrent MACE. Additionally, chronic inflammatory disease state (eg, HIV, viral hepatitis, systemic autoimmune disease) was associated with overall poor outcomes. More recently, similar observations were made by investigators from the YOUNG-MI (The Conundrum of Sex Differences in Outcomes of Young Patients with Acute MI)[15] and VITAL[2] registries that have highlighted the importance of traditional cardiometabolic risk factors along with nontraditional risk enhancers among young adults with CAD. Although the attributable risk of traditional risk factors such as tobacco use, vaping, hypertension, and diabetes may supersede that of nontraditional risk factors among young adults with CCD, the role of

Table 18. Traditional and Nontraditional Risk Factors Associated With CCD in Young Adults

Traditional Risk Factors	Nontraditional Risk Factors
Hypertension (Section 4.2.7, "Blood Pressure Management")	HIV and ART (Section 6.8, "HIV/Autoimmune Disorders")
Obesity and metabolic syndrome (Section 4.2.9, "Weight Management")	Recreational substance use (cocaine and marijuana) (Section 4.2.4, "Alcohol and Substance Use")
Diabetes (Section 4.2.8, "Sodium Glucose Cotransporter 2 Inhibitors and Glucagon Peptide-1 Receptor Agonists")	Systemic inflammatory disorders (IBD, SLE, RA, gout, PsA, AS) and vasculitides
Unhealthy diet and physical inactivity (Section 4.2.1, "Nutrition, including Supplements," and Section 4.2.11, physical activity)	Pregnancy-related complications (IUGR, HDP, gestational diabetes) (Section 6.5, "Women, Including Pregnancy and Hormone Therapy")
Hyperlipidemia (LDL-C, Lp(a)) (Section 4.2.6, "Lipid Management")	Familial hypercholesterolemia
Tobacco use (Section 4.2.3, "Tobacco Products")	Miscellaneous (psychological well-being, sleep quality, social determinants of health (Section 4.1.4, "Social Determinants of Health," and Section 4.2.2, "Mental Health")
Family history of premature CAD	History of chest radiation

ART indicates antiretroviral therapy; AS, ankylosing spondylitis; CCD, chronic coronary disease; Ch9p21, chromosome 9p21 locus; HDP, hypertensive disorders of pregnancy; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; IUGR, intrauterine growth retardation; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); PsA, psoriatic arthritis; RA, rheumatoid arthritis; and SLE, systemic lupus erythematosus.

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Table 19. Nonatherosclerotic Causes of CCD in Young Adults: Evaluation and Management

Cause	Presentation	Management
Kawasaki disease	Late sequelae: coronary artery aneurysm, stenosis, thrombosis, or fistula	Lifelong follow-up with quantitative assessment of luminal dimensions. Low-dose aspirin therapy for small- or medium-sized coronary artery aneurysms. Low-dose aspirin plus anticoagulant therapy for large coronary artery aneurysms.
Coronary artery anomalies	Anomalous left coronary artery from the pulmonary artery Anomalous origin of the coronary artery from the opposite sinus of Valsalva with an interarterial course	Surgical repair – translocation of left coronary artery to aortic root for anomalous left coronary artery from the pulmonary artery. Surgical correction among young adults with interarterial course of coronary artery originating from opposite sinus of Valsalva and symptoms during exercise suggestive of myocardial ischemia.
Myocardial bridging	Exercise-induced ischemia Coronary artery vasospasm Sudden cardiac death	Beta-adrenergic blocking agents in symptomatic patients. Restriction to low-intensity sports. Surgical correction if symptoms refractory to medical therapy.

CCD indicates chronic coronary disease.

these unique risk factors such as chronic inflammation, genetics (Ch9p21 locus, lipoprotein(a)), and recreational drug use remains at the center of clinical optimization. Assessing for and aggressive treatment of nontraditional cardiovascular risk factors (Table 18) such as inflammatory conditions or recreational drug use are important to reduce cardiovascular risk among young adults with CCD.[1-3,16,17] Evaluation for nonatherosclerotic causes of CCD among young adults (coronary anomalies, vasospasm, or spontaneous dissection) should also be prioritized (see Section 6.1, "Existing Heart Diseases and Conditions" and Section 6.5, "Women, Including Pregnancy and Hormone Therapy").

6.4. Cancer

Recommendation for Cancer
Referenced studies that support the recommendation are summarized in the Online Data Supplement.

COR	LOE	Recommendation
1	C-LD	1. In patients with CCD and cancer, a multidisciplinary team including cardiology and oncology expertise is recommended to improve long-term CVD outcomes.[1,2]

Synopsis

Cancer and CCD share mechanistic pathophysiology[3–5] and are the 2 leading causes of death worldwide,[6] sharing multiple risk factors such as sedentary lifestyle, obesity, smoking, diabetes, and age.[4,7] Cancer and CVD increasingly coexist, yet patients with CCD and cancer are often undertreated[4] and are high risk for cardiovascular adverse events. Commonly used chemotherapy and radiation therapy may have cardiac toxicity,[8,9] and some classes of cytotoxic chemotherapy increase CVD risk factors.[10] In 2022, AHA published a scientific statement on cardio-oncology drug interactions, noting communication between oncology and cardiology specialists is warranted.[11] If CCD medications are stopped because of cancer treatment, they should be resumed as soon as possible. In 2019, the AHA provided a scientific statement in favor of the development of cardio-oncology rehabilitation for patients at high risk of developing cardiovascular dysfunction.[2]

Recommendation-Specific Supportive Text

1. A multidisciplinary cardio-oncology team should evaluate the patient before cancer treatment and monitor the patient throughout the course of treatment.[10] Longitudinal registries suggest that cardiovascular outcomes have improved with the introduction of multidisciplinary care teams in cancer treatment. In settings where multidisciplinary teams are unavailable, clinicians should consider referral to relevant subspecialties as appropriate.[1,12] Cardio-oncology is a growing subspecialty that promotes the need for effective cancer treatment while minimizing negative cardiovascular adverse events.[13] The cardio-oncology team is involved in all aspects of the care of cancer patients, from informing pretreatment risk and regimen selection, addressing the complex cardiovascular adverse effects of cancer therapy, and mitigating the heightened long-term risks of CVD in survivorship. This team manages common conditions between subspecialties, such as antiplatelet therapy for venous thromboembolism prophylaxis. Patients with CCD and locally advanced or metastatic cancer can be at increased risk for arterial thrombosis and cardiovascular adverse events. If the patient is not already on an antithrombotic regimen, clinicians may offer thromboprophylaxis with apixaban, rivaroxaban, or low-molecular-weight heparin to selected high-risk outpatients with cancer.[14] Refer to Section 4.1.1 ("Team-Based Approach"), Section 4.1.2 ("Patient Education"), and Section 4.1.4 ("Social Determinants of Health") for management of the patient with CCD and comorbidities.

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6.5. Women, Including Pregnancy and Postmenopausal Hormone Therapy

Recommendations for Women, Including Pregnancy and Postmenopausal Hormone Therapy
Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	Recommendations
Pregnancy		
1	C-LD	1. Women with CCD who are contemplating pregnancy or who are pregnant should be risk-stratified and counseled regarding risks of adverse maternal, obstetric, and fetal outcomes.[1–4]
1	C-LD	2. Women with CCD who are contemplating pregnancy or who are pregnant should receive care from a multidisciplinary cardio-obstetric care team beginning before conception and continuing throughout pregnancy, delivery, and postpartum to improve maternal and fetal outcomes.[1,2,5]
2b	C-LD	3. In women with CCD, continuation of statin use during pregnancy may be considered.[6]
3: Harm	C-LD	4. Women with CCD who are contemplating pregnancy or who are pregnant should not use ACE inhibitors, ARBs, direct renin inhibitors, angiotensin receptor-neprilysin inhibitors, or aldosterone antagonists during pregnancy to prevent harm to the fetus.[2,7,8]
Postmenopausal Hormone Therapy		
3: Harm	A	5. Women with CCD should not receive systemic postmenopausal hormone therapy because of a lack of benefit on MACE and mortality, and an increased risk of venous thromboembolism.[9–11]

Synopsis

CCD remains uncommon among pregnant women ranging from <2% to 3.6% in published registries.[12–14] Physiologic changes in pregnancy that could influence myocardial workload and myocardial perfusion and thus precipitate acute cardiovascular events that include increases in circulating blood volume, stroke volume, heart rate, and cardiac output, decreases in systemic vascular resistance, diastolic BP and LV end-diastolic pressure, physiologic anemia, and a hypercoagulable state.[2,15] Women with CCD who become pregnant are at high risk of adverse maternal and fetal outcomes[1,3] and are best managed by a multidisciplinary cardio-obstetrics team.[16] Pharmacologic therapy should balance maternal benefit and fetal risk.[7] Postmenopausal hormone therapy has been assessed among women with CCD in trials with angiographic endpoints[17–20] and in trials designed to evaluate angina or morbidity and mortality rates.[9,10,21–23] Trials tested either estrogen-only regimens (in women without a uterus) or combined estrogen and progestin regimens (in women with a uterus). None of these trials showed benefits on recurrent cardiovascular events. Venous thromboembolism was significantly increased in these trials. No RCTs exist that have tested transdermal hormone regimens to assess their effect on MACE and mortality.

Recommendation-Specific Supportive Text

1. A systematic review of 37 studies including 124 pregnancies in 116 women with CCD[1] reported cardiovascular complications in 32% of pregnancies, including ischemic cardiovascular events in 9%, and obstetric and fetal/neonatal complications in 58% and 42%, respectively. Only 21% of pregnancies were uncomplicated. In a study of 79 women with CCD (92 pregnancies of at least 24 weeks' gestation), 66% had adverse cardiac events and 14% developed preeclampsia; 25% of infants were delivered preterm, and 25% were born small for gestational age.[13] In the CARPREG II (Pregnancy Outcomes in Women with Heart Disease) prospective registry, a history of CCD was independently associated with adverse cardiac events (odds ratio, 3.0 [95% CI, 1.1-7.6]).[3] Women with CCD, including women with previous SCAD (Section 6.1.1), who are contemplating pregnancy should undergo thorough evaluation and risk stratification using a validated instrument such as the CARPREG

Table 20. CARPREG II Risk Prediction Model

CARPREG II Predictors	Points
Previous cardiac event or arrhythmia	3
Baseline NYHA functional class III to IV or cyanosis	3
Mechanical valve	3
Ventricular dysfunction	2
High-risk left-sided valve disease and LVOT obstruction	2
Pulmonary hypertension	2
CAD	2
High-risk aortopathy	2
No previous cardiac intervention	1
Late pregnancy assessment	1
CARPREG II Score	**Predicted Risk, %**
0 to 1	5
2	10
3	15
4	22
>4	41

The CARPREG (Cardiac Disease in Pregnancy Study) II risk score is based on 10 predictors, shown in the table. Each predictor is assigned a weighted point score. The sum of points represents the risk score. Risk scores are categorized into 5 groups. The predicted and observed frequency of primary cardiac events* in the derivation and validation groups is available at the CARPREG II Study https://doi.org/10.1016/j.jacc.2018.02.076.

*Primary cardiac events were defined as any of these: maternal cardiac death; cardiac arrest; sustained arrhythmia requiring treatment; left-sided HF defined as pulmonary edema; right-sided HF; stroke or TIA; cardiac thromboembolism; MI; and vascular dissection.

CAD indicates coronary artery disease; HF, heart failure; LVOT, left ventricular outflow tract; MI, myocardial infarction; NYHA, New York Heart Association; and TIA, transient ischemic attack.

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Table 21. Safety of Cardiovascular Medications During Pregnancy and Lactation

Medication	Safety in Pregnancy	Safety in Lactation
Arrhythmias		
Adenosine	S	LD
Metoprolol/propranolol	S	LD
Digoxin	S	S
Lidocaine	S	S
Verapamil	LD	LD
Diltiazem	LD	U
Procainamide	LD	LD
Sotalol	LD	U
Flecainide	LD	LD
Propafenone	LD	LD
Amiodarone*	C	C
Heart Failure		
Metoprolol	S	LD
Carvedilol	S	U
Furosemide	S	LD
Bumetanide	S	U
Dopamine	S	U
Dobutamine	S	U
Norepinephrine	S	U
Hydralazine	LD	S
Nitroglycerine	LD	U
Isosorbide dinitrate	LD	U
Torsemide	LD	U
Metolazone	LD	U
Anticoagulants		
Warfarin	LD	S
Unfractionated heparin	S	S
Enoxaparin	S	S
Fondaparinux	LD	U
Argatroban	LD	U
Bivalirudin	LD	U
Antiplatelets		
Aspirin (low dose)	LD	LD
Clopidogrel	LD	LD
Prasugrel	LD	U
Ticagrelor	LD	U
Thrombolytics		
Alteplase	LD	U
Streptokinase	LD	U
Hypertension		
Labetalol	S	LD
Nifedipine	S	S
Alpha-methyldopa (oral)	S	S
Hydralazine	LD	S
Nitroglycerin	LD	U
Nitroprusside	LD	LD
Isosorbide dinitrate	LD	U
Amlodipine	LD	LD
Furosemide	S	LD
Hydrochlorothiazide	LD	S
Clonidine	LD	U
Cautionary Use and Contraindicated in Pregnancy		
Atenolol	C	LD
ACE inhibitor class†	C	LD
ARB class	C	U
Aldosterone antagonists	C	C
Statin class	LD	C
DOAC	C	C
ERAs (eg, bosentan)	C	C

Color key: C, contraindicated; LD, limited data, use with caution; S, considered safe; and U, conflicting data, unknown.

*May be used if other therapies fail.

†Captopril, benazepril, and enalapril are considered safe during lactation.

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; DOAC, direct oral anticoagulants; and ERA, endothelin-receptor antagonists.

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II (Table 20) and be counseled regarding potential risks to mother and fetus.[2,15] Pharmacokinetics of medications may be altered in pregnancy because of changes in absorption, volume of distribution, serum protein binding, extraction ratio, hepatic and renal clearance, uteroplacental flow, and fetal metabolism.[7] Medication regimens should be optimized during family planning to ensure safety throughout pregnancy and lactation.[2,7] Recommendations for selected cardiovascular medications during pregnancy and lactation are summarized in Table 21.

2. A multidisciplinary cardio-obstetrics team (Figure 10) should evaluate the patient before conception and monitor the patient throughout her pregnancy, carefully plan for labor and delivery, and provide close follow-up during the postpartum period to address medication management during lactation, monitor for cardiovascular complications, manage cardiovascular risk factors, and advise on contraception.[5,16] Longitudinal registries suggest that pregnancy outcomes have improved with the introduction of multidisciplinary care teams.[1] In health care settings where multidisciplinary teams are unavailable, clinicians should consider referral to relevant subspecialties as appropriate.
3. Statins have been contraindicated in pregnancy since their approval in 1987. FDA guidance published in July 2021 requested removal of this contraindication from all statin labels.[6] A 2015 US propensity-based

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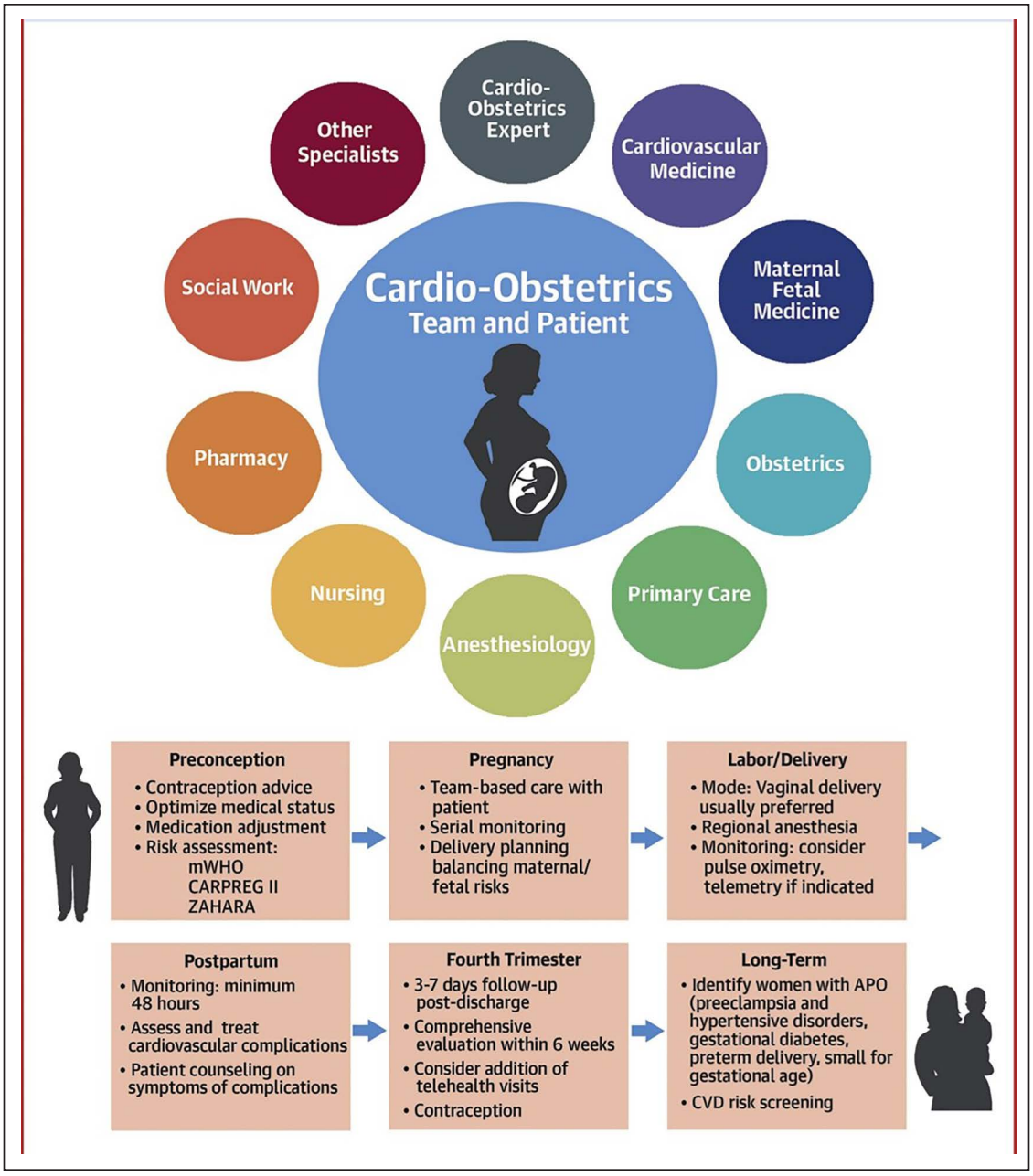

Figure 10. Team-Based Cardio-Obstetrics Model of Care.
The cardio-obstetrics model of care involves multiple specialists working together and with the patient to address issues from preconception, through pregnancy and delivery, and the postpartum period. APO indicates adverse pregnancy outcomes; CARPREG II, Cardiac Disease in Pregnancy study; CVD, cardiovascular disease; mWHO, modified World Health Organization; ZAHARA, Zwangerschap bij Aangeboren HARtAfwijking (Pregnancy in Women With Congenital Heart Disease) study. Modified with permission from Davis MB, et al.[16] Copyright 2021 American College of Cardiology Foundation.

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analysis among 886996 completed pregnancies linked to liveborn infants showed a 1.79-fold increase in risk of fetal malformations among the 1152 pregnancies with first-trimester exposure to statins, but this increase in risk was accounted for by confounders such as preexisting diabetes, lowering the relative risk to 1.07 (95% CI, 0.85-1.37) in adjusted analyses.[24] A 2014 meta-analysis similarly found no increase in birth defects after statin exposure during pregnancy but found an increased risk of miscarriage that the authors attributed to underlying maternal comorbidities.[25] A 2017 analysis of the UK General Practice Research Database showed a 1.64-fold increased risk of fetal loss in statin-exposed pregnancies but could not fully account for differences in baseline characteristics in exposed and unexposed pregnancies.[26] The FDA concluded that data are insufficient at this time to determine whether

there is statin-associated increased risk of miscarriage. Statins remain contraindicated during lactation (Table 21). Lipoprotein apheresis can be considered for women with heterozygous or homozygous familial hypercholesterolemia and CCD.[27]

4. ACE inhibitors, ARBs, direct renin inhibitors, and angiotensin receptor-neprilysin inhibitors can cause renal dysgenesis, oligohydramnios because of fetal oliguria, neonatal anuric renal failure, intrauterine growth retardation, pulmonary hypoplasia, and fetal death, especially when used in the second and third trimester of pregnancy.[8] Benazepril, captopril, and enalapril are safe during lactation.[7] Aldosterone antagonists are contraindicated in pregnancy because of their antiandrogen effects and potential teratogenesis. Aldosterone antagonists are also contraindicated during lactation.[7]
5. Data from secondary prevention trials of hormone therapy[11] concluded that there was no effect on cardiovascular death, nonfatal MI, stroke, angina, or coronary revascularization. A statistically significant increased risk of venous thromboembolism was observed (relative risk, 2.02 [95% CI, 1.13-3.62]). In the angiographic trials,[17–20] no benefit of hormone therapy was seen on progression of disease in native CAD with estrogen only or with estrogen-progestin therapy. The EAGAR (Effects of Aspirin in Gestation and Reproduction) study[20] showed enhanced progression in native coronary arteries yet slowing of disease progression in saphenous vein grafts; the reason for this differential response is unknown. Increased risk of thromboembolism also was documented in a trial of hormone therapy among women with previous venous thromboembolism.[28] Less is known about the risk of oral contraceptives among women with CCD. A recent review on estrogen and thrombosis[29] concluded that combined hormonal contraceptives and injectable depot medroxyprogesterone acetate should be avoided among women with CCD or previous stroke as both forms of contraceptive therapy increase thrombosis risk.[30,31]

   Increased cardiovascular risk has been documented among transwomen with increased rates of venous thromboembolism, acute MI, and stroke compared with ciswomen but not always when compared with cismen.[29,32] This increase in cardiovascular risk is at least in part related to hormone therapy. Whether prevalent CCD further increases risk in hormone-treated transgender women is unknown with future research needed.

6.6. Older Adults

Synopsis

Older patients, defined as ≥75 years of age in accordance with a recent statement published by the AHA, ACC, and American Geriatrics Society,[1] have a high prevalence of CCD and, when present, is more likely to be associated with high-risk anatomical features.[2] Although several retrospective studies, observational studies, and subgroup analyses have suggested that medical therapy[3–6] and revascularization,[7–17] when needed, may be effective in older patients, they are less likely to be treated.[18] A paucity of RCTs with a focus on older patients leaves clinicians with inadequate data to guide their decision-making. The available data are limited by a variable definition of the term older; in fact, some studies have included individuals as young as 60 years of age. Furthermore, many studies comprise patients with both acute and CCD, making it difficult to determine in which clinical scenario a treatment is efficacious. The treatment of CCD in older patients is further complicated by the presence of multiple comorbidities and polypharmacy, both of which can heighten the risk of treatment-related complications. Based on a patient's comorbidities and extent of polypharmacy, scenarios may exist where alternate treatment or procedural approaches (beta blockers,[19] antithrombotic and antiplatelet agents,[9,20–23] coronary angiography,[24] CABG,[25–29] CR[30,31]) may be preferable. For example, a meta-analysis of 6 RCTs comparing short-term versus long-term DAPT in elderly patients.[21] The use of short-term DAPT was not associated with an increase in cardiovascular events but was associated with a significant reduction in major bleeding. Additionally, traditional risk scoring systems in patients with CCD may need to be modified to most accurately assess an older patient's risk.[32,33] Older patients also have an increased prevalence of frailty,[34–37] malnourishment,[38–41] and cognitive decline, all of which may be associated with poor outcomes and treatment response. Equally important, older patients are more likely to prioritize the ability to remain independent, with a focus on maintaining their mobility and functional status rather than reducing their mortality rate.[3] When considering treatment options, team-based care (Section 4.1.1) and shared decision-making

Table 22. The Geriatric 5 Ms

MIND	Mentation, dementia, delirium, depression
MOBILITY	Impaired gait and balance, fall injury prevention
MEDICATIONS	Polypharmacy, deprescribing, optimal prescribing Adverse medication effects and medication burden
MULTICOMPLEXITY	Multimorbidity Complex biopsychosocial situations
MATTERS MOST	Each individual's own meaningful health outcome goals and care preferences

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(Section 4.1.3) are particularly important when caring for older patients. A framework that considers the 5 Ms of geriatric care[42] (Table 22) may be a useful approach to guide these discussions.

6.7. Chronic Kidney Disease

Recommendation for CKD Referenced studies that support the recommendation are summarized in the Online Data Supplement.		
COR	LOE	Recommendation
1	C-LD	1. In patients with CCD and CKD, measures should be taken to minimize the risk of treatment-related acute kidney injury.*[1–3]

*Modified from the 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization.[4]

Synopsis

CKD increases the risk of CAD progression and is associated with poor outcomes after interventions.[5–8] The mortality rate for patients on hemodialysis is ~20% per year, with approximately 50% attributable to a cardiovascular cause.[9–12] Postmortem studies have revealed that patients with CKD not only have a higher burden of atherosclerosis but, also, the plaque features are more advanced, with evidence of increased inflammation.[13–15] Despite the higher prevalence of disease, noninvasive diagnostic testing is often less accurate.[20–24]

Guidance related to the use of pharmacological and interventional therapy is limited by underrepresentation of patients with CKD in clinical trials[16] and attributable to inconsistent definitions of CKD. It is unclear whether medical therapy is as efficacious in patients with CKD because of differences in the risk and benefit balance in the setting of underlying kidney disease.[17,18–21] In the absence of data from dedicated RCTs, patients with CKD should receive similar medical therapy as patients without CKD.[22]

Given the complex interactions, a team-based approach (Section 4.1.1) that includes individuals from the cardiac and renal teams, to include shared decision-making (Section 4.1.3), would be beneficial, especially when considering decisions such as revascularization for which decreased short-term risk must be balanced with long-term benefit.[23,24] For additional reference, please see patient education and SDOH (Sections 4.1.2 and 4.1.4) within this guideline.

Recommendation-Specific Supportive Text

1. In the ISCHEMIA-CKD (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial, patients with a moderate to severe burden of ischemia and estimated glomerular filtration rate [eGFR] of <30 mL/min/1.73 m^2 of body-surface area or the receipt of dialysis did not have improved outcomes with the addition of revascularization to GDMT, suggesting that revascularization can be reserved for patients who remain symptomatic despite medical therapy,[25] clarifying conflicting data from previous studies.[8,26] When PCI is clinically needed, the risk of contrast-induced acute kidney injury (AKI) should not be a reason to withhold it in most patients with CKD.[4] When possible, attempts to minimize the risk of contrast nephropathy should be made through the avoidance of nephrotoxic agents, use of adequate hydration before the administration of iodinated contrast-agent,[27–29] and minimization of the volume of contrast media.[30,31] Additionally, high-dose statins may reduce the occurrence of contrast-induced AKI.[32] The use of radial access may minimize the role of atheroembolism on the development of AKI[33–35]; however, conflicting data exist.[36,37] Delay of CABG in stable patients after angiography beyond 24 hours, when clinically feasible, can also help reduce the risk of AKI.[38] There is no benefit of bicarbonate or N-acetyl-L-cysteine over normal saline for prevention of AKI.[39]

6.8. HIV and Autoimmune Disorders

Recommendations for HIV and Autoimmune Disorders Referenced studies that support the recommendations are summarized in the Online Data Supplement.		
COR	LOE	Recommendations
HIV		
1	B-R	1. In adults with CCD and HIV, antiretroviral therapy is beneficial to decrease the risk of cardiovascular events.[1,2]
2a	B-R	2. In adults with CCD and HIV, it is reasonable to choose antiretroviral therapy regimens associated with more favorable lipid and cardiovascular risk profiles with consideration of drug-drug interactions.[3–5]
3: Harm	C-LD	3. In adults with CCD and HIV, lovastatin or simvastatin should not be administered with protease inhibitors as this may cause harm.[6,7]
Autoimmune Disorders in CCD		
2a	C-LD	4. In adults with CCD and rheumatoid arthritis, initiation and maintenance of disease-modifying antirheumatoid drugs is beneficial to decrease the risk of cardiovascular events.[8–11]
2b	C-LD	5. In adults with CCD and autoimmune diseases, treatment with biologics and other immune modulating therapies that reduce disease activity may be considered to decrease the risk of cardiovascular events.[10,11]
3: Harm	C-LD	6. In patients with CCD and rheumatoid arthritis, high-dose glucocorticoids should not be used long term if alternative therapies are available because of increased cardiovascular risk.[11,12]

Synopsis

HIV and other chronic inflammatory conditions are associated with accelerated atherosclerosis and premature CVD. The 2018 ACC/AHA blood cholesterol guideline

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Table 23. Common Antiretroviral Therapy Drugs and Effects on Lipid Levels

Class	Drug	Effect on Blood Lipids
Protease inhibitors	Atazanavir	Increases HDL-C and decreases LDL-C levels
	Darunavir	Increases HDL-C levels
	Fosamprenavir	Hypertriglyceridemia
	Ritonavir*	Increases HDL-C levels
	Saquinavir	Neutral
	Tipranavir	Dyslipidemia
NRTIs	Abacavir	Increases total cholesterol, LDL-C, and HDL-C levels
	Lamivudine	Increases total cholesterol, LDL-C, and HDL-C levels
	Tenofovir fumarate disoproxil	Lowers LDL levels
	Zidovudine	Hypertriglyceridemia
NNRTIs	Efavirenz	Increases total cholesterol, LDL-C, HDL-C, and triglyceride levels
	Nevirapine	Neutral or decreases lipid levels
	Rilpivirine	Neutral
Integrase inhibitors	Dolutegravir	Neutral
	Raltegravir	Increases HDL levels

*Although ritonavir is a protease inhibitor, this drug is generally used as a pharmacokinetic enhancer.

HDL indicates high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; NNRTI, nonnucleoside reverse-transcriptase inhibitor; and NRTI, nucleoside reverse-transcriptase inhibitor.

Adapted from Hsue PY et al.[6] by permission from Springer Nature, Copyright 2019.

recommends that chronic inflammatory conditions be considered risk-enhancing factors that should guide clinician-patient risk discussion for cholesterol management.[13] Patients with HIV have a higher risk of CAD and MI compared with age- and sex-matched controls.[14] The increased risk may be attributable to HIV itself, the antiretroviral therapy,[15] and to a higher prevalence of traditional, modifiable risk factors.[6] Newer generation antiretroviral therapy regimens have more favorable lipid effects and are associated with improvements in subclinical markers of atherosclerosis. Similarly, although new treatments for autoimmune diseases, including rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematous, and inflammatory bowel diseases, can negatively affect lipid profiles, adequate control of disease activity with steroid-sparing agents should be prioritized and may help lower cardiovascular risk.[10] Because of the rapidly changing and complex pharmacological landscape in treating HIV and other chronic inflammatory conditions, patients should receive care from a multidisciplinary care team that includes infectious disease, rheumatology expertise, or both.

Recommendation-Specific Supportive Text

1. The SMART (Strategies for Management of Antiretroviral Therapy) trial showed that, compared with continuous use of antiretroviral therapy, episodic use of antiretroviral therapy increased risk of opportunistic disease and death from any cause, including CVD.[1] The MI event rate was 1.3 per 100 person-years in the interruption arm versus 0.8 per 100 person-years in the continuous use of antiretroviral therapy arm. Higher CD4 cell count and lower HIV RNA levels are associated with a lower risk of ASCVD.[6,16,17]
2. Excess cardiovascular risk in patients with HIV may be partly attributable to side effects from antiretroviral therapy, including adverse effects on lipid levels. In adults with CCD and HIV, it is reasonable to choose newer generation antiretroviral treatment regimens associated with more favorable lipid and cardiovascular risk profiles.[3–5] These include protease inhibitor regimens with lower doses of ritonavir for boosting and using atazanavir-ritonavir–containing regimens (see Table 23 for commonly used antiretroviral therapy drugs and the effect on lipid levels). In 1 randomized study, switching from a ritonavir-boosted protease inhibitor to a dolutegravir-based regimen was noninferior in maintaining a viral suppression with improvement in lipid levels (7.7% LDL-C reduction).[3] Contemporary US guidelines recommend that individuals with HIV and CVD should switch from an abacavir-containing regimen because of its possible association with increased cardiovascular events.[4,18] Drug interactions are common among patients with HIV on antiretroviral therapy, which should be considered when starting or intensifying statin therapy for management of CCD.[6,7,19,20] Although pravastatin and pitavastatin are least likely to interact with antiretroviral therapy, rosuvastatin and atorvastatin may be preferred for more intense LDL-C reduction in patients with HIV and CCD.[20,21] Management of hypertriglyceridemia in patients with CCD and HIV should follow standard treatment pathways.[22]

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Triglyceride levels ≥500 mg/dL should be treated pharmacologically to reduce the risk of pancreatitis. Drug-drug interactions with protease inhibitors can also occur with antiplatelet drugs like ticagrelor because of its CYP3A metabolism,[23] which may increase the risk of bleeding.

3. Because lovastatin and simvastatin are metabolized by intestinal and liver CYP3A4, the concomitant use of protease inhibitors can increase levels of these statins and may increase the risk of rhabdomyolysis.[6,7,24]
4. Patients with rheumatoid arthritis and other autoimmune disease have residual inflammatory risk, beyond that conferred by traditional CVD risk factors. For patients with rheumatoid arthritis, disease-modifying antirheumatoid drugs such as methotrexate are associated with lower risk of cardiovascular events in observational studies.[10] A single-center observational study found that use of biologic disease–modifying antirheumatoid drugs in patients with rheumatoid arthritis stabilized and decreased plaque as measured by CCTA.[25]
5. Janus kinase inhibitors, tumor necrosis factor inhibitors, and other immunomodulators for the treatment of autoimmune diseases (eg, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and ulcerative colitis) may reduce cardiovascular events by reducing disease activity and inflammation.[11,26,27] These treatments should be used in combination with intensive management of traditional risk factors (see Section 4.2.6, "Lipid Management," Section 4.2.7, "Blood Pressure Management," and Section 4.2.8, "Sodium Glucose Cotransporter 2 Inhibitors and Glucagon-Like Peptide-1 Receptor Agonists").
6. Observational studies suggest that long-term use of higher doses of glucocorticoids (≥5 mg of prednisone) in patients with rheumatoid arthritis are associated with a higher risk of cardiovascular events.[12] This association has not been described with the use of steroid-sparing agents[11] or shorter duration use of steroids (<81 days in 6 months or cumulative doses of <751 mg in 6 months).[12] Using short courses of glucocorticoids for autoimmune disease flares is unlikely to increase cardiovascular risk.

6.9. Cardiac Allograft Vasculopathy in Heart Transplant Recipients

Recommendations for Management of Cardiac Allograft Vasculopathy in Heart Transplant Recipients
Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	Recommendations
1	C-LD	1. In patients with cardiac allograft vasculopathy, statins are recommended for secondary prevention to reduce MACE.[1]

Recommendations for Management of Cardiac Allograft Vasculopathy in Heart Transplant Recipients (Continued)

COR	LOE	Recommendations
2a	C-LD	2. In patients with cardiac allograft vasculopathy, aspirin can be beneficial for secondary prevention to reduce MACE.[2]
2a	C-LD	3. In patients with severe cardiac allograft vasculopathy, revascularization is reasonable in those with suitable anatomy to potentially mitigate the adverse long-term consequences of cardiac allograft vasculopathy.*[3–6]

*Modified from the 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization.[7]

Synopsis

Post–heart transplant cardiac allograft vasculopathy is the leading cause of long-term mortality and retransplantation among heart transplant recipients.[8] The incidence of cardiac allograft vasculopathy increases over time after heart transplant, developing in ~30% of patients at 5 years and ~50% of patients at 10 years.[8] Coronary angiography is the accepted clinical standard for screening and diagnosis of cardiac allograft vasculopathy.[3,9] Intravascular ultrasound is a useful adjunct to angiography and can improve detection of angiographically occult cardiac allograft vasculopathy.[10] Lifestyle modifications and optimal control of cardiovascular risk factors are important for the primary and secondary prevention of cardiac allograft vasculopathy.[3,11] In patients after heart transplant with or without established cardiac allograft vasculopathy, statins, aspirin, and high-intensity interval training delay cardiac allograft vasculopathy progression.[1,2,12] In patients with cardiac allograft vasculopathy, PCI can be beneficial in those with severe, proximal, discrete lesions, and the use of second-generation DES is associated with decreased rates of in-stent restenosis.[4-7] CABG is rarely used in highly selected patients with suitable anatomy, and retransplantation is reserved for patients with severe cardiac allograft vasculopathy not amenable to revascularization.[3] In heart transplant recipients with established cardiac allograft vasculopathy, early substitution of mycophenolate mofetil, azathioprine, or calcineurin inhibitor with a proliferation signal inhibitor can slow cardiac allograft vasculopathy progression but is associated with an increased risk of grade ≥2R rejection.[13–17] CR is addressed in Section 4.2.10.

Recommendation-Specific Supportive Text

1. Multiple RCTs have shown decreased incidence of cardiac allograft vasculopathy with simvastatin or pravastatin initiated early after heart transplant.[18,19] However, in patients with cardiac allograft vasculopathy, RCTs evaluating the safety and efficacy of statins for secondary prevention are lacking. In a retrospective observational study of 409 heart

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transplant recipients with or without established cardiac allograft vasculopathy, early (<2 years) versus late (>2 years) initiation of statin was associated with significantly lower rates of cardiac allograft vasculopathy progression as measured by change in plaque volume and plaque index by intravascular ultrasound, as well as decreased risk of cardiac allograft vasculopathy–related events (allograft failure associated with cardiac allograft vasculopathy, MI, or PCI) and the composite of all-cause death and cardiac allograft vasculopathy–related events, over a median follow-up of 8.2 years.[1] The choice and dose of statin in heart transplant recipients is not well established and will often depend on the other medications (particularly immunosuppressants) that the patient is concomitantly taking (Table 24).[20] A recent retrospective analysis of 346 adult patients who underwent heart transplant between 2006 and 2018 found that moderate/high- versus low-intensity statin therapy was associated with a significant reduction in the primary composite of time to HF hospitalization, MI, revascularization, and all-cause death.[21]

2. Aspirin is frequently initiated early after heart transplant for prevention of cardiac allograft vasculopathy. Although the proposed benefits of aspirin use have not been validated in RCTs, evidence from small retrospective single-center studies support early initiation of aspirin after heart transplant.[2,22–24] In a retrospective observational study of 529 heart transplant recipients with or without established cardiac allograft vasculopathy, early (<1 year) versus late (>1 year) initiation of aspirin was associated with significantly lower rates of cardiac allograft vasculopathy progression as measured by change in plaque volume and plaque index by intravascular ultrasound, as well as decreased risk of all-cause death and cardiac allograft vasculopathy–related graft dysfunction, over a median follow-up of 6.7 years.[2]
3. Data showing improved outcomes with revascularization versus medical therapy alone for cardiac allograft vasculopathy are lacking. However, because increasing severity of cardiac allograft vasculopathy is associated with worse outcomes, revascularization is reasonable in patients with suitable anatomy.[3] PCI can be beneficial in patients with cardiac allograft vasculopathy who present with severe, proximal, discrete lesions.[7] Observational studies showed PCI for cardiac allograft vasculopathy is not only feasible with high procedural success rates but also associated with reliable mid- to long-term angiographic outcomes, especially with the use of second-generation DES.[4–6] PCI with everolimus-eluting stents for cardiac allograft vasculopathy was associated with in-stent restenosis rates of 3% to 5% at 6 to 12 months and 10% at 3 years, which are comparable to the use of everolimus-eluting stents in non–heart transplant CAD.[4–6,25,26] Coronary physiology assessment measuring FFR and the index of microcirculatory resistance early after heart transplant has prognostic significance.[27,28] However, the use of FFR to guide revascularization in patients with cardiac allograft vasculopathy (as opposed to those with non–heart transplant CAD) remains unknown. The use of CABG for severe cardiac allograft vasculopathy is limited by high early mortality rate (36% at 30 days) associated with surgical revascularization in this patient population.[29]

Table 24. Drug-Drug Interactions With Statins and Immunosuppressants and Recommendations for Management

Immunosuppressant	Statin	Effect	Magnitude	Recommendation
Cyclosporine/ tacrolimus/everolimus/ sirolimus*	Atorvastatin	Increased statin exposure through multiple mechanisms. Increased risk for muscle-related toxicity.	Severe 6- to 15-fold increase in AUC of atorvastatin	Limit dose of atorvastatin to 10 mg daily
	Rosuvastatin		Severe 7-fold increase in AUC of rosuvastatin	Limit dose of rosuvastatin to 5 mg daily
	Pravastatin		Severe 5- to 10-fold increase in AUC of pravastatin	Limit dose of pravastatin to 40 mg daily
	Fluvastatin		Moderate 2- to 4-fold increase in AUC of fluvastatin	Limit dose of fluvastatin 40 mg daily
	Simvastatin		Severe 6- to 8-fold increase in AUC of simvastatin	Avoid combination
	Lovastatin		Severe 5- to 20-fold increase in AUC of lovastatin	Avoid combination
	Pitavastatin		Severe 5-fold increase in AUC of pitavastatin	Avoid combination

Magnitude of drug-drug interactions based on AUC increase: minor, >1.25 to <2; moderate, ≥2 to 4.9; and severe, ≥5.
*Changes in magnitude of statin AUC are reported with cyclosporine. Limited data exist with tacrolimus, everolimus, and sirolimus.
AUC indicates area under the curve.
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7. PATIENT FOLLOW-UP: MONITORING AND MANAGING SYMPTOMS

7.1. Follow-Up Plan and Testing in Stable Patients

Recommendations for Follow-Up Plan and Testing in Stable Patients Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	Recommendations
2b	B-R	1. In stable patients with CCD and with previous ACS or coronary revascularization, referral to telehealth programs, community-based programs, or both for lifestyle interventions may be reasonable as an adjunct to usual care to improve management of cardiovascular risk factors.[1–7]
3: No benefit	B-R	2. In patients with CCD without a change in clinical or functional status on optimized GDMT, routine periodic testing with coronary CTA or stress testing with or without imaging is not recommended to guide therapeutic decision-making.[8–10]
3: No benefit	B-R	3. In patients with CCD without a change in clinical or functional status, routine periodic reassessment of LV function is not recommended to guide therapeutic decision-making.[11,12]
3: Harm	B-NR	4. In patients with CCD without a change in clinical or functional status, routine periodic invasive coronary angiography should not be performed to guide therapeutic decision-making.[13–17]

Synopsis

Patients with CCD are at elevated risk for future MACE and should be observed periodically in the outpatient setting.[18,19] Central components of the management of patients with CCD include long-term risk factor modification and active management of GDMT to achieve maximally tolerated doses,[20] with shared decision-making involving effective communication between cardiologists, primary, and specialty care teams (see Section 4.1, "General Approach to Treatment Decisions," Section 4.1.1, "Team-Based Approach," Section 4.1.2, "Patient Education," and Section 4.1.4, "Social Determinants of Health").[21–23] Over the past 2 decades, rates of MACE in patients with CCD have declined, and contemporary studies suggest overall low event rates in patients with CCD on GDMT, especially in the absence of anginal symptoms.[19,24] After index diagnostic evaluation, treatment, and optimization of lifestyle and medical interventions, follow-up testing should be reserved for instances when there has been a significant change in symptom and/or clinical status. Periodic recording of the standard resting 12-lead ECG in patients with CCD may provide a baseline waveform against which future tracings taken during symptoms may be reasonably compared to avoid overdiagnosis of a change in clinical status.[14,15] Patients with CCD who have accelerating symptoms or decreasing functional capacity despite optimized GDMT should undergo assessment as per Section 3 ("Evaluation, Diagnosis, and Risk Stratification"). Recommendations regarding CR can be found in Section 4.2.10.

Recommendation-Specific Supportive Text

1. A Dutch multicenter trial randomized 374 adults <8 weeks after hospitalization for ACS to usual care plus telehealth coaching with the lifestyle intervention "Hartcoach" every 4 weeks versus usual care alone.[1] After 6 months of follow-up, patients randomized to Hartcoach had modest improvement in BMI, waist circumference, physical activity, intake of vegetables, self-management, and anxiety. An Australian trial randomized 430 adults with previous MI to a telephone-delivered 6-month secondary prevention program ("Proactive Heart") versus usual care.[2] Patients in the intervention group had significantly improved health outcomes as assessed by health-related QOL and physical activity surveys, including anxiety outcomes.[3] A subsequent randomized trial of 121 adults found that a 6-month telehealth program (MoodCare) improved depression scores in patients post-ACS compared with usual care,[4] and effects persisted at 1-year follow-up in those with major depressive disorder.[5] In the RESPONSE-2 (Ruxolitinib Efficacy and Safety in Patients with HU Resistant or Intolerant Polycythemia Vera versus Best Available Therapy) trial, nurse-coordinated referral of 711 patients with previous ACS, coronary revascularization, or both and their partners to 3 widely available community-based lifestyle programs in 15 hospitals in the Netherlands led to significant improvements in lifestyle-related factors.[6] Text messaging interventions may[7] or may not[25,26] be beneficial. The cost-effectiveness of such approaches remains uncertain.[27]
2. The evidence base surrounding the long-term prognosis and appropriate management of the spectrum of contemporary patients with CCD is evolving. Routine periodic anatomic or ischemic testing in asymptomatic, nonsedentary patients is not recommended. Limited data are available to guide management of asymptomatic patients with CCD on GDMT who receive functional or anatomic testing and have a positive result. In the ISCHEMIA trial, 5179 patients with stable CAD and site-determined moderate-severe ischemia on stress testing were randomized to invasive versus conservative care strategies, with no difference in the composite primary MACE endpoint at 3.3 years of follow-up.[8] Only patients presenting with daily, weekly, or monthly angina experienced prompt and durable improvement in symptoms

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when randomized to invasive compared with conservative management.[28] In the CLARIFY (Prospective Observational Longitudinal Registry of Patients with Stable Coronary Artery Disease) registry of 32 105 outpatients with CCD across 45 countries, anginal symptoms during noninvasive testing, but not silent ischemia, were associated with increased risk of MACE, including cardiovascular death or nonfatal MI.[9] Recently, the multicenter, POST-PCI (Pragmatic Trial Comparing Symptom-Oriented versus Routine Stress Testing in High-Risk Patients Undergoing Percutaneous Coronary Intervention) RCT compared a strategy of routine functional stress testing (using exercise ECG with or without nuclear myocardial perfusion imaging or stress echocardiography) versus standard care alone 12 months after successful PCI in 1706 high-risk patients. At 2 years of follow-up, no differences were observed between groups in the primary endpoint of composite death, MI or hospitalization for unstable angina.[10]

3. Routine, periodic reassessment of LV function in asymptomatic patients without a change in functional status or clinical intervention is not recommended.[11] In a post-hoc analysis of the RCT MASS II in which patients with multivessel CCD treated by CABG, PCI, or medial therapy underwent evaluation of LVEF before randomization and after 10 years of follow-up (n=350), LVEF was stable over long-term follow-up in the absence of MACE.[12]
4. Asymptomatic patients in the ISCHEMIA trial did not derive a benefit when randomized to invasive compared with conservative management.[8,28] Routine follow-up invasive coronary angiography has been associated with increased revascularization of nonischemic intermediate lesions without an improvement in rates of subsequent cardiac death or MI.[16,17] The ReACT (Randomized Evaluation of Routine Follow-up Coronary Angiography after PCI) trial was a prospective multicenter open-label trial in Japan in which 700 patients were randomized to receive routine follow-up coronary angiography 8 to 12 months after PCI versus clinical follow-up alone.[14] During median follow-up of 4.6 years, no clinical benefit was seen for routine follow-up coronary angiography despite increased early coronary revascularization rates. Routine angiographic follow-up after PCI in patients with diabetes was associated with an increased incidence of revascularization and MACE without a change in death or reinfarction rates.[29] In a contemporary Danish registry of patients with CCD, revascularization in those without ischemia conferred a higher risk of death and MI versus medical therapy alone.[15]

8. OTHER IMPORTANT CONSIDERATIONS

8.1. Cost and Value Considerations

Recommendation for Cost and Value Considerations
Referenced studies that support the recommendation are summarized in the Online Data Supplement.

COR	LOE	Recommendation
1	B-NR	1. When discussing treatment and prevention with patients who have CCD, it is recommended that the health care team discuss out-of-pocket costs for medications at the time of initiating a new medication and at least annually thereafter to preempt cost-related nonadherence.[1–6]

Synopsis

Some new CCD therapies are only available as branded formulations, and their high out-of-pocket costs can impede adoption or increase the risk of cost-related nonadherence.[1,2] High out-of-pocket costs is a frequently cited reason for patients foregoing medications, delaying a prescription refill, or skipping or reducing medication doses.[3] The use of high-cost therapies in a large number of eligible patients increases pharmaceutical spending, which, in the long term, gets passed to the patient in the form of higher insurance premiums (in the case of private insurance) and to the taxpayer in the form of higher taxes (in the case of public insurance). Therefore, clinicians have a key role in ensuring access and adherence to effective therapies by regularly discussing out-of-pocket costs with their patients with CCD as a part of shared decision-making, using lower-cost alternatives when available, and guiding health systems to adopt cost-effective therapies when >1 alternative is appropriate (ie, choosing therapies that require lower incremental spending to generate 1 additional unit of health and meet conventional cost-effectiveness thresholds). For Level of Value Considerations, refer to Table 1. Refer also to the lipid management, SGLT2, and revascularization sections (4.2.6, 4.2.8, and 5.1) for applicable cost-value considerations.

Recommendation-Specific Supportive Text

1. One in 8 persons with CVD in the United States reports cost-related medication nonadherence.[3] Patients may be responsible for hundreds of dollars in out-of-pocket costs for their prescriptions, which can be a barrier to initiating or continuing an effective therapy.[1,2] Most patients report a desire to discuss out-of-pockets with their clinicians, particularly when considering a new therapy.[4–6] Clinicians and their support team should familiarize themselves with out-of-pocket costs for commonly prescribed drugs but recognize that these may vary among patients by benefit design, time of year (eg, whether the annual deductible has been met), and concurrent medications. Clinicians

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or their care support team should identify the best source of out-of-pocket costs in their health systems; in some cases, information may be readily available in the electronic health record at the point of order entry, but in others, clinicians may have to order "test prescriptions" to ascertain coverage. Clinicians or their care support team should review each patient's out-of-pocket costs when starting a new medication and periodically thereafter. Shared decision-making (Section 4.1.3) with patients is paramount because affordability may vary substantially based on the patient's socioeconomic status (Section 4.1.4, "Social Determinants of Health"). Clinicians or their care support team should inform patients of cost-saving approaches such as the use of mail order pharmacies or patient assistance programs or consider lower-cost alternatives when appropriate.

8.2. Evidence Gaps and Areas of Future Research Needs

Although the past decade has seen numerous advancements in the diagnosis and treatment of patients with CCD, several gaps still exist in our understanding. These gaps should serve as areas of future research and are described below.

- With an evolving definition of patients who have CCD, research is needed to determine how advances in noninvasive imaging technology (ie, allowing sensitive detection and quantification of calcified and noncalcified atherosclerotic plaque burden) may affect identification of patients with CCD, their prognostication, and their eligibility for preventive therapies.
- Comprehensive risk scores need to be developed and validated for MACE in patients with CCD in the contemporary era that include patient demographics, medical information, social determinants, and data from noninvasive test results, or invasive test results, or both.
- Although studies have shown deficiencies with clinician-estimation of patient's symptoms, research is needed to understand whether routine use of patient-reported measures in clinical care improve patient-centered outcomes.
- Decision aids that are tested and validated in diverse populations are needed to support shared decision-making in patients with CCD.
- High-quality studies are needed to assess the effect of various substances, including marijuana, on cardiovascular outcomes in patients with CCD.
- With several therapies available to treat symptoms or improve outcomes in patients with CCD, research is needed on how to sequence GDMT in patients with CCD (ie, how to judge relative importance of different components of GDMT in specific patients).
- Randomized trials with longer-term cardiovascular outcomes are needed to determine the effectiveness of interventions that limit sedentary time.
- Research is needed to understand whether the efficacy of therapies used in patients with CCD is uniform across men and women with CCD and across various racial and ethnic groups of patients with CCD that have traditionally been underrepresented in clinical trials.
- Further research is needed to assess the use of personalized medicine approaches, including the assessment of the use of artificial intelligence, text messaging, wearable technology, genomics, and proteomics to improve risk assessment and treatment approaches in diverse populations of patients with CCD.
- Additional research is needed to assess the effect of hybrid CR, as well as home-based CR, on longer-term clinical outcomes and on outcomes for various population subgroups, including women, older adults, and those from underrepresented racial and ethnic groups.
- Future research is needed on patients with CCD on the long-term effect of treatment of mental health conditions (namely depression): (1) patients with a previous (known) diagnosis of mental health condition and concomitant CCD, or (2) patients with a new diagnosis of a mental health condition after MI.
- Future research is needed on the long-term risk of e-cigarette use on cardiovascular health in patients with CCD.
- Further research is needed on whether there is utility for the use of GLP-1 receptor agonists in patients with CCD but not type 2 diabetes for cardiovascular risk reduction. Research is also needed to determine whether there is utility for the combined use of SGLT2 inhibitors and GLP-1 receptor agonists in patients with CCD.
- Further research is needed on the optimal antiplatelet regimen choices for patients with CCD who are 1 year post-MI or PCI.
- Further research is needed on what is the optimal antithrombotic strategy in patients with CCD and atrial fibrillation.
- In patients with CCD and refractory angina, research is needed to assess the utility of neuromodulation and thoracic spinal cord stimulation, therapeutic angiogenesis with cell/gene therapies, coronary sinus occlusion, and shockwave therapy.
- Additional research is needed in populations with SCAD to determine optimal pharmacological management strategy after SCAD and the potential impact of vasculopathy screening on future cardiovascular outcomes.
- As climate change–related extreme environmental events become more severe and more intense,

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high-quality research is needed to examine whether preventative strategies—such as indoor air purifiers and N95 masks during periods of substantial wildfire smoke exposure or public spaces with air-conditioning during extreme heat—are protective in patients with CCD who are at increased risk of cardiovascular events.

- Research is needed to explore how to best integrate SDOH into electronic health records to enable practitioners to coordinate care for patients with CCD challenged with health inequities.
- Although some electronic health records allow estimation of patient out-of-pocket costs for medications, testing, and treatments, more work is needed in development and dissemination of tools to allow clinicians to determine patient costs accurately at the point of care.
- Research is needed to determine whether GDMT is associated with improved outcomes in older adults with CCD or patients with CCD on hemodialysis.
- Studies are needed to assess which interventions lead to effective guideline implementation in clinical practice. Similarly, research is needed to assess the effect of a new guideline release at the patient, clinic, hospital, health care systems, and the community levels.

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ARTICLE INFORMATION

This document was approved by the American College of Cardiology Clinical Policy Approval Committee and the American Heart Association Science Advisory and Coordinating Committee in January 2023, and the American College of Cardiology Science and Quality Committee and the American Heart Association Executive Committee in April 2023.

Supplemental Materials are available with this article at https://www.ahajournals.org/doi/suppl/10.1161/CIR.0000000000001168

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This article has been copublished in the *Journal of the American College of Cardiology*.

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Appendix 1. Author Relationships With Industry and Other Entities–2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Salim S. Virani, Chair	*(Effective February 2023)* Aga Khan University–Vice Provost, Research; Texas Heart Institute–Professional Staff *(Until February 2023)* Baylor College of Medicine–Professor, Cardiovascular Fellowship Program Director; Michael E. DeBakey VA Medical Center for Cardiovascular Disease Prevention (Clinic)–Staff Cardiologist/ Co-Director, VA Advanced Fellowship Program in Health Services Research & Development	None	None	None	NOT RELEVANT • NIH/FIC (DSMB) • Tahir and Jooma Family* • US Department of VA*	NOT RELEVANT • ACC* • ACC.org, Associate Editor for Innovations and Editorial lead, and Editorial lead for Prevention topic collection • ASPC • *Circulation*, Guest Editor • Current Atherosclerosis Reports, Current Cardiology Reports, Section Editor • *Journal of Clinical Lipidology*, Associate Editor • NIH* • NAACME • NLA • Tabba Heart Institute, Steering Committee Member, PAK-SEHAT • WHF†	None
L. Kristin Newby, Vice Chair	Duke University–Professor of Medicine, Division of Cardiology and Duke Clinical Research Institute	RELEVANT • CSL Behring • Medtronic* NOT RELEVANT • Beckman Coulter • NHLBI • NC DHHS	None	None	RELEVANT • Boehringer-Ingelheim NOT RELEVANT • David H. Murdock Institute for Business and Culture • NIH* • NIH (DSMB)† • North Carolina DHHS* • Roche Diagnostics*	NOT RELEVANT • ACC† • AHA† • *American Heart Journal*, Editorial Board† • AstraZeneca Healthcare Foundation† • David H. Murdock Research Institute† • *European Heart Journal-Acute Cardiovascular Care*, Editorial Board† • *JACC Basic Transl Sci* • WHF†	None
Suzanne V. Arnold	St. Luke's Mid America Heart Institute University of Missouri-Kansas City–Professor of Medicine	None	None	None	None	NOT RELEVANT • *Heart*, Associate Editor	None
Vera Bittner	University of Alabama at Birmingham, Division of Cardiovascular Disease–Professor of Medicine; Endowed Scholar in Cardiovascular Disease Prevention; Section Head General Cardiology, Prevention, and Imaging	RELEVANT • Pfizer NOT RELEVANT • ACC*	None	None	RELEVANT • Amgen • Novartis* NOT RELEVANT • Verve Therapeutics (DSMB)	RELEVANT • AstraZeneca* • Dalcor* • Esperion* • Sanofi-Aventis* NOT RELEVANT • AHA* • ACC* • Medscape • NLA	None
LaPrincess C. Brewer	Mayo Clinic–Assistant Professor of Medicine, Preventive Cardiology	None	None	None	NOT RELEVANT • AHA, AHA EPI, Presidential Advisory, SDOH† • NIH • CDC	NOT RELEVANT • ABC† • ACC† • *American Journal of Preventive Cardiology*, Editorial Board • *JAMA*, Editorial Board • Current CV Risk Reports, Section Editor	None
Susan Halli Demeter	Mayo Clinic Arizona–Assistant Professor of Medicine Heart Health & Performance Program Lipid Clinic	None	NOT RELEVANT • Integrity • National Lipid Association/ Paradigm Medical Communication	None	None	NOT RELEVANT • Amgen‡ • Ionis Pharmaceuticals/ Medpace‡ • NLA • PCNA†	None

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Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Dave L. Dixon	Virginia Commonwealth University School of Pharmacy–Associate Professor and Department Chair, Department of Pharmacotherapy & Outcome Science	NOT RELEVANT • APhA	None	None	RELEVANT • Boehringer Ingelheim* NOT RELEVANT • Board of Pharmacy Specialties • CDC* • NIH • Mercatus*	NOT RELEVANT • ACC • ACCP, Cardiology Practice Research Network† • Accreditation Council for Clinical Lipidology† • AHA • Diabetes/Metabolism: Research and Reviews, Editorial Board • *Journal of Cardiovascular Pharmacology* • *Journal of Clinical Lipidology*, Associate Editor† • Medscape • NLA† • PCORI	None
William F. Fearon	Stanford University/ VA Palo Alto Healthcare System–Professor of Medicine	RELEVANT • CathWorks • Siemens NOT RELEVANT • ACC • Gentuity, LLC*	None	None	RELEVANT • Abbott† • Boston Scientific† • Edwards Lifesciences† • Medtronic† NOT RELEVANT • NIH	NOT RELEVANT • *Circulation*, Editorial Board • *Circulation: Cardiovascular Interventions*, Editorial Board • HeartFlow • *International Journal of Cardiology*, Editorial Board • *JACC*, Editorial Board • McGraw Hill • Neovasc Medical Inc. • Stanford University, Abbott‡ • Stanford University, Medtronic‡ • Zoll	None
Beverly Hess	Microsoft–Senior Director (Retired)	None	None	None	None	NOT RELEVANT • AHA Women of Impact, Nominee • AHA, Established Investigators Award Peer Review Panel	None
Heather M. Johnson	Christine E. Lynn Women's Health & Wellness Institute, Department of Preventive Cardiology Boca Regional Hospital; Baptist Health South Florida–Clinical Affiliate; Florida Atlantic University–Associate Professor; University of Wisconsin-Madison–Adjunct Associate Professor	NOT RELEVANT • Best Doctors Advisory Panel • M3 Global Research	NOT RELEVANT • ASPC • Medtelligence† • WomenHeart	None	NOT RELEVANT • NIH*	NOT RELEVANT • AHA • *American Journal of Preventive Cardiology*, Editorial Board† • Applied Radiology† • ASPC† • CureMetrix† • Esperion • NIH	None
Dhruv S. Kazi	Harvard Medical School–Associate Professor; Beth Israel Deaconess Medical Center–Director, Cardiac Critical Care; Smith Center for Outcomes Research–Associate Director	None	None	None	NOT RELEVANT • Harvard Medical School-Institutional Grant, Boston Scientific*	NOT RELEVANT • AHA† • Bayer • *Circulation: Cardiovascular Quality and Outcomes* • Harvard Global Health Institute • Institute for Clinical Economic Review • Lahey Medical Center, Grand Rounds • NIH/NHLBI • Stanford University, Grand Rounds	None
Dhaval Kolte	Massachusetts General Hospital and Harvard Medical School–Instructor in Medicine Department of Medicine, Cardiology Division	None	None	None	None	NOT RELEVANT • *AHJ*, Editorial Board • ACC† • AHA† • Biotronik • Medtronic • NIH • SCAI†	None

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Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Dharam J. Kumbhani	UT Southwestern Medical Center–Associate Professor of Medicine and Section Chief, Interventional Cardiology William Clements University Hospital–Cath Lab Director	NOT RELEVANT • ACC*	None	None	NOT RELEVANT • PCORI	NOT RELEVANT • *Circulation*, Associate Editor*	None
Jim LoFaso	Engineer (Retired)	None	None	None	None	NOT RELEVANT • AHA†	None
Dhruv Mahtta	Baylor College of Medicine–Cardiology Fellow, Department of Medicine, Division of Cardiovascular Disease	None	None	None	None	NOT RELEVANT • *AHJ*, Editor • AstraZeneca • *JAHA*, Editor • Chiesi • *Current Cardiology*, Section Editor • Current Atherosclerosis, Section Editor	None
Daniel B. Mark	Duke University Medical Center–Professor of Medicine; Vice Chief for Academic Affairs Division of Cardiology, Department of Medicine	RELEVANT • Novartis	None	None	RELEVANT • Merck*	RELEVANT • Merck* NOT RELEVANT • *AHJ*, Editor • Elsevier* • Heartflow* • NIH*	NOT RELEVANT • Defendant, Arrhythmia issues, 2020 • Defendant, Acute SOP/CP, 2020 • Defendant, Respiratory Arrest, 2020 • Workers' Compensation Issues, 2020
Margo Minissian	Cedars-Sinai–Executive Director, Geri and Richard Brawerman Nursing Institute; Simms/ Mann Family Foundation Endowed Chair in Nurse Education, Innovation and Research and Assistant Professor, Department of Cardiology	NOT RELEVANT • Medtelligence* • MJH Lifesciences • North American Center for CME, LLC* • Vox Media	None	None	NOT RELEVANT • NIH* • NIHF*	NOT RELEVANT • Brawerman Nursing Institute, Endowed Chair† • NLA • Novo Nordisk • NAMS • MJH Life Sciences, LLC	None
Ann Marie Navar	UT Southwestern Medical Center–Associate Professor of Medicine Department of Medicine, Division of Cardiology	RELEVANT • AstraZeneca* • Amgen* • Bayer* • Boehringer Ingelheim* • Bristol Myers Squibb* • CSL Behring* • Eli Lily and Company • Novartis* • NovoNordisk* • Pfizer* • Janssen Pharmaceutical • New Amsterdam Pharmaceutical NOT RELEVANT • Cerner Corporation	RELEVANT • Vindico	None	RELEVANT • Bristol Myers Squibb* • Esperion* • Janssen Pharmaceuticals • Novartis* • Amgen*	NOT RELEVANT • ACC • AHA • *AHJ* • *American Journal of P reventive Cardiology* • American Society for Preventive Cardiology • Asia Pacific Society of Cardiology • CardioNerds† • *JAMA Cardiology* • NHLBI • NIH • National Forum for Heart Disease & Stroke Prevention	None

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Amit R. Patel	*(Effective January 2022)* University of Virginia Health System–Professor of Medicine; Director, Noninvasive Cardiac Imaging Cardiovascular Division *(through 12/2021)* University of Chicago–Associate Professor; Director Cardiac MRI and CT, Department of Medicine and Radiology	None	NOT RELEVANT • General Electric	None	NOT RELEVANT • Arterys† • ASE* • Circle CVI† • General Electric* • *Journal of Cardiovascular Magnetic Resonance*† • Neosoft† • NIH† • Philips* • Society of Cardiovascular Magnetic Resonance† • Society of Cardiovascular Computed Tomography	NOT RELEVANT • ACC • Amgen • APCA† • Apple* • AstraZeneca • General Electric* • Novartis • Pfizer • Smith & Nephew • The Very Good Food Company, Inc.*	None
Mariann R. Piano	Vanderbilt University School of Nursing–Nancy and Hilliard Travis Professor of Nursing Senior Associate Dean for Research	None	None	None	None	None	None
Fatima Rodriguez	Stanford University School of Medicine–Associate Professor, Section Chief of Preventive Cardiology	RELEVANT • Amgen • Novartis NOT RELEVANT • HealthPals* • Medscape	None	NOT RELEVANT • Carta†	NOT RELEVANT • AHA • NIH	RELEVANT • AstraZeneca NOT RELEVANT • ACC • AHA • *Cardiology and Therapy*, Associate Editor • Medscape • *NEJM Journal Watch Cardiology*, Associate Editor • Novo Nordisk, CEAC*	None
Amy W. Talbot§	American Heart Association/American College of Cardiology Science and Health Advisor, Guidelines	None	None	None	None	None	None
Viviany R. Taqueti	Brigham and Women's Hospital; Harvard Medical School–Director, Cardiac Stress Laboratory	None	None	None	NOT RELEVANT • DOD, Warrior Trial (DSMB)	RELEVANT • Abbott • Broadview Ventures* NOT RELEVANT • ACC • Genetesis • NIH • ASNC, Board Member • NASEM, Committee Member, Identifying New/Improved Diagnostic & Evaluative Teachniques	None
Randal J. Thomas	Mayo Clinic–Professor, Department of Cardiovascular Medicine, Division of Preventive Cardiology	None	None	None	NOT RELEVANT • NHLBI† • NINR†	NOT RELEVANT • AACVPR • AHA • *JRCP*†	None
Sean van Diepen	University of Alberta, Edmonton, Alberta, Canada–Associate Professor, Department of Critical Care Medicine and Division of Cardiology, Department of Medicine	None	None	None	None	NOT RELEVANT • *AHJ* • *Canadian Journal of Cardiology* • *European Heart Journal of Cardiovascular Care* • *JACC Adv.* Sr. Consulting Editor	None

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Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Barbara Wiggins	South Carolina College of Pharmacy–Affiliate Professor Medical University of South Carolina– Clinical Pharmacy Specialist-Cardiology	NOT RELEVANT • LexiComp	None	None	None	NOT RELEVANT • ACC† • *American Journal of Cardiovascular Drugs*, Editorial Board† • PERT Consortium Clinical Protocols Committee† • scPharmaceuticals, (Salaried Employee)	None
Marlene S. Williams	Johns Hopkins Medical Institution Bayview Medical Center–Associate Professor of Medicine, Clinical Director of Cardiology Division of Cardiology, Department of Medicine	NOT RELEVANT • Haemonetics	NOT RELEVANT • National Association for Continuing Education	None	None	NOT RELEVANT • ABC • ACC† • AHA • *American Journal of Cardiovascular Drugs*† • PERT Consortium†	None

This table represents all relationships of committee members with industry and other entities that were reported by authors, including those not deemed to be relevant to this document, at the time this document was under development. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥$5000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. Please refer to https://www.acc.org/guidelines/about-guidelines-and-clinical-documents/relationships-with-industry-policy for definitions of disclosure categories or additional information about the ACC/AHA Disclosure Policy for Writing Committees.

*Significant relationship.

†No financial benefit.

‡This disclosure was entered under the Clinical Trial Enroller category in the ACC's disclosure system. To appear in this category, the author acknowledges that there is no direct or institutional relationship with the trial sponsor as defined in the (ACCF or AHA/ACC) Disclosure Policy for Writing Committees.

§Amy Talbot is an AHA/ACC joint staff member and acts as the Science and Health Advisor for the "2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease." No relevant relationships to report. Nonvoting author on measures and not included/counted in the RWI balance for this writing committee.

AACVPR indicates American Association of Cardiovascular and Pulmonary Rehabilitation; AATS, American Association for Thoracic Surgery; ABC, Association of Black Cardiologists; ACC, American College of Cardiology; ACCF, American College of Cardiology Foundation; ACCP, American College of Clinical Pharmacy; AHA, American Heart Association; *AHJ, American Heart Journal*; APCA, Alliance for Physician Certification and Advancement; APhA, American Pharmacists Association; ASE, American Society of Echocardiography; ASNC, American Society of Nuclear Cardiology; ASPC, American Society of Preventive Cardiology; CDC, US Centers for Disease Control and Prevention; CEAC, Clinical Event Adjudication Committee; CME, continuing medical education; DHHS, US Department of Health and Human Services; DOD, US Department of Defense; DSMB, data and safety monitoring board; ESC, European Society of Cardiology; FIC, Fogarty International Center; *JACC, Journal of the American College of Cardiology; JAMA, Journal of the American Medical Association; JCRP, Journal of Cardiopulmonary Rehabilitation*; NACCME, North American Center for Continuing Medical Education; NAMS, North American Menopause Society; NASEM, National Academies of Sciences, Engineering and Medicine; *NEJM, New England Journal of Medicine*; NHLBI, National Heart, Lung, and Blood Institute; NIH, National Institutes of Health; NLA, National Lipid Association; NINR, National Institute of Nursing Research; PAK-SEHAT, joint collaboration with Getz Pharma and Tabba Heart Institute; PCNA, Preventive Cardiovascular Nurses Association; PCORI, Patient-Centered Outcomes Research Institute; PERT, Pulmonary Embolism Response Team; SCAI, Society for Cardiovascular Angiography and Interventions; UT, University of Texas, VA, Veterans Affairs; WCC, World Congress of Cardiology; and WHF, World Heart Federation.

Appendix 2. Reviewer Relationships With Industry and Other Entities–2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
H. Vernon Anderson	AHA/ACC Chronic Coronary Disease Guideline Peer Review Committee Chair	The University of Texas Health Science Center at Houston	• ACE	None	None	None	None	None
Sunil V. Rao	AHA/ACC Chronic Coronary Disease Guideline Peer Review Committee Vice Chair	New York University	None	None	None	• NHLBI	• NHLBI‡	• Defendant, Cardiac catheterization, 2021
Columbus Batiste II	AHA/ACC Chronic Coronary Disease Peer Review Committee	Kaiser Permanente Riverside and Moreno Valley Medical Centers	None	None	None	None	None	None
Roger Blumenthal	AHA/ACC Chronic Coronary Disease Peer Review Committee	Johns Hopkins University	None	None	None	None	None	None

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Appendix 2. Continued

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Matthew A. Cavender	AHA/ACC Chronic Coronary Disease Peer Review Committee	UNC School of Medicine	• Amgen • Bayer* • Medtronic* • Novo Nordisk* • Zoll	None	None	• Amgen† • Boehringer Ingelheim* • CSL Behring†	• Boston Scientific‡ • Edwards‡ • Novo Nordisk‡	• Third party, medical necessity, 2022*
Anne Carol Goldberg	AHA/ACC Chronic Coronary Disease Peer Review Committee, representing NLA	Washington University School of Medicine	• Akcea • Ionis* • Novartis • Regeneron	• ACC • NLA*		• Amgen* • Arrowhead Pharmaceuticals* • Esperion* • Ionis* • New Amsterdam* • Novartis* • Regeneron* • Sanofi-Aventis*	• ABIM • AHA† • Esperion† • Ionis, TIMI, Lead coordinator, Triglyceride study* • New Amsterdam, National Coordinator for Brooklyn Study* • NLA Foundation† • NLA* • The FH Foundation	None
Cynthia Jackevicius	AHA/ACC Chronic Coronary Disease Peer Review Committee, representing ACCP	Western University of Health Sciences	None	None	None	• CIHR • *Circulation: Cardiovascular Quality and Outcomes*	• AHA • Western University of Health Sciences*	None
Friederike K. Keating	AHA/ACC Chronic Coronary Disease Peer Review Committee	University of Vermont Medical Center	None	None	None	None	• ASNC† • NHLBI‡ • University of Vermont Health Center†	None
Thomas S. Metkus	AHA/ACC Chronic Coronary Disease Peer Review Committee	Johns Hopkins University School of Medicine	• BestDoctors-Telehealth* • McGraw-Hill* • Nova Biomedical • Oakstone-Ebix*	None	None	None	None	None
Leslee J. Shaw	AHA/ACC Chronic Coronary Disease Peer Review Committee	Mount Sinai	None	None	None	None	None	None
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*Significant relationship.

†No financial benefit.

‡This disclosure was entered under the Clinical Trial Enroller category in the ACC's disclosure system. To appear in this category, the author acknowledges that there is no direct or institutional relationship with the trial sponsor as defined in the (ACCF or AHA/ACC) Disclosure Policy for Writing Committees.

ABIM indicates American Board of Internal Medicine; ACC, American College of Cardiology; ACCF, American College of Cardiology Foundation; ACCP, American College of Clinical Pharmacy; ACE, Accreditation for Cardiovascular Excellence; AHA, American Heart Association; ASNC, American Society of Nuclear Cardiology; ASPC, American Society of Preventive Cardiology; CIHR, Canadian Institutes of Health Research; DCRI, Duke Clinical Research Institute; FH, Family Heart; NHLBI, National Heart, Lung, and Blood Institute; NLA, National Lipid Association; PCNA, Preventive Cardiovascular Nurses Association ; STS, Society of Thoracic Surgery; TIMI, Thrombolysis in Myocardial Infarction; and UNC, University of North Carolina.

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AHA/ACC CLINICAL PRACTICE GUIDELINE

2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

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AIM: This clinical practice guideline for the evaluation and diagnosis of chest pain provides recommendations and algorithms for clinicians to assess and diagnose chest pain in adult patients.

METHODS: A comprehensive literature search was conducted from November 11, 2017, to May 1, 2020, encompassing randomized and nonrandomized trials, observational studies, registries, reviews, and other evidence conducted on human subjects that were published in English from PubMed, EMBASE, the Cochrane Collaboration, Agency for Healthcare Research and Quality reports, and other relevant databases. Additional relevant studies, published through April 2021, were also considered.

STRUCTURE: Chest pain is a frequent cause for emergency department visits in the United States. The "2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain" provides recommendations based on contemporary evidence on the assessment and evaluation of chest pain. This guideline presents an evidence-based approach to risk stratification and the diagnostic workup for the evaluation of chest pain. Cost-value considerations in diagnostic testing have been incorporated, and shared decision-making with patients is recommended.

Key Words: AHA Scientific Statements ■ chest pain ■ angina ■ coronary artery disease ■ acute coronary syndrome ■ myocardial ischemia ■ myocardial infarction ■ myocardial injury ■ noncardiac ■ accelerated diagnostic pathway ■ clinical decision pathway ■ sex differences ■ troponins ■ chest pain syndromes ■ biomarkers ■ shared decision-making ■ noncardiac chest pain ■ cardiac imaging

*Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry may apply; see Appendix 1 for detailed information. †ACC/AHA Representative. ‡ACC/AHA Joint Committee on Clinical Practice Guidelines Liaison. §Society of Cardiovascular Computed Tomography Representative. ‖Lay Patient Representative. ¶Society for Academic Emergency Medicine Representative. #Former ACC/AHA Joint Committee member; current member during the writing effort. **Society for Cardiovascular Magnetic Resonance Representative. ††American College of Chest Physicians Representative. ‡‡American Society of Echocardiography Representative. §§Task Force on Performance Measures, Liaison.

ACC/AHA Joint Committee on Clinical Practice Guidelines Members, see page e420.

The American Heart Association requests that this document be cited as follows: Gulati M, Levy PD, Mukherjee D, Amsterdam E, Bhatt DL, Birtcher KK, Blankstein R, Boyd J, Bullock-Palmer RP, Conejo T, Diercks DB, Gentile F, Greenwood JP, Hess EP, Hollenberg SM, Jaber WA, Jneid H, Joglar JA, Morrow DA, O'Connor RE, Ross MA, Shaw LJ. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guideline for the evaluation and diagnosis of chest pain: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2021;144:e368–e454. doi: 10.1161/CIR.0000000000001029

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TOP 10 TAKE-HOME MESSAGES FOR THE EVALUATION AND DIAGNOSIS OF CHEST PAIN

1. **Chest Pain Means More Than Pain in the Chest.** Pain, pressure, tightness, or discomfort in the chest, shoulders, arms, neck, back, upper abdomen, or jaw, as well as shortness of breath and fatigue should all be considered anginal equivalents.
2. **High-Sensitivity Troponins Preferred.** High-sensitivity cardiac troponins are the preferred standard for establishing a biomarker diagnosis of acute myocardial infarction, allowing for more accurate detection and exclusion of myocardial injury.
3. **Early Care for Acute Symptoms.** Patients with acute chest pain or chest pain equivalent symptoms should seek medical care immediately by calling 9-1-1. Although most patients will not have a cardiac cause, the evaluation of all patients should focus on the early identification or exclusion of life-threatening causes.
4. **Share the Decision-Making.** Clinically stable patients presenting with chest pain should be included in decision-making; information about risk of adverse events, radiation exposure, costs, and alternative options should be provided to facilitate the discussion.
5. **Testing Not Needed Routinely for Low-Risk Patients.** For patients with acute or stable chest pain determined to be low risk, urgent diagnostic testing for suspected coronary artery disease is not needed.
6. **Pathways.** Clinical decision pathways for chest pain in the emergency department and outpatient settings should be used routinely.
7. **Accompanying Symptoms.** Chest pain is the dominant and most frequent symptom for both men and women ultimately diagnosed with acute coronary syndrome. Women may be more likely to present with accompanying symptoms such as nausea and shortness of breath.
8. **Identify Patients Most Likely to Benefit From Further Testing.** Patients with acute or stable chest pain who are at intermediate risk or intermediate to high pre-test risk of obstructive coronary artery disease, respectively, will benefit the most from cardiac imaging and testing.
9. **Noncardiac Is In. Atypical Is Out.** "Noncardiac" should be used if heart disease is not suspected. "Atypical" is a misleading descriptor of chest pain, and its use is discouraged.
10. **Structured Risk Assessment Should Be Used.** For patients presenting with acute or stable chest pain, risk for coronary artery disease and adverse events should be estimated using evidence-based diagnostic protocols.

Figure 1 illustrates the take-home messages.

PREAMBLE

Since 1980, the American College of Cardiology (ACC) and American Heart Association (AHA) have translated scientific evidence into clinical practice guidelines with recommendations to improve cardiovascular health. These guidelines, which are based on systematic methods to evaluate and classify evidence, provide a foundation for the delivery of quality cardiovascular care. The ACC and AHA sponsor the development and publication of clinical practice guidelines without commercial support, and members volunteer their time to the writing and review efforts. Guidelines are official policy of the ACC and AHA. For some guidelines, the ACC and AHA partner with other organizations.

Intended Use

Clinical practice guidelines provide recommendations applicable to patients with or at risk of developing cardiovascular disease. The focus is on medical practice

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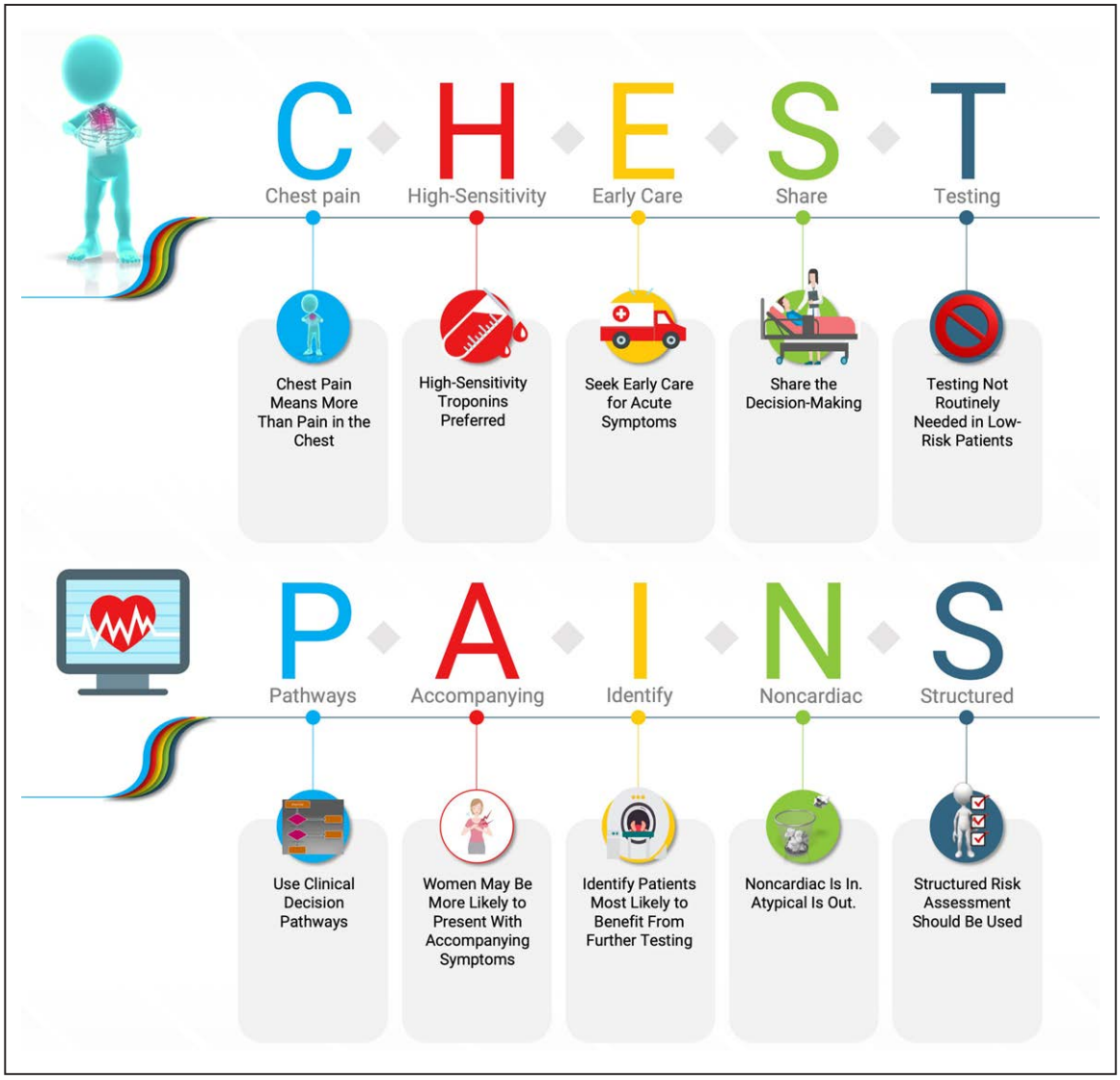

Figure 1. Take-Home Messages for the Evaluation and Diagnosis of Chest Pain

in the United States, but these guidelines are relevant to patients throughout the world. Although guidelines may be used to inform regulatory or payer decisions, the intent is to improve quality of care and align with patients' interests. Guidelines are intended to define practices meeting the needs of patients in most, but not all, circumstances and should not replace clinical judgment.

Clinical Implementation

Management, in accordance with guideline recommendations, is effective only when followed by both practitioners and patients. Adherence to recommendations can be enhanced by shared decision-making between clinicians and patients, with patient engagement in selecting interventions on the basis of individual values, preferences, and associated conditions and comorbidities.

Methodology and Modernization

The ACC/AHA Joint Committee on Clinical Practice Guidelines (Joint Committee) continuously reviews, updates, and modifies guideline methodology on the basis of published standards from organizations, including the Institute of Medicine,[1,2] and on the basis of internal reevaluation. Similarly, presentation and delivery of guidelines are reevaluated and modified in response to evolving technologies and other factors to optimally facilitate dissemination of information to healthcare professionals at the point of care.

Numerous modifications to the guidelines have been implemented to make them shorter and enhance "user friendliness." Guidelines are written and presented in a modular, "knowledge chunk" format, in which each chunk includes a table of recommendations, a brief synopsis, recommendation-specific supportive text and, when

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appropriate, flow diagrams or additional tables. Hyperlinked references are provided for each modular knowledge chunk to facilitate quick access and review.

In recognition of the importance of cost–value considerations, in certain guidelines, when appropriate and feasible, an analysis of value for a drug, device, or intervention may be performed in accordance with the ACC/AHA methodology.[3]

To ensure that guideline recommendations remain current, new data will be reviewed on an ongoing basis by the writing committee and staff. Going forward, targeted sections/knowledge chunks will be revised dynamically after publication and timely peer review of potentially practice-changing science. The previous designations of "full revision" and "focused update" will be phased out. For additional information and policies on guideline development, readers may consult the ACC/AHA guideline methodology manual[4] and other methodology articles.[5-7] The Class of Recommendation (COR) indicates the strength of recommendation, encompassing the estimated magnitude and certainty of benefit in proportion to risk. The Level of Evidence (LOE) rates the quality of scientific evidence supporting the intervention on the basis of the type, quantity, and consistency of data from clinical trials and other sources (Table 1).[4]

Selection of Writing Committee Members

The Joint Committee strives to ensure that the guideline writing committee contains requisite content expertise and is representative of the broader cardiovascular community by selection of experts across a spectrum of backgrounds, representing different geographic regions, sexes, races, ethnicities, intellectual perspectives/biases, and clinical practice settings. Organizations and professional societies with related interests and expertise are invited to participate as partners or collaborators.

Relationships With Industry and Other Entities

The ACC and AHA have rigorous policies and methods to ensure that documents are developed without bias or improper influence. The complete policy on relationships with industry and other entities (RWI) can be found online. Appendix 1 of the guideline lists writing committee members' relevant RWI; for the purposes of full transparency, their comprehensive disclosure information is available in the Supplemental Appendix. Comprehensive disclosure information for the Joint Committee is also available online.

Evidence Review and Evidence Review Committees

In developing recommendations, the writing committee uses evidence-based methodologies that are based on all available data.[4,5] Literature searches focus on randomized controlled trials (RCTs) but also include registries, nonrandomized comparative and descriptive studies, case series, cohort studies, systematic reviews, and expert opinions. Only key references are cited.

An independent evidence review committee is commissioned when there are ≥1 questions deemed of utmost clinical importance and merit formal systematic review to determine which patients are most likely to benefit from a drug, device, or treatment strategy, and to what degree. Criteria for commissioning an evidence review committee and formal systematic review include absence of a current authoritative systematic review, feasibility of defining the benefit and risk in a time frame consistent with the writing of a guideline, relevance to a substantial number of patients, and likelihood that the findings can be translated into actionable recommendations. Evidence review committee members may include methodologists, epidemiologists, clinicians, and biostatisticians. Recommendations developed by the writing committee on the basis of the systematic review are marked "SR."

Guideline-Directed Management and Therapy

The term guideline-directed medical therapy (GDMT) encompasses clinical evaluation, diagnostic testing, and both pharmacological and procedural treatments. For these and all recommended drug treatment regimens, the reader should confirm dosage with product insert material and evaluate for contraindications and interactions. Recommendations are limited to drugs, devices, and treatments approved for clinical use in the United States.

Patrick T. O'Gara, MD, MACC, FAHA
Chair, ACC/AHA Joint Committee on Clinical Practice Guidelines

1. INTRODUCTION

1.1. Methodology and Evidence Review

The recommendations listed in this guideline are, whenever possible, evidence based. An initial extensive evidence review, which included literature derived from research involving human subjects, published in English, and indexed in MEDLINE (through PubMed), EMBASE, the Cochrane Library, the Agency for Healthcare Research and Quality, and other selected databases relevant to this guideline, was conducted from November 11, 2017, to May 1, 2020. Key search words included but were not limited to the following: *acute coronary syndrome, angina, angina pectoris, aortic valve stenosis, biomarker, biomarkers, brain natriuretic peptide, cardiac-gated single photon emission computer-assisted tomography, cardiovascular magnetic resonance, chest pain, CKMB, coronary angiography, coronary arteriosclerosis, coronary artery disease, creatine kinase, creatine kinase MB, echocardiography, electrocardiography, heart valve disease, hypertrophic*

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Table 1. Applying ACC/AHA Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care (Updated May 2019)*

CLASS (STRENGTH) OF RECOMMENDATION	
CLASS 1 (STRONG)	**Benefit >>> Risk**
Suggested phrases for writing recommendations: • Is recommended • Is indicated/useful/effective/beneficial • Should be performed/administered/other • Comparative-Effectiveness Phrases†: – Treatment/strategy A is recommended/indicated in preference to treatment B – Treatment A should be chosen over treatment B	
CLASS 2a (MODERATE)	**Benefit >> Risk**
Suggested phrases for writing recommendations: • Is reasonable • Can be useful/effective/beneficial • Comparative-Effectiveness Phrases†: – Treatment/strategy A is probably recommended/indicated in preference to treatment B – It is reasonable to choose treatment A over treatment B	
CLASS 2b (WEAK)	**Benefit ≥ Risk**
Suggested phrases for writing recommendations: • May/might be reasonable • May/might be considered • Usefulness/effectiveness is unknown/unclear/uncertain or not well-established	
CLASS 3: No Benefit (MODERATE) **(Generally, LOE A or B use only)**	**Benefit = Risk**
Suggested phrases for writing recommendations: • Is not recommended • Is not indicated/useful/effective/beneficial • Should not be performed/administered/other	
Class 3: Harm (STRONG)	**Risk > Benefit**
Suggested phrases for writing recommendations: • Potentially harmful • Causes harm • Associated with excess morbidity/mortality • Should not be performed/administered/other	

LEVEL (QUALITY) OF EVIDENCE‡	
LEVEL A	
• High-quality evidence‡ from more than 1 RCT • Meta-analyses of high-quality RCTs • One or more RCTs corroborated by high-quality registry studies	
LEVEL B-R	**(Randomized)**
• Moderate-quality evidence‡ from 1 or more RCTs • Meta-analyses of moderate-quality RCTs	
LEVEL B-NR	**(Nonrandomized)**
• Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies • Meta-analyses of such studies	
LEVEL C-LD	**(Limited Data)**
• Randomized or nonrandomized observational or registry studies with limitations of design or execution • Meta-analyses of such studies • Physiological or mechanistic studies in human subjects	
LEVEL C-EO	**(Expert Opinion)**
• Consensus of expert opinion based on clinical experience	

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR 1 and 2a; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely-used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

cardiomyopathy, magnetic resonance imaging, mitral valve stenosis, multidetector computed tomography, myocardial infarction, myocardial ischemia, myocardium, NT-proBNP, perfusion imaging, positron-emission tomography, pulmonary hypertension, stable angina, troponin I, troponin T, unstable angina, x-ray computed tomography. Additional relevant studies, published through November 2020 during the guideline writing process, were also considered by the writing committee and added to the evidence tables when appropriate. The final evidence tables are included in the Online Data Supplement and summarize the evidence used by the writing committee to formulate recommendations. References selected and published in the present document are representative and not all-inclusive.

1.2. Organization of the Writing Committee

The writing committee consisted of cardiac intensivists, cardiac interventionalists, cardiac surgeons, cardiologists, emergency physicians, epidemiologists, and a lay/patient representative. The writing committee included representatives from the ACC, AHA, American Society of Echocardiography (ASE), American College of Chest Physicians (CHEST), Society for Academic Emergency Medicine (SAEM), Society of Cardiovascular Computed Tomography (SCCT), and Society for Cardiovascular Magnetic Resonance (SCMR). Appendix 1 lists writing committee members' relevant RWI. For the purposes of full transparency, the writing committee members' comprehensive disclosure information is available in the Supplemental Appendix.

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Table 2. Associated Guidelines and Statements

Title	Organization	Publication Year (Reference)
Guidelines		
Stable ischemic heart disease	ACC/AHA/AATS/PCNA/SCAI/STS	2014[1]* 2012[2]
Atrial fibrillation	AHA/ACC/HRS	2014[3]* 2019[4]
Non-ST elevation ACS	AHA/ACC	2014[5]
Blood cholesterol	AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA	2018[6]
Heart failure	ACC/AHA	2013[7]* 2017[8]
Primary prevention of cardiovascular disease	ACC/AHA	2019[9]
Management of overweight and obesity in adults	AHA/ACC/TOS	2014[10]
ST-elevation myocardial infarction	ACC/AHA	2013[11]
Ventricular arrhythmias and the prevention of sudden cardiac death	AHA/ACC/HRS	2017[12]
Coronary artery bypass graft surgery	ACC/AHA	2011[13]
Hypertrophic cardiomyopathy	ACC/AHA	2020[14]
Percutaneous coronary intervention	ACC/AHA/SCAI	2011[15]* 2015[16]
Secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease	AHA/ACC	2011[17]
Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care—part 9: postcardiac arrest care	AHA	2010[18]* 2019[19]
Prevention, detection, evaluation, and management of high blood pressure in adults	ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA	2017[20]
Statements		
Testing of low-risk patients presenting to the emergency department with chest pain	AHA	2010[21]
Prevention of cardiovascular disease in adults with type 2 diabetes mellitus	AHA/ADA	2015[22]
Prevention and control of seasonal influenza with vaccines	CDC	2018[23]

AACVPR indicates American Association of Cardiovascular and Pulmonary Rehabilitation; AAPA, American Academy of Physician Assistants; AATS, American Association for Thoracic Surgery; ABC, Association of Black Cardiologists; ACC, American College of Cardiology; ACPM, American College of Preventive Medicine; ADA, American Diabetes Association; AGS, American Geriatrics Society; AHA, American Heart Association; APhA, American Pharmacists Association; ASH, American Society of Hypertension; ASPC, American Society for Preventive Cardiology; CDC, Centers for Disease Control and Prevention; ESC, European Society of Cardiology; HRS, Heart Rhythm Society; NHLBI, National Heart, Lung, and Blood Institute; NLA, National Lipid Association; NMA, National Medical Association; PCNA, Preventive Cardiovascular Nurses Association; SCAI, Society for Cardiovascular Angiography and Interventions; STS, Society of Thoracic Surgeons; and TOS, The Obesity Society.

*The full-text guideline and focused update references are provided.

1.3. Document Review and Approval

This document was reviewed by 16 official reviewers nominated by the ACC, the American College of Emergency Physicians, AHA, ASE, American Society of Nuclear Cardiology, CHEST, SAEM, SCCT, and SCMR, and 39 individual content reviewers. Reviewers' RWI information was distributed to the writing committee and is published in this document (Appendix 2).

This document was approved for publication by the governing bodies of the ACC and the AHA and was endorsed by the ASE, CHEST, SAEM, SCCT, and SCMR.

1.4. Scope of the Guideline

The charge of the writing committee was to develop a guideline for the evaluation of acute or stable chest pain or other anginal equivalents, in various clinical settings, with an emphasis on the diagnosis on ischemic causes. This guideline will not provide recommendations on whether revascularization is appropriate or what modality is indicated. Such recommendations can be found in the forthcoming ACC/AHA coronary artery revascularization guideline. In developing the "2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain," the writing committee first reviewed previous published guidelines and related statements. Table 2 contains a list of these publications deemed pertinent to this writing effort and is intended for use as a resource, thus obviating the need to repeat existing guideline recommendations.

1.4.1. Scope of the Problem

Synopsis

After injuries, chest pain is the second most common reason for adults to present to the emergency

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department (ED) in the United States and accounts for >6.5 million visits, which is 4.7% of all ED visits.[1] Chest pain also leads to nearly 4 million outpatient visits annually in the United States.[2] Chest pain remains a diagnostic challenge in the ED and outpatient setting and requires thorough clinical evaluation. Although the cause of chest pain is often noncardiac, coronary artery disease (CAD) affects >18.2 million adults in the United States and remains the leading cause of death for men and women, accounting for >365 000 deaths annually.[3] Distinguishing between serious and benign causes of chest pain is imperative. The lifetime prevalence of chest pain in the United States is 20% to 40%,[4] and women experience this symptom more often than men.[5] Of all ED patients with chest pain, only 5.1% will have an acute coronary syndrome (ACS), and more than half will ultimately be found to have a noncardiac cause.[6] Nonetheless, chest pain is the most common symptom of CAD in both men and women.

1.4.2. Defining Chest Pain

Recommendations for Defining Chest Pain Referenced studies that support the recommendations are summarized in Online Data Supplements 1 and 2.		
COR	**LOE**	**Recommendations**
1	B-NR	1. An initial assessment of chest pain is recommended to triage patients effectively on the basis of the likelihood that symptoms may be attributable to myocardial ischemia.[1-7]
1	C-LD	2. Chest pain should not be described as atypical, because it is not helpful in determining the cause and can be misinterpreted as benign in nature. Instead, chest pain should be described as cardiac, possibly cardiac, or noncardiac because these terms are more specific to the potential underlying diagnosis.

Synopsis

Chest pain is one of the most common reasons that people seek medical care. The term "chest pain" is used by patients and applied by clinicians to describe the many unpleasant or uncomfortable sensations in the anterior chest that prompt concern for a cardiac problem. Chest pain should be considered *acute* when it is new onset or involves a change in pattern, intensity, or duration compared with previous episodes in a patient with recurrent symptoms. Chest pain should be considered *stable* when symptoms are chronic and associated with consistent precipitants such as exertion or emotional stress.

Although the term chest pain is used in clinical practice, patients often report pressure, tightness, squeezing, heaviness, or burning. In this regard, a more appropriate term is "chest discomfort," because patients may not use the descriptor "pain." They may also report a location other than the chest, including the shoulder, arm, neck, back, upper abdomen, or jaw. Despite individual variability, the discomfort induced by myocardial ischemia is often characteristic and therefore central to the diagnosis. For this reason, features more likely to be associated with ischemia have been described as typical versus atypical; however, the latter can be confusing because it is frequently used to describe symptoms considered nonischemic as well as noncardiac. Although other nonclassic symptoms of ischemia, such as shortness of breath, nausea, radiating discomfort, or numbness, may be present, chest pain or chest discomfort remains the predominant symptom reported in men and women who are ultimately diagnosed with myocardial ischemia.[3-7] Pain—described as sharp, fleeting, related to inspiration (pleuritic) or position, or shifting locations—suggests a lower likelihood of ischemia.

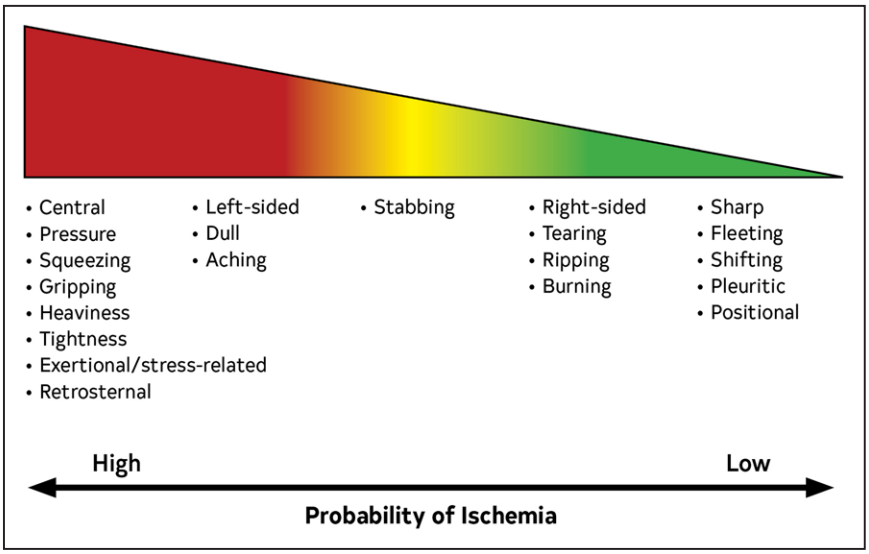

Figure 2. Index of Suspicion That Chest "Pain" Is Ischemic in Origin on the Basis of Commonly Used Descriptors

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Recommendation-Specific Supportive Text

1. Like most visceral discomfort, the sensation produced by myocardial ischemia is characteristically deep, difficult to localize, and usually diffuse. Point tenderness renders ischemia less likely. Reported symptoms lie somewhere on a continuum of higher or lower probability of ischemia based on the presence or absence of specific characteristics (Figure 2). Other clinical elements (eg, duration, provoking and relieving factors, patient age, cardiac risk factors) provide further focus toward or away from ischemia in the diagnostic process. It is essential to ascertain the characteristics of the chest pain directly from the patient for optimal interpretation.[1-7] A patient's history is the most important basis for considering presence or absence of myocardial ischemia, but the source of cardiac symptoms is complex, and their expression is variable. The diagnosis of ischemia may require data beyond history alone. In some patients, what appears to be noncardiac chest pain may be ischemic in origin.
2. Chest pain has been traditionally stratified into "typical" and "atypical" types. Chest pain that is more likely associated with ischemia consists of substernal chest discomfort provoked by exertion or emotional stress and relieved by rest or nitroglycerin. The more classic the chest discomfort is based on quality, location, radiation, and provoking and relieving factors, the more likely it is to be of cardiac ischemic origin. Atypical chest pain is a problematic term. Although it was intended to indicate angina without typical chest symptoms, it is more often used to state that the symptom is noncardiac in origin. As such, we discourage the use of atypical chest pain. Emphasis is more constructively placed on specific aspects of symptoms that suggest their origin in terms of probable ischemia. Of note, chest pain is broadly defined to also include referred pain in the shoulders, arms, jaw, neck, and upper abdomen. To diminish ambiguity, use "cardiac," "possible cardiac," and "noncardiac" to describe the suspected cause of chest pain is encouraged.

1.5. Abbreviations

Abbreviation	Meaning/Phrase
ACS	acute coronary syndrome
AMI	acute myocardial infarction
CABG	coronary artery bypass graft
CAC	coronary artery calcium
CAD	coronary artery disease
CCTA	coronary computed tomographic angiography
CDP	clinical decision pathway
CMR	cardiovascular magnetic resonance
cTn	cardiac troponin
ECG	electrocardiogram
ED	emergency department
EMS	emergency medical services
FFR-CT	fractional flow reserve with computed tomography
GDMT	guideline-directed medical therapy
hs-cTn	high-sensitivity cardiac troponin
ICA	invasive coronary angiography
INOCA	ischemia and no obstructive coronary artery disease
MACE	major adverse cardiovascular events
MBFR	myocardial blood flow reserve
METs	metabolic equivalents
MINOCA	myocardial infarction and nonobstructive coronary arteries
MPI	myocardial perfusion imaging
NSTE-ACS	non–ST-segment–elevation acute coronary syndrome
PCI	percutaneous coronary intervention
PE	pulmonary embolism
PET	positron emission tomography
SIHD	stable ischemic heart disease
SPECT	single-photon emission computed tomography
STEMI	ST-segment–elevation myocardial infarction
TEE	transesophageal echocardiography
TTE	transthoracic echocardiography
VF	ventricular fibrillation
VHD	valvular heart disease
VT	ventricular tachycardia

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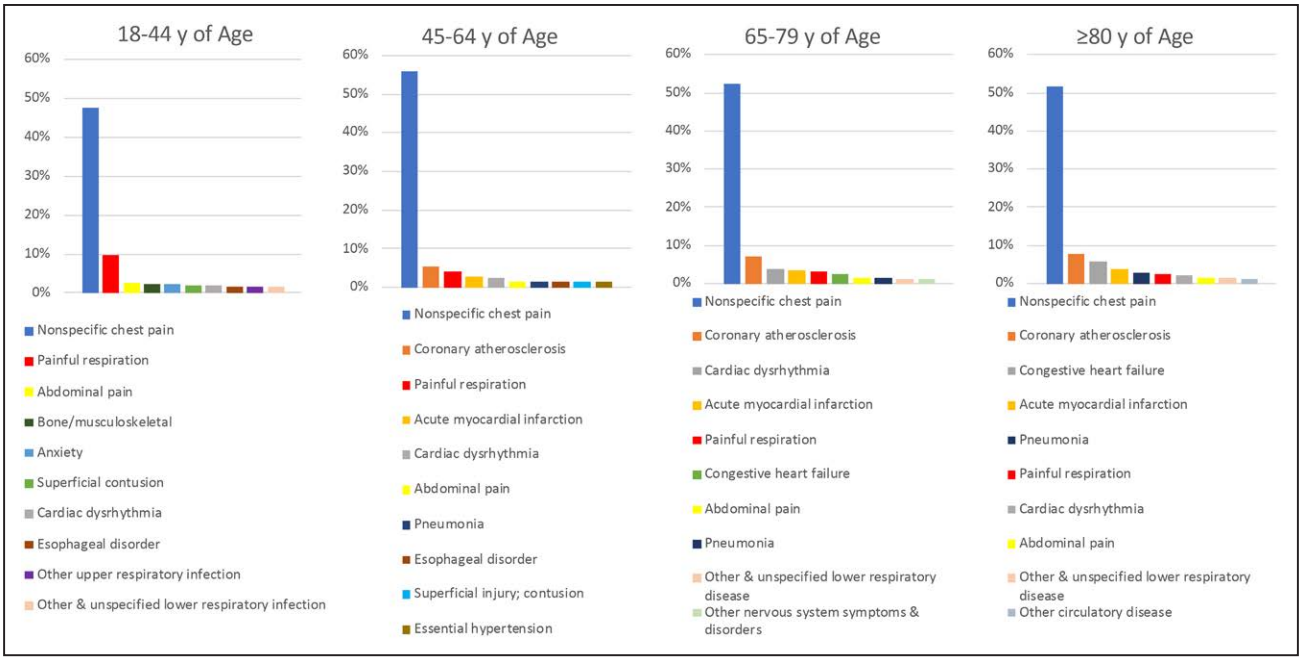

Figure 3. Top 10 Causes of Chest Pain in the ED Based on Age (Weighted Percentage)
Created using data from Hsia RY et al.[3] ED indicates emergency department.

2. INITIAL EVALUATION

2.1. History

Recommendation for History		
COR	**LOE**	**Recommendation**
1	**C-LD**	1. In patients with chest pain, a focused history that includes characteristics and duration of symptoms relative to presentation as well as associated features, and cardiovascular risk factor assessment should be obtained.

Synopsis

Chest pain or chest pain equivalent will be referred to in these guidelines as "chest pain." Patients presenting to the ED with nontraumatic chest pain are a frequent diagnostic challenge.[1] The priorities are: 1) rapid initiation of optimal management in patients with life-threatening conditions such as ACS, aortic dissection, and pulmonary embolism (PE), as well as nonvascular syndromes (eg, esophageal rupture, tension pneumothorax); and 2) deliberate therapy for those with less critical illness. Although there are several life-threatening causes, chest pain usually reflects a more benign condition (Figure 3).[2-4] The initial ECG is important to the evaluation, but history, examination, biomarkers, and other aids remain essential. There is frequently a lack of correlation between intensity of symptoms and seriousness of disease and general similarity of symptoms among different causes of chest pain. A comprehensive history that captures all the characteristics of chest pain (Table 3), including but not limited to its: 1) nature; 2) onset and duration; 3) location and radiation; 4) precipitating factors; 5) relieving factors; and 6) associated symptoms can help better identify potential cardiac causes and should be obtained from all patients.

Recommendation-Specific Supportive Text

1. Angina pectoris is perceived as a retrosternal chest discomfort that builds gradually in intensity (over several minutes), is usually precipitated by stress (physical or emotional) or occurring at rest (as in the case of an ACS) with characteristic radiation (eg, left arm, neck, jaw) and its associated symptoms (eg, dyspnea, nausea, lightheadedness). When actively treated or spontaneously resolving, it dissipates over a few minutes. Relief with nitroglycerin is not necessarily diagnostic of myocardial ischemia and should not be used as a diagnostic criterion, especially because other entities demonstrate comparable response (eg, esophageal spasm).[1,5] Associated symptoms such as shortness of breath, nausea or vomiting, lightheadedness, confusion, presyncope or syncope, or vague abdominal symptoms are more frequent among patients with diabetes, women, and the elderly. A detailed assessment of cardiovascular risk factors, review of systems, past medical history, and family and social history should complement the assessment of presenting symptoms.

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2.1.1. A Focus on the Uniqueness of Chest Pain in Women

Recommendations for a Focus on the Uniqueness of Chest Pain in Women
Referenced studies that support the recommendations are summarized in Online Data Supplements 3 and 4.

COR	LOE	Recommendations
1	B-NR	1. Women who present with chest pain are at risk for underdiagnosis, and potential cardiac causes should always be considered.[1-7]
1	B-NR	2. In women presenting with chest pain, it is recommended to obtain a history that emphasizes accompanying symptoms that are more common in women with ACS.[1-7]

Table 3. Chest Pain Characteristics and Corresponding Causes

Nature
Anginal symptoms are perceived as retrosternal chest discomfort (eg, pain, discomfort, heaviness, tightness, pressure, constriction, squeezing) (Section 1.4.2, Defining Chest Pain).
Sharp chest pain that increases with inspiration and lying supine is unlikely related to ischemic heart disease (eg, these symptoms usually occur with acute pericarditis).
Onset and duration
Anginal symptoms gradually build in intensity over a few minutes.
Sudden onset of ripping chest pain (with radiation to the upper or lower back) is unlikely to be anginal and is suspicious of an acute aortic syndrome.
Fleeting chest pain—of few seconds' duration—is unlikely to be related to ischemic heart disease.
Location and radiation
Pain that can be localized to a very limited area and pain radiating to below the umbilicus or hip are unlikely related to myocardial ischemia.
Severity
Ripping chest pain ("worse chest pain of my life"), especially when sudden in onset and occurring in a hypertensive patient, or with a known bicuspid aortic valve or aortic dilation, is suspicious of an acute aortic syndrome (eg, aortic dissection).
Precipitating factors
Physical exercise or emotional stress are common triggers of anginal symptoms.
Occurrence at rest or with minimal exertion associated with anginal symptoms usually indicates ACS.
Positional chest pain is usually nonischemic (eg, musculoskeletal).
Relieving factors
Relief with nitroglycerin is not necessarily diagnostic of myocardial ischemia and should not be used as a diagnostic criterion.
Associated symptoms
Common symptoms associated with myocardial ischemia include, but are not limited to, dyspnea, palpitations, diaphoresis, lightheadedness, presyncope or syncope, upper abdominal pain, or heartburn unrelated to meals and nausea or vomiting.
Symptoms on the left or right side of the chest, stabbing, sharp pain, or discomfort in the throat or abdomen may occur in patients with diabetes, women, and elderly patients.

ACS indicates acute coronary syndrome.

Synopsis

Most patients who present to the ED with chest pain are women, particularly among those ≥65 years of age.[8] The ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) trial demonstrated that women with moderate-to-severe ischemia are more symptomatic than men.[9] Women are less likely to have timely and appropriate care.[10] This could be explained by the fact that women are more likely to experience prodromal symptoms when they seek medical care.[11] Women may also present with accompanying symptoms (eg, nausea, fatigue, and shortness of breath) more often than men.[12-14] However, chest pain remains the predominant symptom reported by women among those ultimately diagnosed with ACS, occurring with a frequency equal to men.[3,5-7,15,16]

Recommendation-Specific Supportive Text

1. Traditional risk score tools and physician assessments often underestimate risk in women and misclassify them as having nonischemic chest pain.[1,2] The PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial looked at sex differences in the presentation, risk factors, demographics, noninvasive test referrals, and results of 10 003 stable outpatients with suspected CAD.[1] Women commonly presented with chest pain symptoms similar to men but also had a greater prevalence of other symptoms such as palpitations, jaw and neck pain, as well as back pain. Women also had more cardiovascular risk factors, including hypertension (66.6% versus 63.2%; $P<0.001$), hyperlipidemia (68.9% versus 66.3%; $P=0.004$), older age (62.4±7.9 years of age versus 59.0±8.4 years of age, $P<0.001$), cerebral or peripheral artery disease (6.2% versus 4.7%; $P<0.001$), family history of premature CAD (34.6% versus 29.3%; $P<0.001$), and sedentary lifestyle (53.5% versus 43.4%; $P<0.001$). Physician assessments often misclassify chest pain as nonanginal. The BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial reported that women with diabetes had a higher prevalence of angina than their male counterparts, with a lower functional capacity and a lower incidence of obstructive CAD.[16]
2. In the VIRGO (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients) study, men and women ≤55 years of age were equally likely to present with chest pain (defined as pain, pressure, tightness, discomfort; 89.5% versus 87%, respectively). Women were more likely to report ≥3 associated symptoms than men (eg, epigastric symptoms,

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palpitations, and pain or discomfort in the jaw, neck, arms, or between the shoulder blades; 61.9% of women versus 54.8% of men; $P<0.001$).[3] Similar results were found in the YOUNG-MI (Myocardial Infarction) registry where young men and women (≤50 years of age) were equally likely to present with chest pain, although women were more likely to also have other associated symptoms.[7] The HERMES (Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke) study used cardiolinguistic machine learning to record patient-reported symptoms and, in those diagnosed with obstructive CAD, there was no sex difference in the occurrence of chest pain.[6] In a prospective trial of 1941 patients (39% women) with suspected ACS examining the diagnostic value of high-sensitivity cardiac troponin (cTn), chest pain was reported in 92% of women and 91% of men.[5] Additionally, women with acute myocardial infarction (AMI) were more likely to present with "typical" symptoms than men (77% versus 59%; $P=0.007$).

2.1.2. Considerations for Older Patients With Chest Pain

Recommendation for Considerations for Older Patients With Chest Pain		
COR	**LOE**	**Recommendation**
1	C-LD	1. In patients with chest pain who are >75 years of age, ACS should be considered when accompanying symptoms such as shortness of breath, syncope, or acute delirium are present, or when an unexplained fall has occurred.[1]

Synopsis

Increased age is a significant risk factor for ACS. However, it is also a risk factor for comorbidities that are associated with alternative diagnoses associated with chest pain. As a result, a more extensive diagnostic workup is required in older patients. Although patients >75 years of age account for 33% of all cases of ACS, alternative diagnoses are still more common than a cardiac cause of chest pain at presentation.[2,3] A substudy of the PROMISE trial has shown that patients >75 years of age, with stable symptoms suggestive of CAD, are more likely to have a positive noninvasive test and more coronary artery calcification than younger people. For these older patients, when compared with anatomic noninvasive testing for obstructive CAD with cardiac CT, a positive stress test result was associated with increased risk of cardiovascular death or MI.[4]

Recommendation-Specific Supportive Text

1. Patients >75 years of age may have symptoms of shortness of breath, syncope, mental impairment, or abdominal pain, or experienced an unexplained fall. The physician should have a heightened awareness to understand that these symptoms may be associated with ACS, in addition to chest pain.[1]

2.1.3. Considerations for Diverse Patient Populations With Chest Pain

Recommendations for Considerations for Diverse Patient Populations With Chest Pain		
COR	**LOE**	**Recommendations**
1	C-LD	1. Cultural competency training is recommended to help achieve the best outcomes in patients of diverse racial and ethnic backgrounds who present with chest pain.
1	C-LD	2. Among patients of diverse race and ethnicity presenting with chest pain in whom English may not be their primary language, addressing language barriers with the use of formal translation services is recommended.

Synopsis

There are marked racial and ethnic disparities when triaging patients who present for the evaluation of chest pain. Despite a greater number of Black patients presenting with angina pectoris relative to other races, this population is less likely to be treated urgently and less likely to have an ECG performed, samples for cardiac biomarkers drawn, cardiac monitoring performed, or pulse oximetry measured.[1-4] Similar treatment disparities are found with Hispanic patients and those who are covered by Medicaid or are uninsured. Derived from a nationally representative sample from the National Hospital Ambulatory Health Care Survey reflecting an estimated 78 million ED visits in the United States over a 10-year period, these findings have been unchanged over time.[5] Such disparity in the management of chest pain among diverse population subgroups contributes to worse outcomes, including the greater incidence of AMI and fatal coronary events seen in these key population subgroups.[6,7] There are also disparities in the management of patients of South Asian descent who present with ACS, with the diagnosis often missed or delayed, resulting in poor outcomes.[8-11] Consideration of race and ethnicity in the evaluation of patients with suspected ACS and in the outpatient evaluation of symptomatic patients is paramount to improving outcomes. Cultural competency training of providers is recommended to address health disparities in the evaluation and management of diverse patient population subgroups with chest pain.

Recommendation-Specific Supportive Text

1. In patients of various diverse groups presenting with chest pain, cultural competency training of providers to address racial and ethnic disparities may help to improve diagnosis, treatment, and

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outcomes. Attention to race, ethnicity, and sociocultural differences should be considered in the evaluation and management of such patients. Cultural competency training can help address difficulties in the assessment of patients because there may be differences in the description and perception of chest pain among various diverse patient groups. Such training may also help to minimize potential unconscious biases on the part of providers. Disparities in the management of chest pain among diverse populations contribute to worse outcomes, including the greater incidence of MI and fatal coronary events.[1]

2. In patients of various racial and ethnic subgroups presenting with suspected ACS in whom English may not be their primary language, adequately addressing language barriers with the use of language translation is vital to obtain an accurate and complete history. Formal translation services such as those provided through institutions and virtual translation are recommended.

2.1.4. Patient-Centric Considerations

Recommendation for Patient-Centric Considerations		
COR	**LOE**	**Recommendation**
1	C-LD	1. In patients with acute chest pain, it is recommended that 9-1-1 be activated by patients or bystanders to initiate transport to the closest ED by emergency medical services (EMS).[1]

Synopsis

Although chest pain remains one of the most common reasons that patients seek evaluation, among both sexes, there is a tendency for some patients to minimize perceived risk for cardiac disease, resulting in potentially avoidable delays in care.[1] To alleviate this problem, efforts should be made to educate all people regarding their risk for a cardiac event and educate patients about the need for timely care if a heart attack is suspected. Education is essential regarding the need to call 9-1-1, provide transportation by EMS to the nearest ED, initiate early assessment and management of suspected ACS, including transmittal of prehospital ECGs,[2] and intervene if complications occur en route to the ED.[3] The ACC's Early Heart Attack Care guide is a resource to help educate the public about early recognition of potential cardiac symptoms and the importance of activating 9-1-1 for transportation.[4,5]

Recommendation-Specific Supportive Text

1. To ensure the timely delivery of appropriate care, especially reperfusion therapy, it is strongly recommended that patients with acute chest pain be transported to the ED by trained EMS personnel.[2,3] EMS transportation is associated with substantial reductions in ischemic time and treatment delays. Moreover, 1 in 300 patients with chest pain transported to the ED by private vehicle suffers a cardiac arrest en route.[3] Understanding the mode of transportation to the ED for patients with chest pain and educating those who arrive by private vehicle on the associated dangers is an important aspect of management.

2.2. Physical Examination

Recommendation for Physical Examination		
COR	**LOE**	**Recommendation**
1	C-EO	1. In patients presenting with chest pain, a focused cardiovascular examination should be performed initially to aid in the diagnosis of ACS or other potentially serious causes of chest pain (eg, aortic dissection, PE, or esophageal rupture) and to identify complications.

Synopsis

Life-threatening causes of chest pain include, but are not limited to, ACS, PE, aortic dissection, and esophageal rupture. Because ST-segment–elevation myocardial infarction (STEMI) can be recognized on the ECG, the major challenge is to distinguish between non–ST-segment–elevation (NSTE)-ACS and noncardiac chest pain.[1] With an uncomplicated AMI, the examination may be negative. Sudden onset of severe chest pain or back pain associated with limb pulse differential suggest aortic dissection,[2] but sensitivity of the latter finding alone was only 30%.[3] PE may result in tachycardia, dyspnea, and accentuated P2. Noncoronary causes of chest pain include aortic stenosis, aortic regurgitation, and hypertrophic cardiomyopathy, which produces characteristic murmurs and pulse alterations. Chest pain of pericarditis increases in the supine position and may be associated with a friction rub. Stress cardiomyopathy presents in a similar manner as ACS. Chest pain accompanied by a painful, tympanic abdomen may indicate a potentially life-threatening gastrointestinal etiology such as esophageal rupture.[4] Pneumonia may cause localized pleuritic chest pain accompanied by a friction rub. Pneumothorax may be accompanied by pleuritic chest pain and unilateral absence of breath sounds. Tenderness to palpation of the costochondral joints may indicate a musculoskeletal cause. Herpes zoster produces a painful rash in a dermatomal distribution.

Recommendation-Specific Supportive Text

1. Although the causes of chest pain are numerous, the initial evaluation should focus on those

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Table 4. Physical Examination in Patients With Chest Pain

Clinical Syndrome	Findings
Emergency	
ACS	Diaphoresis, tachypnea, tachycardia, hypotension, crackles, S3, MR murmur.[2]; examination may be normal in uncomplicated cases
PE	Tachycardia + dyspnea–>90% of patients; pain with inspiration[7]
Aortic dissection	Connective tissue disorders (eg, Marfan syndrome), extremity pulse differential (30% of patients, type A>B)[8] Severe pain, abrupt onset + pulse differential + widened mediastinum on CXR >80% probability of dissection[9] Frequency of syncope >10%[8], AR 40%–75% (type A)[10]
Esophageal rupture	Emesis, subcutaneous emphysema, pneumothorax (20% patients), unilateral decreased or absent breath sounds
Other	
Noncoronary cardiac: AS, AR, HCM	AS: Characteristic systolic murmur, tardus or parvus carotid pulse AR: Diastolic murmur at right of sternum, rapid carotid upstroke HCM: Increased or displaced left ventricular impulse, prominent *a* wave in jugular venous pressure, systolic murmur
Pericarditis	Fever, pleuritic chest pain, increased in supine position, friction rub
Myocarditis	Fever, chest pain, heart failure, S3
Esophagitis, peptic ulcer disease, gall bladder disease	Epigastric tenderness Right upper quadrant tenderness, Murphy sign
Pneumonia	Fever, localized chest pain, may be pleuritic, friction rub may be present, regional dullness to percussion, egophony
Pneumothorax	Dyspnea and pain on inspiration, unilateral absence of breath sounds
Costochondritis, Tietze syndrome	Tenderness of costochondral joints
Herpes zoster	Pain in dermatomal distribution, triggered by touch; characteristic rash (unilateral and dermatomal distribution)

ACS indicates acute coronary syndrome; AR, aortic regurgitation; AS, aortic stenosis; CXR, chest x-ray; LR, likelihood ratio; HCM, hypertrophic cardiomyopathy; MR, mitral regurgitation; PE, pulmonary embolism; and PUD, peptic ulcer disease.

that are life-threatening, such as ACS, PE, aortic dissection, and esophageal rupture, to facilitate rapid implementation of appropriate treatment.[1] Specific clues can be helpful (Table 4). Chest tenderness on palpation or pain with inspiration markedly reduce the probability of ACS.[1,5,6] Integrating the examination with other elements of the evaluation is crucial to establishing the correct diagnosis.

2.3. Diagnostic Testing

2.3.1. Setting Considerations

Recommendations for Setting Considerations
Referenced studies that support the recommendations are summarized in Online Data Supplement 5.

COR	LOE	Recommendations
1	B-NR	1. Unless a noncardiac cause is evident, an ECG should be performed for patients seen in the office setting with stable chest pain; if an ECG is unavailable the patient should be referred to the ED so one can be obtained.[1-5]
1	C-LD	2. Patients with clinical evidence of ACS or other life-threatening causes of acute chest pain seen in the office setting should be transported urgently to the ED, ideally by EMS.[1-9]
1	C-LD	3. In all patients who present with acute chest pain regardless of the setting, an ECG should be acquired and reviewed for STEMI within 10 minutes of arrival.[1-3,6,7,10]
1	C-LD	4. In all patients presenting to the ED with acute chest pain and suspected ACS, cTn should be measured as soon as possible after presentation.[8,9]
3: Harm	C-LD	5. For patients with acute chest pain and suspected ACS initially evaluated in the office setting, delayed transfer to the ED for cTn or other diagnostic testing should be avoided.

Synopsis

The goals in patients presenting to the ED or office with acute chest pain are: 1) identify life-threatening causes; 2) determine clinical stability; and 3) assess need for hospitalization versus safety of outpatient evaluation and management. These concerns entail consideration of the full extent of clinical data. The ACC/AHA STEMI and NSTE-ACS guidelines categorize chest pain cause into 4 types: STEMI, NSTE-ACS, stable angina, and noncardiac.[6,7] The 12-lead ECG, which should be acquired and interpreted within 10 minutes of arrival to a medical facility[1-7,11] (Section 2.3.2, ECG), is pivotal in the evaluation because of its capacity to identify and triage patients with STEMI to urgent coronary reperfusion. Other ST-T abnormalities consistent with possible ischemia also mandate prompt evaluation in a hospital setting. In both cases, transfer should be by EMS; personal automobile for this purpose is associated with increased risk and should be avoided.[3-5] Patients with stable angina or noncardiac chest pain that is not life-threatening should be managed as outpatients.

Recommendation-Specific Supportive Text

1. The ECG is central to the evaluation of stable angina in the office setting to ensure that ACS

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is not missed.[1,2,6,7] If an ECG cannot be obtained, transfer to the ED should be initiated.

2. Transfer by EMS from the office setting for acute chest pain with suspected ACS or other life-threating conditions is recommended because of the important advantages provided by EMS including: 1) acquisition of a prehospital ECG, which can facilitate reperfusion if ST elevation is present; 2) presence of trained personnel who can provide treatment for chest pain, arrhythmias, and implement defibrillation en route; and 3) shorter travel time to the ED.[1-7,10]
3. Early recognition of STEMI improves outcomes.[1-3,6,7] Therefore, regardless of the setting, an ECG should be obtained and interpreted within 10 minutes of arrival. If this cannot be achieved in the office setting, immediate transfer to the ED by EMS is recommended. A substantial proportion of patients with chest pain are transferred to the ED without a prehospital ECG.[1-3,6,7] This results in an important and avoidable delay in readiness of the ED and reperfusion teams to implement optimally timed reperfusion therapy.[1-7,10]
4. cTn is the most sensitive test for diagnosing acute myocardial injury and, in conjunction with other essential clinical data (eg, history, examination, ECG), its measurement is necessary to implement appropriate therapy.[8,9]
5. Delayed transfer to the hospital for determination of cTn or other diagnostic testing beyond the ECG in the office setting can be detrimental and should be avoided.[1-7,10]

2.3.2. Electrocardiogram

Recommendations for Electrocardiogram
Referenced studies that support the recommendations are summarized in Online Data Supplement 6.

COR	LOE	Recommendations
1	C-EO	1. In patients with chest pain in which an initial ECG is nondiagnostic, serial ECGs to detect potential ischemic changes should be performed, especially when clinical suspicion of ACS is high, symptoms are persistent, or the clinical condition deteriorates.[1]
1	C-EO	2. Patients with chest pain in whom the initial ECG is consistent with an ACS should be treated according to STEMI and NSTE-ACS guidelines.[1,2]
2a	B-NR	3. In patients with chest pain and intermediate-to-high clinical suspicion for ACS in whom the initial ECG is nondiagnostic, supplemental electrocardiographic leads V7 to V9 are reasonable to rule out posterior MI.[3-5]

Synopsis

Patients with chest pain and new ST-elevation, ST depression, or new left bundle branch block on ECG should be treated according to STEMI and NSTE-ACS guidelines.[1,2,6] An initial normal ECG does not exclude ACS. Patients with an initial normal ECG should have a repeat ECG, if symptoms are ongoing, until other diagnostic testing rules out ACS. An ECG may identify other nonischemic causes of chest pain (eg, pericarditis, myocarditis, arrhythmia, electrolyte abnormalities, paced rhythm, hypertrophic cardiomyopathy, pulmonary hypertension, congenital long QT, or normal variant). Figure 4 depicts an algorithm for the role of the ECG to help direct care for individuals presenting with chest pain or chest pain equivalents.

Recommendation-Specific Supportive Text

1. When an ECG is nondiagnostic, it should be compared with previous ECGs, if available.[7] A normal or unchanged ECG is reasonably useful but not sufficient at ruling out ACS.[8-10] Thus, decision-making should not be based solely on a single normal or nondiagnostic ECG. Left ventricular hypertrophy, bundle branch blocks, and ventricular pacing may mask signs of ischemia or injury.[11] Up to 6% of patients with evolving ACS are discharged from the ED with a normal ECG.[12-17] In patients where the initial ECG is normal or is without ST elevation, hyperacute T waves, left bundle branch block, or ST depression, serial ECGs should be performed and management should be guided by new electrocardiographic changes or other diagnostic testing (see Section 2.3.4 on Biomarkers, Section 3.1 on Anatomic Testing, or Section 3.2 on Stress Testing).[7,18-20] The timing for repeat ECG should also be guided by symptoms, especially if chest pain recurs or a change in clinical condition develops.[21]
2. When ST-elevation is present on the initial ECG, management should follow the prescribed STEMI treatment algorithms in associated guidelines.[2,22] Furthermore, if ST depression is identified on the initial ECG, management should follow the NSTE-ACS guidelines.[1]
3. A normal ECG may be associated with left circumflex or right coronary artery occlusions and posterior wall ischemia, which is often "electrically silent"; therefore, right-sided ECG leads should be considered when such lesions are suspected.[2-5]

2.3.3. Chest Radiography

Recommendation for Chest Radiography

COR	LOE	Recommendation
1	C-EO	1. In patients presenting with acute chest pain, a chest radiograph is useful to evaluate for other potential cardiac, pulmonary, and thoracic causes of symptoms.

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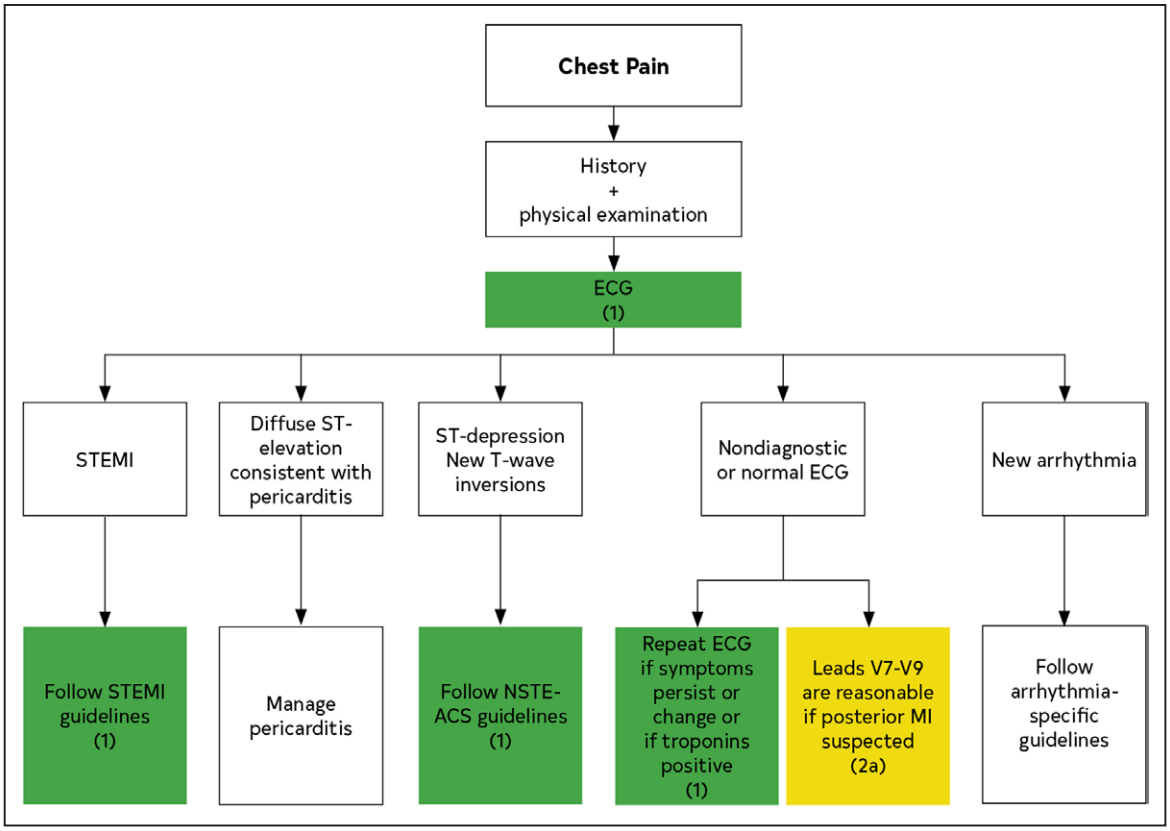

Figure 4. Electrocardiographic-Directed Management of Chest Pain
ECG indicates electrocardiogram; MI, myocardial infarction; NSTE-ACS, non–ST-segment–elevation acute coronary syndrome; and STEMI, ST-segment–elevation myocardial infarction.

Synopsis

Chest radiographs are rapid, noninvasive tests that can be used to screen for several disorders that may present with chest pain. The yield of chest radiography depends on the pretest probability and will thus be higher when history or physical examination point to a greater likelihood of a given diagnosis. However, chest radiographs often do not lead to a diagnosis that requires intervention,[1] and their use should be guided by clinical suspicion.

Recommendation-Specific Supportive Text

1. The AHA/ACC guidelines for NSTE-ACS and heart failure all recommend chest radiographs on presentation, although this should not delay urgent revascularization if it is indicated.[2,3] In patients with acute chest pain and heart failure, chest radiographs are useful to assess heart size and pulmonary congestion, as well as identifying potential pulmonary causes that may have contributed to symptoms. Chest radiographs may demonstrate a widened mediastinum in patients with aortic dissection, although they are not sensitive enough in this setting to rule out the diagnosis.[4] Chest radiographs may be most useful in the evaluation of patients with acute chest pain to detect alternative cardiac, pulmonary, or other conditions that may cause symptoms, including pneumonia, pneumothorax, or rib fractures. Pleural effusions, pulmonary artery enlargement, and infiltrates may suggest PE, which would need to be confirmed by further testing.

2.3.4. Biomarkers

Recommendations for Biomarkers Referenced studies that support the recommendations are summarized in Online Data Supplement 7.		
COR	**LOE**	**Recommendations**
1	B-NR	1. In patients presenting with acute chest pain, serial cTn I or T levels are useful to identify abnormal values and a rising or falling pattern indicative of acute myocardial injury.[1-21]
1	B-NR	2. In patients presenting with acute chest pain, high-sensitivity cTn is the preferred biomarker because it enables more rapid detection or exclusion of myocardial injury and increases diagnostic accuracy.[17,21-25]
1	C-EO	3. Clinicians should be familiar with the analytical performance and the 99th percentile upper reference limit that defines myocardial injury for the cTn assay used at their institution.[23,26]
3: No benefit	B-NR	4. With availability of cTn, creatine kinase myocardial (CK-MB) isoenzyme and myoglobin are not useful for diagnosis of acute myocardial injury.[27-32]

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Synopsis

Cardiovascular biomarkers can be useful for the diagnostic and prognostic assessment of patients with chest pain. Their most important application in clinical practice is for the rapid identification or exclusion of myocardial injury. The preferred biomarker to detect or exclude myocardial injury is cTn (I or T) because of its high sensitivity and specificity for myocardial tissue.[1-21,33] hs-cTn is preferred and can detect circulating cTn in the blood of most "healthy" individuals, with different sex-specific thresholds.[17,21,34] cTn is organ-specific but not disease-specific. Numerous ischemic, noncoronary cardiac, and noncardiac causes of cardiomyocyte injury can result in elevated cTn concentrations.[17,21,24,25] Therefore, interpretation of cTn results requires integration with all clinical information.[17,21]

Although multiple other cardiovascular biomarkers, including some in common clinical use such as natriuretic peptides, have been shown to be associated with the risk of adverse cardiovascular outcomes in patients with chest pain, none have sufficient diagnostic accuracy for myocardial injury to be recommended for that purpose. The use of D-dimer for diagnosis of PE is discussed in Section 4.2.2.

Recommendation-Specific Supportive Text

1. The preferred biomarker to detect or exclude cardiac injury is cTn (I or T) because of its high sensitivity and specificity for myocardial tissue.[1-21] Detection of myocardial cell injury, possibly indicative of AMI, is predicated on a rise or fall of this biomarker in blood.[1,3,4,10-21] A cTn concentration >99th percentile upper reference limit, which is assay-dependent, is an indicator of myocardial injury.[1,9,21] The coefficient of variation at the 99th percentile upper reference limit for each assay should be ≤10%.[8,21]
2. There is ample evidence for the superiority of hs-cTn assays over conventional cTn assays in multiple aspects of evaluation for patients presenting with chest pain with and without AMI.[17,21,24,25,33] The sensitivity and negative predictive values are greater with hs-cTn compared with previous generation assays.[17,21,24,25] In addition, the time interval from onset of chest pain to a detectable concentration at patient presentation is shorter with hs-cTn, affording more rapid rule-in and rule-out algorithms.[22] Although it is sometimes challenging to diagnostically discriminate among these causes of myocardial injury, irrespective of the final diagnosis, the presence of myocardial injury is associated with a higher risk of adverse outcomes among patients with chest pain.[35]
3. The level of detection, 99th percentile upper reference limit, analytical precision, and criteria for a significant delta are assay-specific, including among the many different manufacturers of the same analyte (eg, hs-cTnI). To appropriately apply a cTn assay, clinicians must be familiar with these analytical performance properties for the assay(s) that they use in their practice.[21]
4. Comparative studies have confirmed the superiority of cTn over CK-MB and myoglobin for diagnosis and prognosis of AMI.[27-32] The addition of CK-MB or myoglobin to cTn for evaluation of patients presenting with chest pain is not beneficial.

3. CARDIAC TESTING GENERAL CONSIDERATIONS

For acute and stable chest pain, noninvasive and invasive diagnostic testing is a core component of the evaluation underpinning its importance. Over the past decade, the quality of evidence supporting clinical indications for noninvasive testing has grown dramatically. The approach outlined in this guideline focuses on selective use of testing, optimization of lower cost evaluations, reducing layered testing, and deferring or eliminating testing when the diagnostic yield is low (Figure 5). Reducing unnecessary testing can provide a means to exert cost savings within the diagnostic evaluation of populations.[1] In the same manner, elimination of testing where evidence is lacking and the reduction in testing among low-risk patients for whom deferred testing is appropriate are emphasized in this guideline.

Testing choice will be influenced by site expertise and availability, but knowledge regarding which test may be preferable is useful when selecting between different modalities. Cost should also be considered, when known by the ordering clinician and there is equipoise between available modalities.[2] The exercise ECG is the lowest cost procedure used in the diagnostic evaluation when compared with stress imaging or anatomic procedures, with the exception of coronary artery calcium (CAC) scoring (Figure 6). For all imaging procedures, costs vary by payer and site of services.

The following sections provide a brief overview of the various noninvasive tests available for use in the evaluation of symptomatic patients. Previously, the term known as CAD had been used to define those with a significant obstructive stenosis (ie, ≥50%). In this guideline, we revise the term *known CAD* to include patients with prior anatomic testing (invasive angiography or coronary computed tomographic angiography [CCTA]) with identified nonobstructive atherosclerotic plaque and obstructive CAD. We recognize this is a departure from convention, but our intent was to

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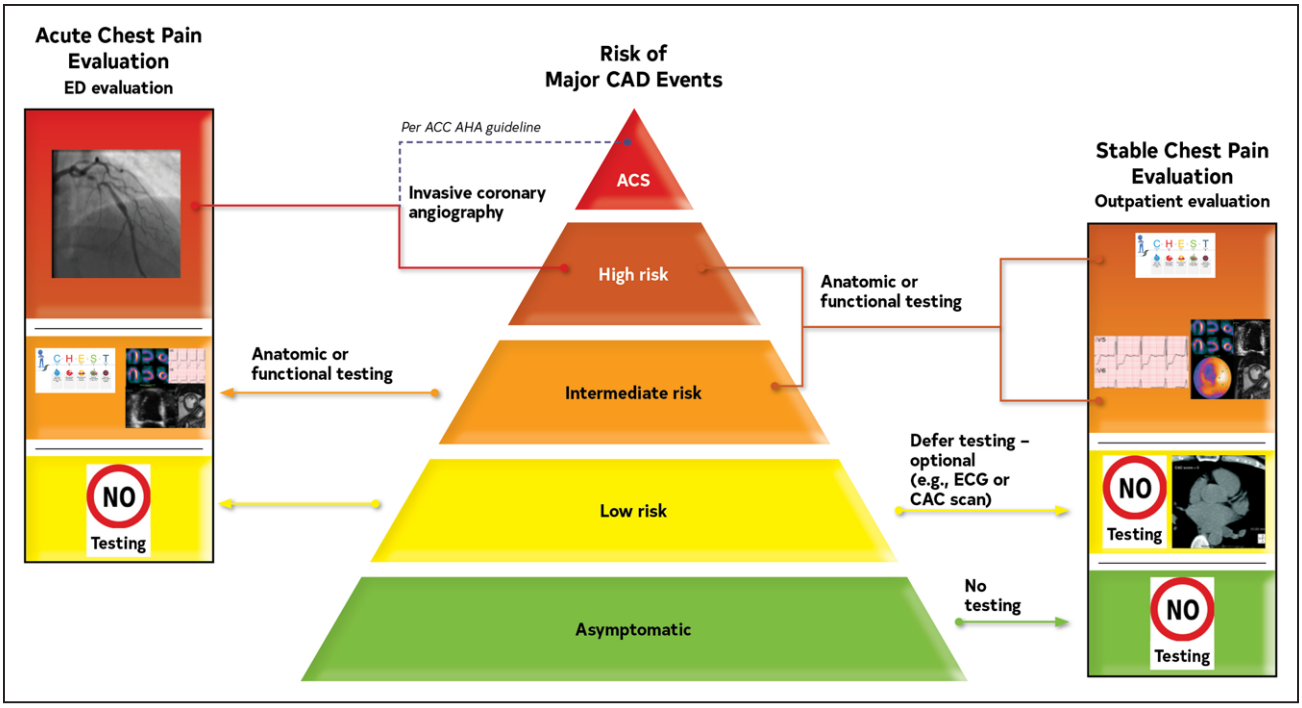

Figure 5. Chest Pain and Cardiac Testing Considerations
The choice of imaging depends on the clinical question of importance, to either a) ascertain the diagnosis of CAD and define coronary anatomy or b) assess ischemia severity among patients with an expected higher likelihood of ischemia with an abnormal resting ECG or those incapable of performing maximal exercise. ACS indicates acute coronary syndrome; CAC, coronary artery calcium; CAD, coronary artery disease; and ECG, electrocardiogram. Please refer to Section 4.1. For risk assessment in acute chest pain, see Figure 9. For risk assessment in stable chest pain, see Figure 11.

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ensure that those with lesser degrees of stenosis who do not require coronary intervention but would benefit from optimized preventive therapy do not get overlooked. However, throughout the document, the term "obstructive," consistent with convention, will be used to indicate CAD with ≥50% stenosis and nonobstructive CAD will be used to indicate CAD <50% stenosis. In addition, the term "high risk CAD" is used to denote patients with obstructive stenosis who have left main stenosis ≥50% or anatomically significant 3-vessel disease (≥70% stenosis).

3.1. Anatomic Testing

3.1.1. Coronary Computed Tomography Angiography

CCTA can visualize and help to diagnose the extent and severity of nonobstructive and obstructive CAD, as well as atherosclerotic plaque composition and high-risk features (eg, positive remodeling, low attenuation plaque).[1-8] Calculation of fractional flow reserve with CT (FFR-CT) provides an estimation of lesion-specific ischemia.[9] Current radiation dosimetry is low for CCTA, with effective doses for most patients in the 3 to 5 mSv range.[10] CCTA contraindications are reported in Table 5 Although in select situations imaging protocols that evaluate the coronary arteries, aorta, and pulmonary arteries may be useful, the general approach should be to use imaging protocols tailored to the most likely diagnosis, rather than a "triple rule out" approach (Figure 6).

3.1.2. Invasive Coronary Angiography

Invasive coronary angiography (ICA) defines the presence and severity of a luminal obstruction of an epicardial coronary artery, including its location, length, and diameter, as well as coronary blood flow.[1,2] For ICA, the primary goal is the characterization and detection of a high-grade obstructive stenosis to define feasibility and necessity of percutaneous or surgical revascularization. The use of physiologic indices (IFR and FFR) provides complementary functional information.[1] Radiation exposure to the patient during an interventional procedure averages 4 to 10 mSv and is dependent on procedural duration and complexity.[3,4]

ICA has a spatial resolution of 0.3 mm; as such, it is impossible to visualize arterioles (diameter of 0.1 mm) that regulate myocardial blood flow.[5] Coronary vascular functional studies can be performed during coronary angiography. Normal angiography does not exclude abnormal coronary vascular function, and it is possible to assess coronary microcirculation and coronary vasomotion. Coronary function testing may assist in manage-

Pretest likelihood of CAD	Low →	No testing necessary →	Option for CAC for ASCVD risk stratification		
	Intermediate-high →	Younger patient (<65 y of age)	**OR**	Less obstructive CAD suspected →	CCTA favored
	Intermediate-high →	Older patient (≥65 y of age)	**OR**	More obstructive CAD suspected →	Stress testing favored

	Favors use of CCTA	Favors use of stress imaging
Goal	• Rule out obstructive CAD • Detect nonobstructive CAD	• Ischemia-guided management
Availability and expertise	• High-quality imaging and expert interpretation routinely available	• High-quality imaging and expert interpretation routinely available
Likelihood of obstructive CAD	• Age <65 y	• Age ≥65 y
Prior test results	• Prior functional study inconclusive	• Prior CCTA inconclusive
Other compelling indications	• Anomalous coronary arteries • Require evaluation of aorta or pulmonary arteries	• Suspect scar (especially if PET or stress CMR available) • Suspect coronary microvascular dysfunction (when PET or CMR available)

Stress testing information					
	ETT	Stress echocardiography	SPECT MPI	PET MPI	Stress CMR MPI
Patient capable of exercise	✓	✓	✓		
Pharmacologic stress indicated		✓	✓	✓	✓
Quantitative flow				✓	✓
LV dysfunction/scar		✓	✓	✓	✓

Figure 6. Choosing the Right Diagnostic Test
ASCVD indicates atherosclerotic cardiovascular disease; CAD, coronary artery disease; CAC, coronary artery calcium; CCTA, coronary computed tomography angiography; CMR, cardiovascular magnetic resonance; ETT, exercise tolerance test; LV, left ventricular; MPI, myocardial perfusion imaging; PET, positron emission tomography and SPECT, single-photon emission computed tomography.

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ment of the underlying condition, in addition to providing prognostic information.[6-8]

3.2. Diagnostic Testing

3.2.1. Exercise ECG

Symptom-limited exercise ECG involves graded exercise until physical fatigue, limiting chest pain (or discomfort), marked ischemia, or a drop in blood pressure occurs.[1] Candidates for exercise ECG are those: a) without disabling comorbidity (eg, frailty, marked obesity [body mass index >40 kg/m^2], peripheral artery disease, chronic obstructive pulmonary disease, or orthopedic limitations) and capable of performing activities of daily living or able to achieve ≥5 metabolic equivalents of exercise (METs)[2]; and b) without

rest ST-T abnormalities (eg, >0.5-mm ST depression, left ventricular hypertrophy, paced rhythm, left bundle branch block, Wolff-Parkinson-White pattern, or digitalis use). Exercise electrocardiographic contraindications are reported in Table 5.

3.2.2. Echocardiography/Stress Echocardiography

Transthoracic echocardiography (TTE) can visualize and aid in the differential diagnosis among the numerous causes of acute chest pain such as acute aortic dissection, pericardial effusion, stress cardiomyopathy, and hypertrophic cardiomyopathy.[1,2] Although TTE does provide information, for patients with acute chest pain, visualization of left and right ventricular function and regional wall motion abnormalities allows for the assessment of CAD risk and may help to guide clinical decision-making. Performance of TTE at the bedside is ideal for patients with acute chest pain and can be done using point-of-care or handheld devices in institutions where such capabilities are available.

After ACS has been ruled out, stress echocardiography can be used to define ischemia severity and for risk stratification purposes. For TTE and stress echocardiography, ultrasound-enhancing agents are helpful for left ventricular opacification when ≥2 contiguous segments or a coronary territory is poorly visualized.[3] Coronary flow velocity reserve in the mid-distal left anterior descending coronary artery has been shown to improve risk stratification and may be helpful in the select patient with known CAD, including nonobstructive CAD.[4-6] Contraindications to stress type (exercise versus pharmacologic) and stress echocardiography are reported in Table 5.

3.2.3. Stress Nuclear (PET or SPECT) Myocardial Perfusion Imaging

After ACS has been ruled out, rest/stress positron emission tomography (PET) or single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) allows for detection of perfusion abnormalities, measures of left ventricular function, and high-risk findings, such as transient ischemic dilation.[1-8] For PET, calculation of myocardial blood flow reserve (MBFR, the ratio of peak hyperemia to resting myocardial blood flow) adds diagnostic and prognostic information over MPI data.[9-14] Radiation exposure, as reported by an average effective dose, is ~3 mSv for rest/stress PET with Rb-82 and ~10 mSv for Tc-99m SPECT; dual-isotope SPECT using thallium is not recommended.[15-17] SPECT/PET contraindications are and contraindications to type of stress test (exercise versus pharmacologic) are reported in Table 5.

3.2.4. Cardiovascular Magnetic Resonance Imaging

Cardiovascular magnetic resonance (CMR) imaging has the capability to accurately assess global and regional left and right ventricular function, detect and localize myocardial ischemia and infarction, and determine myocardial viability. CMR can also detect myocardial edema and microvascular obstruction, which can help differentiate acute versus chronic MI, as well as other causes of acute chest pain, including myocarditis. CMR contraindications are reported in Table 5.

3.3. Cardiac Testing Considerations for Women Who Are Pregnant, Postpartum, or of Child-Bearing Age

This guideline focuses on elective and urgent cardiac testing and, in both circumstances, imaging using ionizing radiation during pregnancy or postpartum while breast feeding should generally be avoided. When imaging is necessary to guide management, the risks and benefits of invasive angiography, SPECT, PET, or CCTA should be discussed with the patient. In all cases for a test deemed clinically necessary, the lowest effective dose of ionizing radiation should be used, including considerations for tests with no radiation exposure (eg, echocardiography, CMR imaging).[1] Radiation risk to the fetus is very small. Iodinated contrast enters the fetal circulation through the placenta and should be used with caution in a pregnant woman. The use of gadolinium contrast with CMR should be discouraged and used only when necessary to guide clinical management and is expected to improve fetal or maternal outcome.[2-5] If contrast is needed for a postpartum woman, breastfeeding may continue because <1% of iodinated contrast is excreted into the breast milk and absorbed into the infant's gastrointestinal tract.[6]

4. CHOOSING THE RIGHT PATHWAY WITH PATIENT-CENTRIC ALGORITHMS FOR ACUTE CHEST PAIN

After initial evaluation, the next step is determining whether further diagnostic testing is needed to establish a diagnosis or formulate a disposition plan. In some cases, there is clearly minimal risk of a serious medical condition although, in others, uncertainty may remain. We provide guidance to help clinicians make this determination within the context of acute and stable chest pain presentations.

The initial assessment of patients presenting with acute chest pain is focused on the rapid identification of patients with immediately life-threatening conditions such that appropriate medical interventions can be initiated. Included among the potentially life-threatening (emergency) causes of chest pain are ACS (Section 4.1), acute aortic syndromes (Section 4.2.1), and PE

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Table 5. Contraindication by Type of Imaging Modality and Stress Protocol

Exercise ECG	Stress Nuclear[1]*	Stress Echocardiography[2-5]	Stress CMR[6]	CCTA[7]*
Abnormal ST changes on resting ECG, digoxin, left bundle branch block, Wolff-Parkinson-White pattern, ventricular paced rhythm (unless test is performed to establish exercise capacity and not for diagnosis of ischemia) Unable to achieve ≥5 METs or unsafe to exercise High-risk unstable angina or AMI (<2 d) ie, active ACS Uncontrolled heart failure Significant cardiac arrhythmias (eg, VT, complete atrioventricular block) or high risk for arrhythmias caused by QT prolongation Severe symptomatic aortic stenosis Severe systemic arterial hypertension (eg, ≥200/110 mm Hg) Acute illness (eg, acute PE, acute myocarditis/pericarditis, acute aortic dissection)	High-risk unstable angina, complicated ACS or AMI (<2 d) Contraindications to vasodilator administration Significant arrhythmias (eg, VT, second- or third-degree atrioventricular block) or sinus bradycardia <45 bpm Significant hypotension (SBP <90 mm Hg) Known or suspected bronchoconstrictive or bronchospastic disease Recent use of dipyridamole or dipyridamole-containing medications Use of methylxanthines (eg, aminophylline, caffeine) within 12 h Known hypersensitivity to adenosine, regadenoson Severe systemic arterial hypertension (eg, ≥200/110 mm Hg)	Limited acoustic windows (eg, in COPD patients) Inability to reach target heart rate Uncontrolled heart failure High-risk unstable angina, active ACS or AMI (<2 d) Serious ventricular arrhythmia or high risk for arrhythmias attributable to QT prolongation Respiratory failure Severe COPD, acute pulmonary emboli, severe pulmonary hypertension Contraindications to dobutamine (if pharmacologic stress test needed) Atrioventricular block, uncontrolled atrial fibrillation Critical aortic stenosis† Acute illness (eg, acute PE, acute myocarditis/pericarditis, acute aortic dissection) Hemodynamically significant LV outflow tract obstruction Contraindications to atropine use: Narrow-angle glaucoma Myasthenia gravis Obstructive uropathy Obstructive gastrointestinal disorders Severe systemic arterial hypertension (eg, ≥200/110 mm Hg) **Use of Contrast Contraindicated in:** Hypersensitivity to perflutren Hypersensitivity to blood, blood products, or albumin (for Optison only)	Reduced GFR (<30 mL/min/1.73 m^2) Contraindications to vasodilator administration Implanted devices not safe for CMR or producing artifact limiting scan quality/interpretation Significant claustrophobia Caffeine use within past 12 h	Allergy to iodinated contrast Inability to cooperate with scan acquisition and/or breath-hold instructions Clinical instability (eg, acute respiratory distress, severe hypotension, unstable arrhythmia) Renal impairment as defined by local protocols Contraindication to beta blockade in the presence of an elevated heart rate and no alternative medications available for achieving target heart rate Heart rate variability and arrhythmia Contraindication to nitroglycerin (if indicated)
For all the imaging modalities, inability to achieve high-quality images should be considered, in particular for obese patients				

ACS indicates acute coronary syndrome; AMI, acute myocardial infarction; AS, aortic stenosis; CCTA, coronary computed tomography angiography; CMR, cardiovascular magnetic resonance imaging; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; LV, left ventricular; MET, metabolic equivalent; MRI, magnetic resonance imaging; PE, pulmonary embolism; SBP, systolic blood pressure; and VT, ventricular tachycardia. Readers should also review each imaging society's guidelines for more details on test contraindications.[1-14]

*Screening for potential pregnancy by history and/or pregnancy testing should be performed according to the local imaging facilities policies for undertaking radiological examinations that involve ionizing radiation in women of child-bearing age.

†Low-dose dobutamine may be useful for assessing for low-gradient AS.

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(Section 4.2.2). Myopericarditis is heterogeneous in its manifestations but can include fulminant myocarditis, which carries a high mortality rate (Section 4.2.3). A subset of noncardiovascular syndromes are also immediately life-threatening, including esophageal rupture (Section 4.3.1), tension pneumothorax, and sickle cell chest crisis. Nonemergency causes of chest pain, such as costochondritis and other musculoskeletal, or gastrointestinal causes, are discussed in Section 4.3. Such nonemergency causes predominate among patients presenting with acute chest pain; therefore, strategies that incorporate routine, liberal use of testing carry the potential for adverse effects of unnecessary investigations and unnecessary cost. Figure 7 provides an overview of this approach.

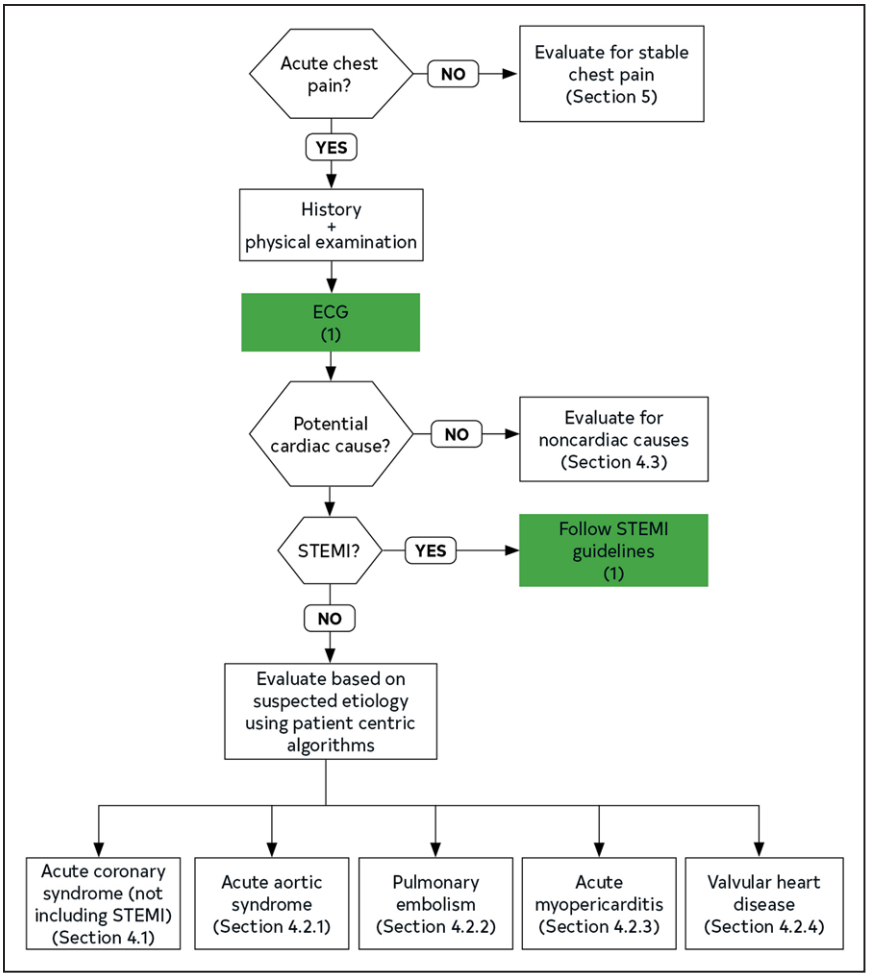

Figure 7. Patient-Centric Algorithms for Acute Chest Pain
ECG indicates electrocardiogram; and STEMI, ST-segment–elevation myocardial infarction.

4.1. Patients With Acute Chest Pain and Suspected ACS (Not Including STEMI)

Recommendations for Patients With Acute Chest Pain and Suspected ACS (Not Including STEMI)
Referenced studies that support the recommendations are summarized in Online Data Supplements 8 and 9.

COR	LOE	Recommendations
1	B-NR	1. In patients presenting with acute chest pain and suspected ACS, clinical decision pathways (CDPs) should categorize patients into low-, intermediate-, and high-risk strata to facilitate disposition and subsequent diagnostic evaluation.[1-14]
1	B-NR	2. In the evaluation of patients presenting with acute chest pain and suspected ACS for whom serial troponins are indicated to exclude myocardial injury, recommended time intervals after the initial troponin sample collection (time zero) for repeat measurements are: 1 to 3 hours for high-sensitivity troponin and 3 to 6 hours for conventional troponin assays.[15-17]
1	C-LD	3. To standardize the detection and differentiation of myocardial injury in patients presenting with acute chest pain and suspected ACS, institutions should implement a CDP that includes a protocol for troponin sampling based on their particular assay.[18,19]

Recommendations for Patients With Acute Chest Pain and Suspected ACS (Not Including STEMI) (Continued)

COR	LOE	Recommendations
1	C-LD	4. In patients with acute chest pain and suspected ACS, previous testing when available should be considered and incorporated into CDPs.[20-24]
2a	B-NR	5. For patients with acute chest pain, a normal ECG, and symptoms suggestive of ACS that began at least 3 hours before ED arrival, a single hs-cTn concentration that is below the limit of detection on initial measurement (time zero) is reasonable to exclude myocardial injury.[13,25-29]

Synopsis

Patients with acute chest pain and suspected ACS cover a spectrum of disease likelihood and stratification into low- versus intermediate- or high-risk groups once STEMI has been excluded (Figure 8). This stratification is important to guide subsequent management. Although most high-risk patients identified by CDPs should undergo cardiac catheterization, these patients still require a clinical assessment to determine if invasive evaluation is appropriate.

Chest pain risk scores provide a summative assessment combining clinical information, such as age, ST

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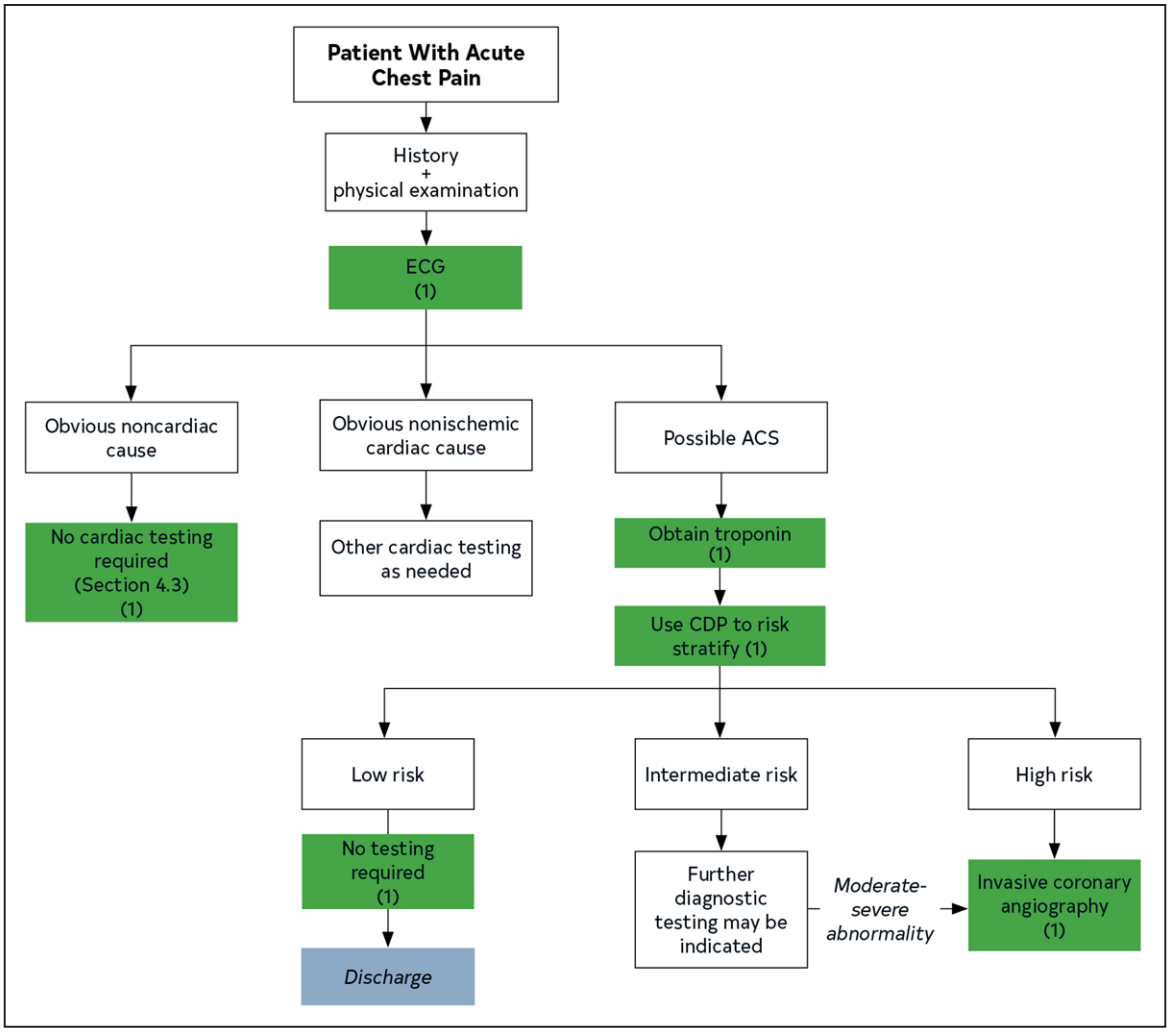

Figure 8. General Approach to Risk Stratification of Patients With Suspected ACS
ACS indicates acute coronary syndrome; CDP, clinical decision pathway; and ECG, electrocardiogram.

segment changes on ECG, symptoms, CAD risk factors, and cTn (Table 6) to estimate a patient's probability of ACS or risk of 30-day major adverse cardiovascular events (MACE).[30-35] Risk scores are essential when conventional cTn assays are used. Based on emerging data, the hs-cTn result may be more predictive than other clinical components of the risk score.[36-43]

Chest pain protocols are intended to add structure to the process of patient evaluation. Although various terms such as accelerated diagnostic protocols or disposition pathways have been used to describe such protocols, they can collectively be referred to as CDPs. CDPs are generally used to help guide disposition, but some also include guidance for cardiac testing of intermediate-risk patients.[30,31,33,34]

Compared with an unstructured clinical assessment, CDPs have been shown to decrease unnecessary testing and reduce admissions while maintaining high sensitivity for detection of acute myocardial injury and 30-day MACE (Table 6). The warranty period of prior cardiac testing should be considered when symptoms are unchanged (Table 7). Low-risk chest pain has been defined in Table 8.

Recommendation-Specific Supportive Text

1. CDPs that are based on cTn results have proven valid and useful in clinical practice.[1-14] Use of unstructured assessment for clinical decision-making often leads to both under- and over-testing. To improve on this, protocols have been developed to rapidly detect (rule in) and to rapidly exclude or "rule out" acute myocardial injury, incorporating time-dependent serial cTn sampling. Some protocols include chest pain risk scores while others do not. CDPs have been shown to help avoid admission or further testing in 21.3% to 43% of eligible patients and should be routinely used in clinical practice.[31,45,50] To standardize the approach to patient care and ensure consistency in decision-making, CDPs should be implemented at the institution level. There are multiple CDPs from which to choose, and

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Table 6. Sample Clinical Decision Pathways Used to Define Risk

	HEART Pathway[31]	EDACS[44]	ADAPT (mADAPT)[45]	NOTR[34]	2020 ESC/hs-cTn*[46,47]	2016 ESC/GRACE[11,38]
Target population	Suspected ACS	Suspected ACS, CP >5 min, planned serial troponin	Suspected ACS, CP >5 min, planned observation	Suspected ACS, ECG, troponin ordered	Suspected ACS, stable	Suspected ACS, planned serial troponin
Target outcome	↑ ED discharge without increasing missed 30-d or 1-y MACE	↑ ED discharge rate without increasing missed 30-d MACE	↑ ED discharge rate without increasing missed 30-d MACE	↑ Low-risk classification without increasing missed 30-d MACE	Early detection of AMI; 30-d MACE	Early detection of AMI
Patients with primary outcome in study population, %	6–22	12	15	5–8	9.8	10–17
Troponin	cTn, hs-cTn	hs-cTn	cTn, hs-cTn	cTn, hs-cTn	hs-cTn	cTn, hs-cTn
Variables used	History ECG Age Risk factors Troponin (0, 3 h)	Age Sex Risk factors History Troponin (0, 2 h)	TIMI score 0-1 No ischemic ECG changes Troponin (0, 2 h)	Age Risk factors Previous AMI or CAD Troponin (0, 2 h)	History ECG hs-cTn (0, 1 or 2 h)	Age HR, SBP Serum Cr Cardiac arrest ECG Cardiac biomarker Killip class
Risk thresholds:						
Low risk	HEART score <3 Neg 0, 3-h cTn Neg 0, 2-h hs-cTn	EDACS score <16 Neg 0, 2 h hs-cTn No ischemic ECG Δ	TIMI score 0 (or <1 for mADAPT) Neg 0, 2-h cTn or hs-cTn No ischemic ECG Δ	Age <50 y <3 risk factors Previous AMI or CAD Neg cTn or hs-cTn (0, 2 h)	Initial hs-cTn is "very low" and Sx onset >3 h ago **Or** Initial hs-cTn "low" and 1– or 2-h hs-cTn Δ is "low"	Chest pain free, GRACE <140 Sx <6 h - hs-cTn <ULN (0, 3 h) Sx >6 h - hs-cTn <ULN (arrival)
Intermediate risk	HEART score 4-6	NA	TIMI score 2-4	NA	Initial hs-cTn is between "low" and "high" **And/Or** 1- or 2-h hs-cTn Δ is between low and high thresholds	T0 hs-cTn = 12–52 ng/L or 1-h Δ = 3–5 ng/L
High risk	HEART score 7-10[48,49]	NA	TIMI score 5-7[49]	NA	Initial hs-cTn is "high" **Or** 1- or 2-h hs-cTn Δ is high	T0 hs-cTn >52 ng/L **Or** Δ 1 h >5 ng/L
Performance	↑ ED discharges by 21% (40% versus 18%) ↓ 30-d objective testing by 12% (69% versus 57%) ↓ length of stay by 12 h (9.9 versus 21.9 h)	More patients identified as low risk versus ADAPT (42% versus 31%)	ADAPT: More discharged ≤6 h (19% versus 11%)	30-d MACE sensitivity =100% 28% eligible for ED discharge	AMI sensitivity >99% 62% Ruled out (0.2% 30-d MACE) 25% Observe 13% Rule in	AMI sensitivity >99% 30-d MACE not studied
AMI sensitivity, %	100	100	100	100	>99	96.7
cTn accuracy: 30-d MACE sensitivity, %	100	100	100	100	NA	NA
hs-cTn accuracy: 30-d MACE sensitivity, %	95	92	93	99	99	--
ED discharge, %	40	49	19 (ADAPT) 39 (mADAPT)	28	--	--

ACS indicates acute coronary syndrome; ADAPT, Accelerated Diagnostic protocol to Assess chest Pain using Troponins; AMI, acute myocardial infarction; CP, chest pain or equivalent; Cr, creatinine; cTn, cardiac troponin; hs-cTn, high-sensitivity cardiac troponin; ECG, electrocardiogram; ED, emergency department; EDACS, emergency department ACS; ESC, European Society of Cardiology; GRACE, Global Registry of Acute Coronary Events; HEART, history, ECG, age, risk factors, troponin; HR, heart rate; hs, high sensitivity; MACE, major adverse cardiovascular events; mADAPT, modified (including TIMI scores of 1) ADAPT; NA, not applicable; neg, negative; NICE, National Institute for Health and Clinical Excellence; NOTR, No Objective Testing Rule; SBP, systolic blood pressure; SSACS, symptoms suggestive of ACS; Sx, symptoms; and ULN, upper limit of normal.

*The terms "very low," "low," "high," "1 h Δ," and "2 h Δ" refer to hs-cTn assay–specific thresholds published in the ESC guideline.[46,47]

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Table 7. Warranty Period for Prior Cardiac Testing

Test Modality	Result	Warranty Period
Anatomic	Normal coronary angiogram CCTA with no stenosis or plaque	2 y
Stress testing	Normal stress test (given adequate stress)	1 y

Table 8 provides a definition used for low-risk chest pain patients. CCTA indicates coronary computed tomographic angiography.

Table 8. Definition Used for Low-Risk Patients With Chest Pain

	Low Risk (<1% 30-d Risk for Death or MACE)
hs-cTn Based	
T-0	T-0 hs-cTn below the assay limit of detection or "very low" threshold if symptoms present for at least 3 h
T-0 and 1- or 2-h Delta	T-0 hs-cTn and 1- or 2-h delta are both below the assay "low" thresholds (>99% NPV for 30-d MACE)
Clinical Decision Pathway Based	
HEART Pathway[20]	HEART score ≤3, initial and serial cTn/hs-cTn < assay 99th percentile
EDACS[14]	EDACS score ≤16; initial and serial cTn/hs-cTn < assay 99th percentile
ADAPT[21]	TIMI score 0, initial and serial cTn/hs-cTn < assay 99th percentile
mADAPT	TIMI score 0/1, initial and serial cTn/hs-cTn < assay 99th percentile
NOTR[15]	0 factors

ADAPT indicates 2-hour Accelerated Diagnostic Protocol to Access Patients with Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarkers; cTn, cardiac troponin; EDACS, Emergency Department Acute Coronary Syndrome; HEART Pathway, History, ECG, Age, Risk Factors, Troponin; hs-cTn, high-sensitivity cardiac troponin; MACE, major adverse cardiovascular events; mADAPT, modified 2-hour Accelerated Diagnostic Protocol to Access Patients with Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarkers; NOTR, No Objective Testing Rule; NPV, negative predictive value; and TIMI, Thrombolysis in Myocardial Infarction.

all generally involve single or serial cTn measurement. Because there are several different manufacturers, the CDP should be based on assay-specific performance thresholds.[4,5] CDPs are more likely to be successful when they incorporate multidisciplinary teams.

2. There are important differences in the performance of highly sensitive and conventional cTn assays. hs-cTn assays may be used to guide disposition by repeat sampling at 1, 2, or 3 hours from ED arrival using the pattern of rise or fall (ie, delta) and the repeat value itself, based on assay-specific diagnostic thresholds.[37-43] When using conventional cTn assays, the sampling timeframe is extended to 3 to 6 hours from ED arrival.[36]
3. CDPs that include risk scores all perform well overall, with 99% to 100% sensitivity for index-visit AMI and 30-day MACE and have been shown to decrease advanced testing to varying degrees and should be used particularly with conventional cTn.[2,13,30-35] However, because sex-specific considerations are not included in all scoring systems, their effectiveness in men and women may not be equal.[51]
4. Previous test results should always be considered in the evaluation of patients with acute chest pain once ACS has been ruled out. In those with recent cardiac testing and normal findings who do not have biomarker evidence of acute myocardial injury, further testing is of limited value, provided that adequate exercise levels were achieved or pharmacologic stress was performed, imaging was of sufficient quality, and there are no changes in symptom frequency or stability at the new visit. The "warranty" intervals (Table 7) for the various cardiac testing modalities differ because of the low number of incident events among patients with a normal CCTA, although patients with normal stress testing may still have significant plaque and a higher event rate.[20-22] The warranty period for a normal stress-rest SPECT is highly variable because it is primarily determined by the type of stress, the patient's clinical characteristics, and left ventricular ejection fraction.[52]
5. To use cTn properly, an understanding of the assay used (high sensitivity or conventional) and the timing of chest pain onset relative to ED arrival is critical.[17,38,39] CDPs that emphasize rapid rule-out based on single hs-cTn concentrations below the limit of detection should be limited to patients whose symptoms started at least 3 hours before ED arrival.[2,5,6,11,14,16,25,40-43,53-55] Unlike high-sensitivity assays, clinical decision-making based on single measurement of conventional cTn has not been validated.[36] If the clinical presentation is still suspicious for ACS or diagnostic uncertainty remains after serial cTn measurement, it may be reasonable to repeat cTn assay later (ie, beyond 3 hours for high-sensitivity and beyond 6 hours for conventional assays).[23,40,41]

4.1.1. Low-Risk Patients With Acute Chest Pain

Recommendations for Low-Risk Patients With Acute Chest Pain
Referenced studies that support the recommendations are summarized in Online Data Supplements 10 and 11.

COR	LOE	Recommendations
1	B-NR	1. Patients with acute chest pain and a 30-day risk of death or MACE <1% should be designated as low risk.[1-11]
2a	B-R	2. In patients with acute chest pain and suspected ACS who are deemed low-risk (<1% 30-day risk of death or MACE), it is reasonable to discharge home without admission or urgent cardiac testing.[12-16]

Synopsis

Low-risk patients are those with symptoms suggestive of ACS and whose probability of MACE within 30 days is

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≤1%.[17] This estimate is based on clinical information that is readily available during the course of evaluation, typically occurring in the ED. There are several methods to determine that a patient is low risk (Table 8) but, invariably, all involve taking an appropriate history and physical examination, demonstration that the ECG is normal, nonischemic, or unchanged from the previous ECG, and cTn measurement at a single point in time (if presentation is >3 hours from symptom onset and using a high-sensitivity assay) or serially[1-11] (with incorporation of a chest pain risk score into the CDP if using a conventional cTn assay). Importantly, there is no evidence to support routine admission or cardiac testing for chest pain patients who are low risk, although outpatient CAC scanning can provide additional information for longer-term risk stratification.

Recommendation-Specific Supportive Text

1. A large proportion of patients presenting to the ED with chest pain are low risk based on a combination of features, including clinical stability, medical history, nonischemic ECG, and absence of acute myocardial injury on cTn measurement. Such individuals have a <1% frequency of ACS or MACE at 30 days.[1-11] Although achieving this with conventional cTn assays requires incorporation of risk scores into a CPD, hs-cTn results can be used on their own. This approach has been validated based on 15 studies including a total of >9600 patients, with a demonstrated negative predictive value for MI or death at 30 days of 99.8%.[11] These findings reflect studies involving both hs-cTnI and hs-cTnT using serial measurement algorithms or a single hs-cTn, provided the final measurement is performed ≥3 hours after the onset of symptoms, without incorporation of risk scores.
2. For this low-risk subset of ED patients who have chest pain, there is no evidence that stress testing or cardiac imaging within 30 days of the index ED visit improves their outcomes.[18] This represents a change from previous guidelines where stress testing within 72 hours was broadly recommended for patients with acute chest pain.[19] However, many of these patients have baseline cardiac risk factors that need to be managed. Pathways to facilitate outpatient follow-up for further evaluation and guideline-directed management of cardiac risk factors should be considered. Among patients presenting to the ED with chest pain, there is a separate group that is at such low risk of having atherosclerotic plaque or 30-day MACE that they do not even need CDP-based risk stratification.

4.1.1.1. Cost-Value Considerations in the Evaluation of Low-Risk Patients

The costs associated with the acute evaluation of chest pain have been examined within systematic reviews, health technology appraisals, and data collected in the observational or randomized clinical trial setting.[1-10] The decision analytic models suggest that the use of hs-Tn can be cost effective as a rule-out for ACS, primarily attributable to prompt discharge of patients without hs-Tn elevations.[2,8,11,12] Moreover, hs-Tn–guided diagnostic strategies also reduced the use of stress testing by nearly one-third.[13] From a large multicenter registry, the reduced time to discharge and use of noninvasive testing contributed to a cost savings of 20%.[13] Nonadherence to management recommendations impact the potential for cost savings.[5] From a randomized trial applying the HEART Pathway, a modest 30-day cost savings of $216 per patient ($P$=0.04) was observed.[6] However, the overall reductions in hospital admission and length of stay impacted population estimates for cost savings from 1 ED registry of 30769 patients presenting before and 23699 patients presenting after implementation of an accelerated diagnostic pathway and resulted in a total cost reduction of $13.5 million (Australian).[7] Thus, improved process efficiency and discharge of low-risk patients largely results in overall cost reductions.

4.1.2. Intermediate-Risk Patients With Acute Chest Pain

Recommendations for Intermediate-Risk Patients With Acute Chest Pain
Referenced studies that support the recommendations are summarized in Online Data Supplements 12 and 13.

COR	LOE	Recommendations
1	C-EO	1. For intermediate-risk patients with acute chest pain, TTE is recommended as a rapid, bedside test to establish baseline ventricular and valvular function, evaluate for wall motion abnormalities, and to assess for pericardial effusion.
2a	A	2. For intermediate-risk patients with acute chest pain, management in an observation unit is reasonable to shorten length of stay and lower cost relative to an inpatient admission.[1-7]

Synopsis

Patients in the ED without high-risk features and not classified as low risk by a CDP fall into an intermediate-risk group. Intermediate-risk patients do not have evidence of acute myocardial injury by troponin but remain candidates for additional cardiac testing. Some may have chronic or minor troponin elevations. This testing often requires more time than is appropriate for an ED visit. These patients may be placed in an inpatient bed or managed in a dedicated observation unit using a chest pain protocol.

Recommendation-Specific Supportive Text

1. Prompt use of TTE allows for an evaluation of cardiac cause for symptoms and evaluation of alternative pathologies for acute chest pain.[8-13] Rapid echocardiographic assessment may facilitate imaging of patients while they are symptomatic. Point-of-care echocardiograms performed at the

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bedside by properly trained clinicians and technicians may be particularly useful.

2. The additional testing needed for intermediate-risk patients often requires more time than is appropriate for an ED visit and is often performed under "observation" outpatient status. These patients may be placed in an inpatient bed or managed in a dedicated observation unit. Relative to care in an inpatient bed, dedicated observation units have been shown to decrease hospital admissions, length of stay, and cost while improving inpatient bed availability and chest pain patient satisfaction.[1-7]

4.1.2.1. Intermediate-Risk Patients With Acute Chest Pain and No Known CAD

Recommendations for Intermediate-Risk Patients With No Known CAD Referenced studies that support the recommendations are summarized in Online Data Supplements 14 and 15.

COR	LOE	Recommendations
		Index Diagnostic Testing
Anatomic Testing		
1	A	1. For intermediate-risk patients with acute chest pain and no known CAD eligible for diagnostic testing after a negative or inconclusive evaluation for ACS, CCTA is useful for exclusion of atherosclerotic plaque and obstructive CAD.[1-11]
1	C-EO	2. For intermediate-risk patients with acute chest pain, moderate-severe ischemia on current or prior (≤1 year) stress testing, and no known CAD established by prior anatomic testing, ICA is recommended.
2a	C-LD	3. For intermediate-risk patients with acute chest pain with evidence of previous mildly abnormal stress test results (≤1 year), CCTA is reasonable for diagnosing obstructive CAD.[12,13]
Stress Testing		
1	B-NR	4. For intermediate-risk patients with acute chest pain and no known CAD who are eligible for cardiac testing, either exercise ECG, stress echocardiography, stress PET/SPECT MPI, or stress CMR is useful for the diagnosis of myocardial ischemia.[1,4,10,14-36]
Sequential or Add-on Diagnostic Testing		
2a	B-NR	5. For intermediate-risk patients with acute chest pain and no known CAD, with a coronary artery stenosis of 40% to 90% in a proximal or middle coronary artery on CCTA, FFR-CT can be useful for the diagnosis of vessel-specific ischemia and to guide decision-making regarding the use of coronary revascularization.[37-43]
2a	C-EO	6. For intermediate-risk patients with acute chest pain and no known CAD, as well as an inconclusive prior stress test, CCTA can be useful for excluding the presence of atherosclerotic plaque and obstructive CAD.
2a	C-EO	7. For intermediate-risk patients with acute chest pain and no known CAD, with an inconclusive CCTA, stress imaging (with echocardiography, PET/SPECT MPI, or CMR) can be useful for the diagnosis of myocardial ischemia.

Synopsis

For patients with recent prior testing and normal findings, no further testing is indicated, given adequate exercise levels were achieved or pharmacologic stress was performed and if imaging was of sufficient quality, provided there are no changes in symptom frequency or stability at the new visit. The intervals (1 year for stress testing, 2 years for CCTA without plaque or stenosis) differ because of a lack of CAD progression and the low number of incident events among patients with a normal CCTA, although patients with normal stress testing may still have significant plaque and a higher event rate.[44-46] With a previously inconclusive or mildly abnormal stress test in the past year, CCTA is recommended, avoiding the potential for inconclusive results if the same type of test is repeated and enabling a more definitive rule-out of obstructive CAD. Among patients who present with acute chest pain who have had moderate-severe abnormalities on previous testing, but no interval anatomic testing, direct referral to ICA may be helpful for diagnosis of obstructive CAD.

Among those without a previous diagnostic evaluation and no known CAD, CCTA or stress testing may be the initial method of testing. Second-line testing may be helpful for patients with an initial inconclusive stress test. Similarly, for intermediate-risk patients with an intermediate stenosis on CCTA, FFR-CT, or stress testing may also be indicated.

ICA is indicated for patients categorized as high risk on a validated risk score (Figure 9). However, patients with an intermediate-risk score may also be candidates for CCTA or ICA if moderate-severe ischemia or significant left ventricular dysfunction is detected on index diagnostic testing.

Although there are several acceptable testing modalities for intermediate-risk patients with acute chest pain, the decision to use one versus another should be guided by local expertise and availability.

Recommendation-Specific Supportive Text

Anatomic Testing

1. In the ED evaluation of patients with acute chest pain, CCTA contributes to a reduced time to diagnosis and prompt discharge, without impacting safety (ie, no difference in death, repeat ED visits, or ACS over 1 to 6 months of follow-up) compared with a standard evaluation including stress testing.[1-4,8,47-50] Long-term prognostic data are limited, but the CATCH (Cardiac CT in the Treatment of Acute Chest Pain) trial showed a relative hazard for CAD events at ~18 months of 0.62 (95% CI: 0.40–0.98; P=0.04) for CCTA versus a standard care strategy.[48] Similar 40-month MACE rates were reported in the PROSPECT (Providing Regional

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Observations to Study Predictors of Events in the Coronary Tree) trial comparing CCTA- versus MPI-directed strategies (*P*=0.29).[10] Similar 2-year outcomes were also reported for stress echocardiography and CCTA (*P*=0.47).[29]

2. In patients who have evidence of moderate or severe ischemia on previous stress testing, who were not revascularized, and who present with acute chest pain, additional noninvasive stress testing is unlikely to result in any change in management. Such patients are assumed to have significant flow-limiting CAD and can proceed directly to an invasive evaluation if coronary revascularization is consistent with the goals of care. A sizeable proportion of patients with moderate-severe ischemia do not undergo ICA[51,52] and may require additional assessment, if repeat symptoms occur.
3. Symptomatic patients with inconclusive or mildly abnormal stress tests often have an increased risk of MACE.[53] Patients with previous stress testing often have atherosclerotic plaque and are at risk for obstructive CAD lesions.[12,13]

Stress Testing

4. Among patients evaluated in the ED who need further testing, exercise ECG is safe with most patients having negative studies and a low risk of ACS.[1,4,10,14-31,54] Stress echocardiography is safe and effective for triage and prompt discharge of patients and is associated with few events among those with normal or low-risk findings over near-term follow-up of up to 6 months.[17,18,36] Prompt stress echocardiography resulted in a reduction in ED and hospital length of stay, compared with CCTA, with similar 2-year MACE rates (*P*=0.47).[29] In the ED evaluation of patients with acute chest pain, a nuclear MPI strategy is similarly safe when compared with CCTA with no difference in MACE (death, ACS, or stroke) over follow-up of 6 to 12 months. Longer-term follow-up data from the PROSPECT trial[10] supported that at ~3.5 years, the rate of MACE was similar between MPI and CCTA (*P*=0.29).[10] Compared with CCTA, use of stress MPI delayed the time to diagnosis by >50%.[1,4] Furthermore, recent observation from 213 patients referred for rest-stress MPI with mildly abnormal hs-cTn values reported no adverse events related to the tests and a modest 13.6% yield for ischemic studies.[55] Single-center, small (n=105) randomized trial evidence suggests that stress CMR is safe without a near-term (90-day) increase in hospital readmission or additional testing.[32-34] From a single-center registry (n=135), stress CMR was associated with a high sensitivity (100%) and specificity (93%) for the detection of obstructive CAD or cardiovascular events at 1 year.[35]

Sequential or Add-on Testing

5. Patients with coronary artery stenosis of 40% to 90% in a proximal or middle coronary segment on CCTA may benefit from measurement of FFR-CT.[37-43] In a large registry of 555 patients, the addition of FFR-CT was safe with no difference in 90-day MACE compared with CCTA alone.[42] No deaths or MI occurred among patients with a negative FFR-CT when revascularization was deferred.
6. CCTA is highly effective at ruling out the presence of plaque or stenosis and may help to clarify risk assessment and subsequent management decisions in patients with no known CAD who have inconclusive stress test results.
7. Patients with acute chest pain who have indeterminate stenosis on CCTA may benefit from having a stress test with imaging to evaluate for myocardial ischemia.[37-43]

4.1.2.1.1. Cost-Value Considerations

Economic evaluations have explored the value of stress echocardiography, CCTA, and stress nuclear imaging. Several observational series report that prompt stress echocardiography in the ED for the evaluation of acute chest pain is associated with significantly lower costs, with no adverse sequelae after early discharge.[1,2] In a single-center randomized trial of 400 patients, prompt stress echocardiography was associated with a reduced rate of hospitalization (*P*=0.026) and length of stay in the ED (*P*<0.0001).[3] The CT-STAT (Systematic Triage of Acute Chest Pain Patients to Treatment) trial reported on the use of CCTA (n=361 patients) compared with stress MPI (n=338 patients) in the acute evaluation of chest pain in the ED.[4] In the CT-STAT trial, the time to diagnosis was 2.9 hours in the CCTA arm and 6.2 hours in the stress MPI arm (*P*<0.0001). Accordingly, median adjusted ED charges were nearly 40% lower for CCTA, compared with stress MPI ($2137 for CCTA versus $3458 for stress MPI; *P*<0.001). Overall, CCTA resulted in improved efficiency with a reduction in length of stay and prompt discharge,[5,6] resulting in cost savings from 15% to 38% when compared with standard care strategies[4,7] and a weighted cost savings of $680.[8]

4.1.2.2. Intermediate-Risk Patients With Acute Chest Pain and Known CAD

Recommendations for Intermediate-Risk Patients With Acute Chest Pain and Known CAD
Referenced studies that support the recommendations are summarized in Online Data Supplements 16 and 17.

COR	LOE	Recommendations
1	A	1. For intermediate-risk patients with acute chest pain who have known CAD and present with new onset or worsening symptoms, GDMT should be optimized before additional cardiac testing is performed.[1,2]

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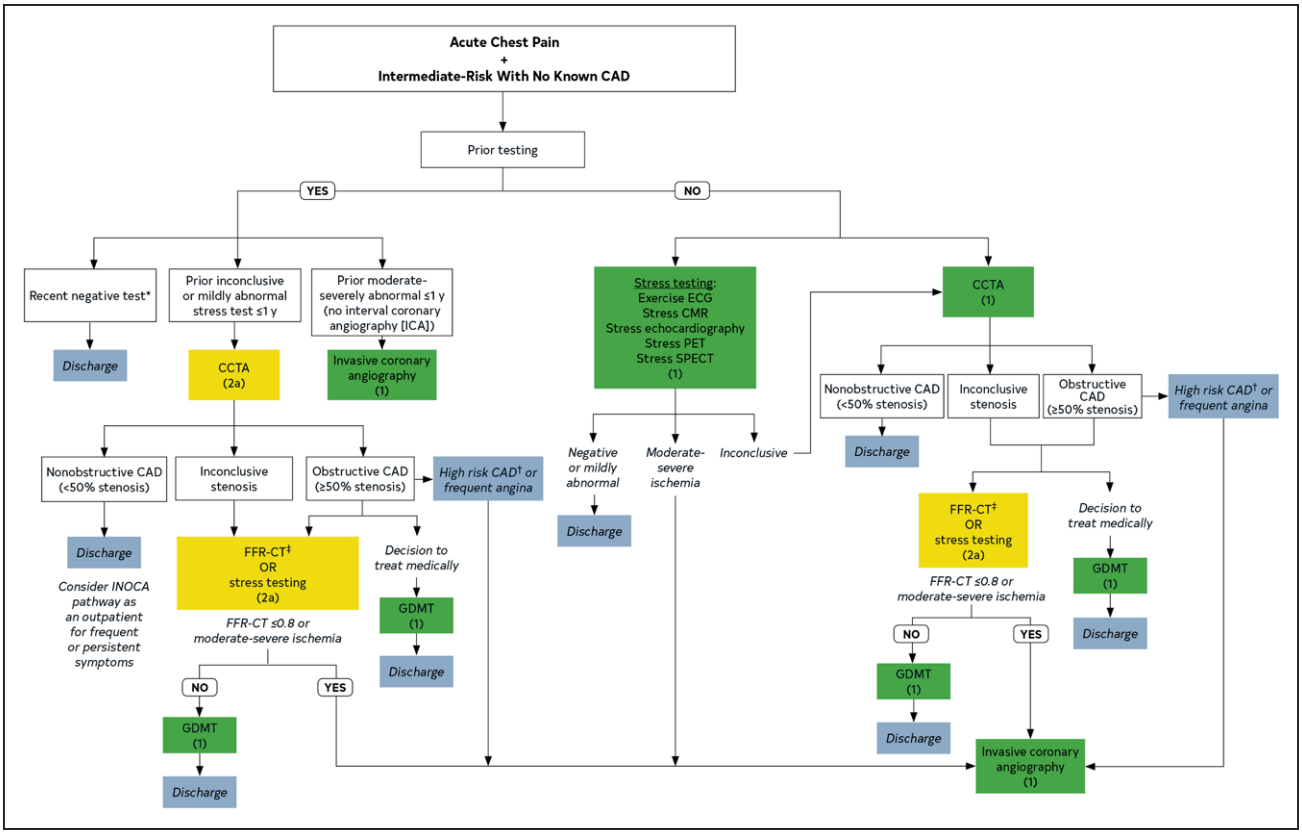

Figure 9. Evaluation Algorithm for Patients With Suspected ACS at Intermediate Risk With No Known CAD

Test choice should be guided by local availability and expertise.

*Recent negative test: normal CCTA ≤2 years (no plaque/no stenosis) OR negative stress test ≤1 year, given adequate stress.

†High-risk CAD means left main stenosis ≥ 50%; anatomically significant 3-vessel disease (≥70% stenosis).

‡For FFR-CT, turnaround times may impact prompt clinical care decisions. However, the use of FFR-CT does not require additional testing, as would be the case when adding stress testing.

CAD indicates coronary artery disease; CCTA, coronary CT angiography; CMR, cardiovascular magnetic resonance imaging; CT, computed tomography; FFR-CT, fractional flow reserve with CT; GDMT, guideline-directed medical therapy; ICA, invasive coronary angiography; INOCA, ischemia and no obstructive coronary artery disease; PET, positron emission tomography; and SPECT, single-photon emission CT.

Recommendations for Intermediate-Risk Patients With Acute Chest Pain and Known CAD (Continued)

COR	LOE	Recommendations
1	A	2. For intermediate-risk patients with acute chest pain who have worsening frequency of symptoms with significant left main, proximal left anterior descending stenosis, or multivessel CAD on prior anatomic testing or history of prior coronary revascularization, ICA is recommended.[3-8]
2a	B-NR	3. For intermediate-risk patients with acute chest pain and known nonobstructive CAD, CCTA can be useful to determine progression of atherosclerotic plaque and obstructive CAD.[9-11]
2a	B-NR	4. For intermediate-risk patients with acute chest pain and coronary artery stenosis of 40% to 90% in a proximal or middle segment on CCTA, FFR-CT is reasonable for diagnosis of vessel-specific ischemia and to guide decision-making regarding the use of coronary revascularization.[12-17]
2a	B-NR	5. For intermediate-risk patients with acute chest pain and known CAD who have new onset or worsening symptoms, stress imaging (PET/SPECT MPI, CMR, or stress echocardiography) is reasonable.[18-21]

Synopsis

Figure 10 includes the evaluation algorithm for patients with known CAD, including patients with nonobstructive and obstructive CAD. In patents with known nonobstructive CAD (ie, a luminal stenosis 1% to 49% on CCTA or ICA or calcified plaque on chest CT), repeat CCTA is recommended unless there is a large enough plaque burden where ischemia is suspected. The use of FFR-CT may be helpful to guide clinical decision-making regarding the use of coronary revascularization.[16] For all other patients with known CAD, stress testing is recommended to guide decisions on optimizing medical management and revascularization.

Recommendation-Specific Supportive Text

1. As shown in many secondary prevention trials, such as the Veterans Affairs Non-Q-Wave myocardial infarction (VANQUISH), COURAGE and ISCHEMIA, GDMT should be assessed in all patients with known CAD and optimized when symptomatic.[2,22,23]

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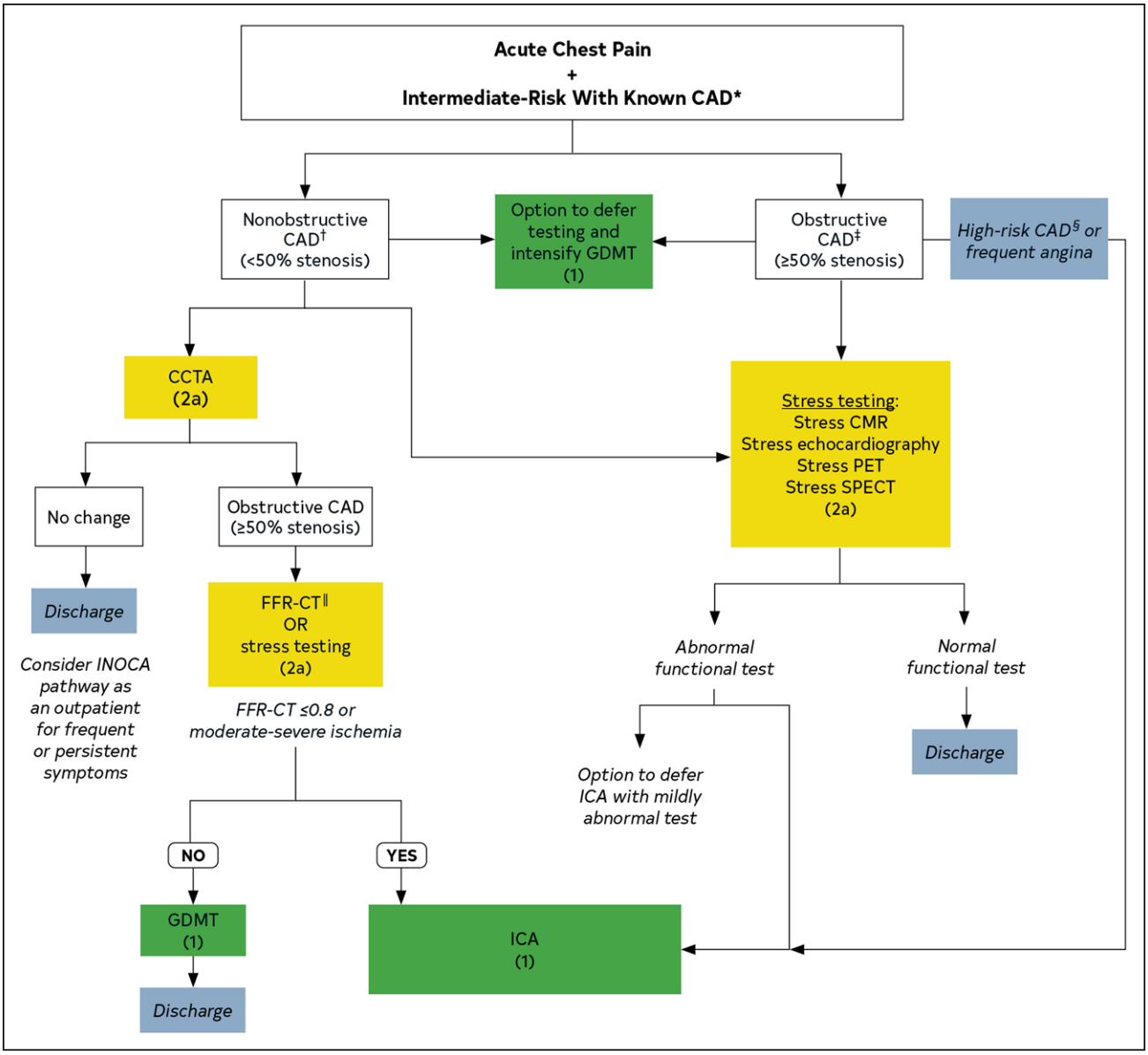

Figure 10. Evaluation Algorithm for Patients With Suspected ACS at Intermediate Risk With Known CAD

Test choice should be guided by local availability and expertise.

*Known CAD is prior MI, revascularization, known obstructive or nonobstructive CAD on invasive or CCTA.

†If extensive plaque is present a high-quality CCTA is unlikely to be achieved, and stress testing is preferred

‡Obstructive CAD includes prior coronary artery bypass graft/percutaneous coronary intervention.

§High-risk CAD means left main stenosis ≥50%; anatomically significant 3-vessel disease (≥70% stenosis).

‖FFR-CT turnaround times may impact prompt clinical care decisions.

ACS indicates acute coronary syndrome; CAD, coronary artery disease; CCTA, coronary CT angiography; CMR, cardiovascular magnetic resonance; CT, computed tomography; FFR-CT, fractional flow reserve with CT; GDMT, guideline-directed medical therapy; ICA, invasive coronary angiography; INOCA, ischemia and no obstructive coronary artery disease; PET, positron emission tomography; and SPECT, single-photon emission CT.

2. ICA is an effective means for diagnosing obstructive CAD and guiding the use of coronary revascularization. For the intermediate-risk patients with a previous history of CAD, ICA is reasonable for patients presenting with frequent weekly or daily symptoms or for those already on GDMT as well as those with high-risk CAD (left main or proximal left anterior descending or multivessel CAD).

3. For patients with previous anatomic testing that revealed nonobstructive CAD, CCTA has been shown to effectively document progressive CAD, including more extensive atherosclerotic plaque or the presence of high-risk plaque features or new obstructive stenosis ≥50%.[9-11,24] Patients in this category also include those patients with a previous CAC scan (or those for whom coronary artery calcification was

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noted as an incidental finding on chest CT) who present to an ED for evaluation of chest pain where concern exists with regard to the extent of noncalcified plaque and potential for underlying obstructive stenosis. However, for patients with extensive plaque, a stress test is preferred.

4. Patients with acute chest pain who have coronary artery stenosis from 40% to 90% on CCTA may benefit from measurement of FFR-CT, especially when the stenosis is proximal or mid-coronary artery.[12-17,25] From 1 large clinical registry, the deferral of coronary revascularization with a normal FFR-CT was safe, with no difference in MACE at 90 days.[16]
5. Most randomized trials that examined the role of stress testing in the ED enrolled patients with no known CAD, with few including patients with obstructive CAD (range: 7%–15%).[18-20] Despite this, assessing the functional significance of obstructive CAD is an important part of ischemia-guided management.[26]

4.1.3. High-Risk Patients With Acute Chest Pain

Recommendations for High-Risk Patients With Acute Chest Pain Referenced studies that support the recommendations are summarized in Online Data Supplements 18 and 19.		
COR	**LOE**	**Recommendations**
Recommendations for High-Risk Patients, Including Those With High-Risk Findings on CCTA or Stress Testing		
1	B-NR	1. For patients with acute chest pain and suspected ACS who have new ischemic changes on electrocardiography, troponin-confirmed acute myocardial injury, new-onset left ventricular systolic dysfunction (ejection fraction <40%), newly diagnosed moderate-severe ischemia on stress testing, hemodynamic instability, and/or a high clinical decision pathway (CDP) risk score should be designated as high risk for short-term MACE.[1-3]
1	C-EO	2. For patients with acute chest pain and suspected ACS who are designated as high risk, ICA is recommended.[4-7]
2a	B-NR	3. For high-risk patients with acute chest pain who are troponin positive in whom obstructive CAD has been excluded by CCTA or ICA, CMR or echocardiography can be effective in establishing alternative diagnoses.[8-12]

Synopsis

Patients with symptoms suggestive of ACS who are at high risk of short-term MACE include those with new ischemic changes on the ECG, troponin-confirmed acute myocardial injury, new-onset left ventricular systolic dysfunction (ejection fraction <40%), newly diagnosed moderate-severe ischemia on stress imaging, and/or a high risk score on CDP.[4,13,14] ICA is indicated for patients with confirmed ACS based on a robust body of randomized trial evidence and clinical practice guideline indications.[4-7] In the patients with a negative initial evaluation, ICA is also indicated for those categorized as high risk on a validated risk stratification instrument.

For high-risk patients with a documented AMI on the index ED evaluation and who demonstrate on CCTA or ICA normal or nonobstructive CAD, CMR and echocardiography are useful for examining alternative causes for symptoms such as nonischemic cardiomyopathy or myocarditis.[8-11]

Recommendation-Specific Supportive Text

1. Patients with acute chest pain and suspected ACS are considered at high risk for short-term MACE if they have new ischemic changes on electrocardiography, troponin-confirmed acute myocardial injury, new-onset left ventricular systolic dysfunction (ejection fraction <40%), newly diagnosed moderate-severe ischemia on stress testing, hemodynamic instability, and/or a high CDP risk score. Risk scores are recommended in guidelines to facilitate the management of patients who present with ACS.[3,15,16]
2. Among patients categorized as high risk, ICA provides a comprehensive assessment of the extent and severity of obstructive CAD. Moreover, the determination of the severity of anatomic CAD is critical to guide the use of coronary revascularization.[6]
3. Approximately 6% to 15% of troponin-positive ACS occurs in the absence of obstructive CAD.[17,18] Additional testing may be helpful to identify the cause that may alter an ensuing therapeutic strategy.[19] Evidence supports that CMR can identify wall motion abnormalities and myocardial edema and distinguish infarct-related scar from non-CAD causes such as myocarditis and nonischemic cardiomyopathy. When performed within 2 weeks of ACS, CMR can be useful to identify MI with nonobstructive CAD (MINOCA) from other causes.[8-11]

4.1.4. Acute Chest Pain in Patients With Prior Coronary Artery Bypass Graft (CABG) Surgery

Recommendations for Acute Chest Pain in Patients With Prior CABG Surgery		
COR	**LOE**	**Recommendations**
1	C-LD	1. In patients with prior CABG surgery presenting with acute chest pain who do not have ACS, performing stress imaging is effective to evaluate for myocardial ischemia or CCTA for graft stenosis or occlusion.[1-7]
1	C-LD	2. In patients with prior CABG surgery presenting with acute chest pain, who do not have ACS[8-14] or who have an indeterminate/nondiagnostic stress test, ICA is useful.[8]

Synopsis

There are many potential causes of acute chest pain in the months after CABG. Musculoskeletal pain from sternotomy remains the most common. However, other

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causes such as myocardial ischemia from acute graft stenosis or occlusion,[1,2] pericarditis, PE, sternal wound infection, or nonunion should also be considered. Post-sternotomy pain syndrome is defined as discomfort after thoracic surgery, persisting for at least 2 months, and without apparent cause.[15] The incidence of post-sternotomy pain syndrome has been found to be as low as 7% and as high as 66%,[16-19] with a higher prevalence in women compared with men within the first 3 months of thoracic surgery (51.4% versus 31.3%; $P<0.01$) but, after 3 months, postoperative sex difference in prevalence was not seen.[20] Graft failure within the first year post-CABG using saphenous venous grafts is usually a result of technical issues, intimal hyperplasia, or thrombosis.[5] Internal mammary artery graft failure within the first-year post-CABG is most commonly attributable to issues with the anastomotic site of the graft.

Reasons for acute chest pain several years after CABG include either graft stenosis or occlusion or progression of disease in a non-bypassed vessel. One year after CABG, ~10% to 20% of saphenous vein grafts fail, while by 10 years, only about half of saphenous vein grafts are patent.[5] In contrast, the internal mammary artery has patency rates of 90% to 95% 10 to 15 years after CABG.[6] Compared with the use of saphenous vein grafts, the use of radial artery grafts for CABG also resulted in a higher rate of patency at 5 years of follow-up.[7] In addition, knowledge of the native coronary anatomy and type of revascularization (complete or incomplete) is useful for interpretation of functional testing.

Recommendation-Specific Supportive Text

1. Acute chest pain in patients with prior CABG may be caused by myocardial ischemia as a result of technical errors at the graft anastomotic site, thrombosis within the graft, graft intimal hyperplasia, or vasospasm within arterial grafts. Progressive atherosclerosis within bypass grafts or the native coronary vessels may also result in acute chest pain caused by myocardial ischemia. Noninvasive stress imaging testing is reasonable in these patients as stress imaging will identify ischemic myocardial territories that will further guide revascularization for patients who are amenable to and are candidates for revascularization. CCTA has a great degree of accuracy with a sensitivity and specificity of detecting complete graft occlusions, 99% and 99%, respectively, when compared with the standard of ICA.[21] Furthermore, CCTA was ideal in assessing bypass grafts because of the large size of these vessels, decreased vessel calcification, and decreased motion of these vessels when compared with native coronary vessels. Evaluation of bypass grafts has been shown to be successful in 93% to 100% of patients.[21] In patients who have acute chest pain without features of ACS, CCTA is especially useful for assessing graft patency and is less robust for assessing native coronary vessel stenosis in this population.[1-7]
2. There are clinical features and stress imaging test features in patients with prior CABG presenting with acute chest pain with no ACS that may indicate a high likelihood of severe ischemic heart disease such as new resting left ventricular systolic dysfunction (left ventricular ejection fraction <35%) not readily explained by noncoronary causes, stress electrocardiographic findings including 2 mm of ST-segment depression at low workload or persisting into recovery, exercise-induced ST-segment elevation, or exercise-induced VT/ventricular fibrillation (VF), severe stress-induced left ventricular systolic dysfunction, stress-induced perfusion abnormalities involving ≥10% of the myocardium, or stress-induced left ventricular dilation. In those with prior CABG with high-risk stress imaging features, referral for ICA is useful provided that these patients are amenable to, and are candidates for, coronary revascularization.[8-14] Patients with prior CABG presenting with acute chest pain without the presence of ACS may have stress imaging features that are equivocal or nondiagnostic for the presence of myocardial ischemia. Equivocal or nondiagnostic stress imaging may be as a result of patient's body habitus, inadequate or suboptimal heart rate, arrhythmias such as atrial fibrillation, left bundle branch block, or patient motion. In these patients, performing an ICA is reasonable when the angiographic findings have a high likelihood of impacting therapeutic decisions.[8]

4.1.5. Evaluation of Patients With Acute Chest Pain Receiving Dialysis

Recommendation for Evaluation of Patients With Acute Chest Pain Receiving Dialysis Referenced studies that support the recommendation are summarized in Online Data Supplement 20.		
COR	**LOE**	**Recommendation**
1	B-NR	1. In patients who experience acute unremitting chest pain while undergoing dialysis, transfer by EMS to an acute care setting is recommended.[1-5]

Synopsis

In 2015, there were nearly 500 000 people in the United States who received maintenance dialysis to treat end-stage renal disease.[1] Chest pain occurs during hemodialysis in 2% to 5% of patients.[6,7] Causes are numerous and related to the high prevalence of severe cardiovascular disease in this population and the dialysis procedure

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itself. Causes include AMI or ACS, pericarditis, PE, pleuritis, hemolysis, gastroesophageal reflux, subclavian steal, and musculoskeletal disorders.[7] Myocardial ischemia is the most frequent serious cause and can be induced by hypotension[6,7] or tachyarrhythmias[2] occurring during dialysis in patients with CAD. AMI in patients undergoing dialysis is less frequently associated with chest pain than in patients who are not on dialysis, but warning signs may include diaphoresis or dyspnea.[3] Unusual but serious causes of chest pain during dialysis are embolism[6] and vessel perforation by catheter.[4,5] When indicated, cardiac testing for patients on dialysis should be the same as those who are not on dialysis.

Recommendation-Specific Supportive Text

1. Because the risk of CAD is relatively high in patients undergoing dialysis, when acute unremitting chest pain occurs during dialysis, a 12-lead ECG should be performed and the patient should be urgently transferred by EMS to an acute care setting for evaluation for cause of symptoms and further clinical engagement.[3]

4.1.6. Evaluation of Acute Chest Pain in Patients With Cocaine and Methamphetamine Use

Recommendation for Evaluation of Acute Chest Pain in Patients With Cocaine and Methamphetamine Use
Referenced studies that support the recommendation are summarized in Online Data Supplement 21.

COR	LOE	Recommendation
2a	B-NR	1. In patients presenting with acute chest pain, it is reasonable to consider cocaine and methamphetamine use as a cause of their symptoms.[1-3]

Synopsis

The most frequent presenting complaint of cocaine abuse is acute chest pain, resulting from ≥1 of the alkaloid's many cardiovascular actions.[1,4,5] Cocaine produces a hyperadrenergic state by blocking neuronal reuptake of norepinephrine and dopamine. The accumulation of these catecholamines increases heart rate and blood pressure, sometimes dramatically. These actions and the drug's simultaneous effect of coronary vasoconstriction and elevated myocardial oxygen demand can produce myocardial ischemia and even infarction in the absence of obstructive CAD. Additional hazardous actions include increased myocardial contractility, cardiac arrhythmias, myocardial toxicity directly or through augmented adrenergic stimulation, increased platelet aggregability, endothelial dysfunction, and hypertensive vascular catastrophes (aortic dissection, cerebrovascular hemorrhage).[4-6]

Methamphetamine has also been shown to lead to myocardial ischemia from mechanisms similar to cocaine. Studies have shown that methamphetamine can result in decreased myocardial perfusion. Like cocaine, methamphetamine also may reduce coronary sinus blood flow.[7] It has been reported that up to 70% of methamphetamine users have an abnormal ECG, with the most common finding being tachycardia.[8] Additional abnormalities on the ECG have been attributed to presence of hypertension, pulmonary artery hypertension, and cardiomyopathy, all of which have been associated with methamphetamine use.[9] General principles for risk stratification of patients with chest pain apply to patients with cocaine or methamphetamine use.[4]

Recommendation-Specific Supportive Text

1. Cocaine and methamphetamine use can be considered in young patients presenting with chest pain and evidence of ACS; the frequency of ACS is <10% among cocaine and methamphetamine users in most studies, and death is rare.[1-4] A person's urine typically tests positive for cocaine or methamphetamine within 1 to 4 hours of consuming the drug and will continue to test positive for 2 to 4 days.

4.1.7. Shared Decision-Making in Patients With Acute Chest Pain

Recommendations for Shared Decision-Making in Patients With Acute Chest Pain
Referenced studies that support the recommendations are summarized in Online Data Supplement 22.

COR	LOE	Recommendations
1	B-R	1. For patients with acute chest pain and suspected ACS who are deemed low risk by a CDP, patient decision aids are beneficial to improve understanding and effectively facilitate risk communication.[1,2]
1	B-R	2. For patients with acute chest pain and suspected ACS who are deemed intermediate risk by a CDP, shared decision-making between the clinician and patient regarding the need for admission, for observation, discharge, or further evaluation in an outpatient setting is recommended for improving patient understanding and reducing low-value testing.[1,2]

Synopsis

Risk communication and shared decision-making using a decision aid such as Chest Pain Choice have been shown to increase patient knowledge, engagement, and satisfaction and decrease the rate of observation unit admission and 30-day cardiac stress testing in both single-center and multicenter randomized trials.[1-3] For low-risk patients, decision aids can facilitate risk communication between the clinician and the patient and increase patients' understanding of their risk and the importance of outpatient follow-up after discharge from

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the ED. For intermediate-risk patients, admission to an observation unit or discharge from the ED with further, timely evaluation in an outpatient setting is acceptable. Decision aids such as Chest Pain Choice can effectively facilitate shared decision-making regarding the need for admission, observation, or discharge for further evaluation in an outpatient setting.[3]

Recommendation-Specific Supportive Text

1. Adult ED patients with acute chest pain who are deemed low risk are frequently admitted for observation and cardiac stress testing or CCTA, resulting in increased cost to the patient and the health care system.[2] Shared decision-making is the process by which patients and clinicians share information and take steps to build consensus about preferred tests and treatments. In shared decision-making, both parties share information: the clinician offers options and describes the potential harms and benefits, and the patient communicates his or her preferences. Patients are prepared with a better understanding of the relevant factors influencing the decision and share responsibility for deciding how to proceed. Shared decision-making rests on the principles of patient centered care, including respect for patient autonomy (ie, that a patient's informed preferences should be the basis for medical action).[4] Decision aids are patient-centered tools designed to facilitate shared decision-making between a patient and the clinician such that patients' values and preferences are incorporated into health care decisions.[5] Shared decision-making, however, can be performed without a decision aid; lack of a decision aid should not preclude attempts at shared decision-making.
2. In a single-center randomized trial of adults presenting to the ED with a chief complaint of chest pain (n=204) who were being considered by the treating clinician for admission to the observation unit for cardiac stress testing, patients randomized to shared decision-making facilitated by the Chest Pain Choice Decision Aid[2,3] had greater knowledge, were more engaged in the decision-making process, and less frequently decided to be admitted to the observation unit for stress testing (58% versus 77%, absolute difference 19%, 95% CI: 6%-31%).[2] There were no MACE after discharge in either group. The decision aid was subsequently tested in a population of 898 patients with greater socioeconomic diversity recruited from 6 EDs across the United States.[1,6] Similar findings were observed. Analysis of health care use in this trial showed fewer cardiac imaging tests and lower overall 45-day health care use in patients randomized to the decision aid.[7,8]

4.2. Evaluation of Acute Chest Pain With Nonischemic Cardiac Pathologies

Recommendation for Evaluation of Acute Chest Pain With Nonischemic Cardiac Pathologies		
COR	**LOE**	**Recommendation**
1	C-EO	1. In patients with acute chest pain in whom other potentially life-threatening nonischemic cardiac conditions are suspected (eg, aortic pathology, pericardial effusion, endocarditis), TTE is recommended for diagnosis.

Synopsis

Alternative nonischemic causes for acute chest pain should be considered if an ischemic cause is not suspected based on initial evaluation. Echocardiography, as a portable bedside noninvasive and almost universally available tool, should be used to unmask some imminently dangerous but potentially treatable cardiac conditions.

TTE is the primary tool to diagnose pericardial effusions with and without tamponade, aortic dissections (TTE and transesophageal echocardiography [TEE]), acute right ventricular dysfunction in the setting of PE, as well as mechanical complications of MI (ventricular septal rupture, free wall rupture, papillary muscle dysfunction and rupture).

Echocardiography can also identify cardiac masses, emboli, or clots in transit, intracardiac shunting, or endocarditis. Furthermore, beyond the anatomic findings, echocardiography can be used to noninvasively assess volume status, pulmonary hypertension, valvular stenosis, and regurgitation. Many of these entities may present with acute chest pain as well as shortness of breath.

Recommendation-Specific Supportive Text

1. Prompt use of TTE allows for an evaluation of cardiac cause for symptoms and evaluation of alternative pathologies for acute chest pain.[1-6] Rapid echocardiographic assessment may facilitate imaging of the patient while symptomatic.

4.2.1. Acute Chest Pain With Suspected Acute Aortic Syndrome

Recommendations for Acute Chest Pain With Suspected Acute Aortic Syndrome		
COR	**LOE**	**Recommendations**
1	C-EO	1. In patients with acute chest pain where there is clinical concern for aortic dissection, computed tomography angiography (CTA) of the chest, abdomen, and pelvis is recommended for diagnosis and treatment planning.
1	C-EO	2. In patients with acute chest pain where there is clinical concern for aortic dissection, TEE or CMR should be performed to make the diagnosis if CT is contraindicated or unavailable.

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Synopsis

Acute aortic syndrome describes diseases involving disruptions in the aortic wall, including aortic dissection, intramural hematoma, and penetrating aortic ulcer.[1] The annual incidence is 2 to 4 cases/100 000, with higher prevalence with genetic conditions that weaken the aortic wall.[2] Prominent risk factors include hypertension atherosclerosis and connective tissue disease. Cocaine use may provoke dissection even without other risk factors.

Acute onset of severe chest or back pain heralds acute aortic dissection in 80% to 90% of patients, sometimes characterized as ripping or tearing.[3] Progression can produce end-organ hypoperfusion, and proximal extension may cause tamponade, severe acute aortic regurgitation, or rarely, STEMI. Intramural hematomas, which differ from dissection by absence of an identifiable intimal flap, have a lesser understood natural history but are typically evaluated and treated in a similar manner to dissections.

Recommendation-Specific Supportive Text

1. A high index of suspicion in appropriate patients, and a coordinated, multidisciplinary evaluation is needed to optimize outcomes. The diagnostic modality of choice in stable patients is CTA, which is both highly sensitive and specific.[4-6] Chest radiographs can show mediastinal widening but may be normal.
2. TTE can show pericardial effusion or aortic regurgitation, and a dissection flap can sometimes be visualized; however, more complete imaging of the aortic arch requires TEE or CT. CMR is sensitive and specific, but CT is usually more expeditious.

4.2.2. Acute Chest Pain With Suspected PE

Recommendations for Acute Chest Pain With Suspected PE
Referenced studies that support the recommendations are summarized in Online Data Supplement 23.

COR	LOE	Recommendations
1	B-NR	1. In stable patients with acute chest pain with high clinical suspicion for PE, CTA using a PE protocol is recommended.[1-4]
1	C-EO	2. For patients with acute chest pain and possible PE, need for further testing should be guided by pretest probability.

Synopsis

The incidence of PE is estimated at 65 cases per 100 000, but some cases are asymptomatic and others undiagnosed.[5,6] One-third of deaths are sudden, and 60% are undiagnosed before death.[7] Risk factors for PE are the same for venous thromboembolism and include inherited hypercoagulable states and acquired risk factors (recent surgery, trauma, immobilization, malignancy, smoking, obesity, oral contraception). Recognition of PE can be challenging because symptoms and clinical signs may be nonspecific. Dyspnea followed by chest pain, classically pleuritic, is the most common presenting symptom.[1] Signs of deep venous thrombosis may be present on examination.[5]

Recommendation-Specific Supportive Text

1. CTA using PE protocol is the diagnostic modality of choice in stable patients; ventilation-perfusion scanning is a second-line alternative in the acute setting.[3,4] Use of clinical prediction rules to select patients for imaging can decrease radiation exposure and cost.[8] Troponin (and brain natriuretic peptide) can be elevated, and echocardiography may reveal acute right ventricular strain consequent to large PEs; troponin and brain natriuretic peptide are both markers for higher mortality rate.[2]
2. Recognition of PE is important because prompt anticoagulation improves outcomes.[2] Clinical assessment combined with pretest risk stratification can help select patients appropriate for diagnostic imaging. In the absence of shock, diagnostic evaluation depends on the clinical assessment of pretest probability.[3] Several prediction rules are available that add predictive value to clinical assessment.[4] D-dimers are highly sensitive but not very specific for the diagnosis of PE in ED patients. Measurement of D-dimers, using age- and sex-specific cutoffs, may be useful in patients at low to intermediate pretest probability; those with negative D-dimers can probably be discharged without further testing, whereas those with positive values should be considered for CTA.[2]

4.2.3. Acute Chest Pain With Suspected Myopericarditis

Recommendations for Acute Chest Pain With Suspected Myopericarditis
Referenced studies that support the recommendations are summarized in Online Data Supplement 24.

COR	LOE	Recommendations
1	B-NR	1. In patients with acute chest pain and myocardial injury who have nonobstructive coronary arteries on anatomic testing, CMR with gadolinium contrast is effective to distinguish myopericarditis from other causes, including myocardial infarction and nonobstructive coronary arteries (MINOCA).[1-6]
1	B-NR	2. In patients with acute chest pain with suspected acute myopericarditis, CMR is useful if there is diagnostic uncertainty, or to determine the presence and extent of myocardial and pericardial inflammation and fibrosis.[7-12]
1	C-EO	3. In patients with acute chest pain and suspected myopericarditis, TTE is effective to determine the presence of ventricular wall motion abnormalities, pericardial effusion, valvular abnormalities, or restrictive physiology.
2b	C-LD	4. In patients with acute chest pain with suspected acute pericarditis, noncontrast or contrast cardiac CT scanning may be reasonable to determine the presence and degree of pericardial thickening.[7,8,13]

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Synopsis

Pericarditis and myocarditis share overlapping common causes and likely form a continuum.[8] In patients with pericarditis, a minimally elevated troponin does not appear to confer a worse prognosis.[14] Most cases of pericarditis in developed nations are viral, although tuberculosis is sometimes a consideration.

Pericarditis classically presents with chest pain that is sharp, pleuritic, and which may be improved by sitting up or leaning forward, although in many instances such findings are not present. A pericardial friction rub may be audible. Widespread ST-elevation with PR depression is the electrocardiographic hallmark, although changes are nonspecific and may be transient.

Clinical manifestations of myocarditis are varied and include chest pain that is often sharp and reflective of epicardial inflammation involving the pericardium. Myocardial dysfunction often causes fatigue and exercise intolerance, and predominance of heart failure distinguishes myocarditis from pericarditis. Troponin is usually elevated.[15]

Recommendation-Specific Supportive Text

1. CMR with late gadolinium enhancement imaging can show characteristic changes of acute myopericarditis, especially if performed early, within 2 weeks of the index presentation. CMR can also frequently distinguish between acute myopericarditis, other cardiomyopathies, and occult MI and other causes of MI and nonobstructive coronary arteries.[1,2]
2. In patients with suspected acute myopericarditis, or if there is diagnostic uncertainty, CMR is useful to determine myocardial edema, thickening, and late enhancement. CMR may also show evidence of pericardial effusions.[2,16] CMR has a sensitivity of 94% to 100% in detecting inflammation of the pericardium.[7-10] CMR features that are suggestive of acute pericarditis include enhancement or thickened pericardium, although such findings can also be seen in the presence of pericardial fibrosis. In addition, increased signal on T2-weighted images correlates with edema, which may be seen in acute myopericarditis. The presence of pericardial adhesions between the visceral and parietal pericardium may be useful in patients with suspected acute pericarditis or pericardial constriction.[7-10]
3. In patients with suspected myopericarditis, echocardiography may show segmental left ventricular wall hypokinesis, which suggests myocardial involvement in patients with myocarditis and is, therefore, a useful tool in these patients. Patients with acute pericarditis may also have echocardiographic findings such as increased pericardial brightness or pericardial effusion with or without tamponade physiology. Some patients with acute pericarditis may also have normal echocardiographic findings.[9,17]
4. In patients with suspected acute pericarditis, cardiac CT with or without contrast may show features that are suggestive of acute pericarditis, such as pericardial thickening or enhancement (after contrast administration). Additionally, CT attenuation values of pericardial effusion can help distinguish between exudative and transudative pericardial fluid. There are limited data on the accuracy of cardiac CT in diagnosing acute pericarditis; a small study showed that pericardial thickening or enhancement was the most accurate single parameter for pericarditis, with sensitivity of 54% to 59% and specificity of 91% to 96%. Therefore, cardiac CT is a reasonable second-line study in these patients.[7,8,13]

4.2.4. Acute Chest Pain With Valvular Heart Disease (VHD)

Recommendations for Acute Chest Pain With VHD		
COR	**LOE**	**Recommendations**
1	C-EO	1. In patients presenting with acute chest pain with suspected or known history of VHD, TTE is useful in determining the presence, severity, and cause of VHD.
1	C-EO	2. In patients presenting with acute chest pain with suspected or known VHD in whom TTE diagnostic quality is inadequate, TEE (with 3D imaging if available) is useful in determining the severity and cause of VHD.
2a	C-EO	3. In patients presenting with acute chest pain with known or suspected VHD, CMR imaging is reasonable as an alternative to TTE and/or TEE is nondiagnostic.

Synopsis

Chest pain may occur in the presence of VHD, particularly stenotic VHD such as aortic valve stenosis and mitral valve stenosis with secondary pulmonary hypertension. Chest pain may also occur after papillary muscle rupture in the setting of MI or in acute degenerative mitral valve disease after spontaneous chordal rupture. Chest pain may also occur in the setting of acute severe aortic insufficiency, which may be related to acute aortic pathology such as an aortic dissection manifesting as severe acute chest pain that may radiate to the back.

The cause of chest pain in patients with aortic valve stenosis may be secondary to coexisting obstructive epicardial CAD[1] or, more commonly, chest pain may occur as a result of coronary microvascular dysfunction[2] in the presence of very elevated left ventricular pressure caused by a high left ventricular afterload, along with the associated left ventricular hypertrophy. The cause of chest pain in patients with severe mitral

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valve stenosis is more likely to be secondary to epicardial obstructive CAD[1] although, less likely, chest pain may occur in isolated mitral valve stenosis resulting from low cardiac output and decreased coronary perfusion.[1]

Recommendation-Specific Supportive Text

1. Patients with VHD may present with chest pain particularly in the setting of stenotic VHD, severe valvular regurgitation in the setting of AMI with ruptured papillary muscle resulting in acute severe mitral valve insufficiency, or acute aortic valve insufficiency in the setting of acute aortic pathology, such as aortic dissection.[3,4] TTE is useful in assessing valvular pathologies because it is widely available and is therefore a good first-line test in these patients to determine the presence, severity, and cause of VHD.[3]
2. The ability to attain adequate 3-dimensional (3D) transthoracic images depends on the ability to obtain adequate 2-dimensional images.[5] In these clinical situations where TTE images are technically inadequate, TEE with 3D images, if required, is useful to determine the severity and cause of VHD.[3,6]
3. There may be clinical situations when TTE and TEE may not be technically adequate to assess the severity and cause of VHD. In such circumstances, CMR may be useful to objectively assess the severity and cause of VHD.[6] The aorta can also be visualized on CMR and can therefore be used to assess acute aortic pathologies accompanying aortic valve insufficiency such as aortic dissection.[4]

4.3. Evaluation of Acute Chest Pain With Suspected Noncardiac Causes

Recommendation for Evaluation of Acute Chest Pain With Suspected Noncardiac Causes		
COR	**LOE**	**Recommendation**
1	C-EO	1. Patients with acute chest pain should be evaluated for noncardiac causes if they have persistent or recurring symptoms despite a negative stress test or anatomic cardiac evaluation, or a low-risk designation by a CDP.

Table 9. Differential Diagnosis of Noncardiac Chest Pain

Respiratory
Pulmonary embolism
Pneumothorax/hemothorax
Pneumomediastinum
Pneumonia
Bronchitis
Pleural irritation
Malignancy
Gastrointestinal
Cholecystitis
Pancreatitis
Hiatal hernia
Gastroesophageal reflux disease/gastritis/esophagitis
Peptic ulcer disease
Esophageal spasm
Dyspepsia
Chest wall
Costochondritis
Chest wall trauma or inflammation
Herpes zoster (shingles)
Cervical radiculopathy
Breast disease
Rib fracture
Musculoskeletal injury/spasm
Psychological
Panic disorder
Anxiety
Clinical depression
Somatization disorder
Hypochondria
Other
Hyperventilation syndrome
Carbon monoxide poisoning
Sarcoidosis
Lead poisoning
Prolapsed intervertebral disc
Thoracic outlet syndrome
Adverse effect of certain medications (eg, 5-fluorouracil)
Sickle cell crisis

Synopsis

The differential diagnosis for noncardiac causes of acute chest pain is quite broad and includes respiratory, musculoskeletal, gastrointestinal, psychological, and other causes (Table 9). Of these, musculoskeletal causes are the most common, including costochondritis, muscle strain, and potential consequences of recent or occult chest trauma such as rib fracture. Various gastrointestinal causes, commonly esophageal, can present with chest pain, including gastrointestinal reflux and esophageal dysmotility as well as gastritis from either medications or peptic ulcer disease. Respiratory causes are less frequent but potentially more serious and include PE, pneumonia, and pneumothorax. Many patients will have dyspnea in addition to chest pain. Psychological causes are usually diagnoses of exclusion but merit consideration in the right context.

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Recommendation-Specific Supportive Text

1. If acute myocardial injury is ruled out, alternative diagnoses merit consideration in patients with persistent or recurrent symptoms. Clinical risk assessment, with implementation of CDPs when appropriate, is the key to selecting patients for further diagnostic evaluation and also to choosing among potential diagnostic modalities.

4.3.1. Evaluation of Acute Chest Pain With Suspected Gastrointestinal Syndromes

Recommendation for Evaluation of Acute Chest Pain With Suspected Gastrointestinal Syndromes		
COR	**LOE**	**Recommendation**
2a	**C-LD**	1. In patients with recurrent acute chest pain without evidence of a cardiac or pulmonary cause, evaluation for gastrointestinal causes is reasonable.

Synopsis

Among outpatients who present with chest pain, approximately 10% to 20% have a gastrointestinal cause.[1] Gastrointestinal pain may result from stimulation of chemoreceptors by acid or hyperosmolar substances, of mechanoreceptors by abnormal contraction or distention, or of thermoreceptors.[2] Some patients have abnormal perceptions of otherwise normal stimuli. Gastroesophageal reflux disease is the most likely cause for recurring unexplained chest pain of esophageal origin.[3] Chest pain caused by gastroesophageal reflux disease can mimic myocardial ischemia and may be described as squeezing or burning. The duration can be minutes to hours, often occurs after meals or at night, and can worsen with stress. Depending on the severity, it may or may not resolve spontaneously or with antacids. Esophagitis not related to reflux may be caused by medications, underlying infections such as candidiasis, or radiation injury. Allergic conditions are associated with eosinophilic esophagitis, which is diagnosed by biopsy. Esophageal motility disorders such as achalasia, distal esophageal spasm, and nutcracker esophagus are less common but can present as squeezing retrosternal pain or spasm, often accompanied by dysphagia.

Recommendation-Specific Supportive Text

1. The first step in evaluation of potential esophageal chest pain is a careful history. Although the clinical presentation often does not provide adequate clues to distinguish cardiac from esophageal pain, some symptoms may be suggestive of an esophageal cause, such as heartburn, regurgitation, or dysphagia, and relief with antacid or antisecretory agents. These symptoms, however, are not sufficiently specific to be fully diagnostic. A history of use of medications such as nonsteroidal anti-inflammatory agents, potassium supplements, iron, or bisphosphonates should be sought. Physical examination is often unrevealing. When an esophageal cause of chest pain is suspected, upper endoscopy should be considered.[4] Symptoms and signs that merit early evaluation (usually within 2 weeks) include dysphagia, odynophagia, gastrointestinal bleeding, unexplained iron deficiency anemia, weight loss, and recurrent vomiting. Patients without these symptoms may merit a trial of empiric acid suppression therapy.[5] If an upper endoscopy is normal and the symptoms persist despite a trial of acid suppression, consideration should be given to additional evaluation, such as esophageal function testing and pH monitoring, to exclude other esophageal causes.[6]

4.3.2. Evaluation of Acute Chest Pain With Suspected Anxiety and Other Psychosomatic Considerations

Recommendation for Evaluation of Acute Chest Pain With Suspected Anxiety and Other Psychosomatic Considerations Referenced studies that support the recommendation are summarized in Online Data Supplement 25.		
COR	**LOE**	**Recommendation**
2a	**B-R**	1. For patients with recurrent, similar presentations for acute chest pain with no evidence of a physiological cause on prior diagnostic evaluation including a negative workup for myocardial ischemia, referral to a cognitive-behavioral therapist is reasonable.[1-14]

Synopsis

Although the heart-brain relationship is well established,[15-17] its clinical relevance has been enhanced by recognition of stress cardiomyopathy.[18,19] Less dramatic than the latter syndrome but highly prevalent is recurrent chest pain despite angiographically normal coronary arteries and no definable cardiac disease, including an assessment for INOCA.[1-14] Chest pain in these patients has been variously labeled angina, angina-like, "atypical" angina, or noncardiac chest pain based on its deviation from characteristic ischemic cardiac discomfort. Prognosis of patients with noncardiac chest pain is largely devoid of cardiac complications.[4,9,20-23] The close association of this symptom with psychological syndromes such as anxiety, panic attack, depression, somatoform disorder, and cardiophobia suggests that there may be a psychogenic origin in many patients. These factors have also raised consideration of mechanisms for noncardiac chest pain such as central nervous system-visceral inter-

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actions, low pain thresholds, hyperbody vigilance, sympathetic activation, as well as anxiety, depression, and panic disorder.[6,7,9,14,23-30] It has been reported that these patients undergo extensive and repetitive cardiac testing and have low referral to cognitive-behavioral therapists, suggesting a lost opportunity for pharmacologic or cognitive-behavioral therapy.[6]

Recommendation-Specific Supportive Text

1. Most low-risk patients presenting to the ED or office setting with chest pain do not have life-threatening conditions. Diagnoses may include psychological entities such as somatization or noncardiac chest pain.[1-13] It has been reported that in low-risk chest pain patients without evidence of cardiac disease, depression, anxiety, and gastroesophageal syndromes each exceeded CAD by almost 10-fold.[7] Additionally, care of these patients often includes multiple tests, high cost, and avoidable radiation exposure (5.0 mSv).[6] A low rate (<10%) of clinician inquiry, documentation, or referral has also been noted for psychological factors, even in chest pain patients with self-reported anxiety.[6,7] A systematic review of therapy for patients with chest pain, no evidence of cardiac disease, and psychological disorders revealed that antidepressants and anxiolytics had mixed evidence for efficacy,[10] but a Cochrane database of psychotherapy (17 RCTs) for such patients revealed a 32% reduction in chest pain frequency[11] for a 3-month interval. Approaches using cognitive-behavioral methods were most effective.[11] These results were limited by small study cohorts and patient heterogeneity; however, they do suggest benefit from consideration of psychogenic factors in patients who continue to seek evaluation for chest pain despite previous definitive, negative workups.

4.3.3. Evaluation of Acute Chest Pain in Patients With Sickle Cell Disease

Recommendations for Evaluation of Acute Chest Pain in Patients With Sickle Cell Disease
Referenced studies that support the recommendations are summarized in Online Data Supplement 25.

COR	LOE	Recommendations
1	B-NR	1. In patients with sickle cell disease who report acute chest pain, emergency transfer by EMS to an acute care setting is recommended.[1-5]
1	C-LD	2. In patients with sickle cell disease who report acute chest pain, ACS should be excluded.[3-5]

Synopsis

Acute chest syndrome is a leading cause of death for patients with sickle cell disease.[1,2] Patients with sickle cell disease who are experiencing chest pain require prompt evaluation.[3] Although chest pain occurs in most, other manifestations of acute chest syndrome include shortness of breath, fever, arm and leg pain, and the presence of a new density on chest radiography. Older adolescents and adults with sickle cell disease who present with chest pain and shortness of breath should be evaluated for AMI or myocardial ischemia.[4] AMI occurs in patients with sickle cell disease at a relatively early age, usually without the traditional risk factors for ACS. Death from ACS in patients with sickle cell disease is significantly high in age-, sex-, and race-matched controls.[5]

Recommendation-Specific Supportive Text

1. In patients with sickle cell disease who experience chest pain, ACS is associated with significant morbidity and mortality rates. These patients should be transferred to an acute care setting by EMS when there is clinical suspicion of ACS.
2. The recommended diagnostic evaluation for all adults with sickle cell disease who have a clinical presentation concerning for acute chest syndrome includes an ECG, troponin test, complete blood count with white blood cell differential, reticulocyte count, anteroposterior and lateral chest radiograph, and blood and sputum cultures.

5. EVALUATION OF PATIENTS WITH STABLE CHEST PAIN

5.1. Patients With No Known CAD Presenting With Stable Chest Pain

Stable chest pain is a symptom of myocardial ischemia characterized by chest pain that is provoked with stress (physical or emotional). Risk status in suspected stable ischemic heart disease (SIHD) is not well defined. Figure 11 provides a description of SIHD risk estimates.[1]

5.1.1. Pretest Risk Probability to Guide Need for Stress and Anatomic Tests

In the evaluation of symptomatic patients with suspected CAD, use of validated scores to predict the pretest probability of obstructive CAD may be useful to identify low-risk patients for whom testing may be deferred. It is preferable to use contemporary estimates such as those published in the past 10 years, such as the pretest probability proposed by Juarez-Orozco et al.[1] in preference to scores from historical patient series, which may overestimate the frequency of obstructive CAD. Alternatively, low-risk patients may be those <40 years of age or who have symptoms that have a low likelihood of representing ischemia (Section 5.1.2). When available, information on the presence and amount of CAC may be useful for enhancing the pretest probability of obstructive CAD, as shown in Figure 11.[2] This information can be ob-

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Pretest Probabilities of Obstructive CAD in Symptomatic Patients
(A) according to age, sex, and symptoms;
(B) according to age, sex, symptoms, and CAC

Age, y	Chest Pain		Dyspnea	
	Men	Women	Men	Women
30–39	≤4	≤5	0	3
40–49	≤22	≤10	12	3
50–59	≤32	≤13	20	9
60–69	≤44	≤16	27	14
70+	≤52	≤27	32	12

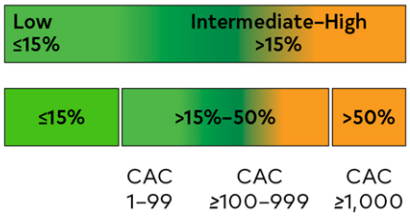

Figure 11. Pretest Probabilities of Obstructive CAD in Symptomatic Patients According to Age, Sex, and Symptoms
Modified from Juarez-Orozco et al[1] and Winther et al.[2] 1) The pretest probability shown is for patients with anginal symptoms. Patients with lower-risk symptoms would be expected to have lower pretest probability. 2) The darker green– and orange-shaded regions denote the groups in which noninvasive testing is most beneficial (pretest probability >15%). The light green–shaded regions denote the groups with pretest probability of CAD ≤15% in which the testing for diagnosis may be considered based on clinical judgment.[1] 3) If CAC is available, it can also be used to estimate the pretest probability based on CAC score.[2] CAC indicates coronary artery calcium; and CAD, coronary artery disease.

tained from performing a CAC scan or, when available, from a visual estimation of CAC based on prior noncardiac chest CT. Among the remaining patients classified as intermediate-high risk, selective testing may improve diagnosis of CAD and for risk stratification purposes.[1-5]

5.1.2. Low-Risk Patients With Stable Chest Pain and No Known CAD

Recommendations for Low-Risk Patients With Stable Chest Pain and No Known CAD
Referenced studies that support the recommendations are summarized in Online Data Supplements 27 and 28.

COR	LOE	Recommendations
1	B-NR	1. For patients with stable chest pain and no known CAD presenting to the outpatient clinic, a model to estimate pretest probability of obstructive CAD is effective to identify patients at low risk for obstructive CAD and favorable prognosis in whom additional diagnostic testing can be deferred.[1-5]
2a	B-R	2. For patients with stable chest pain and no known CAD categorized as low risk, CAC testing is reasonable as a first-line test for excluding calcified plaque and identifying patients with a low likelihood of obstructive CAD.[6-9]
2a	B-NR	3. For patients with stable chest pain and no known CAD categorized as low risk, exercise testing without imaging is reasonable as a first-line test for excluding myocardial ischemia and determining functional capacity in patients with an interpretable ECG.[10]

Synopsis

Over the past several decades, patient presentation and observed obstructive CAD prevalence has changed, thus affecting patient selection for diagnostic testing. Current observations in the United States include:

- Typical exertional angina prevalence is generally low (<10%), with more patients presenting without the classic demand-related symptoms.[11] Symptoms can be infrequent (ie, on a weekly or monthly basis),[12,13] which challenges the diagnostic evaluation.
- Among patients undergoing a diagnostic evaluation, there is a relatively low prevalence of obstructive CAD and ischemia (ie, ~10%).[11,14,15]
- Traditional pretest risk scores largely overestimate disease probability and contribute to overtesting.[16-19]
- Current testing patterns result in a high normal coronary angiography rate (upward of 50%–60%).[20,21] For the aforementioned reasons, use of a contemporary pretest probability estimates to define low-risk patients not requiring additional diagnostic testing is a primary goal of the initial evaluation of symptomatic patients with suspected CAD.[5] Even when contemporary pretest probability estimates are used, they have a low specificity for identifying patients with obstructive CAD. A CAC score of zero can be useful to identify patients with stable chest pain who are low risk, have a low likelihood of obstructive CAD, and a low risk of future

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cardiovascular events.[7] Additionally, exercise testing without imaging is also reasonable to perform in low-risk individuals with stable chest pain and no known CAD to exclude myocardial ischemia and assess functional capacity[10] (Figure 12).

Recommendation-Specific Supportive Text

1. There are several pretest probability scores for use in symptomatic patients with suspected CAD. Older pretest probability scores, such as the Diamond-Forrester model developed in 1979, estimates the probability of obstructive CAD, resulting in significant overestimation in contemporary patients referred for noninvasive imaging, particularly women.[1] Newer pretest probability estimates are available.[4] The CAD Consortium models include basic (age, sex, symptoms, and hospital setting); clinical (basic model + risk factors: diabetes, hypertension, hyperlipidemia, and smoking); and extended (clinical model + CAC) versions. Each new variant is better than older models, and the addition of variables within each model level improves prediction.[3] A major strength of these models is the extensive validation in different hospitals, settings, and countries. Another updated model to estimate the pretest probability of obstructive CAD was recently developed[4,22] and has been recommended by the ESC guidelines, further reinforcing that the prevalence of obstructive CAD among symptomatic patients is substantially lower than predicted estimates.
2. Among symptomatic patients, a CAC score of zero identifies a low-risk cohort of patients who may not require additional diagnostic testing; most events occur among patients with detectable CAC (eg, 84% in the PROMISE trial).[7,9] Several randomized trials evaluated the role of CAC in guiding selective use of follow-up testing, including CCTA.[6,7] From the CRESCENT 1 (Comprehensive Cardiac CT Versus Exercise Testing in Suspected Coronary Artery Disease) trial, 350 symptomatic patients were randomized to CAC scanning versus exercise ECGs.[7] Only patients with detectable CAC or high pretest risk (141/242) underwent follow-up CCTA. At 1 year, the CAC arm was associated with a reduction in cardiovascular disease events when compared with those who underwent exercise testing alone (P=0.011).
3. Exercise testing was shown to be an effective diagnostic strategy in low-risk symptomatic women from the WOMEN (What Is the Optimal Method for Ischemia Evaluation in Women) trial, when compared with exercise MPI.[10] Using this approach, there was no significant difference in CAD death or hospitalization for an ACS or heart failure, with either test, but exercise testing alone provided significant cost savings.

5.1.3. Intermediate-High Risk Patients With Stable Chest Pain and No Known CAD

Recommendations for Intermediate-High Risk Patients With Stable Chest Pain and No Known CAD
Referenced studies that support the recommendations are summarized in Online Data Supplements 29 and 30.

COR	LOE	Recommendations
		Index Diagnostic Testing
Anatomic Testing		
1	A	1. For intermediate-high risk patients with stable chest pain and no known CAD, CCTA is effective for diagnosis of CAD, for risk stratification, and for guiding treatment decisions.[1-12]
Stress Testing		
1	B-R	2. For intermediate-high risk patients with stable chest pain and no known CAD, stress imaging (stress echocardiography, PET/SPECT MPI or CMR) is effective for diagnosis of myocardial ischemia and for estimating risk of MACE.[8,13-35]
2a	B-R	3. For intermediate-high risk patients with stable chest pain and no known CAD for whom rest/stress nuclear MPI is selected, PET is reasonable in preference to SPECT, if available to improve diagnostic accuracy and decrease the rate of nondiagnostic test results.[36-39]
2a	B-R	4. For intermediate-high risk patients with stable chest pain and no known CAD with an interpretable ECG and ability to achieve maximal levels of exercise (≥5 METs), exercise electrocardiography is reasonable.[8,13,15,40-45]
2b	B-NR	5. In intermediate-high risk patients with stable chest pain selected for stress MPI using SPECT, the use of attenuation correction or prone imaging may be reasonable to decrease the rate of false-positive findings.[46-51]
Assessment of Left Ventricular Function		
1	B-NR	6. In intermediate-high risk patients with stable chest pain who have pathological Q waves, symptoms or signs suggestive of heart failure, complex ventricular arrhythmias, or a heart murmur with unclear diagnosis, use of TTE is effective for diagnosis of resting left ventricular systolic and diastolic ventricular function and detection of myocardial, valvular, and pericardial abnormalities.[13,14,52]
Sequential or Add-on Testing: What to Do if Index Test Results are Positive or Inconclusive		
2a	B-NR	7. For intermediate-high risk patients with stable chest pain and known coronary stenosis of 40% to 90% in a proximal or middle coronary segment on CCTA, FFR-CT can be useful for diagnosis of vessel-specific ischemia and to guide decision-making regarding the use of coronary revascularization.[12,53-58]
2a	B-NR	8. For intermediate-high risk patients with stable chest pain after an inconclusive or abnormal exercise ECG or stress imaging study, CCTA is reasonable.[5,59-63]
2a	B-NR	9. For intermediate-high risk patients with stable chest pain and no known CAD undergoing stress testing, the addition of CAC testing can be useful.[64-70]

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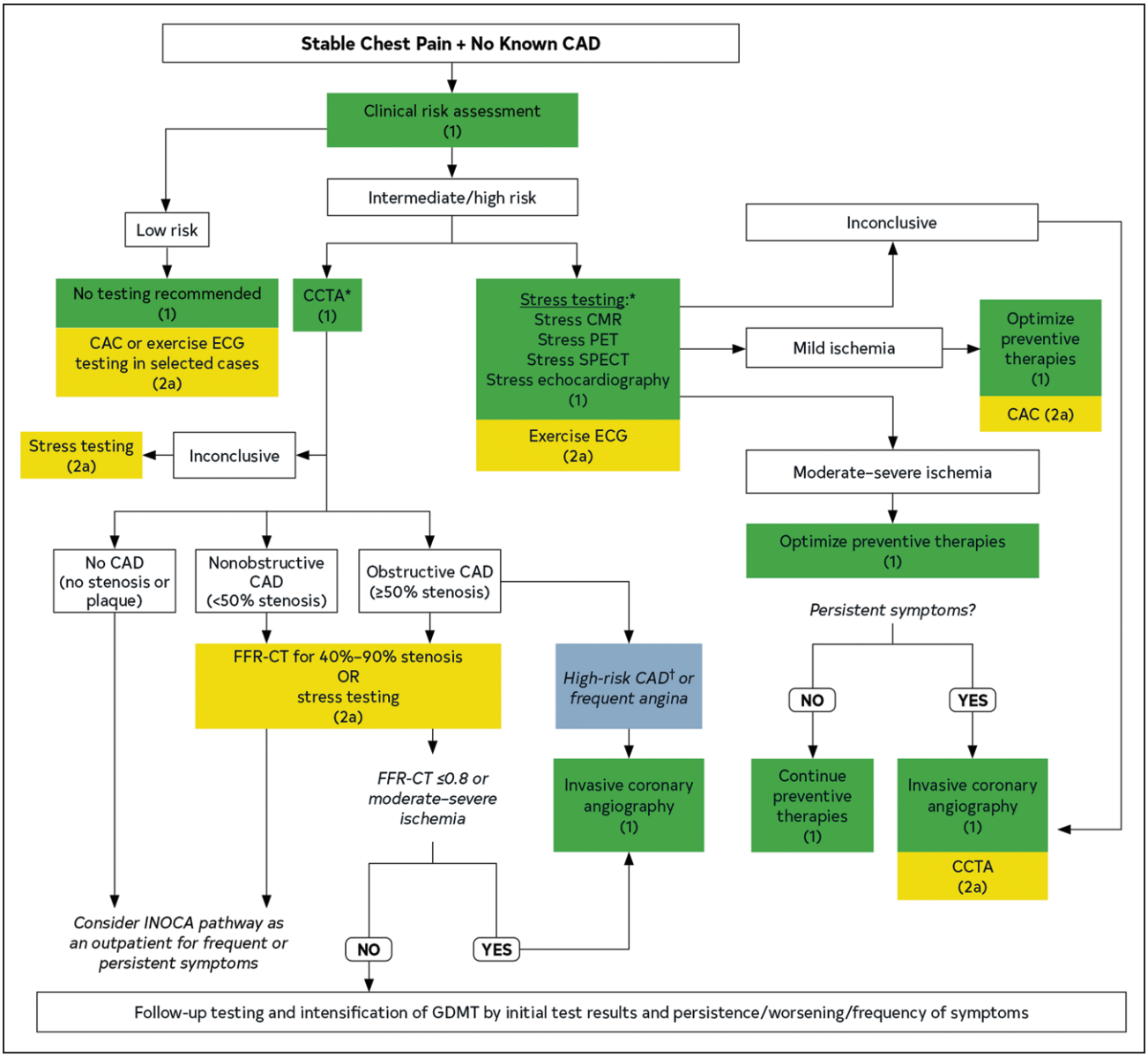

Figure 12. Clinical Decision Pathway for Patients With Stable Chest Pain and No Known CAD

Test choice should be guided by local availability and expertise.

*Test choice guided by patient's exercise capacity, resting electrocardiographic abnormalities; CCTA preferable in those <65 years of age and not on optimal preventive therapies; stress testing favored in those ≥65 years of age (with a higher likelihood of ischemia). †High-risk CAD means left main stenosis ≥50%; anatomically significant 3-vessel disease (≥70% stenosis).

CAD indicates coronary artery disease; CCTA, coronary CT angiography; CMR, cardiovascular magnetic resonance imaging; CT, computed tomography; FFR-CT, fractional flow reserve with CT; GDMT, guideline-directed medical therapy; INOCA, ischemia and no obstructive CAD; PET, positron emission tomography; and SPECT, single-photon emission CT.

Recommendations for Intermediate-High Risk Patients With Stable Chest Pain and No Known CAD (Continued)		
Sequential or Add-on Testing: What to Do if Index Test Results are Positive or Inconclusive (continued)		
2a	B-NR	10. For intermediate-high risk patients with stable chest pain after inconclusive CCTA, stress imaging is reasonable.[13,14,20-23,40,71-76]
2b	C-EO	11. For intermediate-high risk patients with stable chest pain after a negative stress test but with high clinical suspicion of CAD, CCTA or ICA may be reasonable.

Synopsis

The approach to the diagnostic evaluation of patients with no known CAD who are at intermediate to high risk (Figure 12) should be guided by the ability to achieve high-quality imaging as well as local availability and expertise. Intermediate-high risk patients have modest rates of obstructive CAD (~10%–20%) and risk of clinical events (~1%–2% per year).[1,5,8,77-80] CCTA is preferable in those <65 years of age and not on optimal preventive therapies, while stress testing may be advantageous in those

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≥65 years of age, because they have a higher likelihood of ischemia and obstructive CAD.[34-36,81-83] Although previous guidelines supported direct referral to ICA among patients with stable chest pain, contemporary randomized trials support that candidates for elective coronary angiography may be safely triaged using CCTA[1,84] or noninvasive stress testing.[34,35]

Patient characteristics and existing contraindications for a given test modality (Tables 5 and 6) should be considered when choosing a diagnostic test. Imaging of obese patients, especially those with morbid obesity (body mass index >40), can be challenging and requires careful consideration of available equipment. In obese patients, contrast enhancement is useful to improve imaging quality. In certain patients, it may be important to undergo exercise testing so to collect data on the hemodynamic or symptomatic response to exercise. In patients selected for stress imaging who are able to exercise, exercise testing is preferred over pharmacologic stress to improve the diagnostic and prognostic information of the test. Although PET and SPECT are grouped together, PET has improved diagnostic and prognostic performance, especially when quantitative assessment of MBF can be performed.[36-39]

Irrespective of the test performed, an overarching goal of the evaluation of symptomatic patients is to identify those who would benefit from GDMT, as defined by the 2014 SIHD guidelines, the 2018 cholesterol-lowering guidelines, and the 2019 prevention guidelines.[13,85-87] For this evaluation, the patient should be engaged in a process of shared decision-making before determining the final choice of the cardiac test modality and in guiding the pathway for treatment decisions.

Recommendation-Specific Supportive Text

Anatomic Testing

1. Clinical trials report a higher diagnostic sensitivity for CCTA compared with stress testing for detecting obstructive CAD on ICA.[2-4,37,38,88] CCTA without stenosis or plaque has a low CAD event rate. From the PROMISE trial, the 3-year CAD event rate for negative test findings was 0.9% for CCTA versus 2.1% for stress testing.[17]Randomized trials comparing the effectiveness of CCTA versus stress testing report similar near-term effectiveness (at ~2–3 years of follow-up).[7,8,10-12,89] In the SCOT-HEART (Scottish Computed Tomography of the Heart) trial, the addition of CCTA to standard of care resulted in a reduction in 5-year CAD death or AMI when compared with standard care alone (predominantly exercise ECG) (HR: 0.59; 95% CI: 0.41-0.84; P=0.004).[9] From a prespecified analysis from the PROMISE trial, patients with diabetes who underwent CCTA had a lower risk of cardiovascular death or MI when compared with those randomized to stress testing (adjusted HR: 0.38; 95% CI: 0.18-0.79; P=0.01).[6] Especially for patients with nonobstructive and obstructive CAD, CCTA more often prompts initiation and intensification of preventive and anti-ischemic therapies than other diagnostic strategies.[6,89-96] Several randomized trials compared the effectiveness of CCTA versus direct referral to ICA among symptomatic patients.[1,5] From the CONSERVE trial, a strategy of initial CCTA was associated with lower cost but similar 1-year MACE rates (death, ACS, stroke, urgent/emergency coronary revascularization, or cardiac hospitalization) as direct ICA (4.6% versus 4.6%).[5]

Stress Testing

2. The prognostic value of stress echocardiography has been demonstrated in large observational series with low rates of CAD events for patients with normal test results, particularly those with good exercise tolerance.[71,72,97-99] In the PROMISE trial, patients randomized to stress testing had no difference in the primary outcome of death, ACS, or major procedural complications as compared to CCTA.[100] For stress nuclear imaging, multicenter registries support effective risk stratification based on rest/stress measures of MPI and left ventricular function,[13,21,27,28,98,101,102] with recent evidence on the prognostic value of stress PET.[26,37,38,103,104] Randomized trials have compared the effectiveness of rest/stress MPI with other noninvasive tests, such as CMR[105] and CCTA, revealing similar 1- to 3-year outcomes. Two multicenter trials have evaluated the effectiveness of a CMR-guided strategy as compared to standard testing approaches.[34,35] The CE-MARC 2 multicenter trial (n=1 202) revealed that both CMR and SPECT MPI were associated with similar rates (ie, 7.1%–7.5%) of unnecessary invasive angiography (defined as a no CAD stenosis ≥70% or a normal invasive FFR) compared with standard testing for chest pain (28.8%; P<0.001).[34] The MR-INFORM trial randomized 918 patients with typical angina and multiple risk factors or a positive exercise ECG to a CMR strategy versus invasive FFR strategy.[35] The CMR strategy was associated with less coronary revascularization (P=0.005) and a similar event rate (death, AMI, or target vessel revascularization; P=0.91).
3. Although PET and SPECT are grouped together, PET has improved diagnostic and prognostic performance, especially when quantitative assessment of MBF can be performed.[36-39] A recent clinical trial (n=475) reported a higher diagnostic accuracy with stress PET MPI compared with other stress test modalities.[38]

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4. Diagnostic accuracy of the exercise ECG is lower (ie, sensitivity and specificity range, 60%–77%) than stress imaging, but prognostication remains a useful goal.[13,41] In the WOMEN trial including 824 symptomatic women, exercise ECG was equally effective when compared with exercise SPECT MPI, with similar 2-year CAD event rates (2.0% versus 2.3%; P=0.59).[40] Failure to complete the first stage of the Bruce protocol (or <5 METs) or to achieve 85% of age-predicted fitness level increases CAD event risk.[13,41-45] Patients exercising to Bruce stage III or >10 METs with a negative ECG have a low risk of CAD events. In patients with submaximal exercise or for those with an ischemic ECG ≥1.0 mm ST depression, additional stress imaging may improve risk detection and guide clinical management.[41] Marked ischemia (eg, ≥2.0 mm at reduced workloads) or high Duke or Lauer scores signify increased risk among women and men[13,41,42,44]; such patients may benefit from additional testing (anatomic or stress testing).
5. Use of attenuation correction algorithms and prone imaging can reduce MPI artifacts.[46-51]

Assessment of Left Ventricular Function

6. Clinical practice guidelines and appropriate use criteria support use of TTE as appropriate for the assessment of regional and global left ventricular function.[13,14] The likelihood of abnormal findings increases when TTE is performed selectively among higher risk patients, such as those with electrocardiographic Q waves or heart failure symptoms, complex ventricular arrhythmias, or a heart murmur.[52]

Sequential or Add-on Testing: What to Do if Index Test Results are Positive or Inconclusive

7. The use of FFR-CT is supported by several studies,[56,57,104] including one reporting improved diagnostic accuracy with FFR-CT versus coronary CT alone when applying invasive FFR as the gold standard.[56] Several multinational registries have examined the utility of FFR-CT with regards to guiding clinical decision-making and the safety of deferring coronary revascularization in patients with a negative FFR-CT.[12,26,53,54] In the ADVANCE registry, FFR-CT changed treatment recommendations in two-thirds of 5083 patients, and there were no MACE at 90 days for patients with a negative FFR-CT.[54] FFR-CT is most beneficial when measured in a coronary stenosis of 40% to 90% severity located in a proximal or mid-coronary artery segment.[54,106,107]
8. Use of CCTA after stress testing can diagnose or exclude obstructive CAD and identify patients who may benefit from referral to ICA.[5,59-61,63] The ISCHEMIA trial used CCTA after site-determined moderate-severe ischemia to exclude patients with nonobstructive CAD and identifying those with significant left main stenosis who benefit from prompt referral to ICA.[63,108] Half of the screen failures for the ISCHEMIA trial were identified by CCTA including those with nonobstructive CAD or unprotected left main CAD.
9. Observational registry data suggest that adding CAC can improve risk assessment, reduce diagnostic uncertainty, help detect atherosclerotic plaque, and guide preventive management.[64-70,94,109,110]
10. After an initial exercise ECG, data support an improved diagnostic accuracy and improved risk stratification with further stress imaging, such as with stress echocardiography,[13,14,71,72] nuclear MPI,[20-23,40,73-76] or CMR.[35,111-113]
11. For the symptomatic patients with negative stress test findings, selective use of CCTA or invasive coronary angiography can help detect obstructive CAD and atherosclerotic plaque and reduce diagnostic certainty.

5.2. Patients With Known CAD Presenting With Stable Chest Pain

Recommendations for Patients With Known CAD Presenting With Stable Chest Pain
Referenced studies that support the recommendations are summarized in Online Data Supplement 31.

COR	LOE	Recommendations
1	A	1. For patients with obstructive CAD and stable chest pain, it is recommended to optimize GDMT.[1-3]
1	C-EO	2. For patients with known nonobstructive CAD and stable chest pain, it is recommended to optimize preventive therapies.[4,5]

Synopsis

In patients with known CAD, clinicians should opt to intensify GDMT first, if there is an opportunity to do so, and defer testing. Although GDMT exists for obstructive CAD, there are no current guidelines that are specific to nonobstructive CAD. Thus, adhering to atherosclerotic CV prevention guidelines is recommended.[4,5]

Recommendation-Specific Supportive Text

1. ACC/AHA clinical practice guidelines for treatment of patients with stable CAD recommend optimization of anti-ischemic and preventive therapies with the goal to reduce the patient's angina burden and improve clinical outcomes.[6,7]
2. For all patients with a history of CAD risk factors, optimized preventive therapy should be used according to ACC/AHA clinical practice guidelines.[4,5]

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5.2.1. Patients With Obstructive CAD Who Present With Stable Chest Pain

Recommendations for Patients With Obstructive CAD Who Present With Stable Chest Pain
Referenced studies that support the recommendations are summarized in Online Data Supplements 32 and 33.

COR	LOE	Recommendations
		Index Diagnostic Testing
Anatomic Testing		
1	A	1. For patients with obstructive CAD who have stable chest pain despite GDMT and moderate-severe ischemia, ICA is recommended for guiding therapeutic decision-making.[1-4]
1	A	2. For patients with obstructive CAD who have stable chest pain despite optimal GDMT, those referred for ICA without prior stress testing benefit from FFR or instantaneous wave free ratio.[3,5-7]
1	B-R	3. For symptomatic patients with obstructive CAD who have stable chest pain with CCTA-defined ≥50% stenosis in the left main coronary artery, obstructive CAD with FFR with CT ≤0.80, or severe stenosis (≥70%) in all 3 main vessels, ICA is effective for guiding therapeutic decision-making.[4,8]
2a	B-NR	4. For patients who have stable chest pain with previous coronary revascularization, CCTA is reasonable to evaluate bypass graft or stent patency (for stents ≥3 mm).[9-13]
Stress Testing		
1	B-NR	5. For patients with obstructive CAD who have stable chest pain despite optimal GDMT, stress PET/SPECT MPI, CMR, or echocardiography is recommended for diagnosis of myocardial ischemia, estimating risk of MACE, and guiding therapeutic decision-making.[14-36]
2a	B-R	6. For patients with obstructive CAD who have stable chest pain despite optimal GDMT, when selected for rest/stress nuclear MPI, PET is reasonable in preference to SPECT, if available, to improve diagnostic accuracy and decrease the rate of nondiagnostic test results.[37]
2a	B-NR	7. For patients with obstructive CAD who have stable chest pain despite GDMT, exercise treadmill testing can be useful to determine if the symptoms are consistent with angina pectoris, assess the severity of symptoms, evaluate functional capacity and select management, including cardiac rehabilitation.[4,38-40]
2a	B-NR	8. For patients with obstructive CAD who have stable chest pain symptoms undergoing stress PET MPI or stress CMR, the addition of MBFR is useful to improve diagnosis accuracy and enhance risk stratification.[31-36]

Synopsis

In patients with known CAD, physicians should opt to intensify GDMT first, if there is an opportunity to do so, and defer testing. In patients with a history of obstructive CAD, previous AMI, or previous coronary revascularization, assessing the severity of ischemia may be useful to guide clinical decision-making regarding the use of ICA and intensify preventive and anti-ischemic therapy. Imaging should be considered in those with new onset or persistent stable chest pain (Figure 13). In patients with frequent angina or severe stress-induced ischemia, referral to ICA or CCTA is an option.[4] Among individuals with known obstructive CAD or ischemic heart disease who have stable symptoms, exercise treadmill testing may be useful for assessing functional capacity, assessing the type and severity of symptoms, and informing the role of coronary revascularization, cardiac rehabilitation, or anti-anginal therapy.[4,38-40]

Recommendation-Specific Supportive Text

Anatomic Testing

1. SIHD randomized trials reveal a pattern that ischemia-guided percutaneous coronary intervention (PCI) results in an improvement in angina when compared with medical therapy alone.[1-4,41] In the ISCHEMIA trial, a total of 5179 patients with stable CAD and site-determined moderate-severe ischemia on stress testing were randomized to invasive versus conservative care strategies.[4] No difference in the composite primary MACE endpoint was observed at ~3.3 years of follow-up. Patients presenting with daily, weekly, or monthly angina had a prompt and durable improvement in symptoms when randomized to invasive compared with conservative management.[41]
2. Coronary revascularization after identification of suspected lesion-specific ischemia (FFR ≤0.80 or instantaneous wave-free ratio ≤0.89) in obstructive CAD is associated with improved event-free survival compared with the use of PCI determined by anatomy alone.[3,5,6,42]
3. In a patient presenting with new or recurrent chest pain symptoms, progression of CAD (ie, new or worsening stenosis or more extensive nonobstructive atherosclerotic plaque) may be characterized using CCTA.[43,44] Detection of nonobstructive CAD often results in prompt initiation and intensification of preventive and anti-ischemic therapies with CCTA.[45-50] There is a high degree of concordance between CCTA- and ICA-determined obstructive CAD.[33,51-55] CCTA-defined left main stenosis (nonobstructive and ≥50% stenosis) is associated with a high CAD event risk.[56,57] Coronary revascularization confers a survival benefit among patients with left main CAD.[58] From randomized trials, major clinical outcomes in patients with left main CAD are similar with CABG and PCI at near-term follow-up of 1 to 2 years, although repeat revascularization rates are higher after PCI.[58]

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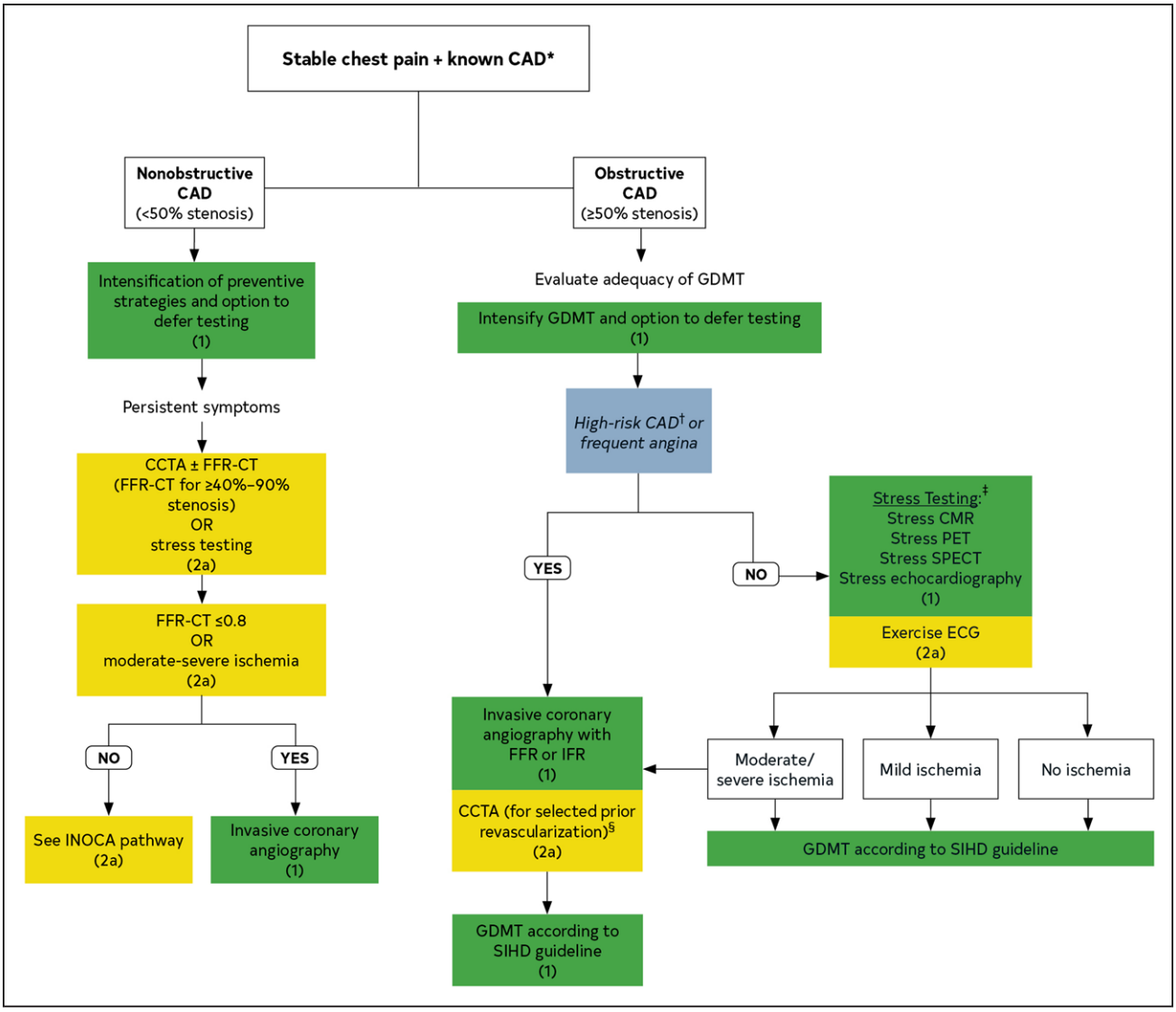

Figure 13. Clinical Decision Pathway for Patients With Stable Chest Pain (or Equivalent) Symptoms With Prior MI, Prior Revascularization, or Known CAD on Invasive Coronary Angiography or CCTA, Including Those With Nonobstructive CAD

Test choice should be guided by local availability and expertise.

*Known CAD means prior MI, revascularization, known obstructive CAD, nonobstructive CAD.

†High-risk CAD means left main stenosis ≥50%; or obstructive CAD with FFR-CT ≤0.80.

‡Test choice guided by the patient's exercise capacity, resting electrocardiographic abnormalities.

§Patients with prior CABG or stents >3.0 mm. *Follow-up Testing and Intensification of GDMT Guided by Initial Test Results and Persistence / Worsening / Frequency of Symptoms and Shared Decision Making.*

CABG indicates coronary artery bypass graft; CAD, coronary artery disease; CCTA, coronary CT angiography; CMR, cardiovascular magnetic resonance imaging; CT, computed tomography; ECG, electrocardiogram; FFR-CT, fractional flow reserve with CT; GDMT, guideline-directed medical therapy; ICA, invasive coronary angiography; iFR, instant wave-free ratio; INOCA, ischemia and no obstructive coronary artery disease; MI, myocardial infarction; MPI, myocardial perfusion imaging; PET, positron emission tomography; SIHD, stable ischemic heart disease; and SPECT, single-photon emission CT.

4. CCTA has been shown to be accurate for the assessment of native vessel CAD and bypass graft patency with high accuracy (~96%) and concordance (82%–>93%) to ICA; it may also be useful to assess patency of proximal large stents (≥3 mm) if such information is known at the time of presentation.[9-13] Several controlled clinical trials have evaluated the concordance of FFR-CT with invasive FFR.[59-62] Diagnostic sensitivity of FFR-CT compared with invasive FFR is high.[32,60]

Stress Testing

5. Observational findings reveal that patients with moderate-severe ischemia on PET and SPECT MPI have an improved outcome with early coronary

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revascularization.[20,34,63-65] Patients with moderate-severe ischemia on PET (≥10% ischemic myocardium) treated with PCI reported an improvement in angina when compared with those treated medically.[20] Prespecified substudies from therapeutic strategy trials for SIHD also evaluated the role of rest/stress nuclear MPI to assess residual ischemia severity among patients with known CAD who were treated with medical therapy alone or when combined with revascularization.[1,2,14-18]
Clinical trials of CMR have included subgroups with obstructive CAD, including 76% and 49% in the MR-IMPACT and MR-IMPACT2 studies, respectively, showing generally comparable diagnostic accuracy to stress SPECT MPI.[23,24] Several large, multicenter registries reveal that stress CMR effectively risk stratifies patients with known CAD.[27-30] In a multicenter registry of 2496 patients with a history of CAD, an abnormal stress CMR had a nearly 2-fold increased mortality hazard.[27] From the SPINS Registry (Stress CMR Perfusion Imaging in the United States), patients with known CAD with MPI ischemia and scarring by late gadolinium enhancement had a relative hazard of 1.5 to 2.1 for CV death or nonfatal MI.[30] Prognosis worsens for patients by the extent and severity of inducible wall motion abnormalities on stress echocardiography.[66,67] Recent randomized trial evidence supports the role of stress echocardiography to guide clinical decision-making. From the ORBITA (Objective Randomized Blinded Investigation With Optimal Medical Therapy in Stable Angina) trial, there was a greater reduction in the stress echocardiographic wall motion score among patients with single-vessel CAD treated with PCI compared with placebo ($P<0.0001$).[68] In a secondary analysis, there was an interaction between the baseline stress echocardiographic wall motion score and the efficacy of PCI for improved angina at 6 weeks of follow-up.[69] That is, PCI-treated patients with a wall motion score ≥1 were more often angina-free compared with those in the placebo arm.
6. Evidence supports that the improved diagnostic accuracy of PET MPI is helpful in the patient with known CAD. In a randomized trial of 322 symptomatic patients with known CAD, the presence of low- and high-risk stress PET findings was associated with lower and higher rates of ICA when compared with SPECT MPI ($P=0.001$).[37] In this trial, nearly 1 in 5 patients with low-risk SPECT MPI findings underwent ICA, a rate more than twice that of stress PET MPI. Based on such evidence, PET is preferable over SPECT when both are available.
7. Observational studies of patients with CAD and stable chest pain have demonstrated that exercise treadmill testing can be useful by evaluating the relation of symptoms to graded stress testing, thereby helping to confirm the diagnosis of angina pectoris; assessing symptom severity; and selecting appropriate management: medical therapy, revascularization, and/or cardiac rehabilitation.[4,38-40]

Secondary Diagnostic Testing: For the Assessment of Vascular Territory Flow or Vessel-Specific Ischemia

8. Measurement of MBFR, when reduced, reflects abnormalities of flow within the epicardial coronary arteries and/or microvasculature and independently predicts risk of major CAD events. This can be effectively accomplished using PET[31,70,71] or CMR.[28] Normal MBFR may be helpful in excluding high risk anatomy, although reduced levels may provide a better estimate of disease extent and severity. In the presence of nonobstructive CAD, reduced MBFR may signify coronary microvascular dysfunction, especially among women.[70]

5.2.1.1. Patients With Prior CABG Surgery With Stable Chest Pain

Recommendations for Patients With Prior CABG Surgery With Stable Chest Pain

COR	LOE	Recommendations
1	C-LD	1. In patients who have had prior CABG surgery presenting with stable chest pain whose noninvasive stress test results show moderate-to-severe ischemia,[1-7] or in those suspected to have myocardial ischemia with indeterminate/nondiagnostic stress test, ICA is recommended for guiding therapeutic decision-making.[1]
2a	C-LD	2. In patients who have had prior CABG surgery presenting with stable chest pain who are suspected to have myocardial ischemia, it is reasonable to perform stress imaging or CCTA to evaluate for myocardial ischemia or graft stenosis or occlusion.[8-15]

Synopsis

In patients with prior CABG who have stable chest pain, it is important to assess medical therapies and optimize all guideline-directed therapies.[1] ICA can be useful to guide therapeutic decision-making in those with frequent angina that has not improved with medical therapy.[1-9] In those whose symptoms do improve after optimizing medical therapy, evaluation with stress testing can be useful to assess the degree of myocardial ischemia and determine which patients may benefit from coronary angiography.[6,10] CCTA can also be used to detect graft patency but is often less robust for assessing native coronary vessel stenosis in those with prior CABG, because of high degree of nondiagnostic segments.[8-15]

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Recommendation-Specific Supportive Text

1. There are stress test features in patients with prior CABG and presenting with stable chest pain that may indicate a high likelihood of severe ischemic heart disease such as stress electrocardiographic findings including 2 mm of ST-segment depression at low workload or persisting into recovery, exercise-induced ST-segment elevation, or exercise-induced VT/VF, severe stress-induced left ventricular systolic dysfunction, stress-induced perfusion abnormalities involving ≥10% myocardium or stress-induced left ventricular dilation. In these patients with prior CABG and high-risk imaging features, referral for ICA is reasonable provided that these patients are amenable to and are candidates for coronary revascularization.[1-7] Patients with prior CABG presenting with stable chest pain may have stress imaging features that are equivocal or nondiagnostic for the presence of myocardial ischemia. Equivocal or nondiagnostic stress tests may be a result of patient's body habitus, inadequate or suboptimal heart rate, arrhythmias such as atrial fibrillation, left bundle branch block, or patient motion. In these patients, performing an ICA is reasonable when the angiographic findings have a high likelihood of impacting therapeutic decisions.[1]
2. Stable chest pain due to myocardial ischemia may occur in patients with prior CABG because of progression of atherosclerosis in the native coronary arteries or within the bypass grafts. Noninvasive stress imaging testing is reasonable in these patients to identify ischemic myocardial territories that will further guide revascularization for patients who are amenable to and are candidates for revascularization. Furthermore, stress imaging also assists in stratifying patients to determine the degree of likelihood for severe ischemic heart disease, which will assist in therapeutic decisions.[8-10,12-14] CCTA has a great degree of accuracy with a sensitivity and specificity of detecting complete graft occlusions, 99% and 99%, respectively, when compared with the standard of ICA.[15] Furthermore, CCTA was ideal in assessing bypass grafts attributable to the large size of these vessels, decreased vessel calcification and decreased motion of these vessels when compared with native coronary vessels, with successful evaluation of bypass grafts in 93% to 100% of patients.[15] In patients who have stable chest pain and are previously known to have borderline graft stenosis or are suspected to have new graft stenosis, CCTA is useful for assessing graft patency but less robust for assessing native coronary vessel stenosis in this population because of high degree of nondiagnostic segments.[8-15]

5.2.2. Patients With Known Nonobstructive CAD Presenting With Stable Chest Pain

Recommendations for Patients With Known Nonobstructive CAD Presenting With Stable Chest Pain
Referenced studies that support the recommendations are summarized in Online Data Supplements 34 and 35.

COR	LOE	Recommendations
		Index Diagnostic Testing
Anatomic Testing		
2a	B-NR	1. For symptomatic patients with known nonobstructive CAD who have stable chest pain, CCTA is reasonable for determining atherosclerotic plaque burden and progression to obstructive CAD, and guiding therapeutic decision-making.[1-7]
2a	B-NR	2. For patients with known coronary stenosis from 40% to 90% on CCTA, FFR can be useful for diagnosis of vessel-specific ischemia and to guide decision-making regarding the use of ICA.[8-14]
Stress Testing		
2a	C-LD	3. For patients with known extensive nonobstructive CAD with stable chest pain symptoms, stress imaging (PET/SPECT, CMR, or echocardiography) is reasonable for the diagnosis of myocardial ischemia.[15-24]

Synopsis

For patients with known nonobstructive CAD (luminal narrowing 1%–49%), CCTA can be useful for detection of new or worsening obstructive stenosis, atherosclerotic disease progression, and identification of high-risk plaque features, such as low attenuation plaque or positive remodeling[1,2,5-7,25] (Figure 13). Similarly, stress imaging is reasonable to detect myocardial ischemia and can help guide further management and treatment of ischemic burden.[15-24]

Irrespective of the test performed, an overarching goal of the evaluation of symptomatic patients with known nonobstructive CAD is to identify those who would benefit from intensification of preventive therapy, as defined by the 2018 cholesterol-lowering guidelines and the 2019 prevention guidelines.[26-29] For this evaluation, the patient should be engaged in a process of shared decision-making before determining the final choice of the cardiac testing modality and in guiding the pathway for treatment decisions.

Recommendation-Specific Supportive Text

Anatomic Testing

1. Atherosclerosis is a progressive disease that worsens over time,[1] with nonobstructive CAD

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consistently identified as precursor for ACS.[3-6] From the PROMISE trial, nonobstructive CAD was associated with a 3-fold increase in MACE risk over ~2 years of follow-up.[3] Additional analyses from the SCOT-HEART and PROMISE trials reveal that high-risk atherosclerotic plaque features are associated with an elevated MACE risk among patients with nonobstructive CAD.[4,5] CCTA commonly identifies patients with nonobstructive CAD but can further define compositional alterations within the plaque (ie, noncalcified plaque) and positive remodeling.[4,5,7,25,30] These plaque features have been associated with inducible ischemia, identified as precursors for ACS, and independently predict MACE.[5,6,31] Recently, Williams et al reported that a low attenuation plaque burden was associated with a >6-fold increase in incident MI for patients with nonobstructive CAD.[4]

2. Controlled clinical trials reveal that FFR-CT improves diagnostic accuracy over and above obstructive CAD on CCTA when compared with invasive FFR.[12,13] Multinational registries have examined the use of FFR-CT with regards to the use to drive clinical decision-making regarding the use of follow-up ICA and the safety of deferring coronary revascularization in patients with a negative FFR-CT.[8-11] From the ADVANCE (Assessing Diagnostic Value of Noninvasive FFR-CT in Coronary Care) registry, FFR-CT changed treatment recommendations in two-thirds of patients, and there were no MACE at 90 days for patients with a negative FFR-CT.[10] From the SYNTAX 3 trial,[14] FFR-CT was performed in 223 patients. Treatment recommendations and selection of vessels for revascularization were guided by FFR-CT in ~20% of patients.

Stress Testing

3. Approximately 20% to 30% of patients with nonobstructive CAD will demonstrate ischemia.[15-24] Patients who experience ischemia with nonobstructive CAD (INOCA – see Section 5.2.3) benefit from assessment of functional significance of an intermediate coronary stenosis as it provides insight into the patient's presenting symptoms and can help guide clinical management.

5.2.3. Patients With Suspected Ischemia and No Obstructive CAD (INOCA)

Recommendations for myocardial blood flow measurements using PET, echocardiography, and CMR are found in Section 5.2.2.

Recommendations for Patients With INOCA
Referenced studies that support the recommendations are summarized in Online Data Supplements 36 and 37.

COR	LOE	Recommendations
2a	B-NR	1. For patients with persistent stable chest pain and nonobstructive CAD and at least mild myocardial ischemia on imaging, it is reasonable to consider invasive coronary function testing to improve the diagnosis of coronary microvascular dysfunction and to enhance risk stratification.[1-4]
2a	B-NR	2. For patients with persistent stable chest pain and nonobstructive CAD, stress PET MPI with MBFR is reasonable to diagnose microvascular dysfunction and enhance risk stratification.[5-11]
2a	B-NR	3. For patients with persistent stable chest pain and nonobstructive CAD, stress CMR with the addition of MBFR measurement is reasonable to improve diagnosis of coronary myocardial dysfunction and for estimating risk of MACE.[12-14]
2b	C-EO	4. For patients with persistent stable chest pain and nonobstructive CAD, stress echocardiography with the addition of coronary flow velocity reserve measurement may be reasonable to improve diagnosis of coronary myocardial dysfunction and for estimating risk of MACE.

Synopsis

Signs and symptoms of ischemia occur because of focal obstructive CAD, but INOCA is common and may result from alterations in flow within the microvasculature. Thus, many symptomatic patients without obstructive CAD on previous workup may be candidates for assessment of coronary microvascular dysfunction and other causes of INOCA.[1] Patients at highest risk for coronary microvascular dysfunction include women, those with hypertension, diabetes, and other insulin-resistant states.[15] There is substantive evidence that testing focusing on documentation of coronary or microvascular flow abnormalities can aid in the diagnosis of microvascular angina, and abundant evidence supports that the addition of flow alterations improves risk stratification. Invasive coronary reactivity testing allows for the assessment of vasospasm, in addition to nonendothelial–dependent and endothelium-dependent microvascular reactivity.[2,4] From the National Institutes of Health-NHLBI-sponsored WISE (Women's Ischemia Syndrome Evaluation), impaired coronary flow reserve (ie, <2.32) among women with no obstructive CAD was associated with an elevated hazard for major CAD events with lengthy follow-up of 10 years (P=0.03).[2] Among women with no obstructive

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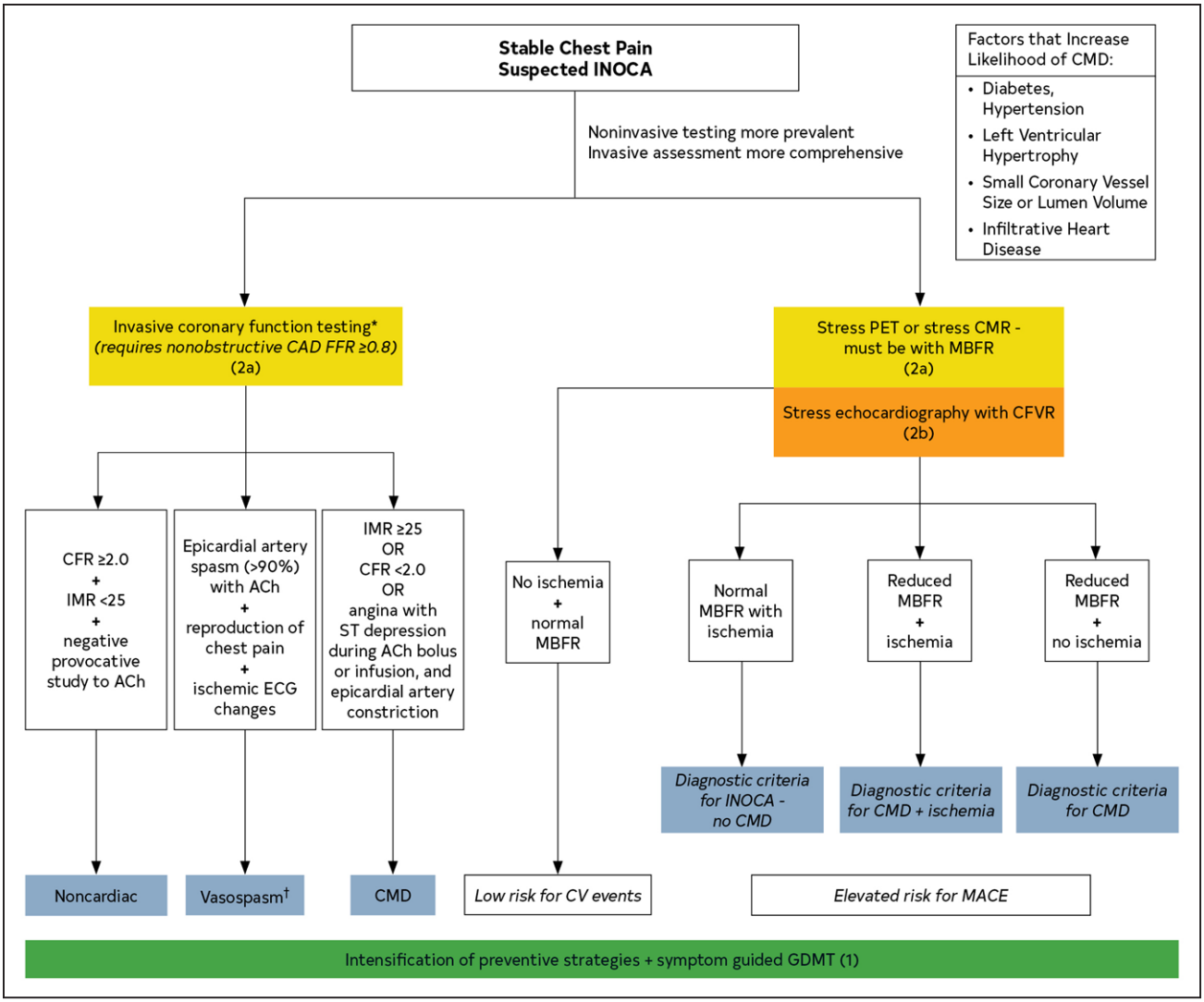

Figure 14. Clinical Decision Pathway for INOCA

Test choice should be guided by local availability and expertise.

*Ford T et al.[16] †Cannot exclude microvascular vasospasm.

ACh indicates acetylcholine; CAD, coronary artery disease; CFR, coronary flow reserve; CFVR, coronary flow velocity reserve; CMD, coronary microvascular dysfunction; CV, cardiovascular; FFR, fractional flow reserve; GDMT, guideline-directed medical therapy; IMR, index of microcirculatory restriction; INOCA, ischemia and no obstructive CAD; MACE, major adverse cardiovascular events; and MBFR, myocardial blood flow reserve.

CAD, epicardial vasoconstriction was also significantly associated with higher rates of hospitalization for angina (P=0.0002).[2] Prognostic evidence is available supporting the novel contribution of PET MBFR techniques; several reports also note a benefit using CMR and echocardiographic techniques. A proposed diagnostic evaluation pathway is outlined in Figure 14.

Recommendation-Specific Supportive Text

1. Evidence supports a role for invasive coronary reactivity testing, including prognostic evidence from the WISE study.[1,2] The CorMicA (Coronary Microvascular Angina) trial enrolled symptomatic patients (74% women) without obstructive CAD and positive invasive coronary reactivity testing (n=76 patients to intervention and 75 to the blinded control group). The intervention consisted of anti-ischemic therapy using beta-blockers and angiotensin-converting enzyme inhibitors along with preventive care (statins) and lifestyle changes, including smoking cessation, and was associated with a significant improvement in angina and quality of life over 6 months (P=0.001).[4,16] This small trial did not report any differences in 6-month MACE (P=0.8).
2. PET measurement of peak myocardial blood flow and MBFR, when reduced, reflects abnormalities

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of flow within the epicardial coronary arteries and microvasculature and independently predicts risk of major CAD events.[5-7,17] PET measurement of MBFR improves risk stratification, including for patients with nonobstructive CAD, especially women, for whom coronary microvascular dysfunction is suspected.[18]

3. CMR has been used to evaluate MBFR. When validated against invasive coronary physiology measures, pixel-wise quantitative myocardial perfusion mapping by CMR was able to identify coronary microvascular dysfunction in a small study that included 23 patients with nonobstructive CAD.[19] The addition of coronary flow reserve improves prognostication.[12-14] Stress CMR studies of MBFR have shown reasonable agreement with PET (n=21).[20]
4. Stress echocardiography assessing coronary flow velocity reserve in the left anterior descending artery with Doppler can currently be combined with wall motion analysis during vasodilator stress echocardiography. Limited data have shown that abnormal coronary flow velocity reserve (≤2) adds incremental value to the prognostic stratification achieved with clinical and angiographic data for events such as death and nonfatal MI in patients with angiographically normal or near-normal coronary arteries and preserved at-rest regional and global left ventricular function at baseline and during stress.[21]

5.3. Cost-Value Considerations in Diagnostic Testing

A general concept regarding cost is that layered testing (ie, when a test is followed by more tests) leads to higher costs. To minimize the potential needs for downstream testing, clinicians should select the test that is most likely to answer a particular question.

5.3.1. CCTA and CAC Scanning Cost-Value Considerations

In the outpatient setting, long-term costs were generally similar between CCTA and stress testing strategies.[1] Higher invasive angiography rates after CCTA are matched by a greater use of downstream stress testing after initial stress testing, resulting in minimal differences in cost at 2 to 3 years of follow-up.[1,2] From the CONSERVE (Coronary Computed Tomographic Angiography for Selective Cardiac Catheterization) trial, 823 patients were randomized to a selective versus direct referral strategy to ICA. Enrollment was limited to patients with nonemergent indications for ICA.[3] The selective referral arm included CCTA-guided use of ICA. Cumulative diagnostic costs were $1183 for the selective arm and $2755 for the direct referral arm of the CONSERVE trial (57% lower costs). In the CCTA-guided arm, follow-up stress testing was applied and contributed to reduced referrals to ICA.

A recent tiered testing strategy was evaluated in both the CRESCENT I and II trials.[2,4] From the CRESCENT I trial, CAC was used as the index test, with follow-up CCTA used only in patients with detectable CAC or for those with a high pretest risk.[2] In this trial, nearly 40% of patients did not undergo CCTA, which reduced diagnostic evaluation costs; no events were reported in this subgroup. By comparison, nearly half of those randomized to the exercise ECG had additional confirmatory diagnostic testing. Overall, 1-year costs were significantly lower in the CAC tiered testing protocol (16% cost savings; $P<0.0001$).[2] Moreover, 1-year MACE-free survival was higher in the CAC-guided testing arm (97%) compared with exercise ECG (90%; HR: 0.32; $P=0.011$).

5.3.2. Exercise Electrocardiographic Cost-Value Considerations

The economic evidence for the exercise ECG supports that tiered testing may offset its reduced diagnostic accuracy.[1,2] In a decision model, tiered testing of exercise ECG followed by selective stress echocardiography resulted in improved diagnostic accuracy and favorable cost-effective ratios when compared with other testing strategies.[2] In a Medicare cohort, observed 180-day costs were lowest for the exercise ECG when compared with stress echocardiography, MPI, or CCTA.[3] Randomized trial data on cost are available and from the PROMISE trial initial test costs were $174 for exercise ECG, >50% lower than that of other imaging procedures.[4] At 3-years of follow-up, the mean cost difference was $1731 higher for CCTA (n=4818) when compared with the exercise ECG (n=858); however, the 95% CIs for cost differences was wide ($2 to $3519), and there was no overall difference by randomization.[4] Overall, results from the PROMISE trial showed that stress testing was associated with similar costs and CAD outcomes over ~3 years of follow-up.[4,5] In a randomized trial of 824 symptomatic women, cumulative procedural costs were nearly 50% lower for exercise ECG versus MPI SPECT ($P<0.0001$), with no difference in 2-year event-free survival ($P=0.59$).[6]

5.3.3. Stress Echocardiographic Cost-Value Considerations

Several cost-effectiveness models have reported an increased incremental cost-effectiveness ratio for stress echocardiography, compared with exercise ECG and

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other diagnostic procedures.[1-4] In these models, cost-effectiveness was influenced by an improved diagnostic accuracy for stress echocardiography, which led to longer life expectancy.[1] In a recent systematic review, the evidence supports that stress echocardiography or stress MPI are cost-effective for those patients at intermediate pretest risk.[5] The improved CAD detection for exercise echocardiography resulted in fewer office and ED visits and hospital days, yielding a 20% cost savings when compared with the exercise ECG.[6] There were 2204 patients that underwent stress echocardiography in the PROMISE trial, and 3-year mean costs were similar to that of CCTA (CCTA − stress echocardiography mean cost difference: −$363; 95% CI: −$1562 to $818).[7]

5.3.4. Stress Nuclear MPI Cost-Value Considerations

Among intermediate-risk patients, evidence synthesis supports that stress MPI is a cost-effective test option.[1] From the SPARC (Study of Myocardial Perfusion and Coronary Anatomy Imaging Roles in Coronary Artery Disease) registry, observed 2-year mortality rate was highest for PET MPI (5.5%) compared with CCTA (0.7%) or SPECT MPI (1.6%), with 2-year cost highest for patients undergoing PET.[2] In the PROMISE trial, nearly two-thirds of patients underwent stress MPI, and the mean cost was similar when compared with CCTA.[3] Mean costs were also similar in a randomized trial of 457 patients comparing stress MPI with exercise ECG ($P>0.05$).[4] Among higher-likelihood patients in the UK enrolled in the CECaT (Cost Effectiveness of Noninvasive Cardiac Testing) trial, MPI SPECT was the most cost-effective approach.[5]

5.3.5. Stress CMR Cost-Value Considerations

A synthesis of this cost evidence reveals a pattern whereby CMR perfusion and scar imaging is associated with a favorable incremental cost-effectiveness ratio of <$50 000 per quality-adjusted life years saved.[1,2] From a single report, a CMR strategy informed by the CE-MARC trial was more cost-effective than stress MPI, largely because of the higher diagnostic accuracy for CMR.[2] However, the most cost-effective strategy was that of initial exercise ECG followed by selective stress CMR and invasive angiography; for this tiered testing approach, additional testing was deemed appropriate in the setting of abnormal or inconclusive findings. In a decision model for intermediate pretest risk patients, a strategy of CMR followed by selective ICA had projected reduced costs by ~25% when compared with direct referral to ICA.[2,3] From the Stress CMR Perfusion Imaging in the United States registry,[4] patients with negative findings for ischemia and scar had low downstream costs.[5]

6. EVIDENCE GAPS AND FUTURE RESEARCH

Chest pain is one of the most common symptoms for which a person seeks medical care, and it should therefore be the target of substantial research investigation.

1. For patients with ACS, considerable success has been achieved in reducing door-to-balloon times for STEMI, but little progress has been made in reducing the important delays from symptom onset to presentation. Further research is needed to develop approaches to shorten this interval including studies of other methods of evaluating patients with chest pain using technologies that permit acquisition and transmission of ECGs from home and remote evaluations (eg, telehealth) for those with acute symptoms.[1,2]
2. An important, increasing patient population includes women and men with angina and ACS associated with angiographically normal or nonobstructive coronary arteries.[3,4] Prognosis is not benign, pathophysiology has not been clarified, and optimal therapy is unclear in these heterogeneous groups, which are now considered in terms of INOCA[5] and MINOCA.[6] Adequately identifying patients with INOCA, and completing an evaluation to make such a diagnosis, is necessary but often not done, regardless of whether chest pain is assessed in the ED, inpatient, or outpatient setting. Further investigation to clarify disease mechanisms in these challenging syndromes is needed to provide the basis for therapeutic advances.
3. One of the initial challenges in the evaluation of patients with chest pain, either in the emergency or office setting, is symptom classification. Methods to elicit symptoms and clusters of symptoms that provide improved pretest probabilities of symptomatic CAD may be aided with machine-learning algorithms. It is already clear that some common dogma about chest pain descriptions, such as differences between men and women, may not be as prevalent as has been reported[7] and may impede care of both sexes if they do not fit preconceived notions of the clinical significance of their symptoms. However, reducing the differences in both sex and racial differences in treatment and outcomes are important future goals of research and clinical care.
4. Clinical risk stratification and decision tools will likely continue to grow in popularity because they are incorporated into electronic health records, but it would be useful to test them in large randomized trials to rigorously determine their

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benefit in terms of improved outcomes or lower costs before widespread implementation.[1] hs-cTn assays are now the global standard of care for identifying myocardial injury, although questions remain about whether minimal elevations, which carry prognostic value, are actionable in a manner that improves outcomes. Trials evaluating various medical and procedural strategies would be useful including diagnostic and therapeutic algorithms for MINOCA. The number of potential questions that could be addressed will demand innovative trial designs to use resources efficiently and meaningfully.

5. Increasingly, randomized trials will be performed to determine which diagnostic tests can be eliminated from initial and follow-up care, both to streamline management algorithms and to decrease health care costs. In part, this approach will encompass evaluation of where patients with chest pain should be initially evaluated and monitored. Comparison of the various imaging modalities in randomized trials should help refine test selection and use.[8]

   Thus, the diagnosis and management of chest pain will remain a fertile area of investigation, with randomized evaluations complementing insights provided by registries of patients presenting with chest pain.[9-12] In the future, registries will more frequently serve as platforms within which to conduct randomized trials. Accreditation activities coupled with registry participation will also need to be evaluated to determine if they not only improve processes of care but also affect clinical endpoints.[12] Assessment of long-term outcomes, patient-centered metrics, and cost will be integrated into these studies to enhance the evidence base for care of patients presenting with chest pain with greater precision.

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ARTICLE INFORMATION

This document was approved by the American College of Cardiology Clinical Policy Approval Committee in May 2021, the American Heart Association Science Advisory and Coordinating Committee in May 2021, the Society of Cardiovascular Computed Tomography in July 2021, the Society for Academic Emergency Medicine in June 2021, the Society for Cardiovascular Magnetic Resonance in June 2021, the American College of Chest Physicians in June 2021, the American Society of Echocardiography in June 2021, the American Heart Association Executive Committee in July 2021, and the American College of Cardiology Science and Quality Committee in July 2021.

The Comprehensive RWI Data Supplement table is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/CIR.0000000000001029.

This article has been copublished in the *Journal of the American College of Cardiology*.

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APPENDIX

Appendix 1. Author Relationships With Industry and Other Entities (Relevant)–2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Martha Gulati (Chair)	The University of Arizona Phoenix–Professor of Medicine & Chief of Cardiology	None	None	None	None	None	None
Phillip D. Levy (Vice Chair)	Wayne State University–Professor and Associate Chair for Research, Department of Emergency Medicine; Assistant Vice President for Translational Science and Clinical Research Innovation	• Apex Innovation* • AstraZeneca • AstraZeneca, Hospital Quality Foundation • Beckman Coulter • Boehringer Ingelheim • Bristol-Myers Squibb • Cardiorentis • Novartis* • Ortho Diagnostics* • Pfizer • Roche* • Sciex • Shire* • Siemens* • The Medicines Company • Trevena • ZS Pharma	None	• Carbon Lifeform Innovations† • Mespere†	• Amgen* • Bristol-Myers Squibb* • Cardiorentis* • Edwards Lifesciences* • Gilead Sciences* • Novartis* • Pfizer* • Roche* • Shire* • Trevena	• Amgen* • Edwards* • E.R. Squibb & Sons, L.L.C. • Janssen Pharmaceuticals • Roche	None
Debabrata Mukherjee (Vice Chair)	Texas Tech University Health Sciences Center El Paso–Chairman, Department of Medicine	None	None	None	None	None	None
Ezra Amsterdam	UC Davis Medical Center–Professor, Department of Internal Medicine	None	None	None	None	None	None
Deepak L. Bhatt	Brigham and Women's Hospital Heart & Vascular Center–Executive Director of Interventional Cardiovascular Programs; Harvard Medical School–Professor of Medicine	• Daiichi Sankyo • Pfizer*	None	None	• Abbott* • Amarin* • Amgen* • AstraZeneca* • Bayer* • Boehringer Ingelheim* • Bristol-Myers Squibb* • Cardax* • Chiesi* • Eisai* • Eli Lilly* • Ethicon* • FlowCo† • Forest Laboratories* • Idorsia* • Ironwood* • Ischemix* • Medtronic* • Merck* • Pfizer* • PhaseBio* • PLx Pharma* • Regeneron* • Roche* • Sanofi-aventis* • Synaptic* • Takeda† • The Medicines Company*	• Amarin Pharma Inc.* • AstraZeneca* • Biotronik‡ • Boehringer Ingelheim* • Boston Scientific‡ • Cardax† • Merck† • Novartis • PhaseBio† • PLx Pharma† • Regado Biosciences† • Sanofi-aventis* • St. Jude Medical‡ • Svelte‡	None

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Appendix 1. Continued

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Kim K. Birtcher	University of Houston College of Pharmacy–Clinical Professor	None	None	None	None	None	None
Ron Blankstein	Harvard Medical School–Associate Professor of Medicine and Radiology, Co-Director, Cardiovascular Imaging Training Program; Brigham and Women's Hospital–Associate Physician, Preventive Cardiology; Director, Cardiac Computed Tomography	• Amgen • Astellas Inc • EKOS Corp.	None	None	• Amgen† • Astellas Pharma† • Gilead Sciences† • Sanofi-aventis†	• Sanofi US Services*	None
Jack Boyd	Stanford University–Clinical Assistant Professor, Department of Cardiothoracic Surgery	• Esculon/Centese • Sorin	None	None	None	None	None
Renee P. Bullock-Palmer	Deborah Heart & Lung Center–Director, Women's Heart Center; Director, Non-Invasive Cardiac Imaging	None	None	None	None	None	None
Theresa Conejo	Nazareth Hospital–Heart Failure Coordinator	None	None	None	None	None	None
Deborah B. Diercks	UT Southwestern–Professor and Chair, Department of Emergency Medicine	• ETHealthcare • Janssen Pharmaceuticals • Novartis*	None	None	• Abbott* • Bristol-Myers Squibb† • Ortho Clinical† • Roche* • Siemens	• E.R. Squibb & Sons, L.L.C.* • Konica Minolta Healthcare Americans, Inc.	None
Federico Gentile	Centro Cardiologico Gentile, Naples, Italy–Director	None	None	None	None	None	None
John P. Greenwood	Leeds Institute of Cardiovascular and Metabolic Medicine–Mautner Chair of Cardiology, Division of Biomedical Imaging	None	None	None	None	None	None
Erik P. Hess	University of Alabama at Birmingham–Professor of Emergency Medicine and Vice Chair for Research, Department of Emergency Medicine	• Gilead Sciences*	None	None	• Gilead Sciences*	None	None
Steven M. Hollenberg	Cooper Medical School of Rowan University–Professor of Medicine; Cooper University Hospital–Director, Coronary Care Unit	None	None	None	None	None	None
Wael A. Jaber	Cleveland Clinic Lerner College of Medicine–Professor of Medicine, Department of Cardiovascular Medicine and Fuad Jubran Endowed Chair in Cardiovascular Medicine, Heart and Vascular Institute	None	None	None	None	None	None
Hani Jneid	Baylor College of Medicine–Associate Professor of Medicine; The Michael DeBakey VA Medical Center–Director of Interventional Cardiology Research	None	None	None	None	None	None

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Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
José A. Joglar	University of Texas Southwestern Medical Center–Professor of Internal Medicine, Fellowship Program Director, Clinical Cardiac Electrophysiology, Elizabeth Thaxton Page and Ellis Batten Page, Professorship in Clinical Cardiac Electrophysiology Research	None	None	None	None	None	None
David A. Morrow	Brigham and Women's Hospital–Director, Levine Cardiac Intensive Care Unit; Harvard Medical School–Professor of Medicine, Cardiovascular Division	• Abbott • Aralez Pharmaceuticals* • AstraZeneca* • Bayer* • Daiichi Sankyo • diaDexus • Gilead Sciences • GlaxoSmithKline* • Merck* • Novartis* • Pfizer* • Roche* • Verseon	None	None	• Abbott* • Amgen* • AstraZeneca* • BRAHMS* • Daiichi-Sankyo* • Eisai Corporation* • GlaxoSmithKline* • Johnson & Johnson* • Medicines Company* • Merck* • Novartis* • Pfizer* • Regeneron* • Roche* • Singulex* • Takeda Pharmaceuticals*	• Roche*	None
Robert E. O'Connor	University of Virginia–Professor and Chair, Department of Emergency Medicine	None	None	None	None	• Cardiorentis Ltd.†	None
Michael A. Ross	Emory University School of Medicine–Professor, Department of Emergency Medicine; Emory Healthcare–Chief of Service, Observation Medicine; Emory University Hospital Chest Pain Center–Medical Director	None	None	None	None	None	None
Leslee J. Shaw	Icahn School of Medicine, Mount Sinai–Professor	None	None	None	None	• Covanos, Inc–Scientific Advisory Board†	None

This table represents the relationships of committee members with industry and other entities that were determined to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the writing committee during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥$5 000 of the fair market value of the business entity, or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted.

According to the ACC/AHA, a person has a *relevant* relationship IF: a) the *relationship or interest* relates to the same or similar subject matter, intellectual property or asset, topic, or issue addressed in the *document;* or b) the *company/entity* (with whom the relationship exists) makes a drug, drug class, or device addressed in the *document* or makes a competing drug or device addressed in the *document*; or c) the *person or a member of the person's household*, has a reasonable potential for financial, professional or other personal gain or loss as a result of the issues/content addressed in the *document*. Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry and other entities may apply.

*Significant relationship.

†No financial benefit.

‡This disclosure was entered under the Clinical Trial Enroller category in the ACC's disclosure system. To appear in this category, the author acknowledges that there is no *direct* or *institutional* relationship with the trial sponsor as defined in the ACC/AHA Disclosure Policy for Writing Committees.

ACC indicates American College of Cardiology; AHA, American Heart Association; ASE, American Society of Echocardiography; CHEST, American College of Chest Physicians; SAEM, Society for Academic Emergency Medicine; SCCT, Society of Cardiovascular Computed Tomography; SCMR, Society for Cardiovascular Magnetic Resonance; UC, University of California; UT, University of Texas; and VA, Veterans Affairs.

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Appendix 2. Reviewer Relationships With Industry and Other Entities (Comprehensive)–2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain

Reviewer	Representation	Employ-ment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Sana M. Al-Khatib	Content Reviewer–AHA	Duke University Medical Center	• Medtronic • Milestone Pharmaceuticals	None	None	• Abbott • Medtronic* • NHLBI* • PCORI* • US Food and Drug Administration*	• Abbott • AHA* • Bristol-Myers Squibb • Medtronic • Pfizer	None
Mouaz Al-Mallah	Official Reviewer–American Society of Nuclear Cardiology	Houston Methodist	• Pfizer	None	None	• Siemens†	• Amgen • GE Healthcare‡* • Pfizer • Siemens	None
Jayashri R. Aragam	Official Reviewer–American Society of Echocardiography	West Roxbury VA Hospital, Harvard Medical School	None	None	None	None	None	None
Ragavendra Baliga	Content Reviewer–ACC/AHA	Ohio State University Hospital	None	None	None	None	• Baliga's *Textbook of Internal Medicine* with 1480 MCQs, Editor-in-Chief† • Elsevier, Deputy Editor† • Lippincott Williams & Wilkins • McGraw-Hill Cardiology Textbook, Editor-in-Chief • Oxford University Press & Przewodnik praktyczny jak stosowac statyny, Termedia Wydawnictwa Medyczne, Editor • Oxford University Press, Series Editor • Springer, Co Editor-in-Chief • W.B. Saunders/ Elsevier, *250 Cases in Clinical Medicine, Third Edition*	None
Joshua A. Beckman	Content Reviewer–ACC/AHA Joint Committee on Clinical Practice Guidelines	Vanderbilt University Medical Center	• Amgen • GlaxoSmithKline* • JanOne • Janssen Pharmaceuticals* • Sanofi-aventis*	None	• EMX† • JanaCare†	• Bayer (DSMB) • Novartis (DSMB)	• Amgen • GlaxoSmithKline • Vascular Interventional Advances*	None
Daniel S. Berman	Official Reviewer–AHA	Cedars-Sinai Medical Center	• Bayer* • Cedars-Sinai Medical Center* • General Electric	None	None	None	• Amgen* • Bayer • Cedars-Sinai Medical Center • GE Healthcare*	None
Kelley Branch	Content Reviewer–Society of Cardiovascular Computed Tomography	University of Washington	• Bayer* • Janssen Pharmaceuticals*	None	None	• Bayer* • Locke Foundation Grant* • Novartis‡	• AstraZeneca • Bayer* • Janssen Pharmaceuticals • Novartis • Sanofi-aventis	None
Andrew Choi	Official Reviewer–Society of Cardiovascular Computed Tomography	The George Washington University School of Medicine	None	None	• Cleerly, Inc.*	None	None	None
Melissa A. Daubert	Official Reviewer–AHA	Duke University Medical Center	None	None	None	None	• 4D Molecular Contrafect • Heartflow • NIH • Roche • Verliy	None

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Reviewer	Representation	Employ-ment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Lisa de las Fuentes	Content Reviewer–ACC/AHA Joint Committee on Clinical Practice Guidelines	Washington University	• Acceleron • Altavant • Arena • Bayer • Express Scripts • Gilead Sciences • Johnson & Johnson • Mentor Planning and Consulting • Phase Bio • V-wave • WebMD*	• Bayer* • Simply Speaking*	None	• Acceleron* • Altavant* • Bayer • Complexa* • Johnson & Johnson* • Liquidia* • Medtronic* • NIH* • Reata • Trio Analytics* • United Therapeutics* • University of Kentucky (DSMB) • University of Toronto (DSMB)†	• ACC† • AHA† • *Circulation* Journals • Pulmonary Hypertension Association*	None
Anita Deswal	Content Reviewer–ACC/AHA Joint Committee on Clinical Practice Guidelines	UT MD Anderson Cancer Center	None	None	None	None	• ACC • AHA • HFSA†	None
Dave L. Dixon	Content Reviewer–ACC/AHA Joint Committee on Clinical Practice Guidelines	Virginia Commonwealth University School of Pharmacy	• American Pharmacists Association	None	None	• Centers for Disease Control and Prevention* • Community Pharmacy Foundation*	• Accreditation Council for Clinical Lipidology† • American College of Pharmacy Cardiology Practice Research Network† • American Pharmacists Association • National Lipid Association†	None
John U. Doherty	Official Reviewer–ACC	Jefferson University Hospitals	None	None	None	None	None	None
Maros Ferencik	Content Reviewer–Society of Cardiovascular Computed Tomography	Oregon Health & Science University	• Biograph*	None	• AHA, Fellow to Faculty Award*	• NIH*	• HeartFlow‡	None
Lee A. Fleisher	Content Reviewer–ACC/AHA Joint Committee on Clinical Practice Guidelines	Centers for Medicare & Medicaid Services (CMS)	None	None	None	• NIH	None	None
Mario Garcia	Content Reviewer–AHA/ACC	Montefiore Medical Center	None	None	None	None	• Abiomed • Medtronic Vascular, Inc. • Novartis • Philips	None
Seth Gemme	Official Reviewer–American College of Emergency Physicians	Baystate Medical Center	• Roche Diagnostics	None	None	None	None	None
Zachary D. Goldberger	Content Reviewer–ACC/AHA Joint Committee on Clinical Practice Guidelines	University of Wisconsin School of Medicine and Public Health	None	None	None	None	None	None
Bulent Gorenek	Content Reviewer–ACC/AHA Joint Committee on Clinical Practice Guidelines	Eskisehir Osmangazi University	• AstraZeneca • Sandoz	None	None	None	None	None

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Reviewer	Representation	Employ-ment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Norrisa Haynes	Content Reviewer–ACC/AHA Joint Committee on Clinical Practice Guidelines	University of Pennsylvania	None	None	None	None	None	None
Adrian F. Hernandez	Content Reviewer–ACC/AHA Joint Committee on Clinical Practice Guidelines	Duke University	• Amgen • AstraZeneca* • Bayer • Biofourmis • Boehringer Ingelheim • Boston Scientific* • Cytokinetics • Daiichi Sankyo • Eli Lilly • Merck* • Myokardia • Novartis* • Pfizer • Relypsa • Sanofi-aventis* • Xogenex	None	None	• American Regent • AstraZeneca* • Eidos (DSMB) • Genentech • GlaxoSmithKline* • Janssen Pharmaceuticals • Merck • NIH† • Novartis* • PCORI† • Verily*	• AHA† • AstraZeneca • Boston Scientific • CSL Behring • Janssen Pharmaceuticals* • Merck • Novartis • Genentech* • Relypsa • Sanofi-aventis	• Defendant, Patent Dispute, 2019
Mark A. Hlatky	Content Reviewer–ACC/AHA Joint Committee on Clinical Practice Guidelines	Stanford University School of Medicine	• ACC, Global Advisory Committee • Blue Cross Blue Shield Center for Effectiveness Evaluation* • The Medicines Company	None	None	• HeartFlow* • NHLBI (DSMB) • St. Jude	• George Institute†	None
Stephen Hoole	Content Reviewer–ACC	Royal Papworth Hospital, UK	• Abbott* • Bayer • Boston Scientific	• AstraZeneca • Bayer • Novo Nordisk	None	• Abbott* • AstraZeneca*	None	None
W. Schuyler Jones	Content Reviewer–ACC/AHA Joint Committee on Clinical Practice Guidelines	Duke University	• Amgen • Bayer* • Janssen Pharmaceuticals* • Pfizer	None	None	• Bristol-Myers Squibb • Janssen Pharmaceuticals • Patient-Centered Outcomes Research Institute	• Abbott* • Amgen • AstraZeneca • Boehringer Ingelheim • Cardiovascular Systems Inc.* • Janssen Pharmaceuticals • ZOLL Medical	None
Michael Kontos	Content Reviewer–ACC	Virginia Commonwealth University Health	None	None	None	None	• ACC* • NIH‡ • Society for Academic Emergency Medicine† • VCSQUI† • VHAC†	None
Raymond Kwong	Official Reviewer–Society for Cardiovascular Magnetic Resonance	Brigham and Women's Hospital	None	None	None	• Alnylam, Inc* • MyoKardia* • NIH	• Bayer • Siemens • Society for Cardiovascular Magnetic Resonance†	None
Glenn N. Levine	Content Reviewer–Former Chair of the ACC/AHA Task Force on Clinical Practice Guidelines	Baylor College of Medicine	None	None	None	None	None	• Defendant, In-hospital death, 2020 • Defendant, In-hospital death, 2019*
Jonathan Lindner	Official Reviewer–American Society of Echocardiography	Oregon Health & Science University	None	None	None	• Bracco† • GE Healthcare • GE Lifesciences† • Pfizer†	• Lantheus Medical Imaging, Inc.	None

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Reviewer	Representation	Employ-ment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
G.B. John Mancini	Content Reviewer–ACC	Vancouver Hospital Research Pavillion, Professor of Medicine	• Amgen • AstraZeneca • Bayer • Boehringer Ingelheim • Eli Lilly • Esperion • HLS Therapeutics • Merck • Pfizer • Regeneron • Sanofi-aventis	• Amgen • HLS Therapeutics • Sanofi-aventis	None	• Novo Nordisk • NovartisPle	None	None
Daniel B. Mark	Content Reviewer–ACC/AHA Joint Committee on Clinical Practice Guidelines	Duke University	None	None	None	None	• HeartFlow* • Merck*	None
Jim McCord	Content Reviewer–ACC/AHA	Henry Ford Health System	• Beckman • Roche* • Siemens*	None	None	• Abbott* • Beckman Diagnostics* • Roche* • Siemens	• ACC Accreditation Services, Board Member†	None
C. Noel Bairey Merz	Content Reviewer–ACC/AHA	Cedars-Sinai Heart Institute	• Med Intelligence	None	None	• California Institute for Precision Medicine* • DOD Warrior* • NIH-NIA* • Sanofi-aventis* • WISE pre-HFpEF*	• Bayer, Advisory Board • iRhythm*	None
Nicholas L. Mills	Content Reviewer–ACC	BHF Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, Scotland	• Abbott • Laboratories • LumiraDx • Roche Diagnostics • Siemens Healthineers	None	None	None	None	None
James Min	Content Reviewer–ACC/AHA	• Cleerly, Inc.	None	None	• Cleerly, Inc.	• NIH	• Ablative Solutions • Arineta • Memphis Meats	None
L. Kristin Newby	Content Reviewer–ACC	Duke University	• Beckman-Coulter • BioKier • Bristol-Myers Squibb • CSL • Medtronic • NHLBI • Quidel • Roche Diagnostics	None	None	• Boehringer Ingelheim • David H. Murdock Institute for Business and Culture • NIH • North Carolina DHHS	• AHA† • ACC, Oregon Chapter • AstraZeneca† • Boehringer Ingelheim • David H. Murdock Research Institute† • *JACC*, Deputy Editor* • Roche Diagnostics	None
Patrick T. O'Gara	Content Reviewer–ACC/AHA Joint Committee on Clinical Practice Guidelines	Brigham and Women's Hospital	None	None	None	None	• Edwards Lifesciences† • *JAMA Cardiology** • NIH* • Medtrace† • Medtronic† • Medtronic Vascular, Inc.	None

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Reviewer	Representation	Employ-ment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Kevin O'Neil	Content Reviewer–American College of Chest Physicians	Wilmington Health, PLLC	None	None	None	None	• American Board of Internal Medicine • Astellas Pharma • Commission on Accreditation for Respiratory Care† • Genentech • Genzyme • GlaxoSmith Kline • Insmed • Otsuka • America Pharmaceuticals • Philips • Resmed Corp • Sunovion Pharmaceuticals	None
W. Frank Peacock	Content Reviewer–AHA	Baylor College of Medicine	• Abbott • AstraZeneca • Instrumentation Laboratories • Janssen Pharmaceuticals* • Medicure • Pharma Inc. • Quidel • Relypsa • Siemens	None	• Comprehensive Research Associates* • Emergencies in Medicine†	• Roche*	• Abbott • Aseptiscope* • Astellas Pharma • AstraZeneca • Beckman Coulter, Inc.* • Boehringer Ingelheim* • DiaSorin S.P.A.* • E.R. Squibb & Sons, L.L.C.* • Instrumentation Laboratory Company* • Janssen Pharmaceuticals* • Medicure Pharma Inc. • Quidel • Relypsa • Roche* • Salix Pharmaceutical Division of Bausch Health US, LLC • Siemens*	None
Carl Pepine	Content Reviewer–ACC/AHA	University of Florida	• Caladrius • Biosciences • Elsevier • Slack Inc.* • Verily • XyloCor	None	None	• Biocardia* • Brigham and Women's Hospital* • CSL Behring* • Cytori Therapeutics*‡ • DCRI* • GE Healthcare • InVentive Health Clinical, LLC‡ • Mesoblast* • NIH‡ • NIH/NHLBI* • Pfizer • Sanofi-aventis‡ • US Department of Defense*	None	None
Andrea L. Price	Content Reviewer–ACC	Indiana University Health	None	None	• Quality Informatics Synergies, LLC	• ACC, Accreditation Foundation Board*	None	None
Susan B. Promes	Official Reviewer–American College of Emergency Physicians	Penn State Health Milton S. Hershey Medical Center	None	None	None	None	None	None
Tanveer Rab	Content Reviewer–ACC	Emory University	None	None	None	None	None	None
Harish Ramakrishna	Content Reviewer–ACC	Mayo Clinic	None	None	None	None	None	None

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Reviewer	Representation	Employ-ment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Basmah Safdar	Official Reviewer–Society for Academic Emergency Medicine	Yale School of Medicine	None	None	None	None	• OrthoClinical* • Roche*	None
Michael Salerno	Content Reviewer–Society for Cardiovascular Magnetic Resonance	University of Virginia	None	None	None	• NIH*	• Heartflow • Siemens	• Defendant, SPECT Camera Malfunction, 2020
Ada Stefanescu Schmidt	Content Reviewer–ACC	University of Toronto; Harvard University	None	None	None	None	None	None
Prem Soman	Official Reviewer–American Society of Nuclear Cardiology	University of Pittsburgh Medical Center	• Alnylam Pharma • Eidos • Pfizer	None	None	None	• Astellas • Pharma* • Pfizer	None
Jacqueline Tamis-Holland	Content Reviewer–ACC/AHA Joint Committee on Clinical Practice Guidelines	Mount Sinai Morningside Hospital	None	None	None	• Internal-Minneapolis Heart Institute† • The NGS Predict Study‡	• Abbott† • AHA† • Bronx Lebanon Hospital, Cardiology Fellowship Program Director† • Medscape/Heart.org • NIH†‡ • NYS†	None
James Thomas	Content Reviewer–ACC/AHA	Northwestern Medicine	• Abbott • Caption Health* • Edwards Lifesciences* • General Electric • Shire North American Group Inc.*	None	None	• Abbott • Caption Health • General Electric	• Abbott • Caption Health* • Edwards Lifesciences* • Medtronic Vascular, Inc. • Shire North American Group Inc.	None
Todd Villines	Official Reviewer–Society of Cardiovascular Computed Tomography and ACC	University of Virginia Health System	None	None	None	None	None	None
Andrew R. Waxler	Official Reviewer–ACC	Penn State Health	None	• Amarin* • Regeneron* • Sanofi-aventis*	None	None	• Abbott • Amarin* • Amgen • Boehringer Ingelheim • DalCor Pharmaceuticals • Janssen Pharmaceuticals • Novartis • Penn State-St. Joseph Medical Center Foundation, Board Member† • Penn State–St. Joseph Medical Center Pharmacy and Therapeutics, Committee Member† • Portola • Regeneron • Sanofi-aventis • The Medicines Company • ZOLL Medical	None

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Reviewer	Representation	Employ-ment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Nanette K. Wenger	Content Reviewer–AHA	Emory University	• Amarin Pharma, Inc. • AstraZeneca • Janssen Pharmaceuticals	None	None	• AstraZeneca† • Boehringer Ingelheim • US Department of Defense • Duke Clinical Research Institute† • NHLBI† • ZOLL Medical†	None	None
Joseph Woo	Content Reviewer–ACC/AHA Joint Committee on Clinical Practice Guidelines	Stanford University School of Medicine	None	None	None	None	• NIH*	None
Sammy Zakaria	Official Reviewer–American College of Chest Physicians	Johns Hopkins University School of Medicine	None	None	None	None	None	None
Mark J. Zucker	Official Reviewer–American College of Chest Physicians	Newark Beth Israel Medical Center	None	None	None	None	None	None

This table represents all relationships of reviewers with industry and other entities that were reported at the time of peer review, including those not deemed to be relevant to this document, at the time this document was under review. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥$5000 of the fair market value of the business entity, or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. Names are listed in alphabetical order within each category of review. Please refer to https://www.acc.org/guidelines/about-guidelines-and-clinical-documents/relationships-with-industry-policy for definitions of disclosure categories or additional information about the ACC/AHA Disclosure Policy for Writing Committees.

*Significant relationship.

†No financial benefit.

‡This disclosure was entered under the Clinical Trial Enroller category in the ACC's disclosure system. To appear in this category, the author acknowledges that there is no direct or institutional relationship with the trial sponsor as defined in the (ACCF or AHA/ACC) Disclosure Policy for Writing Committees.

ACC indicates American College of Cardiology; ACCF, American College of Cardiology Foundation; AHA, American Heart Association; ASE, American Society of Echocardiography; ASNC, American Society of Nuclear Cardiology; CHEST, American College of Chest Physicians; DCRI, Duke Clinical Research Institute; DHHS, Department of Health and Human Services; DOD, Department of Defense; DSMB, data and safety monitoring board; HFSA, Heart Failure Society of America; *JACC*, *Journal of the American College of Cardiology*; NHLBI, National Heart, Lung, and Blood Institute; NIA, National Institute on Aging; NIH, National Institutes of Health; NYS, New York state; PCORI, Patient-Centered Outcomes Research Institute; SAEM, Society for Academic Emergency Medicine; SCCT, Society of Cardiovascular Computed Tomography; SCMR, Society for Cardiovascular Magnetic Resonance; UT, University of Texas; VCSQI, Virginia Cardiac Services Quality Initiative; VA, Veterans Affairs; and VHAC, Virginia Heart Attack Coalition.

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ESC European Society of Cardiology

European Heart Journal (2024) **45**, 3415–3537
https://doi.org/10.1093/eurheartj/ehae177

ESC GUIDELINES

2024 ESC Guidelines for the management of chronic coronary syndromes

Developed by the task force for the management of chronic coronary syndromes of the European Society of Cardiology (ESC)

Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS)

Authors/Task Force Members: Christiaan Vrints *†, (Chairperson) (Belgium), Felicita Andreotti *†, (Chairperson) (Italy), Konstantinos C. Koskinas‡, (Task Force Co-ordinator) (Switzerland), Xavier Rossello ‡, (Task Force Co-ordinator) (Spain), Marianna Adamo (Italy), James Ainslie (United Kingdom), Adrian Paul Banning (United Kingdom), Andrzej Budaj (Poland), Ronny R. Buechel (Switzerland), Giovanni Alfonso Chiariello (Italy), Alaide Chieffo (Italy), Ruxandra Maria Christodorescu (Romania), Christi Deaton (United Kingdom), Torsten Doenst [1] (Germany), Hywel W. Jones (United Kingdom), Vijay Kunadian (United Kingdom), Julinda Mehilli (Germany), Milan Milojevic [1] (Serbia), Jan J. Piek (Netherlands), Francesca Pugliese (United Kingdom), Andrea Rubboli (Italy), Anne Grete Semb (Norway), Roxy Senior (United Kingdom), Jurrien M. ten Berg (Netherlands), Eric Van Belle (France), Emeline M. Van Craenenbroeck (Belgium), Rafael Vidal-Perez (Spain), Simon Winther (Denmark), and ESC Scientific Document Group

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Councils: Council for Cardiology Practice.

Working Groups: Cardiovascular Pharmacotherapy, Cardiovascular Surgery, Coronary Pathophysiology and Microcirculation, Thrombosis.

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¶ ***Professor Jean-Philippe Collet sadly passed away during the development of these guidelines. Professor Collet's contribution to these guidelines was, as always, highly valued.***

All experts involved in the development of these guidelines have submitted declarations of interest, which are reported in a supplementary document to the guidelines. See the *European Heart Journal* online or https://www.escardio.org/Guidelines for supplementary documents as well as evidence tables.

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Keywords Guidelines • Antianginal therapy • Antithrombotic therapy • Atherosclerosis • Clinical likelihood • Chronic coronary syndromes • Coronary artery disease • Diagnostic testing/algorithm • Heart team • Lipid-lowering therapy • Microvascular disease • Myocardial ischaemia • Myocardial revascularization • Outcomes • PROMS/PREMS • Shared decision-making • Stable angina • Vasospasm

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Abbreviations and acronyms

99mTc	Technetium-99m
ACE-I	Angiotensin-converting enzyme inhibitor
Ach	Acetylcholine
ACS	Acute coronary syndrome(s)
AF	Atrial fibrillation
AKI	Acute kidney injury
ALPHEUS	Assessment of Loading with the $P2Y_{12}$ Inhibitor Ticagrelor or Clopidogrel to Halt Ischemic Events in Patients Undergoing Elective Coronary Stenting
ANOCA	Angina with non-obstructive coronary arteries
ARB	Angiotensin receptor blocker

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ARC-HBR	Academic Research Consortium for High Bleeding Risk
ARNI	Angiotensin receptor neprilysin inhibitor
ART	Antiretroviral therapy
ASCVD	Atherosclerotic cardiovascular disease
ASE	American Society of Echocardiography
AUGUSTUS	Open-Label, 2 × 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban versus Vitamin K Antagonist and Aspirin versus Aspirin Placebo in Patients with Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention
BARC	Bleeding Academic Research Consortium
b.i.d.	bis in die (twice daily)
BMI	Body mass index
BP	Blood pressure
b.p.m.	Beats per minute
CABG	Coronary artery bypass grafting
CAC	Coronary artery calcification
CACS	Coronary artery calcium score
CACS-CL	CACS + risk-factor-weighted clinical likelihood (RF-CL) model
CAD	Coronary artery disease
CANTOS	Canakinumab Antiinflammatory Thrombosis Outcome Study
CAPRIE	Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events
CCB	Calcium channel blocker
CCS	Chronic coronary syndrome(s)
CCTA	Coronary computed tomography angiography
CFC	Coronary flow capacity
CFR	Coronary flow reserve
CFVR	Coronary flow velocity reserve
CHA_2DS_2-VASc	Congestive heart failure or left ventricular dysfunction, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74, sex category (female)
CI	Confidence interval
CKD	Chronic kidney disease
CMD	Coronary microvascular dysfunction
CMR	Cardiac magnetic resonance
COLCOT	Colchicine Cardiovascular Outcomes Trial
COMPASS	Cardiovascular Outcomes for People Using Anticoagulation Strategies
COURAGE	Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation
CRT	Cardiac resynchronization therapy
CT	Computed tomography
CVD	Cardiovascular disease
CYP2C19	Cytochrome P450 2C19
CYP3A4	Cytochrome P450 3A4
CZT	Cadmium–zinc–telluride
DAPT	Dual antiplatelet therapy
DEFINE GPS	Distal Evaluation of Functional Performance with Intravascular Sensors to Assess the Narrowing Effect: Guided Physiologic Stenting
DES	Drug-eluting stent
DEFINE-FLAIR	Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation
DHP	Dihydropyridine
DM	Diabetes mellitus
DOAC	Direct oral anticoagulant
dPR	Diastolic pressure ratio
DSE	Dobutamine stress echocardiography
EACTS	European Association for Cardio-Thoracic Surgery
EACVI	European Association of Cardiovascular Imaging
ECG	Electrocardiogram
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ESC	European Society of Cardiology
EXCEL	Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization
FAME	Fractional Flow Reserve versus Angiography for Multivessel Evaluation
FFR	Fractional flow reserve
FFR-CT	Coronary computed tomography angiography-derived fractional flow reserve
FREEDOM	Strategies for Multivessel Revascularization in Patients with Diabetes
GDMT	Guideline-directed medical therapy
GI	Gastrointestinal
GIP	Glucose-dependent insulinotropic polypeptide
GLOBAL LEADERS	Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs. aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent (DES): a multicentre, open-label, randomized superiority trial
GLP-1	Glucagon-like peptide-1
GUSTO	Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries
HbA1c	Glycated haemoglobin
HBR	High bleeding risk
HDL-C	High-density lipoprotein cholesterol
HF	Heart failure
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HIV	Human immunodeficiency virus
HMR	Hyperaemic myocardial velocity resistance
HOST-EXAM	Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis-EXtended Antiplatelet Monotherapy
HR	Hazard ratio
hs-CRP	High-sensitivity C-reactive protein
HSR	Hyperaemic stenosis resistance
i.c.	Intracoronary
i.v.	Intravenous
ICA	Invasive coronary angiography
ICD	Implantable cardioverter defibrillator
ICFT	Invasive coronary functional testing
iFR	Instantaneous wave-free ratio
iFR-SWEDEHEART	Instantaneous Wave-free Ratio versus Fractional Flow Reserve in Patients with Stable Angina Pectoris or Acute Coronary Syndrome
ILIAS	Inclusive Invasive Physiological Assessment in Angina Syndromes
IMR	Index of microcirculatory resistance
INOCA	Ischaemia with non-obstructive coronary arteries
INR	International normalized ratio
IQR	Interquartile range

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ISCHEMIA	Initial Invasive or Conservative Strategy for Stable Coronary Disease (trial)
ISR	In-stent restenosis
ISTH	International Society on Thrombosis and Haemostasis
IVUS	Intravascular ultrasound
LAD	Left anterior descending
LBBB	Left bundle branch block
LDL-C	Low-density lipoprotein cholesterol
LGE	Late gadolinium enhancement
LIMA	Left internal mammary artery
LITA	Left internal thoracic artery
LMCA	Left main coronary artery
LMCAD	Left main coronary artery disease
LODOCO2	LOw-DOse COlchicine 2
LOE	Level of evidence
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MACCE	Major adverse cardiac or cerebrovascular events
MACE	Major adverse cardiovascular events
MASTER-DAPT	Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation with an Abbreviated versus Standard DAPT Regimen
MBF	Myocardial blood flow
MCE	Myocardial contrast echocardiography
MCS	Mechanical circulatory support
MFR	Myocardial flow reserve
mHealth	Mobile device-based healthcare
MI	Myocardial infarction
MIDCAB	Minimally invasive direct coronary artery bypass
MRA	Mineralocorticoid receptor antagonist
MRI	Magnetic resonance imaging
MRR	Microvascular resistance reserve
MVA	Microvascular angina
MVD	Multivessel disease
NNH	Number needed to harm
NNT	Number needed to treat to prevent an adverse event
NOBLE	Nordic–Baltic–British Left Main Revascularisation Study
NSTEMI	Non-ST-segment elevation myocardial infarction
NTG	Nitroglycerine
NYHA	New York Heart Association
OAC	Oral anticoagulant
OCT	Optical coherence tomography
OR	Odds ratio
ORBITA	Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina
ORBITA-COSMIC	Coronary Sinus Reducer Objective Impact on Symptoms, MRI Ischaemia and Microvascular Resistance
PAD	Peripheral artery disease
PAR	Protease-activated receptor
PARR-2	F-18-Fluorodeoxyglucose Positron Emission Tomography Imaging-Assisted Management of Patients with Severe Left Ventricular Dysfunction and Suspected Coronary Disease: a Randomized, Controlled Trial
PCI	Percutaneous coronary intervention
PCSK9	Proprotein convertase subtilisin/kexin type 9
Pd/Pa	Distal coronary pressure to aortic pressure ratio
PDE-5	Phosphodiesterase-5
PEGASUS-TIMI 54	Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin Thrombolysis In Myocardial Infarction
PESA	Progression of Early Subclinical Atherosclerosis
PET	Positron emission tomography
PRECISE-DAPT	PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual AntiPlatelet Therapy
PRECOMBAT	Randomized Trial of Stents versus Bypass Surgery for Left Main Coronary Artery Disease (trial)
PRIZE	Precision Medicine with Zibotentan in Microvascular Angina
PROM	Patient-reported outcome measure
PROMISE	Prospective Multicenter Imaging Study for Evaluation of Chest Pain
PTP	Pre-test probability
QFR	Quantitative flow ratio
QoL	Quality of life
R3F	French FFR Registry
RAAS	Renin–angiotensin–aldosterone system
RCT	Randomized controlled trial
REVIVED-BCIS2	Percutaneous Revascularization for Ischemic Left Ventricular Dysfunction
RF-CL	Risk-factor-weighted clinical likelihood
RFR	Relative flow reserve
RIPCORD	Routine Pressure Wire Assessment Influence Management Strategy at Coronary Angiography for Diagnosis of Chest Pain trial
RR	Relative risk
RWTA	Regional systolic wall-thickening abnormalities
SAPT	Single antiplatelet therapy
SCORE2	Systematic Coronary Risk Estimation 2
SCORE2-OP	Systematic Coronary Risk Estimation 2–Older Persons
SCOT-HEART	Scottish Computed Tomography of the Heart
SELECT	Semaglutide Effects on Cardiovascular Outcomes in People With Overweight or Obesity
SGLT2	Sodium–glucose cotransporter 2
SLE	Systemic lupus erythematosus
SPECT	Single-photon emission computed tomography
STEMI	ST-segment elevation myocardial infarction
STICH	Surgical Treatment for Ischemic Heart Failure
STS-PROM	Society of Thoracic Surgeons Predicted Risk of Mortality
SURMOUNT	Efficacy and Safety of Tirzepatide Once Weekly in Participants Without Type 2 Diabetes Who Have Obesity or Are Overweight With Weight-Related Comorbidities: A Randomized, Double-Blind, Placebo-Controlled Trial
SYNTAX	SYNergy between PCI with TAXUS and Cardiac Surgery
THEMIS	The Effect of Ticagrelor on Health Outcomes in diabEtes Mellitus patients Intervention Study
TID	Transient ischaemic dilatation
TIMI	Thrombolysis In Myocardial Infarction
Tx	Thromboxane

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TWILIGHT	Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention
vFFR	Vessel fractional flow reserve
VKA	Vitamin K antagonist
VSA	Vasospastic angina
VTE	Venous thrombo-embolism
WARRIOR	Women's IschemiA Trial to Reduce Events in Non-ObstRuctIve CORonary Artery Disease
WOMEN	What is the Optimal Method for Ischemia Evaluation of Women
X-ECG	Exercise ECG testing

1. Preamble

Guidelines evaluate and summarize available evidence with the aim of assisting health professionals in proposing the best diagnostic or therapeutic approach for an individual patient with a given condition. Guidelines are intended for use by health professionals, and the European Society of Cardiology (ESC) makes its guidelines freely available.

ESC Guidelines do not override the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient or the patient's caregiver where appropriate and/or necessary. It is also the health professional's responsibility to verify the rules and regulations applicable in each country to drugs and devices at the time of prescription and to respect the ethical rules of their profession.

ESC Guidelines represent the official position of the ESC on a given topic and are regularly updated when warranted by new evidence. ESC Policies and Procedures for formulating and issuing ESC Guidelines can be found on the ESC website (https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Guidelines-development/Writing-ESC-Guidelines). These guidelines update and replace the previous version from 2019 and partly replace the myocardial revascularization guidelines from 2018.

The Members of this task force were selected by the ESC to include professionals involved in the medical care of patients with this pathology, as well as patient representatives and methodologists. The selection procedure included an open call for authors and aimed to include members from across the whole of the ESC region and from relevant ESC Subspecialty Communities. Consideration was given to diversity and inclusion, notably with respect to gender and country of origin. The task force performed a critical review and evaluation of the published literature on diagnostic and therapeutic approaches including assessment of the risk–benefit ratio. The strength of every recommendation and the level of evidence supporting them were weighed and scored according to predefined scales as outlined in *Tables 1* and *2* below. Patient-reported outcome measures (PROMs) and patient-reported experience measures (PREMs) were also evaluated as the basis for recommendations and/or discussion in these guidelines. The task force followed ESC voting procedures and all approved recommendations were subject to a vote and achieved at least 75% agreement among voting members. Members of the task force with declared interests on specific topics were asked to abstain from voting on related recommendations.

The experts of the writing and reviewing panels provided declaration of interest forms for all relationships that might be perceived as real or potential sources of conflicts of interest. Their declarations of interest were reviewed according to the ESC declaration of interest rules, which can be found on the ESC website (http://www.escardio.org/guidelines) and have been compiled in a report published in a supplementary document with the guidelines. Funding for the development of ESC Guidelines is derived entirely from the ESC with no involvement of the healthcare industry.

The ESC Clinical Practice Guidelines (CPG) Committee supervises and co-ordinates the preparation of new guidelines and is responsible

Table 1 Classes of recommendations

Classes of recommendations	Definition	Wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended or is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

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Table 2 Levels of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

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for the approval process. In addition to review by the CPG Committee, ESC Guidelines undergo multiple rounds of double-blind peer review by external experts, including members from across the whole of the ESC region, all National Cardiac Societies of the ESC and from relevant ESC Subspecialty Communities. After appropriate revisions, the guidelines are signed off by all the experts in the task force. The finalized document is signed off by the CPG Committee for publication in the *European Heart Journal*.

ESC Guidelines are based on analyses of published evidence, chiefly on clinical trials and meta-analyses of trials, but potentially including other types of studies. Evidence tables summarizing key information from relevant studies are generated early in the guideline development process to facilitate the formulation of recommendations, to enhance comprehension of recommendations after publication, and reinforce transparency in the guideline development process. The tables are published in their own section of the ESC Guidelines and are specifically related to the recommendation tables.

Off-label use of medication may be presented in these guidelines if a sufficient level of evidence shows that it can be considered medically appropriate for a given condition. However, the final decisions concerning an individual patient must be made by the responsible health professional giving special consideration to:

- The specific situation of the patient. Unless otherwise provided for by national regulations, off-label use of medication should be limited to situations where it is in the patient's interest with regard to the quality, safety, and efficacy of care, and only after the patient has been informed and has provided consent.
- Country-specific health regulations, indications by governmental drug regulatory agencies and the ethical rules to which health professionals are subject, where applicable.

2. Introduction

The 2019 ESC (European Society of Cardiology) Guidelines for the diagnosis and management of chronic coronary syndromes introduced the term chronic coronary syndromes (CCS)[1] to describe the clinical presentations of coronary artery disease (CAD) during stable periods, particularly those preceding or following an acute coronary syndrome (ACS). CAD was defined as the pathological process characterized by atherosclerotic plaque accumulation in the epicardial arteries, whether obstructive or non-obstructive. Based on expanded pathophysiological concepts, a new, more comprehensive definition of CCS is introduced:

> 'CCS are a range of clinical presentations or syndromes that arise due to structural and/or functional alterations related to chronic diseases of the coronary arteries and/or microcirculation. These alterations can lead to transient, reversible, myocardial demand vs. blood supply mismatch resulting in hypoperfusion (ischaemia), usually (but not always) provoked by exertion, emotion or other stress, and may manifest as angina, other chest discomfort, or dyspnoea, or be asymptomatic. Although stable for long periods, chronic coronary diseases are frequently progressive and may destabilize at any moment with the development of an ACS.'

Of note, 'disease' refers to the underlying coronary pathology, and 'syndrome' refers to the clinical presentation.

2.1. Evolving pathophysiological concepts of chronic coronary syndromes

Our understanding of the pathophysiology of CCS is transitioning from a simple to a more complex and dynamic model. Older concepts

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considered a fixed, focal, flow-limiting atherosclerotic stenosis of a large or medium coronary artery as a *sine qua non* for inducible myocardial ischaemia and ischaemic chest pain (angina pectoris). Current concepts have broadened to embrace structural and functional abnormalities in both the macro- and microvascular compartments of the coronary tree that may lead to transient myocardial ischaemia. At the macrovascular level, not only fixed, flow-limiting stenoses but also diffuse atherosclerotic lesions without identifiable luminal narrowing may cause ischaemia under stress;[2,3] structural abnormalities such as myocardial bridging[4] and congenital arterial anomalies[5] or dynamic epicardial vasospasm may be responsible for transient ischaemia. At the microvascular level, coronary microvascular dysfunction (CMD) is increasingly acknowledged as a prevalent factor characterizing the entire spectrum of CCS;[6] functional and structural microcirculatory abnormalities may cause angina and ischaemia even in patients with non-obstructive disease of the large or medium coronary arteries [angina with non-obstructive coronary arteries (ANOCA); ischaemia with non-obstructive coronary arteries (INOCA)].[6] Finally, systemic or extracoronary conditions, such as anaemia, tachycardia, blood pressure (BP) changes, myocardial hypertrophy, and fibrosis, may contribute to the complex pathophysiology of non-acute myocardial ischaemia.[7]

The risk factors that predispose to the development of epicardial coronary atherosclerosis also promote endothelial dysfunction and abnormal vasomotion in the entire coronary tree, including the arterioles that regulate coronary flow and resistance,[8–10] and adversely affect myocardial capillaries,[6,11–14] leading to their rarefaction. Potential consequences include a lack of flow-mediated vasodilation in the epicardial conductive arteries[9] and macro- and microcirculatory vasoconstriction.[15] Of note, different mechanisms of ischaemia may act concomitantly.

2.2. Chronic coronary syndromes: clinical presentations (*Figure 1*)

In clinical practice, the following, not entirely exclusive, CCS patients seek outpatient medical attention: (i) the symptomatic patient with reproducible stress-induced angina or ischaemia with epicardial obstructive CAD; (ii) the patient with angina or ischaemia caused by epicardial vasomotor abnormalities or functional/structural microvascular alterations in the absence of epicardial obstructive CAD (ANOCA/INOCA); (iii) the non-acute patient post-ACS or after a revascularization; (iv) the non-acute patient with heart failure (HF) of ischaemic or cardiometabolic origin. A further growing category (v) are the asymptomatic individuals in whom epicardial CAD is detected during an imaging test for refining cardiovascular risk assessment,[16] screening for personal or professional purposes, or as an incidental finding for another indication.[17] Patients may experience a variable and unpredictable course, transitioning between different types of CCS and ACS presentations throughout their lifetime.

The clinical presentations of CCS are not always specific for the mechanism causing myocardial ischaemia; thus, symptoms of dysfunctional microvascular angina (MVA) may overlap with those of vasospastic or even obstructive large–medium artery angina. Furthermore, it is important to note that CCS doesn't always present as classical angina pectoris and symptoms may vary depending on age and sex. Sex-stratified analyses indicate that women with suspected angina are usually older and have a heavier cardiovascular risk factor burden, more frequent comorbidities, non-anginal symptoms such as dyspnoea and fatigue, and greater prevalence of MVA than men.[18–21]

2.3. Changing epidemiology and management strategies

Contemporary primary prevention,[16] including lifestyle changes and guideline-directed medical therapy (GDMT), has led to a decline of the age-standardized prevalence[22,23] of obstructive epicardial coronary atherosclerosis in patients with suspected CCS.[24–28] As a consequence, the diagnostic and prognostic risk prediction models applied in the past to identify obstructive epicardial CAD in patients with suspected angina pectoris have required updating and refinement.[27,29,30] Initial use of coronary computed tomography angiography (CCTA)[31,32] for detecting and assessing epicardial coronary atherosclerosis is increasingly being adopted since it has shown similar performance to non-invasive stress testing for detecting segmental myocardial ischaemia.[33–35] Invasive coronary angiography (ICA), classically used to detect anatomically significant stenoses, has expanded to become a functional test[36] that includes refined haemodynamic assessment of epicardial stenoses, provocative testing for the detection of epicardial or microvascular spasm,[37–40] and a functional assessment of CMD.[41–43] Moreover, there is a growing interest in non-invasive imaging methods such as stress positron emission tomography (PET)[44,45] or stress magnetic resonance imaging (MRI),[46] which allow accurate assessment of the coronary microcirculation in a quantitative manner.

Medical therapy for CCS patients, including antithrombotic strategies, anti-inflammatory drugs, statins and new lipid-lowering, metabolic, and anti-obesity agents, has significantly improved survival after conservative treatment, making it harder to demonstrate the benefits of early invasive therapy.[47] However, revascularization can still benefit patients with obstructive CAD at high risk of adverse events, not only for symptom relief[48–52] but also to prevent spontaneous myocardial infarction (MI) and cardiac death and, in some groups, to improve overall survival[53–56] during long-term follow-up. Recently, revascularization through percutaneous coronary intervention (PCI) was shown to provide more angina relief than a placebo procedure in patients with stable angina and evidence of ischaemia, on minimal or no antianginal therapy, confirming the beneficial effects of revascularization.[52]

The present guidelines deal with the assessment and diagnostic algorithm in patients with symptoms suspected of CCS (*Section 3*) and their treatment (*Section 4*), special subgroups of CCS patients (*Section 5*) and finally, long-term follow-up and care (*Section 6*).

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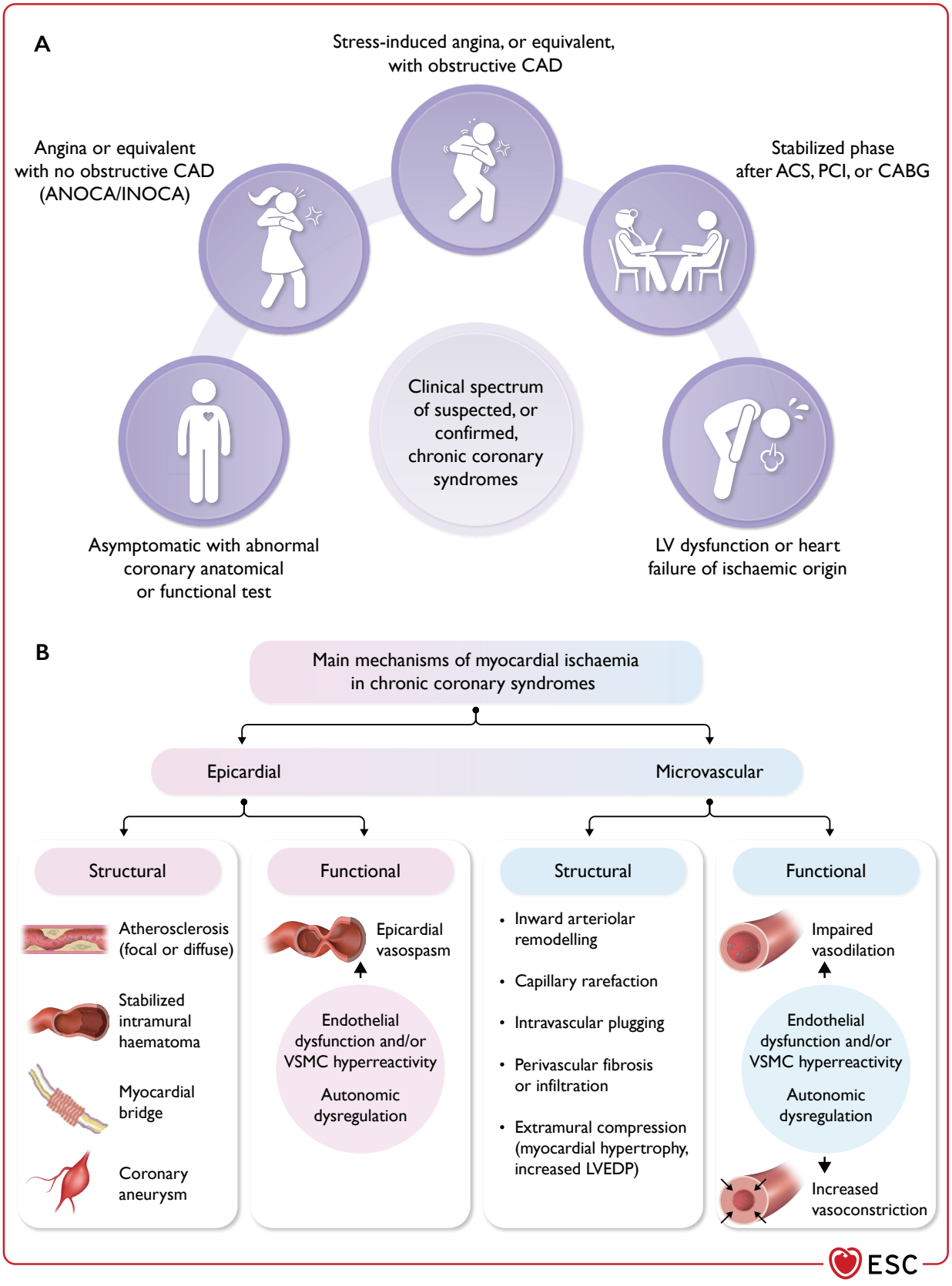

Figure 1 (Central Illustration) Clinical presentations of chronic coronary syndrome and mechanisms of myocardial ischaemia. ACS, acute coronary syndrome; ANOCA, angina with non-obstructive coronary arteries; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS, chronic coronary syndrome; INOCA, ischaemia with non-obstructive coronary arteries; LV, left ventricular; LVEDP, left ventricular end-diastolic pressure; PCI, percutaneous coronary intervention; VSMC, vascular smooth muscle cell.

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2.4. What is new

The 2024 Guidelines contain a number of new and revised recommendations, which are summarized in *Tables 3* and *4*, respectively.

Table 3 New major recommendations in 2024

Recommendations	Class[a]	Level[b]
History taking and risk factor assessment and resting electrocardiogram in individuals with suspected chronic coronary syndrome—*Section 3*		
In individuals reporting symptoms of suspected myocardial ischaemic origin, a detailed assessment of cardiovascular risk factors, medical history, and symptom characteristics (including onset, duration, type, location, triggers, relieving factors, time of day) is recommended.	I	C
Symptoms like chest pain triggered by emotional stress; dyspnoea or dizziness on exertion; pain in the arms, jaw, neck, or upper back; or fatigue should be considered as potential angina equivalents.	IIa	B
Basic biochemistry in the initial diagnostic management of individuals with suspected chronic coronary syndrome—*Section 3*		
• Additionally, high-sensitivity C-reactive protein and/or fibrinogen plasma levels should be considered.	IIa	B
Likelihood of obstructive atherosclerotic coronary artery disease in the initial diagnostic management of individuals with suspected chronic coronary syndrome—*Section 3*		
It is recommended to estimate the pre-test likelihood of obstructive epicardial CAD using the Risk Factor-weighted Clinical Likelihood model.	I	B
It is recommended to use additional clinical data (e.g. examination of peripheral arteries, resting ECG, resting echocardiography, presence of vascular calcifications on previously performed imaging tests) to adjust the estimate yielded by the Risk Factor-weighted Clinical Likelihood model.	I	C
In individuals with a *very low* (≤5%) pre-test likelihood of obstructive CAD, deferral of further diagnostic tests should be considered.	IIa	B
In individuals with a *low* (>5%–15%) pre-test likelihood of obstructive CAD, CACS should be considered to reclassify subjects and to identify more individuals with very low (≤5%) CACS-weighted clinical likelihood.	IIa	B
In individuals with an initially low (>5%–15%) likelihood of obstructive CAD, exercise ECG and detection of atherosclerotic disease in non-coronary arteries may be considered to adjust the pre-test likelihood estimate.	IIb	C
Ambulatory electrocardiogram in the initial diagnostic management of individuals with suspected chronic coronary syndrome—*Section 3*		
Ambulatory ECG monitoring should be considered in subjects with suspected vasospastic angina.	IIa	B
Non-invasive anatomical imaging tests in the initial diagnostic management of individuals with suspected obstructive coronary artery disease—coronary computed tomography angiography, if available and supported by local expertise—*Section 3*		
In individuals with suspected CCS and low or moderate (>5%–50%) pre-test likelihood of obstructive CAD, CCTA is recommended to diagnose obstructive CAD and to estimate the risk of MACE.	I	A
Non-invasive tests in the initial diagnostic management of individuals with suspected chronic coronary syndrome—stress echocardiography, if available and supported by local expertise—*Section 3*		
In individuals with suspected CCS and moderate or high (>15%–85%) pre-test likelihood of obstructive CAD, stress echocardiography is recommended to diagnose myocardial ischaemia and to estimate the risk of MACE.	I	B
During stress echocardiography, when two or more contiguous myocardial segments are not visualized, it is recommended to use commercially available intravenous ultrasound contrast agents (microbubbles) to improve diagnostic accuracy.	I	B
During stress echocardiography, myocardial perfusion using commercially available intravenous ultrasound contrast agents (microbubbles) is recommended to improve diagnostic accuracy and to refine risk stratification beyond wall motion.	I	B
During stress echocardiography, Doppler left anterior descending coronary artery flow reserve may be considered to improve risk stratification beyond wall motion and to assess microvascular function.	IIb	B
Non-invasive functional myocardial imaging tests in the initial diagnostic management of individuals with suspected chronic coronary syndrome—resting and stress single-photon emission computed tomography/positron emission tomography—cardiac magnetic resonance imaging, if available and supported by local expertise—*Section 3*		
In individuals with suspected CCS and moderate or high (>15%–85%) pre-test likelihood of obstructive CAD, SPECT or, preferably, PET myocardial perfusion imaging is recommended to: • diagnose and quantify myocardial ischaemia and/or scar; • estimate the risk of MACE; • quantify myocardial blood flow (PET).	I	B
In patients selected for PET or SPECT myocardial perfusion imaging, it is recommended to measure CACS from unenhanced chest CT imaging (used for attenuation correction) to improve detection of both non-obstructive and obstructive CAD.	I	B
In individuals with suspected CCS and moderate or high (>15%–85%) pre-test likelihood of obstructive CAD, CMR perfusion imaging is recommended to diagnose and quantify myocardial ischaemia and/or scar and estimate the risk of MACE.	I	B

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Indications for invasive coronary angiography in individuals with suspected obstructive coronary artery disease—*Section 3*		
When ICA is indicated, radial artery access is recommended as the preferred access site.	I	A
When ICA is indicated, it is recommended to have coronary pressure assessment available and to use it to evaluate the functional severity of intermediate non-left main stem stenoses prior to revascularization.	I	A
In individuals with de novo symptoms highly suggestive of obstructive CAD that occur at a low level of exercise, ICA with a view towards revascularization is recommended as first diagnostic test after clinical assessment by a cardiologist.	I	C
Functional assessment of epicardial artery stenosis severity during invasive coronary angiography—*Section 3*		
During ICA, selective assessment of functional severity of intermediate diameter stenoses is recommended to guide the decision to revascularize, using the following techniques:		
• FFR/iFR (significant ≤0.8 or ≤0.89, respectively);	I	A
• QFR (significant ≤0.8).	I	B
In addition:		
• CFR/HSR/CFC should be considered as a complementary investigation;	IIa	B
• resting invasive measurement of Pd/Pa, dPR, RFR, or angiography-derived vessel FFR may be considered as alternative parameters.	IIb	C
Systematic and routine wire-based coronary pressure assessment of all coronary vessels is not recommended.	III	A
Selection of individual diagnostic tests in individuals with suspected chronic coronary syndrome—*Section 3*		
To rule out obstructive CAD in individuals with low or moderate (>5%–50%) pre-test likelihood, CCTA is recommended as the preferred diagnostic modality.	I	B
CCTA is recommended in individuals with low or moderate (>5%–50%) pre-test likelihood of obstructive CAD if functional imaging for myocardial ischaemia is not diagnostic.	I	B
Invasive coronary angiography with the availability of invasive functional assessments is recommended to confirm or exclude the diagnosis of obstructive CAD or ANOCA/INOCA in individuals with an uncertain diagnosis on non-invasive testing.	I	B
In patients with a known intermediate coronary artery stenosis in a proximal or mid coronary segment on CCTA, CT-based FFR may be considered.	IIb	B
Definition of high risk of adverse events		
An initial stratification of risk of adverse events is recommended based on basic clinical assessment (e.g. age, ECG, anginal threshold, diabetes, CKD, LVEF).	I	B
The use of one or more of the following test results is recommended to identify individuals at high risk of adverse events: • exercise ECG: o Duke Treadmill Score < −10; • stress SPECT or PET perfusion imaging: o area of ischaemia ≥10% of the LV myocardium; • stress echocardiography: o ≥3 of 16 segments with stress-induced hypokinesia or akinesia; • stress CMR: o ≥2 of 16 segments with stress perfusion defects or o ≥3 dobutamine-induced dysfunctional segments; • CCTA: o left main disease with ≥50% stenosis, o three-vessel disease with ≥70 stenosis, or o two-vessel disease with ≥70% stenosis, including the proximal LAD or o one-vessel disease of the proximal LAD with ≥70% stenosis and FFR-CT ≤0.8	I	B
Cardiovascular risk, lifestyle changes, and exercise interventions in patients with established chronic coronary syndrome—*Section 4*		
An informed discussion on CVD risk and treatment benefits tailored to individual patient needs is recommended.	I	C
Multidisciplinary behavioural approaches to help patients achieve healthy lifestyles, in addition to appropriate pharmacological management, are recommended.	I	A
Aerobic physical activity of at least 150–300 min per week of moderate intensity or 75–150 min per week of vigorous intensity and reduction in sedentary time are recommended.	I	B
Home-based cardiac rehabilitation and mobile health interventions should be considered to increase patients' long-term adherence to healthy behaviours, and to reduce hospitalizations or cardiac events.	IIa	B
Antianginal drugs in patients with chronic coronary syndrome—*Section 4*		
It is recommended to tailor the selection of antianginal drugs to the patient's characteristics, comorbidities, concomitant medications, treatment tolerability, and underlying pathophysiology of angina, also considering local drug availability and cost.	I	C
Ivabradine should be considered as add-on antianginal therapy in patients with left ventricular systolic dysfunction (LVEF <40%) and inadequate control of symptoms, or as part of initial treatment in properly selected patients.	IIa	B

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Ivabradine is not recommended as add-on therapy in patients with CCS, LVEF >40%, and no clinical heart failure.	III	B
Combination of ivabradine with non-DHP-CCB or other strong CYP3A4 inhibitors is not recommended.	III	B
Antithrombotic therapy in patients with chronic coronary syndrome—*Section 4*		
Long-term antithrombotic therapy in patients with chronic coronary syndrome and no clear indication for oral anticoagulation		
In CCS patients with a prior MI or PCI, clopidogrel 75 mg daily is recommended as a safe and effective alternative to aspirin monotherapy.	I	A
After CABG, aspirin 75–100 mg daily is recommended lifelong.	I	A
In CCS patients *without* prior MI or revascularization but with evidence of significant obstructive CAD, aspirin 75–100 mg daily is recommended lifelong.	I	B
Lipid-lowering drugs in patients with chronic coronary syndrome—*Section 4*		
Lipid-lowering treatment with an LDL-C goal of <1.4 mmol/L (55 mg/dL) and a ≥50% reduction in LDL-C vs. baseline is recommended.	I	A
For patients who are statin intolerant and do not achieve their goal on ezetimibe, combination with bempedoic acid is recommended.	I	B
For patients who do not achieve their goal on a maximum tolerated dose of statin and ezetimibe, combination with bempedoic acid should be considered.	IIa	C
Sodium–glucose cotransporter 2 inhibitors and/or glucagon-like peptide-1 receptor agonists in patients with chronic coronary syndrome—*Section 4*		
SGLT2 inhibitors with proven CV benefit are recommended in patients with T2DM and CCS to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication.	I	A
The GLP-1 receptor agonist semaglutide should be considered in CCS patients without diabetes, but with overweight or obesity (BMI ≥27 kg/m^2), to reduce CV mortality, MI, or stroke.	IIa	B
Anti-inflammatory drugs in patients with chronic coronary syndrome—*Section 4*		
In CCS patients with atherosclerotic CAD, low-dose colchicine (0.5 mg daily) should be considered to reduce myocardial infarction, stroke, and need for revascularization.	IIa	A
Revascularization in patients with chronic coronary syndrome—*Section 4*		
Informed and shared decisions		
For complex clinical cases, to define the optimal treatment strategy, in particular when CABG and PCI hold the same level of recommendation, a Heart Team discussion is recommended, including representatives from interventional cardiology, cardiac surgery, non-interventional cardiology, and other specialties if indicated, aimed at selecting the most appropriate treatment to improve patient outcomes and quality of life.	I	C
It is recommended that the decision for revascularization and its modality be patient-centred, considering when possible patient preferences, health literacy, cultural circumstances, and social support.	I	C
Revascularization to improve outcomes		
In CCS patients with LVEF ≤35%, it is recommended to choose between revascularization or medical therapy alone, after careful evaluation, preferably by the Heart Team, of coronary anatomy, correlation between coronary artery disease and LV dysfunction, comorbidities, life expectancy, individual risk-to-benefit ratio, and patient perspectives.	I	C
Assessment of procedural risks and post-procedural outcomes		
Intracoronary imaging guidance by IVUS or OCT is recommended for performing PCI on anatomically complex lesions, in particular left main stem, true bifurcations and long lesions.	I	A
Intracoronary pressure measurement (FFR or iFR) or computation (QFR):		
• is recommended to guide lesion selection for intervention in patients with multivessel disease;	I	A
• should be considered at the end of the procedure to identify patients at high risk of persistent angina and subsequent clinical events;	IIa	B
• may be considered at the end of the procedure to identify lesions potentially amenable to treatment with additional PCI.	IIb	B
Choice of revascularization modality		
It is recommended that physicians select the most appropriate revascularization modality based on patient profile, coronary anatomy, procedural factors, LVEF, patient preferences and outcome expectations.	I	C
Mode of revascularization in patients with chronic coronary syndrome		
Left main disease		
In CCS patients at low surgical risk with significant left main coronary stenosis, CABG:		
• is recommended over medical therapy alone to improve survival;	I	A
• is recommended as the overall preferred revascularization mode over PCI, given the lower risk of spontaneous myocardial infarction and repeat revascularization.	I	A
In CCS patients with significant left main coronary stenosis of low complexity (SYNTAX score ≤22), in whom PCI can provide equivalent completeness of revascularization to that of CABG, PCI is recommended as an alternative to CABG, given its lower invasiveness and non-inferior survival.	I	A

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Management of chronic coronary syndrome patients with chronic heart failure—*Section 5*		
In HF patients with LVEF ≤35% in whom obstructive CAD is suspected, ICA is recommended with a view towards improving prognosis by CABG, taking into account the risk-to-benefit ratio of the procedures.	I	B
In HF patients with LVEF >35% and suspected CCS with low or moderate (>5%–50%) pre-test likelihood of obstructive CAD, CCTA or functional imaging is recommended.	I	C
In patients with HFpEF with angina or equivalent symptoms and normal or non-obstructive epicardial coronary arteries, PET or CMR perfusion or invasive functional coronary testing should be considered to detect or rule out coronary microvascular dysfunction.	IIa	B
In selected patients with HFrEF undergoing high-risk PCI for complex CAD, the use of a microaxial flow pump may be considered in experienced centres.	IIb	C
It is recommended that CCS patients with heart failure be enrolled in a multidisciplinary heart failure management programme to reduce the risk of heart failure hospitalization and to improve survival.	I	A
Sacubitril/valsartan is recommended as a replacement for an ACE-I or ARB in CCS patients with HFrEF to reduce the risk of heart failure hospitalization and death.	I	B
Diagnosis and management of patients with angina/ischaemia with non-obstructive coronary arteries—*Section 5*		
Management of ANOCA/INOCA		
In symptomatic patients with ANOCA/INOCA, medical therapy based on coronary functional test results should be considered to improve symptoms and quality of life.	IIa	A
For the management of endothelial dysfunction, ACE-I should be considered for symptom control.	IIa	B
For the management of microvascular angina associated with reduced coronary/myocardial blood flow reserve, beta-blockers should be considered for symptom control.	IIa	B
For the treatment of isolated vasospastic angina: • calcium channel blockers are recommended to control symptoms and to prevent ischaemia and potentially fatal complications;	I	A
• nitrates should be considered to prevent recurrent episodes.	IIa	B
In patients with evidence of overlapping endotypes, combination therapy with nitrates, calcium channel blockers, and other vasodilators may be considered.	IIb	B
Older, female, high bleeding risk, comorbid, and socially/geographically diverse patients—*Section 5*		
Similar guideline-directed cardiovascular preventive therapy is recommended in women and men.	I	C
Bleeding risk assessment is recommended using the PRECISE-DAPT score, the qualitative ARC-HBR tool or other, validated methods.	I	B
Attention to interaction between antiretroviral treatment and statins is recommended in patients with HIV.	I	B
Socioeconomic, geographical, and under-investigated groups		
Continued targeted efforts are recommended: • to increase delivery of safe and effective cardiac care to all CCS patients, especially those of lower socioeconomic classes, and • to enhance inclusion in future clinical trials of geographical, social, or other groups that are currently underrepresented.	I	C
Screening for coronary artery disease in asymptomatic individuals—*Section 5*		
When coronary artery calcification findings are available from previous chest CT scans, using these findings to enhance risk stratification and guide treatment of modifiable risk factors should be considered.	IIa	C
Coronary artery calcium scoring (CACS) may be considered to improve risk classification around treatment decision thresholds.	IIb	C
Adherence to medical therapy and lifestyle changes—*Section 6*		
Mobile health interventions (e.g. using text messages, apps, wearable devices) are recommended to improve patient adherence to healthy lifestyles and medical therapy.	I	A
Behavioural interventions are recommended to improve adherence.	I	B
Simplifying medication regimens (e.g. using fixed-dose drug combinations) is recommended to increase patient adherence to medications.	I	B
Multiprofessional and family involvement is recommended to promote adherence, in addition to patient education and involvement.	I	C
Recurrent or refractory angina/ischaemia		
In patients with refractory angina leading to poor quality of life and with documented or suspected ANOCA/INOCA, invasive coronary functional testing is recommended to define ANOCA/INOCA endotypes and appropriate treatment, considering patient choices and preferences.	I	B

ACE-I, angiotensin-converting enzyme inhibitor; ANOCA, angina with non-obstructive coronary arteries; ARB, angiotensin receptor blocker; ARC-HBR, Academic Research Consortium for High Bleeding Risk; BMI, body mass index; CABG, coronary artery bypass grafting; CACS, coronary artery calcium score; CAD, coronary artery disease; CCB, calcium channel blocker; CCS, chronic coronary syndrome; CCTA, coronary computed tomography angiography; CFC, coronary flow capacity; CFR, coronary flow reserve; CKD, chronic kidney disease; CMR, cardiac magnetic resonance; CT, computed tomography; CV, cardiovascular; CVD, cardiovascular disease; CYP3A4, cytochrome P450 3A4; DHP, dihydropyridine; dPR, diastolic pressure ratio; ECG, electrocardiogram; FFR, fractional flow reserve; FFR-CT, coronary computed tomography angiography-derived fractional flow reserve; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HIV, human immunodeficiency virus; HSR, hyperaemic stenosis resistance; ICA, invasive coronary angiography; iFR, instantaneous wave-free ratio; INOCA, ischaemia with non-obstructive coronary arteries; IVUS, intravascular ultrasound; LAD, left anterior descending; LDL-C, low-density lipoprotein cholesterol; LV, left ventricular; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; MCS, mechanical circulatory support; MI, myocardial infarction; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; Pd/Pa, distal coronary pressure to aortic pressure ratio; PET, positron emission tomography; PRECISE-DAPT, PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual AntiPlatelet Therapy; QFR, quantitative flow ratio; RFR, relative flow reserve; SGLT2, sodium–glucose cotransporter 2; SPECT, single-photon emission computed tomography; T2DM, type 2 diabetes mellitus.

[a]Class of recommendation.

[b]Level of evidence.

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Table 4 Revised recommendations

Recommendations in 2019 version	Class[a]	Level[b]	Recommendations in 2024 version	Class[a]	Level[b]
Recommendations for antianginal drugs in patients with chronic coronary syndrome—*Section 4*					
Nicorandil, ranolazine, ivabradine, or trimetazidine should be considered as a second-line treatment to reduce angina frequency and improve exercise tolerance in subjects who cannot tolerate, have contraindications to, or whose symptoms are not adequately controlled by beta-blockers, CCBs, and long-acting nitrates.	IIa	B	Long-acting nitrates or ranolazine should be considered as add-on therapy in patients with inadequate control of symptoms while on treatment with beta-blockers and/or CCBs, or as part of initial treatment in properly selected patients.	IIa	B
In selected patients, the combination of a beta-blocker or a CCB with second-line drugs (ranolazine, nicorandil, ivabradine, and trimetazidine) may be considered for first-line treatment according to heart rate, blood pressure, and tolerance.	IIb	B	Nicorandil or trimetazidine may be considered as add-on therapy in patients with inadequate control of symptoms while on treatment with beta-blockers and/or CCBs, or as part of initial treatment in properly selected patients.	IIb	B
Antithrombotic therapy in patients with chronic coronary syndrome—*Section 4*					
Aspirin 75–100 mg daily is recommended in patients with a previous MI or revascularization.	I	A	In CCS patients with a prior MI or remote PCI, aspirin 75–100 mg daily is recommended lifelong after an initial period of DAPT.	I	A
Clopidogrel 75 mg daily is recommended as an alternative to aspirin in patients with aspirin intolerance.	I	B	In CCS patients with a prior MI or remote PCI, clopidogrel 75 mg daily is recommended as a safe and effective alternative to aspirin monotherapy.	I	A
Clopidogrel 75 mg daily may be considered in preference to aspirin in symptomatic and asymptomatic patients with either PAD or a history of ischaemic stroke or transient ischaemic attack.	IIb	B			
Aspirin 75–100 mg daily may be considered in patients without a history of MI or revascularization, but with definitive evidence of CAD on imaging.	IIb	C	In patients *without* prior MI or revascularization but with evidence of significant obstructive CAD, aspirin 75–100 mg daily is recommended lifelong.	I	B
Antithrombotic therapy post-percutaneous coronary intervention in patients with chronic coronary syndrome and no indication for oral anticoagulation—*Section 4*					
Aspirin 75–100 mg daily is recommended following stenting.	I	A	In CCS patients with no indication for oral anticoagulation, DAPT consisting of aspirin 75–100 mg and clopidogrel 75 mg daily for up to 6 months is recommended as the default antithrombotic strategy after PCI-stenting.	I	A
Clopidogrel 75 mg daily following appropriate loading (e.g. 600 mg or >5 days of maintenance therapy) is recommended, in addition to aspirin, for 6 months following coronary stenting, irrespective of stent type, unless a shorter durations (1–3 months) is indicated due to risk of occurrence of life-threatening bleeding.	I	A			
Clopidogrel 75 mg daily following appropriate loading (e.g. 600 mg or >5 days of maintenance therapy) may be considered for 1 month in patients with very high risk of life-threatening bleeding.	IIb	C	In patients at high bleeding risk but not at high ischaemic risk, it is recommended to discontinue DAPT 1–3 months after PCI and continue single antiplatelet therapy.	I	A
Clopidogrel 75 mg daily following appropriate loading (e.g. 600 mg or >5 days of maintenance therapy) should be considered for 3 months in patients with a higher risk of life-threatening bleeding.	IIa	A	Stopping DAPT after 1–3 months from PCI-stenting may be considered in patients who are not at high bleeding risk nor at high risk of ischaemic events.	IIb	B

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Long-term antithrombotic therapy in patients with chronic coronary syndrome and an indication for oral anticoagulation—*Section 4*					
When oral anticoagulation is initiated in a patient with AF who is eligible for a NOAC, a NOAC is recommended in preference to a VKA.	I	A	In CCS patients with a long-term indication for OAC, an AF-therapeutic-dose of VKA alone or, preferably, of DOAC alone (unless contraindicated) is recommended lifelong.	I	B
Long-term OAC therapy (NOAC or VKA with time in therapeutic range >70%) is recommended in patients with AF and a CHA_2DS_2-VASc score ≥2 in males and ≥3 in females.	I	A			
Long-term OAC therapy (NOAC or VKA with time in therapeutic range >70%) should be considered in patients with AF and a CHA_2DS_2-VASc score of 1 in males and 2 in females.	IIa	B			
Aspirin 75–100 mg daily (or clopidogrel 75 mg daily) may be considered in addition to long-term OAC therapy in patients with AF, history of MI, and at high risk of recurrent ischaemic events who do not have a high bleeding risk.	IIb	B			
Antithrombotic therapy post-percutaneous coronary intervention in chronic coronary syndrome patients and an indication for oral anticoagulation—*Section 4*					
After uncomplicated PCI, early cessation (≤1 week) of aspirin and continuation of dual therapy with an OAC and clopidogrel should be considered if the risk of stent thrombosis is low, or if concerns about bleeding risk prevail over concerns about the risk of stent thrombosis, irrespective of the type of stent used.	IIa	B	After uncomplicated PCI in CCS patients with concomitant indication for OAC: • early cessation of aspirin (≤1 week); • followed by continuation of OAC and clopidogrel: o up to 6 months in patients not at high ischaemic risk or o up to 12 months in patients at high ischaemic risk; • followed by OAC alone; is recommended.	I	A
Triple therapy with aspirin, clopidogrel, and an OAC for ≥1 month should be considered when the risk of stent thrombosis outweighs the bleeding risk, with the total duration (≤6 months) decided according to assessment of these risks and clearly specified at hospital discharge.	IIa	C	Continuation of aspirin up to 1 month after PCI, in addition to OAC and clopidogrel, should be considered in patients at high thrombotic risk or with anatomical/procedural characteristics judged to outweigh the bleeding risk.	IIa	B
Recommendations for lipid-lowering drugs in patients with chronic coronary syndrome—*Section 4*					
Statins are recommended in all patients with CCS.	I	A	A high-intensity statin up to the highest tolerated dose to reach the LDL-C goals is recommended for all patients with CCS.	I	A
Diagnosis and management of patients with angina/ischaemia with non-obstructive coronary arteries—*Section 5*					
Guidewire-based CFR and/or microcirculatory resistance measurements should be considered in patients with persistent symptoms, but coronary arteries that are either angiographically normal or have moderate stenoses with preserved iwFR/FFR.	IIa	B	In persistently symptomatic patients despite medical treatment with suspected ANOCA/INOCA (i.e. anginal symptoms with normal coronary arteries or non-obstructive lesions at non-invasive imaging, or intermediate stenoses with normal FFR/iFR at coronary arteriography) and poor quality of life, invasive coronary functional testing is recommended to identify potentially treatable endotypes and to improve symptoms and quality of life, considering patient choices and preferences.	I	B
Intracoronary acetylcholine with ECG monitoring may be considered during angiography, if coronary arteries are either angiographically normal or have moderate stenoses with preserved iwFR/FFR, to assess microvascular vasospasm.	IIb	B			
Diagnostic tests for vasospastic angina—*Section 5*					
Ambulatory ST-segment monitoring should be considered to identify ST-segment deviation in the absence of increased heart rate.	IIa	C	In individuals with suspected vasospastic angina and frequent symptoms, ambulatory ST-segment monitoring should be considered to identify ST-segment deviation during angina.	IIa	B

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Screening for coronary artery disease in asymptomatic individuals—*Section 5*					
Total risk estimation using a risk-estimation system such as SCORE is recommended for asymptomatic adults >40 years of age without evidence of CVD, diabetes, CKD, or familial hypercholesterolaemia.	I	C	Opportunistic screening of healthy individuals for cardiovascular risk factors and to estimate risk of future cardiovascular events using scoring systems, e.g. SCORE2 and SCORE2-OP, is recommended to detect individuals at high risk and guide treatment decisions.	I	C
Diagnosis of disease progression in patients with established chronic coronary syndrome—*Section 6*					
Risk stratification is recommended in patients with new or worsening symptom levels, preferably using stress imaging or, alternatively, exercise stress ECG.	I	B	Risk stratification is recommended in patients with new or worsening symptoms, preferably using stress imaging.	I	C
2018 ESC/EACTS Guidelines on myocardial revascularization	**Class[a]**	**Level[b]**	**Recommendations in 2024 version**	**Class[a]**	**Level[b]**
Recommendations for revascularization in patients with chronic coronary syndrome—*Section 4*					
Revascularization to improve outcomes					
In CCS patients with LV ejection fraction ≤35%					
In patients with one- or two-vessel disease, PCI should be considered as an alternative to CABG when complete revascularization can be achieved.	IIa	C	In selected CCS patients with functionally significant MVD and LVEF ≤35% who are at high surgical risk or not operable, PCI may be considered as an alternative to CABG.	IIb	B
In patients with three-vessel disease, PCI should be considered based on the evaluation by the Heart Team of the patient's coronary anatomy, the expected completeness of revascularization, diabetes status, and comorbidities.	IIa	C			
Anatomically and clinically based recommendations for revascularization in chronic coronary syndrome—*Section 4*					
Left main disease					
Left main disease with low SYNTAX score (0–22), PCI.	I	A	In CCS patients with significant left main coronary stenosis of low complexity (SYNTAX score ≤22), in whom PCI can provide equivalent completeness of revascularization to that of CABG, PCI is recommended as an alternative to CABG, given its lower invasiveness and non-inferior survival.	I	A
Left main disease with intermediate SYNTAX score (23–32), PCI.	IIa	A	In CCS patients with significant left main coronary stenosis of intermediate complexity (SYNTAX score 23–32), in whom PCI can provide equivalent completeness of revascularization to that of CABG, PCI should be considered, given its lower invasiveness and non-inferior survival.	IIa	A
Left main with multivessel disease					
For left main disease with high SYNTAX score (≥33), PCI.	III	B	In CCS patients at high surgical risk, PCI may be considered over medical therapy alone.	IIb	B
Multivessel disease and diabetes					
For CCS patients with diabetes and three-vessel disease with low SYNTAX score 0–22, PCI.	IIb	A	In CCS patients at very high surgical risk, PCI should be considered over medical therapy alone to reduce symptoms and adverse outcomes.	IIa	B
For CCS patients with diabetes and three-vessel disease with intermediate or high SYNTAX score (>22), PCI.	III	A			
Single- or double-vessel disease involving the proximal LAD					
For one or two-vessel disease with proximal LAD stenosis, CABG, or PCI are recommended.	I	A	In CCS patients with significant single- or double-vessel disease involving the proximal LAD and insufficient response to guideline-directed medical therapy, CABG or PCI is recommended over medical therapy alone to improve symptoms and outcomes.	I	A
			In CCS patients with complex significant single- or double-vessel disease involving the proximal LAD, less amenable to PCI, and insufficient response to guideline-directed medical therapy, CABG is recommended over PCI to improve symptoms and reduce revascularization rates.	I	B

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Single- or double-vessel disease not involving the proximal LAD					
For one or two-vessel disease without proximal LAD stenosis PCI is recommended.	I	C	In symptomatic CCS patients with single- or double-vessel disease not involving the proximal LAD and with insufficient response to guideline-directed medical therapy, PCI is recommended to improve symptoms.	I	B
For one or two-vessel disease without proximal LAD stenosis, CABG may be considered.	IIb	C	In symptomatic CCS patients with single- or double-vessel disease not involving the proximal LAD and with insufficient response to guideline-directed medical therapy, not amenable to revascularization by PCI, CABG may be considered to improve symptoms.	IIb	C

AF, atrial fibrillation; ANOCA, angina with non-obstructive coronary arteries; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCB, calcium channel blocker; CCS, chronic coronary syndrome; CFR, coronary flow reserve; CHA_2DS_2-VASc, congestive heart failure or left ventricular dysfunction, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74, sex category (female); CKD, chronic kidney disease; CVD, cardiovascular disease; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; EACTS, European Association for Cardio-Thoracic Surgery; ECG, electrocardiogram; ESC, European Society of Cardiology; FFR, fractional flow reserve; iFR(iwFR), instantaneous wave-free ratio; INOCA, ischaemia with non-obstructive coronary arteries; LAD, left anterior descending; LDL-C, low-density lipoprotein cholesterol; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MVD, multivessel disease; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; SCORE2, Systematic Coronary Risk Estimation 2; SCORE-OP, Systematic Coronary Risk Estimation 2–Older Persons; SYNTAX, SYNergy Between PCI with TAXUS and Cardiac Surgery; VKA, vitamin K antagonist.
[a]Class of recommendation.
[b]Level of evidence.

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3. Stepwise approach to the initial management of individuals with suspected chronic coronary syndrome

Managing individuals with suspected CCS involves four steps (*Figure 2*):

STEP 1. The first step is a general clinical evaluation that focuses on assessing symptoms and signs of CCS, differentiating non-cardiac causes of chest pain and ruling out ACS. This initial clinical evaluation requires recording a 12-lead resting electrocardiogram (ECG), basic blood tests, and in selected individuals, chest X-ray imaging and pulmonary function testing. This evaluation can be done by the general practitioner.

STEP 2. The second step is a further cardiac examination, including echocardiography at rest to rule out left ventricular (LV) dysfunction and valvular heart disease. After that, it is recommended to estimate the clinical likelihood of obstructive CAD to guide deferral or referral to further non-invasive and invasive testing.

STEP 3. The third step involves diagnostic testing to establish the diagnosis of CCS and determine the patient's risk of future events.

STEP 4. The final step includes lifestyle and risk-factor modification combined with disease-modifying medications. A combination of antianginal medications is frequently needed, and coronary revascularization is considered if symptoms are refractory to medical treatment or if high-risk CAD is present. If symptoms persist after obstructive CAD is ruled out, coronary microvascular disease and vasospasm should be considered.

3.1. STEP 1: General clinical examination

3.1.1. History, differential diagnosis, and physical examination

Careful and detailed history taking is the initial step in diagnostic management for all clinical scenarios within the spectrum of CCS. Although chest pain or discomfort (*Figure 3*) is the most cardinal symptom of CCS, it must be emphasized that many patients do not present with characteristic anginal symptoms and that the symptomatology may vary with age, sex, race, socioeconomic class, and geographical location. In contemporary studies, only 10% to 25% of patients with suspected CCS present with angina with classic aggravating and relieving factors, while 57% to 78% have symptoms less characteristic of angina and 10% to 15% have dyspnoea on exertion.[33,57]

While older studies suggested that women were more likely to experience less characteristic chest pain symptoms,[58] recent data show that anginal chest pain is equally prevalent in both men and women, albeit with slightly different characteristics.[59] Symptoms were classified as non-characteristic angina in over two-thirds of the patients of both sexes.[21,60] Of note, the absence of anginal symptoms does not preclude CCS, as it may be absent in patients with diabetes with autonomic neuropathy or in elderly patients with a very sedentary lifestyle despite very severe obstructive CAD. Of course, chest pain is not always angina (i.e. of ischaemic origin), since it can be related to non-coronary (e.g. pericarditis) or non-cardiovascular conditions.[61,62]

Anginal pain symptoms have been traditionally classified as "typical, atypical, or non-anginal/non-cardiac" based on the location of the pain, as well as precipitating and relieving factors. Although angina that meets all three characteristics, with retrosternal chest discomfort provoked by exertion or emotional stress and relieved by rest or nitroglycerine, is highly suggestive of ischaemia caused by obstructive CAD, these characteristics are rarely all present when ischaemia is caused by microvascular dysfunction and vasospasm. Furthermore, patients with "typical" vs. "atypical" angina included in the PRECISE study had similar 1-year outcomes,[57] highlighting the limited prognostic value of symptom classification on typicality of angina used in obstructive CAD prediction models. Because this terminology to describe anginal symptoms no longer aligns with current concepts of CCS, it should be replaced by a detailed description of symptoms (Figure 3). It is important to thoroughly evaluate chest pain, including an objective exclusion of myocardial ischaemia caused by obstructive CAD, microvascular disease, and/or coronary vasospasm, before classifying it as non-cardiac.

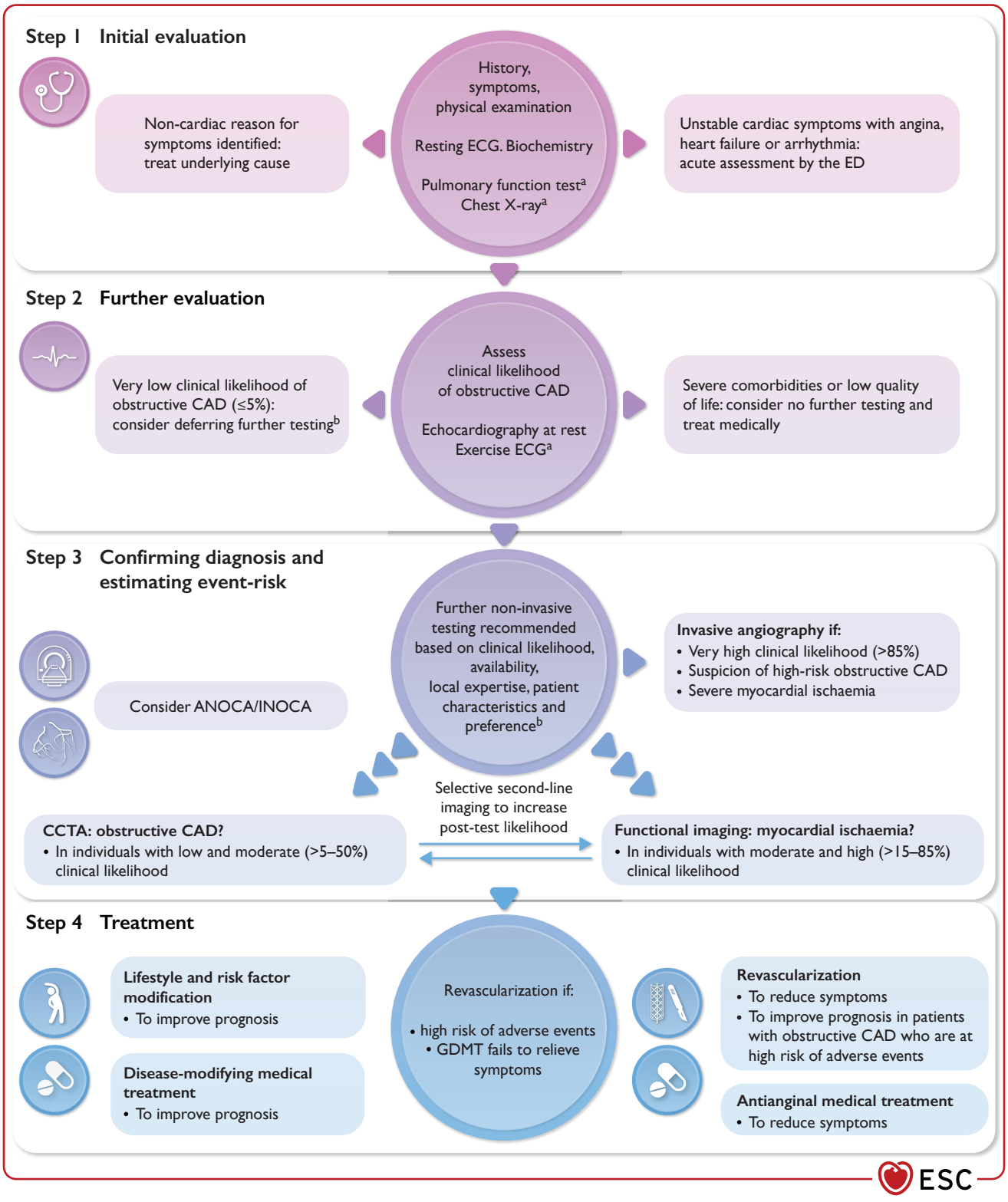

Figure 2 Stepwise approach to the initial management of individuals with suspected chronic coronary syndrome. ANOCA, angina with non-obstructive coronary arteries; CAD, coronary artery disease; CCS, chronic coronary syndrome; CCTA, coronary computed tomography angiography; ECG, electrocardiogram; ED, emergency department; GDMT, guideline-directed medical therapy; INOCA, ischaemia with non-obstructive coronary arteries. [a]In selected patients. [b]Consider also coronary spasm or microvascular dysfunction.

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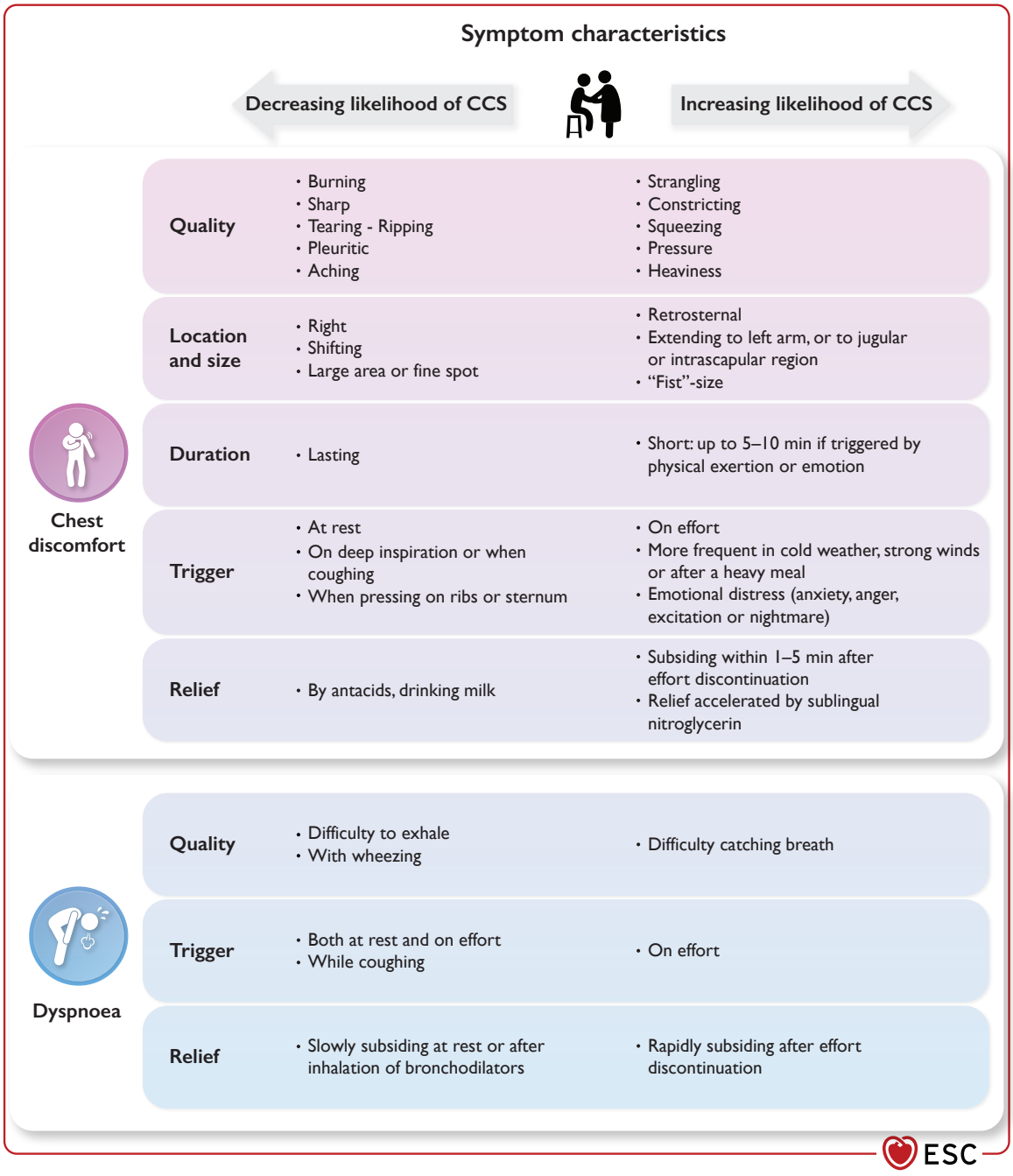

Figure 3 Main CCS symptoms: angina and exertional dyspnoea. CCS, chronic coronary syndrome.

The Canadian Cardiovascular Society classification is still widely used as a grading system for effort-induced angina to quantify the threshold at which symptoms occur with physical activities (*Table 5*). Importantly, the severity of symptoms is not well associated with the severity of obstructive CAD and appears to differ by sex. Women have more frequent angina, independent of less extensive epicardial CAD, and less severe myocardial ischaemia than men.[63] Angina at rest is not always indicative of severe, fixed obstructive CAD, as it may also occur in patients with transient epicardial or microvascular coronary vasospasm.

It is essential to document coronary risk factors during history taking, as they may be modifiable and will be used for the pre-test likelihood estimation of obstructive CAD. Smoking cessation counselling starts with a quantitative assessment of prior and current tobacco use to make the risk factor more evident to the patient. In addition, detailed family history looking for premature cardiovascular disease (CVD) or sudden cardiac death should always be obtained. If available, cholesterol levels help define familial hypercholesterolaemia.[64] It is also essential to assess the presence of comorbidities that affect the likelihood of CAD and overall survival. Because of their high prevalence in CCS patients, diabetes, chronic obstructive pulmonary disease, kidney disease, and peripheral and cerebral vascular disease are particularly relevant.

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Table 5 Grading of effort angina severity according to the Canadian Cardiovascular Society

Grade	Description of angina severity[66]	
I	Angina only with strenuous exertion	Presence of angina during strenuous, rapid, or prolonged ordinary activity (walking or climbing the stairs)
II	Angina with moderate exertion	Slight limitation of ordinary activities when they are performed rapidly, after meals, in the cold, in the wind, under emotional stress, or during the first few hours after waking up, but also walking uphill, climbing more than one flight of ordinary stairs at a normal pace, and in normal conditions
III	Angina with mild exertion	Having difficulties walking one or two blocks or climbing one flight of stairs at a normal pace and conditions
IV	Angina at rest	No exertion is needed to trigger angina

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Recent-onset anginal symptoms with changing frequency or intensity should raise the suspicion that a coronary atherosclerotic plaque may be destabilizing. In these patients, the diagnostic algorithm recommended by the 2023 ESC Guidelines for the management of patients with acute coronary syndromes should be used to rule out an acute event.[65]

When investigating suspected CCS, it is important to perform a thorough physical examination that includes BP measurement and body mass index (BMI) calculation, to assess the presence of anaemia, hypertension, valvular heart disease, LV hypertrophy, or arrhythmias. It is also recommended to search for evidence of non-coronary vascular disease, which may be asymptomatic (palpation of peripheral pulses; auscultation of carotid and femoral arteries), and signs of other comorbid conditions, such as thyroid disease, renal disease, or diabetes. This should be used in the context of other clinical information, such as the presence of cough or stinging pain, making CCS less likely. One should also try to reproduce the symptoms by palpation and test the effect of sublingual nitroglycerine to classify the symptoms.

3.1.2. Basic testing: 12-lead electrocardiogram and biochemistry

Basic testing in individuals with suspected CCS includes a 12-lead ECG, standard laboratory tests, resting echocardiography, and, in selected patients, a chest X-ray, and a pulmonary function test if dyspnoea is the main symptom. Such tests can be done on an outpatient basis.

3.1.2.1. Electrocardiogram

The paradigm of diagnosing myocardial ischaemia has, for almost a century, been based on detecting repolarization abnormalities, mainly in the form of ST-segment depressions or T wave abnormalities. Thus, the resting 12-lead ECG remains an indispensable component of the initial evaluation of a patient with chest pain.[67]

A normal resting ECG is frequently recorded after an anginal attack. However, even in the absence of repolarization abnormalities, the ECG at rest may suggest CCS indirectly, through signs of previous MI (pathological Q or R waves) or conduction abnormalities [mainly left bundle branch block (LBBB) and impaired atrioventricular conduction]. Atrial fibrillation (AF) is not rarely associated with CCS.[68] ST-segment depression during supraventricular tachyarrhythmias, however, is not a strong predictor of obstructive CAD.[69–72]

The ECG can be crucial for diagnosing transient myocardial ischaemia by recording dynamic ST-segment changes during ongoing angina. Vasospastic angina (VSA) should be suspected when observing typical transient ST-segment elevations or depressions with U-wave changes during an angina attack at rest.[73]

Long-term ambulatory ECG monitoring can be considered in selected patients to detect ischaemia during anginal episodes unrelated to physical activities. ECG changes suggesting ischaemia on ambulatory ECG monitoring are frequent in women but do not correlate with findings during stress testing.[74] Ambulatory ECG monitoring may also reveal 'silent' ischaemia in patients with CCS, but therapeutic strategies targeting it have not demonstrated clear survival benefits.[75,76]

Recommendation Table 1 — Recommendations for history taking, risk factor assessment, and resting electrocardiogram in individuals with suspected chronic coronary syndrome (see also Evidence Table 1)

Recommendations	Class[a]	Level[b]
History taking and risk factor assessment		
In individuals reporting symptoms of suspected myocardial ischaemic origin, a detailed assessment of cardiovascular risk factors, medical history, and symptom characteristics (including onset, duration, type, location, triggers, relieving factors, time of day) is recommended.	I	C
Symptoms like chest pain triggered by emotional stress; dyspnoea or dizziness on exertion; pain in the arms, jaw, neck, or upper back; or fatigue should be considered as potential angina equivalents.[18,33,57,59,77]	IIa	B
Resting ECG		
If clinical or ECG assessment suggests ACS rather than CCS, immediate referral to the emergency department and/or repeated measurement of blood troponin, preferably using high-sensitivity or ultrasensitive assays, to rule out acute myocardial injury, is recommended.[78,79]	I	B
A resting 12-lead ECG is recommended in all individuals reporting chest pain (unless an obvious non-cardiac cause is identified), particularly during, or immediately after, an episode suggestive of myocardial ischaemia.	I	C
Using ST-segment deviations during supraventricular tachyarrhythmias, particularly during re-entrant atrioventricular tachycardias, per se, as reliable evidence of obstructive CAD, is not recommended.[80–84]	III	B

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ACS, acute coronary syndrome; CAD, coronary artery disease; CCS, chronic coronary syndrome; ECG, electrocardiogram.
[a]Class of recommendation.
[b]Level of evidence.

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3.1.2.2. Biochemical tests

Laboratory blood tests identify potential causes of ischaemia (e.g. severe anaemia, hyperthyroidism), cardiovascular risk factors (e.g. lipids, fasting glucose), and yield prognostic information (e.g. renal disease, inflammation). When fasting plasma glucose and glycated haemoglobin (HbA1c) are both inconclusive, an additional oral glucose tolerance test is useful.[85,86]

A lipid profile, including total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides, allowing calculation of low-density lipoprotein cholesterol (LDL-C), is necessary in every person with suspected CCS to refine his/her risk profile and guide treatment.[16,64] Fasting values are needed to characterize severe dyslipidaemia or follow-up hypertriglyceridaemia,[64] but not in other situations.[87] Elevated lipoprotein(a) is a marker of cardiovascular risk, particularly early-onset atherosclerotic disease;[88] lipoprotein(a)-lowering strategies are currently being investigated in phase 3 cardiovascular outcomes trials.[89–91] Given that circulating lipoprotein(a) levels are genetically determined and do not fluctuate substantially over a lifetime,[89,91] a single measure is sufficient in persons with suspected CCS.[92]

Renal dysfunction increases the likelihood of CAD and has a negative impact on prognosis.[93–95] Glomerular filtration rate (GFR) also impacts renally cleared drugs. It is reasonable to also measure uric acid levels, as hyperuricaemia is frequent, and may affect renal function.

If there is a clinical suspicion of CAD instability, biochemical markers of myocardial injury—such as troponin T or troponin I—should be measured, preferably using high-sensitivity assays, and management should follow the 2023 ESC Guidelines for the management of patients with acute coronary syndromes.[65] If high-sensitivity assays are employed, low troponin levels can be detected in many patients with stable angina. Increased troponin levels are associated with adverse outcomes,[96–100] and small studies have indicated a possible incremental value in diagnosing obstructive CAD,[101–104] but larger trials are needed to verify the utility of systematic assessment in individuals suspected of CCS. While multiple biomarkers may be useful for prognostication, they do not yet have a role in diagnosing obstructive CAD, but some promising results have been published.[105–108] Measuring NT-proBNP helps confirm or exclude suspected HF.

Markers of inflammation such as C-reactive protein[109–113] and fibrinogen[114–118] are predictors of an individual's risk of CAD and can predict cardiovascular event risk in CCS patients,[99,111] but their value is limited beyond traditional risk factors.[111] However, in patients taking contemporary statins, high-sensitivity C-reactive protein (hs-CRP) was a stronger predictor for future cardiovascular events and death than LDL-C.[119,120] These patients may benefit from additional LDL-C reduction through adjunctive lipid-lowering therapies, such as ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition,[121] inclisiran, and bempedoic acid.[122–124] Elevated hs-CRP levels in patients taking statins and PCSK9 inhibitors may indicate residual inflammatory risk that could be further reduced through inflammation modulation.[119,125,126] Experimental inhibition of interleukin-6, a pivotal factor in atherothrombosis, resulted in a marked parallel reduction of C-reactive protein and fibrinogen in patients with chronic kidney disease (CKD) and high cardiovascular risk.[127]

Recommendation Table 2 — Recommendations for basic biochemistry in the initial diagnostic management of individuals with suspected chronic coronary syndrome (see also Evidence Table 2)

Recommendations	Class[a]	Level[b]
The following blood tests are recommended in all individuals to refine risk stratification, diagnose comorbidities, and guide treatment:		
• lipid profile including LDL-C;[64,128]	I	A
• full blood count (including haemoglobin);[129–133]	I	B
• creatinine with estimation of renal function;[134]	I	B
• glycaemic status with HbA1c and/or fasting plasma glucose.[16,86,135,136]	I	B
In patients with suspected CCS, it is recommended to assess thyroid function at least once.[137,138]	I	B
Additionally, hs-CRP and/or fibrinogen plasma levels should be considered.[109–118,121,125]	IIa	B

CCS, chronic coronary syndrome; HbA1c, glycated haemoglobin; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol.
[a]Class of recommendation.
[b]Level of evidence.

3.2. STEP 2: Further evaluation

3.2.1. Pre-test clinical likelihood of obstructive atherosclerotic coronary artery disease

The diagnosis of CCS is based on interpreting the individual's symptoms, balancing the impact of age, sex, risk factors, and comorbidities on the likelihood that CCS is present, and choosing the most appropriate diagnostic test to confirm the clinically suspected diagnosis. To aid diagnosis, prediction tables for obstructive CAD can be used that integrate these clinical factors and provide guidance on selecting diagnostic tests based on their capacities to rule in and rule out obstructive atherosclerotic CAD. Importantly, these models do not include the probability of ANOCA/INOCA, which always needs to be considered if symptoms persist after deferral of further testing or diagnostic testing that excludes obstructive CAD.

The tables used to estimate the likelihood of obstructive CAD as confirmed by ICA were initially based on the Diamond–Forrester approach, which considered sex, age, and angina symptoms.[25] However, these tables have had to be updated several times owing to the declining prevalence of obstructive CAD at invasive angiography in contemporary Western cohorts.[26,29] The overestimation of obstructive CAD prevalence has limited the utility of these tables in clinical routine and in accurately estimating the post-test likelihood of obstructive CAD by diagnostic imaging methods.[1,29,30]

The 2019 ESC Guidelines for the diagnosis and management of CCS introduced the concept of clinical likelihood as a more comprehensive and individualized assessment of the probability of obstructive CAD.[1]

Compared with a basic pre-test probability model, incorporation of risk factors in the basic pre-test likelihood model (based on age, sex, and

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symptoms) leads to improved prediction of obstructive CAD, down-classifies more individuals to very low and low likelihood of disease, and maintains high calibration.[30,139,140] The Risk-Factor-weighted Clinical Likelihood (RF-CL) model includes sex, age, angina symptoms, and number of risk factors without losing diagnostic accuracy compared with more advanced models requiring computed calculation (*Figure 4*).[139,141,142] The RF-CL model increases three-fold the number of subjects categorized as at very low (≤5%) likelihood of obstructive CAD compared with the ESC pretest probability (ESC-PTP) model (38% vs. 12%),[139] while predicting annualized event rates of MI and death of 0.5%, 1.1%, and 2.1% for individuals having very low, low, and moderate likelihood of obstructive CAD, respectively.[143]

Individual adjustment of the likelihood may be necessary for individuals with severe single risk factors or comorbidities associated with an increased prevalence of obstructive CAD, which are not reflected in the RF-CL model, e.g. familial hypercholesterolaemia, severe kidney dysfunction, rheumatic/inflammatory diseases, and peripheral artery disease (PAD).

Exercise ECG testing may modify the likelihood of obstructive CAD and can be used in patients with low (>5%–15%) clinical likelihood, in whom a negative test allows reclassification to the very low (≤5%) clinical likelihood group with a favourable prognosis.[144] However, CCTA as a first-line diagnostic test can give more accurate information and has been associated with fewer angina symptoms during follow-up than a strategy with exercise ECG as the first investigation.[145–148] In addition, more adverse events were observed in randomized trials with an exercise ECG than with a CCTA-based diagnostic strategy.[34,146] However, exercise ECG remains clinically useful for reproducing anginal symptoms, which have a prognostic value.[149,150]

In contrast to exercise ECG, visualization of calcified atherosclerotic plaque in the coronary artery significantly impacts the clinical likelihood of atherosclerotic obstructive CAD. Coronary artery calcification (CAC) can be measured using the coronary artery calcium score (CACS), which is derived from an ECG-gated non-contrast-enhanced computed tomography (CT) scan. Alternatively, the presence of CAC can be evaluated qualitatively by visually inspecting the coronary arteries on a previous non-cardiac chest CT scan, if available. The absence of CAC (CACS = 0) has a very high negative predictive value (>95%) for obstructive CAD.[151] Of note, in younger patients, obstructive CAD is rare, but when present, a higher percentage (58% of those younger than 40 years) have a CACS of 0 compared with older patients with obstructive CAD (9% among those aged 60 to 69 years).[152]

Small, randomized studies have shown that further testing can safely be deferred in patients without CAC, without increased event rates during follow-up.[146,153] Finally, in a larger prospective observational study, absence of CAC alone was sufficient to define a low-risk group with no need for further testing with improved accuracy compared with basic clinical prediction models.[154] The combination of CACS with the RF-CL model [CACS + RF-CL (the Coronary Artery Calcium Score-Weighted Clinical Likelihood—CACS-CL)] showed the strongest potential to effectively defer cardiac testing compared with other clinical prediction models or CACS alone (adjustment of the estimation of the clinical likelihood of obstructive CAD).[139,154] With the CACS-CL model, substantially more individuals (54%) compared with the RF-CL model (38%) were categorized as having a very low clinical likelihood of obstructive CAD in the external validation cohorts.[139] Finally, the CACS-CL model was superior to other clinical prediction models in predicting MI and death during follow-up.[143]

Detection of atherosclerotic disease in non-coronary arteries with ultrasound or CT scans of, e.g. the aorta, and the carotid or femoral arteries, may increase the clinical likelihood of obstructive CAD,[155–158] and the risk for future CVD events.[159,160] However, how accurately the detection of non-coronary atherosclerotic disease impacts the likelihood estimation of obstructive CAD needs further investigation.

In general, individuals with a very low (≤5%) likelihood of obstructive CAD do not require further diagnostic testing unless symptoms persist and non-cardiac causes have been excluded. In patients with a low (>5%–15%) likelihood of obstructive CAD, the benefit of diagnostic testing is uncertain but may be performed if symptoms are limiting and require clarification. Patients with moderate (>15%–50%), high (>50%–85%), and very high (>85%) likelihood of obstructive CAD are encouraged to undergo further diagnostic testing.

By using pre-test likelihood estimates and diagnostic imaging-test positive and negative likelihood ratios, it is possible to calculate the post-test probability of obstructive CAD. Hence, pre-test likelihood estimation is useful to guide non-invasive diagnostic test strategies for detecting obstructive CAD (*Section* 3.3.4).

Recommendation Table 3 — Recommendations for estimating, adjusting and reclassifying the likelihood of obstructive atherosclerotic coronary artery disease in the initial diagnostic management of individuals with suspected chronic coronary syndrome (see also Evidence Table 3)

Recommendations	Class[a]	Level[b]
It is recommended to estimate the pre-test likelihood of obstructive epicardial CAD using the Risk Factor-weighted Clinical Likelihood model.[139,140,142,143,161,162]	I	B
It is recommended to use additional clinical data (e.g. examination of peripheral arteries, resting ECG, resting echocardiography, presence of vascular calcifications on previously performed imaging tests) to adjust the estimate yielded by the Risk Factor-weighted Clinical Likelihood model.[163]	I	C
In individuals with a *very low* (≤5%) pre-test likelihood of obstructive CAD, deferral of further diagnostic tests should be considered.[139,164]	IIa	B
In individuals with a *low* (>5%–15%) pre-test likelihood of obstructive CAD, CACS should be considered to reclassify subjects and to identify more individuals with very low (≤5%) CACS-weighted clinical likelihood.[139,143,165]	IIa	B
In individuals with an initially low (>5%–15%) likelihood of obstructive CAD, exercise ECG and detection of atherosclerotic disease in non-coronary arteries may be considered to adjust the pre-test likelihood estimate.[144,166]	IIb	C

CACS, coronary artery calcium score; CAD, coronary artery disease; ECG, electrocardiogram.
[a]Class of recommendation.
[b]Level of evidence.

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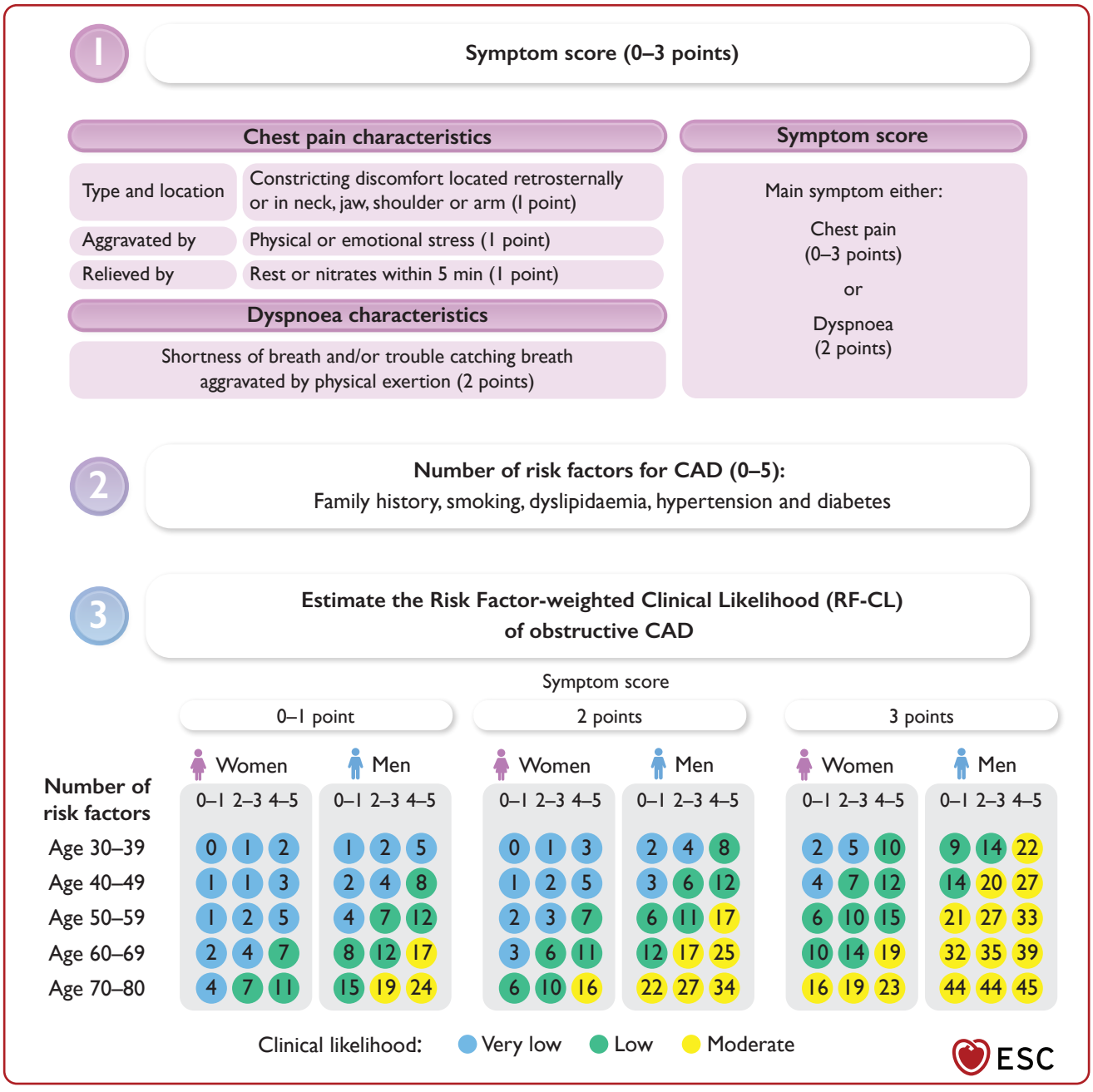

Figure 4 Estimation of the clinical likelihood of obstructive coronary artery disease. CAD, coronary artery disease; RF-CL, risk factor-weighted clinical likelihood. Data derived from Winther *et al.*[139] The symptom score replaces the previous, potentially misleading terminology, that defined presence of three chest pain characteristics as 'typical' angina (here = 3 points), two of three characteristics as 'atypical' angina (here = 2 points), and no or one characteristic as 'non-cardiac/non-anginal' (here = 0–1 point). Family history of CAD is defined as 1 or more first-degree relatives with early signs of CAD (men <55 and women <65 years of age); smoking, as current or past smoker; dyslipidaemia, hypertension, and diabetes, as present at the time of diagnosis. Values in the lower panel are the clinical likelihood estimates expressed as %.

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3.2.2. Transthoracic echocardiography and cardiac magnetic resonance at rest

An echocardiographic study will provide important information about cardiac function and anatomy. Patients with CCS have often preserved left ventricular ejection fraction (LVEF).[167] A decreased LV function and/or regional wall motion abnormalities may increase the suspicion of ischaemic myocardial damage,[167] and a pattern of LV dysfunction following the anatomical perfusion territory of the coronary arteries is typical in patients who have already had an MI.[168,169] The detection of regional wall motion abnormalities can be challenging by visual assessment, and detection of early systolic lengthening, decreased systolic shortening, or post-systolic shortening by strain imaging techniques,[170–172] or new parameters such as global myocardial work,[173] may be helpful in individuals with apparently normal LV function but with clinical suspicion of CCS. Diastolic LV dysfunction has been reported to be an early sign of ischaemic myocardial dysfunction and may also be indicative of microvascular dysfunction.[174,175]

Echocardiography can help in detecting alternative causes of chest pain (e.g. pericarditis) and in diagnosing valvular heart diseases, ischaemic HF, and most cardiomyopathies,[176] though these diseases may co-exist with obstructive CAD. The use of an echocardiographic contrast agent can be helpful in patients with poor acoustic windows.[177]

Cardiac magnetic resonance (CMR) is an alternative in patients with suspected CAD when the echocardiogram (having used ultrasound contrast agent) is inconclusive.[178] Cardiac magnetic resonance can assess global and regional function,[179] and the use of late gadolinium enhancement (LGE) CMR can reveal a typical pattern of scarred myocardium in patients who have already experienced an MI.[180] Moreover, CMR provides information on myocardial ischaemia through the evaluation of stress-induced perfusion defects.[181]

The strongest predictor of long-term survival is systolic LV function. Hence, risk stratification through the assessment of systolic LV function is useful in all symptomatic individuals with suspected CCS. Mortality increases as LVEF declines.[182] Management of patients with either angina or HF symptoms, with reduced LVEF ≤40% or mildly reduced LVEF 41%–49%, is described in *Section 4*.

Recommendation Table 4 — Recommendations for resting transthoracic ultrasound and cardiac magnetic resonance imaging in the initial diagnostic management of individuals with suspected chronic coronary syndrome (see also Evidence Table 4)

Recommendations	Class[a]	Level[b]
A resting transthoracic echocardiogram is recommended: to measure LVEF, volumes and diastolic function; • identify regional wall motion abnormalities; • identify non-coronary cardiac disease (e.g. hypertrophy, cardiomyopathy, valve disease, pericardial effusion); • assess right ventricular function and estimate systolic pulmonary artery pressure; to refine risk stratification and guide treatment.[167,183,184]	I	B
CMR, if available, may be considered as an alternative imaging test in individuals with inconclusive echocardiographic evaluation.[185,186]	IIb	C

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CMR, cardiac magnetic resonance; LVEF, left ventricular ejection fraction.
[a]Class of recommendation.
[b]Level of evidence.

3.2.3. Exercise electrocardiogram testing

Exercise ECG testing is low cost, does not use ionizing radiation, is widely accessible, and remains an alternative for diagnostic testing depending on local resources and individual characteristics.

The classical exercise ECG, involving graded exercise until the occurrence of fatigue, limiting chest pain or discomfort, significant ischaemic ECG changes, arrhythmias, excessive hypertension, a BP drop or after reaching 85% of the maximal predicted heart rate, has been the mainstay of the examination techniques used in clinical cardiology for assessing individuals with suspected CCS. Exercise ECG testing has a lower diagnostic performance of obstructive CAD compared with modern functional imaging and CCTA,[148] which, therefore, should be preferred as a first-line test in subjects with suspected CCS. Several clinical trials have confirmed that a strategy based on anatomical[34,146,187,188] or functional imaging[189] simplifies the diagnosis, enables the targeting of preventive therapies and interventions, and potentially reduces the risk of MI compared with usual care based on exercise ECG. In addition, two randomized trials showed that patients reported fewer anginal complaints during follow-up when randomized to CCTA as an index investigation for stable chest pain compared with exercise ECG.[145,146]

Although the Scottish Computed Tomography of the Heart (SCOT-HEART) trial favoured CCTA as first-line test in CCS, a *post hoc* analysis suggested that abnormal results of exercise ECG remain a specific indicator of obstructive CAD, and are associated with future coronary revascularization and risk of MI.[188] Exercise ECG testing with clearly abnormal results was most predictive for these outcomes; however, in a large proportion of individuals who underwent exercise ECG, particularly those with normal or inconclusive results, there was still a significant amount of unrecognized non-obstructive and obstructive CAD, which can be detected by additional CCTA imaging.[188] In the WOMEN trial (What is the Optimal Method for Ischemia Evaluation of Women), including low-risk symptomatic women, exercise ECG was equally effective compared with exercise myocardial perfusion scintigraphy, with a similar 2-year incidence of major adverse cardiovascular events (MACE), defined as CAD death, or hospitalization for an ACS or HF, while providing significant diagnostic cost savings.[190] Individuals exercising >10 metabolic equivalents with a negative exercise ECG and a low-risk Duke Treadmill Score have a good prognosis with limited need for downstream testing and revascularization.[166,191] Patients with marked ischaemia at a low workload and a high-risk Duke Treadmill Score may benefit from further anatomical or functional testing. In regions with limited access to functional imaging or CCTA, or in individuals with a low (>5%–15%) pre-test likelihood of obstructive CAD,[144] exercise ECG remains, therefore, useful for risk stratification and prognostication.[144] Particularly, in subjects with a low (>5%–15%) likelihood of obstructive CAD, a negative exercise ECG may help to down-classify patients into the very low likelihood (<5%) class, in whom further testing can be deferred.[144]

An exercise ECG is of no diagnostic value in patients with ECG abnormalities at rest that prevent interpretation of the ST-segment changes during stress (i.e. LBBB, paced rhythm, Wolff–Parkinson–White syndrome, ≥0.1 mV ST-segment depression on resting ECG, or treatment with digitalis). In patients with known CAD, exercise ECG may be considered in selected patients to complement their clinical evaluation for assessing symptoms, ST-segment changes, exercise tolerance, arrhythmias, BP response, and event risk.

In summary, due to its low sensitivity (58%) and specificity (62%), exercise ECG testing has low diagnostic performance for the diagnosis of obstructive CAD[148] and should mainly be used for risk stratification.

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Recommendation Table 5 — Recommendations for exercise ECG in the initial diagnostic management of individuals with suspected chronic coronary syndrome (see also Evidence Table 5)

Recommendations	Class[a]	Level[b]
Exercise ECG is recommended in selected patients[c] for the assessment of exercise tolerance, symptoms, arrhythmias, BP response, and event risk.	I	C
Exercise ECG may be considered as an alternative test to rule in and rule out CAD when non-invasive imaging tests are unavailable.[148,166,188,190,191]	IIb	B
An exercise ECG may be considered to refine risk stratification and treatment.[188]	IIb	B
In individuals with a low (>5%–15%) pre-test likelihood of obstructive CAD, an exercise ECG may be considered to identify patients in whom further testing can be deferred.[144]	IIb	C
Exercise ECG is not recommended for diagnostic purposes in patients with ≥0.1 mV ST-segment depression on resting ECG, left bundle branch block or who are being treated with digitalis.	III	C
In individuals with a low or moderate (>5%–50%) pre-test likelihood of obstructive CAD, an exercise ECG is not recommended to rule out CAD if CCTA or functional imaging tests are available.[148]	III	C

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BP, blood pressure; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; ECG, electrocardiogram.
[a]Class of recommendation.
[b]Level of evidence.
[c]When this information will have an impact on diagnostic strategy or management.

3.2.4. Chest X-ray

Chest X-ray is commonly utilized in the evaluation of patients experiencing chest pain. However, in the context of CCS, it does not yield specific information for accurate diagnosis or risk stratification. The test may provide assistance in assessing patients with suspected HF. Additionally, chest X-ray may prove beneficial in diagnosing pulmonary conditions that often co-exist with CAD, or in ruling out other potential causes of chest pain.

3.2.5. Ambulatory electrocardiogram monitoring

Ambulatory ECG monitoring can assist in evaluating patients with chest pain and palpitations. It can also help in detecting and evaluating silent myocardial ischaemia, as well as suspected VSA.[192–194]

Recommendation Table 6 — Recommendations for chest X-ray in the initial diagnostic management of individuals with suspected chronic coronary syndrome (see also Evidence Table 6)

Recommendations	Class[a]	Level[b]
A chest X-ray should be considered for individuals with: • signs and symptoms suggestive of heart failure; • suspected acute pulmonary disease; • suspected aortic, non-coronary cardiac, or other thoracic causes of chest pain.	IIa	C

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[a]Class of recommendation.
[b]Level of evidence.

Recommendation Table 7 — Recommendations for ambulatory ECG monitoring in the initial diagnostic management of individuals with suspected chronic coronary syndrome (see also Evidence Table 7)

Recommendations	Class[a]	Level[b]
Ambulatory ECG monitoring is recommended in subjects with chest pain and suspected arrhythmias.	I	C
Ambulatory ECG monitoring should be considered in subjects with suspected vasospastic angina.[192–194]	IIa	B

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ECG, electrocardiogram.
[a]Class of recommendation.
[b]Level of evidence.

3.3. STEP 3: Confirming the diagnosis

3.3.1. Anatomical imaging: coronary computed tomography angiography

Through the intravenous (i.v.) injection of contrast agent, CCTA allows direct anatomical visualization of the coronary artery lumen and wall. CCTA offers a practical, non-invasive test, with proven diagnostic performance in detecting obstructive coronary artery stenoses when compared with ICA.[32,148]

Obstructive coronary stenoses have typically been defined using visual thresholds of either 50% or 70% diameter reduction. It is accepted that not all anatomical stenoses above such thresholds, especially those of moderate (50%–69%) stenosis severity, are haemodynamically or functionally significant[195] or induce myocardial ischaemia.[196] Depending on the clinical context, it may be necessary to complement CCTA with functional data either from non-invasive imaging techniques or from invasive angiography with fractional flow reserve (FFR) (see *Section 3.3.3.2*), when the haemodynamic consequence of a stenosis is deemed questionable for management options.

While several earlier trials (publication date during or before 2016) reported a higher rate of *downstream ICA* in patients receiving CCTA compared with functional imaging,[197] this was no longer observed in more recent trials (publication date after 2016). Moreover, increased downstream use of invasive procedures was linked to non-adherence to guideline recommendations as these procedures were used significantly less when the guidelines were adopted.[198]

Coronary computed tomography angiography-derived fractional flow reserve (FFR-CT) can complement CCTA by providing values of model-based computational FFR along the coronary tree. FFR-CT has shown good agreement with invasive FFR,[199] and has clinical utility by reducing the number of unnecessary ICA procedures.[200] However, in patients with severe disease at CCTA, FFR-CT has less impact on patient management.[201] FFR-CT does not require pharmacological stress, additional contrast agent injection, or radiation exposure. FFR-CT, however, is not ubiquitous and depends on image quality. Nevertheless, the rejection rate is reported to be quite low in real-world data with newest-generation scanners.[202–204]

3.3.1.1. Computed tomography perfusion imaging

Computed tomography perfusion imaging, performed under pharmacological stress, has been validated against several reference standards, including single-photon computed tomography (SPECT) and

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invasive FFR. It has shown adequate diagnostic performance in selected cohorts,[205,206] and a potential to reduce the number of unnecessary downstream invasive angiography procedures, when compared with functional tests (mostly symptom-limited exercise ECG).[153] While CT perfusion imaging could complement CCTA during the same visit, this technique requires the administration of a pharmacological stressor, contrast agent, and further patient irradiation. Imaging techniques and analysis methods are not yet widely standardized (e.g. static and dynamic imaging techniques, visual and quantitative assessment).[207–209]

3.3.1.2. Prognosis, plaque features, and opportunity to improve outcomes

The SCOT-HEART trial demonstrated a small but significant decrease of the combined endpoint of cardiovascular death or non-fatal MI (from 3.9% to 2.3% during 5-year follow-up) in patients in whom CCTA was performed in addition to routine testing (exercise ECG).[34] In a *post hoc* analysis of this trial, CCTA features (low-attenuation plaque, positive remodelling, spotty calcifications, and napkin-ring sign) conferred an increased risk of death or non-fatal MI, although these plaque features were not independent of CACS.[210] Systematically evaluating adverse plaque features by CCTA can be challenging due to technical limitations (spatial resolution) and patient characteristics (calcifications).

A network meta-analysis of randomized trials suggested that diagnostic testing with CCTA was associated with clinical outcomes similar to those with functional imaging in patients with suspected stable CAD.[197] In another pairwise meta-analysis, CCTA showed a lower rate of MI compared with functional testing, but the absolute per cent risk difference was small (0.4%).[211]

In the available randomized trials comparing CCTA and functional testing (all testing a diagnostic strategy),[33,210,212] test reporting and patient management variability could in part help explain the improved outcomes observed in the CCTA arm of SCOT-HEART. In this trial, CCTA findings, including non-obstructive atherosclerosis, emphasized the need to trigger the start or intensification of medical treatment. Increased standardization in reporting CCTA to encompass key plaque features (accepting inherent limitations) will be warranted to systematically harvest prognostic information and help fine-tune risk management strategies.[213]

3.3.1.3. Recognized pre-requisites for coronary computed tomography angiography

Generally, a slow and regular heart rate, and compliance with breath-holding instructions are necessary to achieve good image quality. This includes suitability to receive pre-medication (typically oral or i.v. beta-blockers) when needed. Kidney function and allergy to contrast agents should be assessed prior to referral. Temporal and spatial resolution remain technical limitations and can hinder precision in adjudicating coronary stenosis severity. This is most problematic in older patients with heavily calcified coronary arteries, in whom functional testing may be more appropriate than CCTA. Contemporary CT technology (64-slice technology or above) and a well-trained imaging team can help mitigate these limitations and must be considered a pre-requisite for CCTA.

Recommendation Table 8 — Recommendations for non-invasive anatomical imaging tests in the initial diagnostic management of individuals with suspected chronic coronary syndrome—coronary computed tomography angiography, if available, and supported by local expertise (see also Evidence Table 8)

Recommendations	Class[a]	Level[b]
In individuals with suspected CCS and low or moderate (>5%–50%) pre-test likelihood of obstructive CAD, CCTA is recommended to diagnose obstructive CAD and to estimate the risk of MACE.[33,34,145,212,214–221]	I	A
CCTA is recommended in individuals with low or moderate (>5%–50%) pre-test likelihood of obstructive CAD to refine diagnosis if another non-invasive test is non-diagnostic.[222]	I	B
CCTA is not recommended in patients with severe renal failure (eGFR <30 mL/min/1.73 m^2), decompensated heart failure, extensive coronary calcification, fast irregular heart rate, severe obesity, inability to cooperate with breath-hold commands, or any other conditions that can make obtaining good imaging quality unlikely.	III	C

CAD, coronary artery disease; CCS, chronic coronary syndrome; CCTA, coronary computed tomography angiography; eGFR, estimated glomerular filtration rate; MACE, major adverse cardiovascular events.
[a]Class of recommendation.
[b]Level of evidence.

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3.3.2. Functional imaging

3.3.2.1. Stress echocardiography

Stress echocardiography is used to detect myocardial ischaemia by assessing regional systolic wall-thickening abnormalities (RWTA) during stress. It relies on inducing myocardial ischaemia by increasing myocardial oxygen demand beyond the myocardial blood supply. Because ischaemia starts in the subendocardium, which contributes to more than 50% of systolic myocardial wall thickening, stress testing will precipitate wall-thickening abnormalities in the perfusion territory of narrowed coronary arteries. Stress modalities used to increase myocardial oxygen demand are exercise (treadmill or bicycle), or i.v. administration of dobutamine, or vasodilators (adenosine, dipyridamole, regadenoson) combined with atropine (to increase heart rate adequately—a major determinant of oxygen demand). Stress echocardiography using demand stress has provided diagnostic accuracy and risk-stratification capabilities similar to those obtained with other contemporary functional imaging testing modalities.[148,223] The advantages of stress echocardiography are that it is widely available, low-cost, can be performed and interpreted at the bedside, rapid, free of ionizing radiation, and can be repeated without safety concerns.[224–227] Although stress echocardiography is operator-dependent, which may compromise reproducibility, the technique is within reach of every cardiology department or office. Compromised image quality, especially in obese and chronic obstructive pulmonary disease subjects, is a significant

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limitation. RWTA may not occur if the myocardial oxygen demand increase is inadequate or if the induced perfusion abnormalities are not large enough (<10% of the myocardium), such as in mild atherosclerotic CAD or single-vessel obstructive CAD.[228] As stress echocardiography relies on RWTA as a marker of ischaemia, it may under-estimate ischaemia in patients with microvascular disease not affecting the subendocardium as in ANOCA/INOCA.[36]

Ultrasound contrast agents considerably enhance the quality of diagnostic images obtained during stress echocardiography. These microbubbles, consisting of stable gas and shells about the size and rheology of red blood cells, can pass through the pulmonary microcirculation and induce a dense opacification of the left heart chambers. The enhanced image quality and endocardial border definition by using ultrasound contrast agents markedly improve the accuracy of stress echocardiography.[229,230] Ultrasound contrast agents may be required in individuals with obesity and chronic obstructive pulmonary disease and must be used in all cases if it is evident at baseline that all segments may not be visible during stress. Passage of ultrasound contrast agents through the myocardium allows assessment of myocardial perfusion simultaneously with regional wall motion, improving the sensitivity of stress echocardiography (better detection of single-vessel and microvascular disease) and risk stratification beyond RWTA.[231–235] The use of ultrasound contrast agents during stress echocardiography for assessing regional and global LV function is strongly recommended by the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE) guidelines—both class I indications. Similarly, myocardial perfusion assessment has received a class I recommendation by the EACVI and a class IIa recommendation by the ASE.[177,236] Ultrasound contrast agents are generally safe, but rare cases of anaphylactic reactions have been reported.[237]

Measurement of the coronary flow velocity reserve (CFVR) based on Doppler flow velocity recordings at rest and during stress in the left anterior descending (LAD) artery, and assessment of lung congestion through the visualization of B-lines on lung ultrasound, can easily be added to routine stress echocardiography procedures. In a prospective observational multicentre study, a reduced CFVR was often accompanied by RWTA, abnormal LV contractile reserve, and pulmonary congestion during stress, and showed independent value over RWTA in predicting an adverse outcome.[238] The inclusion of these additional parameters in routine stress echocardiography procedures provides insights on coronary microcirculatory dysfunction.

Finally, carotid ultrasound may be performed in the same session with stress echocardiography to assess extracoronary atherosclerosis; while this does not add value for confirming a CCS diagnosis per se, it provides incremental prognostic value beyond myocardial ischaemia.[239,240]

Recommendation Table 9 — Recommendations for non-invasive tests in the initial diagnostic management of individuals with suspected chronic coronary syndrome —stress echocardiography, if available, and supported by local expertise (see also Evidence Table 9)

Recommendations	Class[a]	Level[b]
In individuals with suspected CCS and moderate or high (>15%–85%) pre-test likelihood of obstructive CAD, stress echocardiography is recommended to diagnose myocardial ischaemia and to estimate the risk of MACE.[33,241–246]	I	B
During stress echocardiography, when two or more contiguous myocardial segments are not visualized, it is recommended to use commercially available intravenous ultrasound contrast agents (microbubbles) to improve diagnostic accuracy.[177,229,236,247,248]	I	B
During stress echocardiography, myocardial perfusion using commercially available intravenous ultrasound contrast agents (microbubbles) is recommended to improve diagnostic accuracy and to refine risk stratification beyond wall motion.[177,230,232,236,249–254]	I	B
During stress echocardiography, Doppler left anterior descending coronary artery flow reserve may be considered to improve risk stratification beyond wall motion and to assess microvascular function.[177,238,255]	IIb	B

CAD, coronary artery disease; CCS, chronic coronary syndrome; MACE, major adverse cardiovascular events.
[a]Class of recommendation.
[b]Level of evidence.

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3.3.2.2. *Myocardial perfusion scintigraphy—single-photon emission computed tomography*

Myocardial perfusion SPECT imaging relies on the myocardial uptake and retention of a radiopharmaceutical. Technetium-99m (99mTc)-based tracers are the most commonly used radiopharmaceuticals, whereas Thallium 201 (201Tl) should be avoided as it is associated with higher radiation exposure. Myocardial perfusion SPECT produces images of regional myocardial tracer retention, which reflects relative regional myocardial blood flow (MBF). Myocardial hypoperfusion is characterized by relative reduced radionuclide tracer uptake and retention during vasodilatation or stress, compared with the uptake and retention at rest. The inherent need for a normally perfused myocardial reference territory allowing for visualization of the myocardium with relative hypoperfusion constitutes the main limitation of SPECT (and stress CMR), particularly in multivessel CAD. Coronary calcium scoring from non-contrast-enhanced CT, acquired for attenuation correction, as well as transient ischaemic dilatation (TID) and reduced post-stress ejection fraction (EF) are important non-perfusion predictors of severe obstructive CAD.

Ischaemia can be demonstrated by physical exercise or through the administration of pharmacological stressors (e.g. dobutamine) or vasodilators (e.g. dipyridamole, adenosine, or regadenoson). Pharmacological agents are indicated in patients who cannot exercise adequately or may be used as an alternative or an adjunct to exercise stress. The possibility to use physical exercise and/or different pharmacological stressors in combination with the wide-spread availability of the technique and the lack of absolute contraindications contributes to the high versatility and applicability of myocardial perfusion SPECT in clinical routine.

SPECT myocardial perfusion imaging is associated with good accuracy for the detection of flow-limiting coronary lesions,[148,256–258] and has been shown to provide prognostic information[223,259] and to improve patient management in a randomized controlled trial (RCT).[178]

Newer-generation SPECT cameras based on cadmium–zinc–telluride (CZT) semiconductor detector technology enable a substantial reduction in radiation dose exposure and acquisition time, as well as an increased diagnostic accuracy[260] and absolute quantification of MBF. Hence, its diagnostic performance for multivessel CAD has improved substantially.[261]

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However, non-obstructive coronary atherosclerosis not linked with ischaemia remains undetected by functional testing in general.

If available, assessment of myocardial perfusion using SPECT is recommended in patients with suspected CCS with moderate or high pre-test likelihood of obstructive CAD (15%–85%) or known CCS. Importantly, if non-contrast-enhanced CT for attenuation correction is acquired, this allows for additional CAC scoring, providing important information for risk stratification even in the absence of flow-limiting coronary lesions.

3.3.2.3. Positron emission tomography-computed tomography

Similarly to myocardial perfusion SPECT imaging, PET also relies on radiopharmaceuticals. Contrary to SPECT, however, the radionuclides commonly used (i.e. ^{13}N-ammonia, ^{15}O-water, and ^{82}Rubidium) are short-lived, with half-lives in the range of minutes, requiring production of these radionuclides *ad hoc* for every investigation. As attenuation correction is mandatory, PET is routinely performed in combination with non-contrast-enhanced CT. Scans are performed during both rest and infusion of pharmacological stressors (e.g. dobutamine) or vasodilators (e.g. dipyridamole, adenosine, or regadenoson).

While myocardial perfusion PET-CT produces retention images depicting relative differences in regional MBF similar to those from SPECT—albeit with superior image quality and at much lower radiation dose exposure—the unique strength of PET-CT imaging is its ability to provide robust absolute quantitative measures of MBF. Measuring MBF with cardiac PET does not increase radiation or imaging time. Several measurements of MBF can be routinely obtained, including MBF during hyperaemia, MBF at rest, the MBF reserve, and the relative MBF reserve, and confer added diagnostic and prognostic value beyond relative perfusion assessment.[262,263]

Quantitative measures of MBF offer the ability to assess individuals with known or suspected diffusely impaired MBF, e.g. with multivessel CAD, or microvascular dysfunction.[45,264] In general, PET-CT myocardial perfusion imaging is associated with high accuracy for detecting flow-limiting coronary lesions,[148,258,265] and has been shown to provide prognostic information.[223,262,263] In several head-to-head comparisons, PET-CT myocardial perfusion imaging outperformed other functional imaging modalities.[257,266–269] However, whether the superiority in diagnostic accuracy leads to improved clinical effectiveness and post-test management remains to be elucidated.[270] In a large retrospective study, a low MBF reserve measured by PET independently predicted mortality and helped identify patients with a survival benefit from early revascularization with PCI or coronary artery bypass grafting (CABG) beyond the extent of myocardial ischaemia.[271]

Limitations of PET-CT arise from its limited availability compared with other imaging modalities. Furthermore, methodological heterogeneity exists, particularly regarding thresholds for abnormality of quantitative measurements. Finally, physical exercise is challenging to perform.

If available, assessment of myocardial perfusion using PET-CT is particularly recommended in obese patients (due to the high photon energy), in young patients (due to the low radiation dose exposure), and in those with known or suspected diffusely impaired MBF, e.g. those with multivessel CAD or microvascular dysfunction.[264] Notably, the mandatory non-contrast-enhanced CT for attenuation correction allows for additional CAC scoring, providing essential information for risk stratification even in the absence of flow-limiting coronary lesions.

3.3.2.4. Cardiac magnetic resonance imaging

Aside from providing highly accurate and reproducible assessments of overall cardiac anatomy, cardiac volumes, function, and tissue characterization, CMR also offers the ability to assess myocardial perfusion, which relies on the first-pass myocardial perfusion of gadolinium-based contrast agents.

Recently, CMR methods using various parameters for quantitative MBF assessment have been introduced. However, the diagnostic performance of these parameters varies extensively among studies, and standardized protocols and software are lacking.[272] Therefore, visual assessment of perfusion defects is currently used in clinical practice. Myocardial perfusion imaging by stress CMR combines high spatial resolution with the absence of ionizing radiation. This has been shown to provide high diagnostic accuracy in detecting flow-limiting coronary lesions,[148,257,258] prognostic value,[223,273–275] and improving patient management.[178,276] Pharmacological vasodilators (e.g. adenosine or regadenoson) or stressors (e.g. dobutamine) are commonly applied, as physical exercise is challenging to perform. In conjunction with a dobutamine infusion, wall motion abnormalities induced by ischaemia can also be detected.[277] Of note, and as for all non-invasive imaging modalities used for assessing myocardial perfusion, incorporating all available imaging and non-imaging information as part of an integrative approach is mandatory. For CMR, a multiparametric protocol, including LV function and assessment of LGE along with myocardial perfusion, increases the ability to rule in or rule out obstructive CAD in suspected CCS.[278]

Coronary magnetic resonance angiography allows non-invasive visualization of the coronary arteries.[279] However, CMR angiography remains primarily a research tool due to limitations arising from long imaging times, low spatial resolution, and operator dependency. General limitations of CMR for myocardial perfusion arise from its limited availability, the claustrophobia experienced by patients, duration of image acquisition,[280] and possible contraindications to CMR [e.g. non-conditional pacemakers and implantable cardioverter defibrillators (ICDs)] or to gadolinium-based contrast agents (e.g. renal failure due to the potential risk of nephrogenic systemic fibrosis). Finally, and contrary to SPECT/CT or PET-CT, stress CMR does not currently provide information on presence or absence of coronary calcifications.

If available, and if no contraindications are met, stress CMR is recommended as an option in patients with suspected CCS with moderate or high (>15%–85%) pre-test likelihood of obstructive CAD or known CCS, particularly if additional information on cardiac function and tissue characterization is warranted.

Recommendation Table 10 — Recommendations for non-invasive functional myocardial imaging tests in the initial diagnostic management of individuals with suspected chronic coronary syndrome—resting and stress single-photon emission computed tomography/positron emission tomography—cardiac magnetic resonance imaging, if available, and supported by local expertise (see also Evidence Table 10)

Recommendations	Class[a]	Level[b]
In individuals with suspected CCS and moderate or high (>15%–85%) pre-test likelihood of obstructive CAD, stress SPECT or, preferably, PET myocardial perfusion imaging is recommended to: • diagnose and quantify myocardial ischaemia and/or scar; • estimate the risk of MACE; • quantify myocardial blood flow (PET).[33,44,223,257,263,268,270,271,281–288]	I	B

Continued

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In patients selected for PET or SPECT myocardial perfusion imaging, it is recommended to measure CACS from unenhanced chest CT imaging (used for attenuation correction) to improve detection of both non-obstructive and obstructive CAD.[289–293]	I	B
In individuals with suspected CCS and moderate or high (>15%–85%) pre-test likelihood of obstructive CAD, stress CMR perfusion imaging is recommended to diagnose and quantify myocardial ischaemia and/or scar and estimate the risk of MACE.[148,273,276,278,294–297]	I	B

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CACS, coronary artery calcium score; CAD, coronary artery disease; CCS, chronic coronary syndrome; CMR, cardiac magnetic resonance; CT, computed tomography; MACE, major adverse cardiovascular events; PET, positron emission tomography; SPECT, single-photon emission computed tomography.
[a]Class of recommendation.
[b]Level of evidence.

3.3.2.5. Non-invasive testing for microvascular dysfunction

Angina/ischaemia with non-obstructive coronary arteries (ANOCA/INOCA) may be caused by transient and/or sustained impairments in the supply–demand of myocardial perfusion. Functional disorders leading to ANOCA/INOCA (e.g. MVA and VSA) are more common in women than in men.[298,299] A recent meta-analysis reported an overall prevalence of MVA of 41% and VSA of 40% in selected patients without obstructive CAD.[299] However, the true prevalence in unselected patient populations with suspected CCS remains unclear. Patients with ANOCA/INOCA have increased morbility/mortality,[300,301] impaired quality of life (QoL), and weigh on health resource utilization. Early, accurate, and preferably non-invasive diagnosis is, therefore, of importance.

The possibility of a microcirculatory origin of angina should be considered in individuals with symptoms suggestive of myocardial ischaemia and coronary arteries that are either normal or with non-obstructive lesions on CCTA or ICA. Several measurements that rely on quantifying blood flow through the coronary circulation are used to describe the function of the microvasculature to identify cases of MVA. Among the non-invasive imaging modalities, transthoracic Doppler echocardiography has been used as a non-invasive means to measure coronary blood flow but is limited to the assessment of the LAD artery and is affected by high inter- and intra-operator variability.[302,303] Furthermore, this modality cannot distinguish between impairment of coronary flow caused by epicardial CAD or coronary microcirculatory dysfunction.

A more direct and accurate microvascular function assessment is based on MBF measurement. This is commonly achieved by PET-CT myocardial perfusion imaging.[299] PET allows for the quantification of MBF (expressed as millilitres per minute per gram of myocardium) and myocardial flow reserve (MFR). The latter reflects the magnitude of the increase in MBF that can be achieved by maximal coronary vasodilation conferred by vasodilators, such as adenosine or regadenoson. Since the microvasculature primarily determines vascular resistance, MFR measures the ability of the microvasculature to respond to a stimulus and therefore represents small vessel function. An MFR of less than 2.0 (2.5 for non-obstructive CAD) is often considered abnormal for PET.[304] Of note, however, no definitive references are available across imaging modalities due to the moderate correlation among different MBF estimates.[264]

Recently, quantitative CMR has been proposed as an emerging technique for the assessment of microvascular dysfunction through MBF quantification but is currently limited to experienced centres.[275] Quantitative myocardial perfusion can also be achieved by myocardial contrast echocardiography (MCE) through destruction–reperfusion imaging and analysis of the time–intensity curves from different regions of interest in the myocardium.[231,233–235] Of note, MCE assesses capillary blood flow, and capillaries comprise 90% of the microvasculature. Measuring MBF at rest and during hyperaemia allows calculation of MBF reserve, which is associated with severity of coronary stenoses in patients with stable angina. In a meta-analysis, MBF reserve had high accuracy for predicting flow-limiting CAD.[231] However, in the absence of obstructive CAD, reduced MBF reserve by MCE depicts microcirculatory abnormalities. Transthoracic Doppler evaluation of the LAD artery is also used to assess coronary flow reserve (CFR) during stress hyperaemia and has prognostic value.[238,255,305,306]

In contrast, the diagnosis of VSA ideally relies on the results of provocation tests in the catheterization laboratory through selective intracoronary acetylcholine (Ach) infusion (see *Section 5.2.5.2*).

It is important to note that there is only a modest correlation between the values of MBF reserve measured by different techniques and modalities.[269,305,307]

3.3.3. Invasive tests

Invasive coronary angiography has undergone significant advancements over time. It is no longer just an angiographic technique that provides *anatomical* information about the presence of coronary atherosclerosis and luminal obstructions of the epicardial coronary arteries. It can also determine the *functional* consequences of these obstructions on coronary blood flow [FFR and instantaneous wave-free ratio (iFR)] by direct measurement of the coronary BP[49,308–311] or by calculating the coronary pressure drop across a stenosis based on two or more angiographic projections.[312] Furthermore, new technologies allow measurement of CFR and microvascular resistance, and protocols have been introduced for testing the presence of coronary vasospasm.[36,39]

3.3.3.1. Invasive coronary angiography

Invasive coronary angiography with available coronary pressure assessment[49,308–311,313] is indicated in patients with a very high (>85%) clinical likelihood of obstructive CAD,[1] in particular those with severe symptoms refractory to antianginal treatment, or characteristic angina or dyspnoea at a low level of exercise[1,47] or left ventricle dysfunction suggesting extensive obstructive CAD.[47,182,314,315]

Invasive coronary angiography/coronary pressure assessment is also indicated if non-invasive assessment suggests high event risk—e.g. CCTA shows ≥50% left main stenosis, or ≥70% proximal LAD stenosis with single or two-vessel CAD, or ≥70% proximal three-vessel CAD[56,182,316,317]—or when any stress test shows moderate to severe inducible ischaemia[316] or when symptoms are highly suggestive for obstructive CAD. In all the above situations, ICA/coronary pressure assessment is performed for additional risk stratification[318–320] and to determine a potential revascularization approach (see *Section 4.4*).[49,308,309,313]

Invasive coronary angiography/coronary pressure assessment may also be indicated to confirm or exclude the diagnosis of obstructive CAD in patients with uncertain results on non-invasive testing.[316]

Given the frequent mismatch between the angiographic and haemodynamic severities of coronary stenoses, coronary pressure assessment should be readily available to complement ICA investigation for clinical decision-making.[321–326]

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In patients with suspected ANOCA/INOCA and an ICA/coronary pressure assessment disclosing no significant epicardial CAD, additional invasive investigations including index of microcirculatory resistance (IMR), CFR and, if necessary, invasive vasoreactivity testing using Ach (or ergonovine)[36] as part of a complete 'invasive coronary functional testing' (ICFT) can be performed.

Performing ICA is not exempt from potential complications. Given that femoral diagnostic catheterization has been associated with a 0.5%–2.0% composite rate of major complications, mainly bleeding requiring blood transfusions,[327] radial access is now the standard access when possible. Radial access has been associated with reduced mortality and reduced major bleeding while allowing rapid ambulation.[327] Still, the composite ICA rate of death, MI, or stroke through radial access is of the order of 0.1%–0.2%.[327] The decision to perform ICA should balance benefits and risks, as well as potential therapeutic consequences, of the investigation that should be part of the process of shared clinical decision-making. Patients should be adequately informed of these aspects ahead of the procedure.

Recommendation Table 11 — Recommendations for invasive coronary angiography in the diagnostic management of individuals with suspected chronic coronary syndrome (see also Evidence Table 11)

Recommendations	Class[a]	Level[b]
When ICA is indicated, radial artery access is recommended as the preferred access site.[327–330]	I	A
When ICA is indicated, it is recommended to have coronary pressure assessment available and to use it to evaluate the functional severity of intermediate non-left main stem stenoses[c] prior to revascularization.[49,195,308,313,321,322,325,331–333]	I	A
Invasive coronary angiography is recommended to diagnose obstructive CAD in individuals with a very high (>85%) clinical likelihood of disease, severe symptoms refractory to guideline-directed medical therapy, angina at a low level of exercise, and/or high event risk.	I	C
In individuals with de novo symptoms highly suggestive of obstructive CAD that occur at a low level of exercise, ICA with a view towards revascularization is recommended as first diagnostic test after clinical assessment by a cardiologist.	I	C
When ICA is indicated, measurement of FFR/iFR should be considered to evaluate the functional severity of intermediate left main stem stenoses[c] prior to revascularization.[331,334,335]	IIa	A
When ICA is indicated, IVUS should be considered to evaluate the severity of intermediate stenoses of left main stem[c] prior to revascularization.[336,337]	IIa	B

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CAD, coronary artery disease; FFR, fractional flow reserve; ICA, invasive coronary angiography; iFR, instantaneous wave-free ratio; IVUS, intravascular ultrasound.
[a]Class of recommendation.
[b]Level of evidence.
[c]Typically 40%–90% for non–left main stem stenoses and 40%–70% for left main stem stenoses by visual estimate. For ICA in the diagnostic management of individuals with suspected ANOCA/INOCA, see *Section 5.3.* (Specific groups).

3.3.3.2. Functional assessment of epicardial stenosis severity to guide coronary revascularization

When non-invasive stress tests are inconclusive or not performed, identifying the artery responsible for ischaemia during ICA can be challenging, especially in cases with multivessel CAD or coronary stenoses of intermediate severity (typically around 40%–90% for non-left main stem stenoses or 40%–70% for left main stem stenoses by visual estimate). In such cases, recording wire-based intracoronary pressure during maximal hyperaemia to calculate FFR or at rest to measure iFR is recommended to improve risk assessment and clinical decision-making and to reduce clinical events.[318–320] This has been confirmed by large clinical outcome studies such as FAME 1,[308] FAME 2,[49] DEFINE-FLAIR (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation),[310] iFR-SWEDEHEART (Instantaneous Wave-free Ratio versus Fractional Flow Reserve in Patients with Stable Angina Pectoris or Acute Coronary Syndrome),[311] R3F (French FFR Registry),[313] and RIPCORD (Routine Pressure Wire Assessment Influence Management Strategy at Coronary Angiography for Diagnosis of Chest Pain trial).[309] Haemodynamic relevance, as defined by FFR of ≤0.80, or iFR of ≤0.89, correlates poorly with diameter stenosis by visual assessment. In the PRIME-FFR [Insights From the POST-IT (Portuguese Study on the Evaluation of FFR-Guided Treatment of Coronary Disease) and R3F Integrated Multicenter Registries—Implementation of FFR (Fractional Flow Reserve) in Routine Practice][322] and FAME (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) study,[195] 31% of the 40%–49% stenoses were haemodynamically significant while only 35% of the 50%–70% stenoses were haemodynamically relevant, and of the 71%–90% stenoses, 20% were not. Only an estimated diameter stenosis of >90% predicted haemodynamic relevance with high accuracy (96% correct classification). The discordance between angiographical and functional assessment of coronary stenosis severity varies with age, presence of CMD and lesion-specific factors.[338,339] Lesions in the left main or proximal LAD are more likely to result in a significant FFR, as they supply a larger myocardial mass than those in smaller arteries. As a result, the optimal angiographic cut-off value for functionally non-significant stenosis is 43% for the left main and 55% for small vessels.[339] This implies that the threshold for functional assessment for larger arteries should be set at 40% diameter stenosis.

Large management studies showed that integration of FFR to ICA is associated with treatment reclassification in 30%–50% of cases in the R3F, POST-IT, RIPCORD, and DEFINE-REAL studies.[309,313,340,341] Subsequently, many other non-hyperaemic pressure parameters were introduced [distal coronary pressure to aortic pressure ratio (Pd/Pa), diastolic pressure ratio (dPR), relative flow reserve (RFR)], with good correlation with FFR or iFR, but without available clinical outcome data. It is interesting to note that both separate and pooled analyses of the patients included in those studies reveal that 'FFR/iFR-based reclassification' does not have any significant effect on the number of patients recommended for revascularization.[342]

Meta-analyses of the 5-year outcome of patients managed with iFR and FFR as part of the randomized DEFINE-FLAIR and DEFINE-SWEDEHEART studies have reported a 2% absolute increase in all-cause mortality in those managed with iFR.[343,344] This was not associated with any unplanned revascularization or non-fatal MI rate increase.[343,344] Although it was initially hypothesized that this mortality excess could be related to a higher proportion of 'inappropriate' revascularization deferral with iFR compared with FFR (50% vs. 45%),[343] it is reassuring that iFR-based deferral is as safe as FFR-based deferral up to 5 years.[345]

In patients with multivessel CAD, systematic FFR measurement of all epicardial vessels has been proposed to select appropriate therapy, but

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recent studies (RIPCORD2 and FUTURE) did not demonstrate any clinical outcome improvement compared with angiography alone.[346,347] Therefore, intracoronary pressure measurement in patients with multivessel CAD should only be performed on intermediate lesions.

Several recent studies using either FFR or iFR suggest that the pattern of pressure drop along the coronary artery (focal vs. progressive) recorded during a pullback is important to select patients who will benefit more from PCI.[2,348–352] Longitudinal functional vessel interrogation can therefore be helpful in patients with serial lesions or diffuse CAD.

New 3D angiographically derived wireless coronary pressure parameters, such as quantitative flow ratio (QFR) or vessel fractional flow reserve (vFFR), are at different stages of clinical investigation[325,353,354] (NCT03729739) and have important features that may help to increase the use of coronary pressure measurement during ICA significantly. These technologies have indeed the unique advantage of providing both distal coronary pressure measures and a coronary pressure map along the coronary vessel without requiring the use of any pressure wire. The lack of benefits shown in some recent FFR trials demonstrates that it is not sufficient to validate such new coronary pressure indexes against FFR alone to demonstrate their clinical value, and it is important to also show benefit in a direct comparative trial vs. angiography. In that context, the results of the FAVOR III China study[355] are important, demonstrating an improved clinical outcome in the QFR-guided group compared with the angiography-guided group, driven by fewer MIs and ischaemia-driven revascularizations.

The combined measurements of pressure and flow (measured by Doppler or thermodilution) may further reduce the number of interventions. Patients with lesions and concordant normal FFR and CFR have an excellent prognosis. Patients with lesions and discordant results between FFR and CFR have a similar prognosis to that of patients with lesions and concordant abnormal FFR and CFR, treated with PCI. Lesions with an abnormal FFR but normal CFR pertain to a good clinical outcome up to 5 years of follow-up if left untreated.[356–358] Moreover, hyperaemic stenosis resistance (HSR), by measuring the pressure gradient across a lesion divided by flow, is an excellent index for both diagnostic and prognostic purposes.[359,360] The recently introduced continuous thermodilution technique for measuring absolute coronary flow presents an alternative method for determining CFR. Additionally, this method allows for evaluation of the microvascular resistance reserve (MRR), a novel index for assessing coronary microvascular function.[361–364]

Coronary flow capacity (CFC) integrates hyperaemic flow and CFR and is useful for both diagnostic purposes as well as the evaluation of the result after PCI.[365–368]

Intravascular imaging techniques [e.g. intravascular ultrasound (IVUS) or optical coherence tomography (OCT)] have demonstrated good diagnostic accuracy in predicting FFR, especially in stenoses located in the left main stem.[369,370] They are reasonable options to assess left main stenosis severity and prognosis; increasing left main plaque burden was associated with long-term all-cause and cardiac mortality in patients not undergoing revascularization.[371]

While coronary pressure thresholds, specifically 0.80 for FFR and 0.89 for iFR, are crucial in aiding clinical decision-making, particularly in the case of deferring revascularization when FFR/iFR exceeds the ischaemic threshold,[310,372] they must be considered alongside other parameters. These include a careful assessment of the patient's symptoms and the results of non-invasive stress testing to determine the need for revascularization.

Recommendation Table 12 — Recommendations for functional assessment of epicardial artery stenosis severity during invasive coronary angiography to guide revascularization (see also Evidence Table 12)

Recommendations	Class[a]	Level[b]
During ICA, selective assessment of functional severity of intermediate[c] diameter stenoses is recommended to guide the decision to revascularize, using the following techniques:		
• FFR/iFR (significant ≤0.8 or ≤0.89, respectively);[49,308,310,311,313,321–323,332,373]	I	A
• QFR (significant ≤0.8).[325,355,374,375]	I	B
In addition:		
• CFR/HSR/CFC should be considered as a complementary investigation;[359,360,366–368,376]	IIa	B
• resting invasive measurement of Pd/Pa, dPR, RFR, or angiography-derived vessel FFR may be considered as alternative parameters.[353,377]	IIb	C
Systematic and routine wire-based coronary pressure assessment of all coronary vessels is not recommended.[346,347]	III	A

CFC, coronary flow capacity; CFR, coronary flow reserve; dPR, diastolic pressure ratio; FFR, fractional flow reserve; HSR, hyperaemic stenosis resistance; ICA, invasive coronary angiography; iFR, instantaneous wave-free ratio; Pd/Pa, distal coronary pressure to aortic pressure ratio; QFR, quantitative flow ratio; RFR, relative flow reserve.
[a]Class of recommendation.
[b]Level of evidence.
[c]Typically around 40%–90% for non-left main stem or 40%–70% for left main stem by visual estimate.

3.3.3.3. Assessment of microvascular dysfunction

Detailed discussion of microvascular dysfunction by invasive coronary functional testing is provided in *Section 5.2.5.2*. After nitroglycerine, adenosine is administered to assess endothelium-independent vasodilation [CFR, IMR, and hyperaemic myocardial velocity resistance (HMR)]. Coronary flow reserve can be calculated using bolus thermodilution (as baseline transit time divided by hyperaemic transit time) or continuous thermodilution (as the ratio of hyperaemic and resting absolute coronary flow), or Doppler flow velocity (hyperaemic flow velocity divided by baseline flow velocity).[307,378,379] The IMR is calculated as the product of distal coronary pressure at maximal hyperaemia multiplied by the hyperaemic mean transit time. Increased IMR (≥25 U) indicates microvascular dysfunction.[380,381] It is important to note that continuous thermodilution-derived measurements have shown higher reproducibility than similar measurements derived from bolus thermodilution.[382]

Angiography-derived index of coronary microcirculatory resistance (angio-IMR) allows microcirculation assessment without using intracoronary wires.[383]

3.3.3.4. Testing for coronary vasospasm

Vasoreactivity testing explores endothelium-dependent mechanisms of CMD and epicardial and microvascular vasomotor tone disorders.[36,73,384]

The most established approach for coronary vasoreactivity testing is by intracoronary infusion of Ach, although other substances like ergonovine have been proposed.[384,385] The methodology is described in detail in *Section 5.2.5.2.2*.

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3.3.4. Diagnostic algorithm and selection of appropriate tests

After estimation of the pre-test likelihood of obstructive epicardial CAD based on the RF-CL model (*Figure 4* and *Figure 5*),[139] further diagnostic testing is dependent on the clinical scenario, general condition, QoL, presence of comorbidities, local availability and expertise for different diagnostic techniques, and importantly patient expectations and preferences (*Figure 6*; *Table 6*).

In patients with severe comorbidities or severe frailty or very low QoL that all contribute to a limited life expectancy, in whom revascularization is judged to be futile, the diagnosis of CCS can be made clinically, and managed with medical therapy and lifestyle changes alone. If CCS diagnosis is uncertain in such patients, establishing a diagnosis using non-invasive functional imaging for myocardial ischaemia before treatment is reasonable.

Individual adjustment of the clinical likelihood should always be considered based on the clinical CCS scenario including ECG and echocardiography findings (*Figure 5*, *Section 2*). Further diagnostic testing can be deferred in patients with a very low (≤5%) likelihood of obstructive CAD. Based on the CACS-CL model, in patients with a low (>5%–15%) likelihood of obstructive CAD, CACS can be considered to re-estimate the likelihood of obstructive CAD.[139,165,141,154] Further diagnostic testing can also be deferred in patients reclassified based on CACS from a low to a very low (<5%) likelihood of

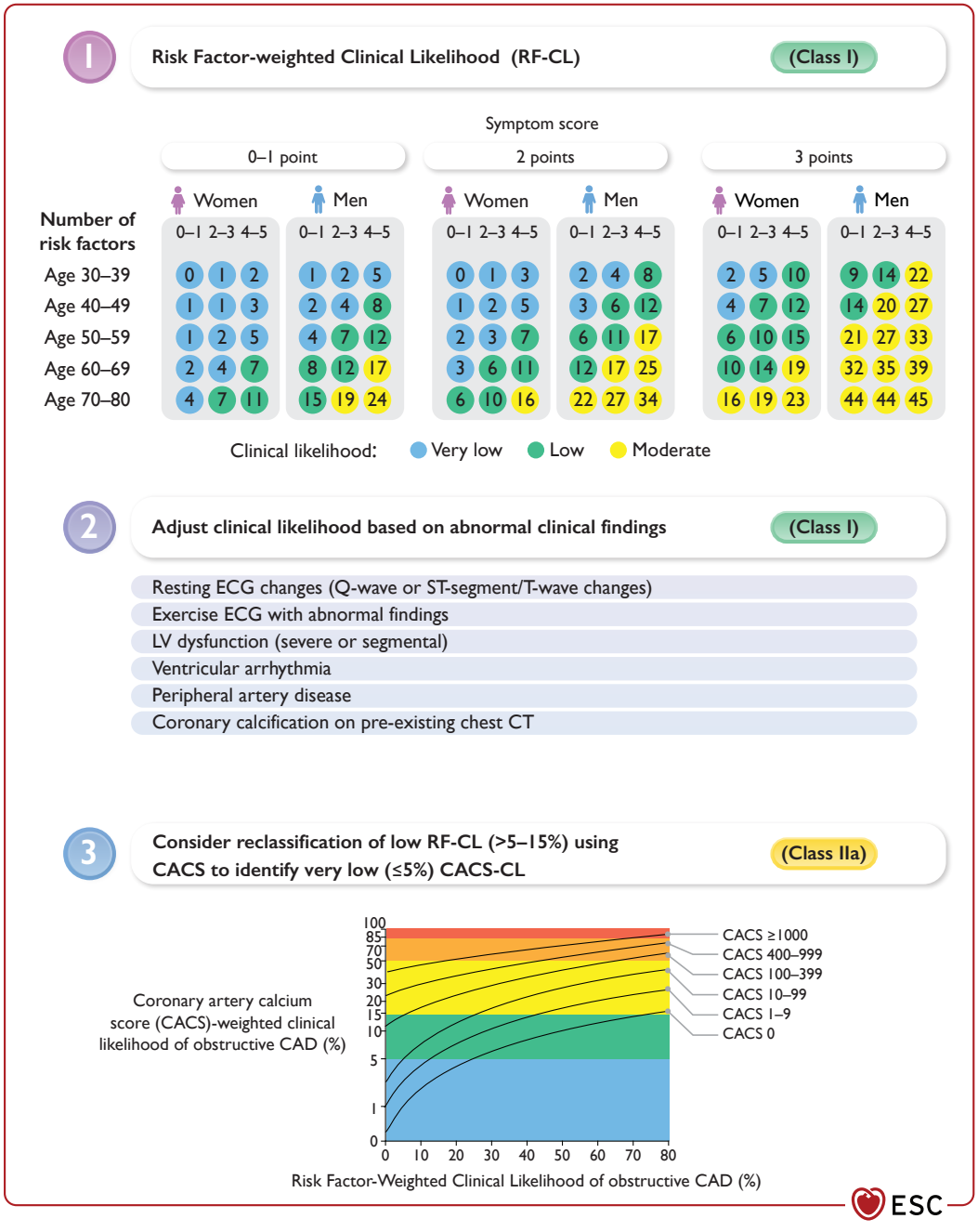

Figure 5 Adjustment and reclassification of the estimated clinical likelihood of obstructive coronary artery disease. CACS, coronary artery calcium score; CACS-CL, coronary artery calcium score + RF-CL model; CAD, coronary artery disease; CT, computed tomography; ECG, electrocardiogram; LV, left ventricular; RF-CL, risk factor-weighted clinical likelihood.

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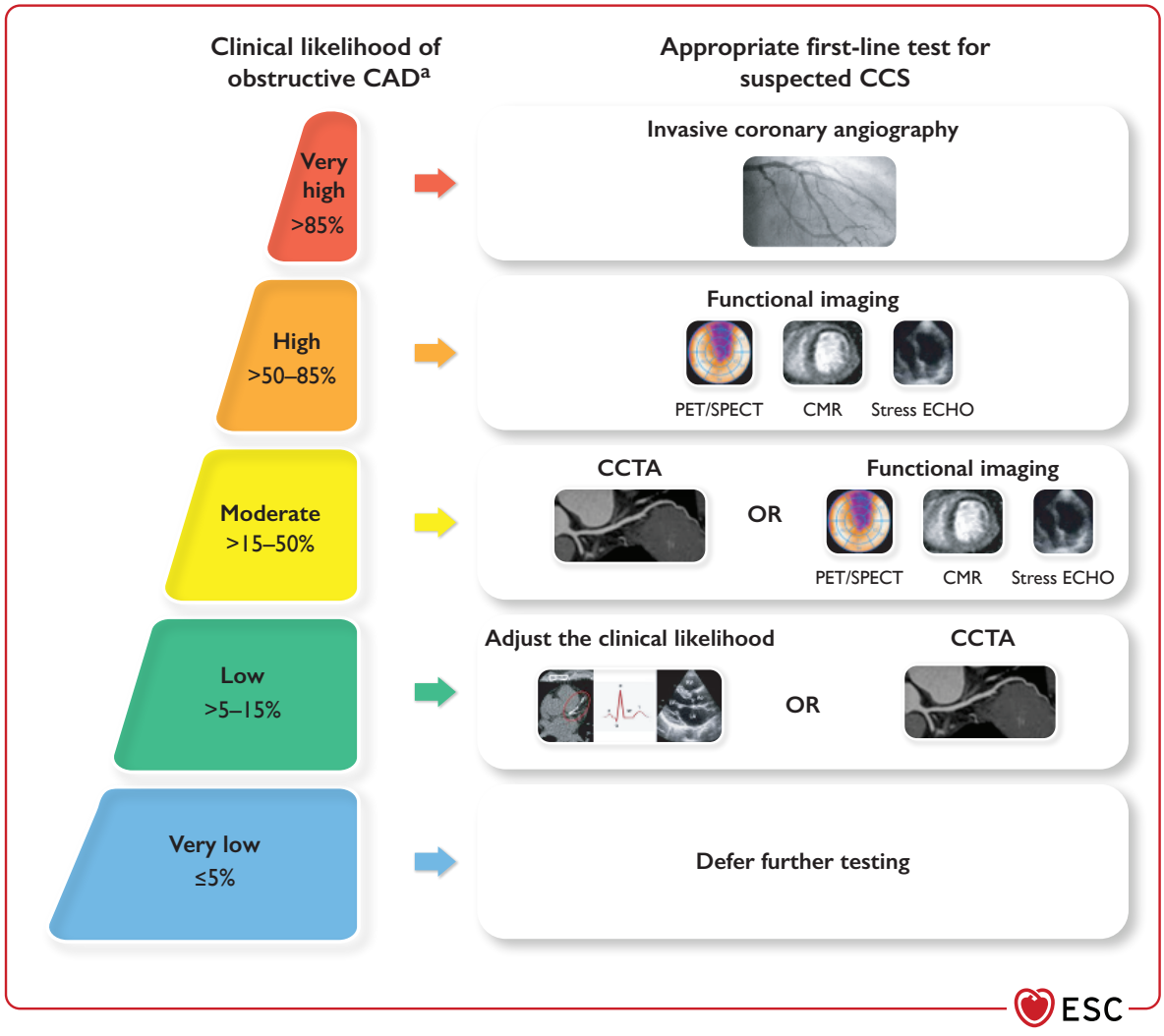

Figure 6 Appropriate first-line testing in symptomatic individuals with suspected chronic coronary syndrome. CAD, coronary artery disease; CACS-CL, coronary artery calcium score + RF-CL model; CCS, chronic coronary syndrome; CCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance; ECHO, echocardiography; PET, positron emission tomography; RF-CL, risk factor-weighted clinical likelihood; SPECT, single-photon emission computed tomography. [a]The clinical likelihood of obstructive CAD should be estimated based on the RF-CL model (*Figure 4*). Individual adjustment of the RF-CL values is in some cases needed based on abnormal clinical finding (*Figure 5*) or highly suspicious symptoms. Beyond the CACS-CL no methods are validated to give accurate adjusted values to the RF-CL and the adjusted values is therefore based on clinical judgment.

obstructive CAD (*Figure 5*).[143] Conversely, if CACS is high and there are clinical findings indicating that the RF-CL model may be underestimating the likelihood of obstructive CAD, further diagnostic testing should be selected based on the adjusted clinical likelihood and coronary calcium burden. It is important to note that patients with a very low and low (≤15%) likelihood of obstructive CAD constitute approximately 85% of individuals with *de novo* symptoms suspected of CCS.[27,30,139] Most can be treated conservatively without the need for further testing as they have no stenoses or non-obstructive CAD with a very low incidence of events during long-term follow-up.[27,139,143]

Individuals with a moderate or high (>15%–85%) likelihood of obstructive CAD should be referred for non-invasive anatomical or functional imaging to establish the diagnosis and assess the risk for future cardiac events. There is growing support for using CCTA as a first-line test in the group with a low or moderate (15%–50%) likelihood.[27,31,32,139,386] Given the low prevalence of CAD in this group of patients and its high negative predictive value, CCTA is the most effective diagnostic method to rule out obstructive CAD. Moreover, besides its strength in ruling out CAD, CCTA offers direct visualization of non-obstructive CAD, which may trigger intensification of preventive measures. The use of CCTA as a first-line test is supported by large, randomized trials showing equivalence in health outcomes with functional testing[33] and even superiority compared with usual care using exercise ECG.[34]

In patients with a very high (≥85%) clinical likelihood of obstructive CAD, symptoms unresponsive to medical therapy, or angina at a low level of exercise, and an initial clinical evaluation (including echocardiogram and, in selected patients, exercise ECG) that indicates a high event risk, proceeding directly to ICA without further diagnostic testing is a reasonable option. Under such circumstances, the indication for revascularization of stenoses with a diameter reduction of <90% should be guided by coronary pressure assessment (*Figure 6*; *Table 6*).

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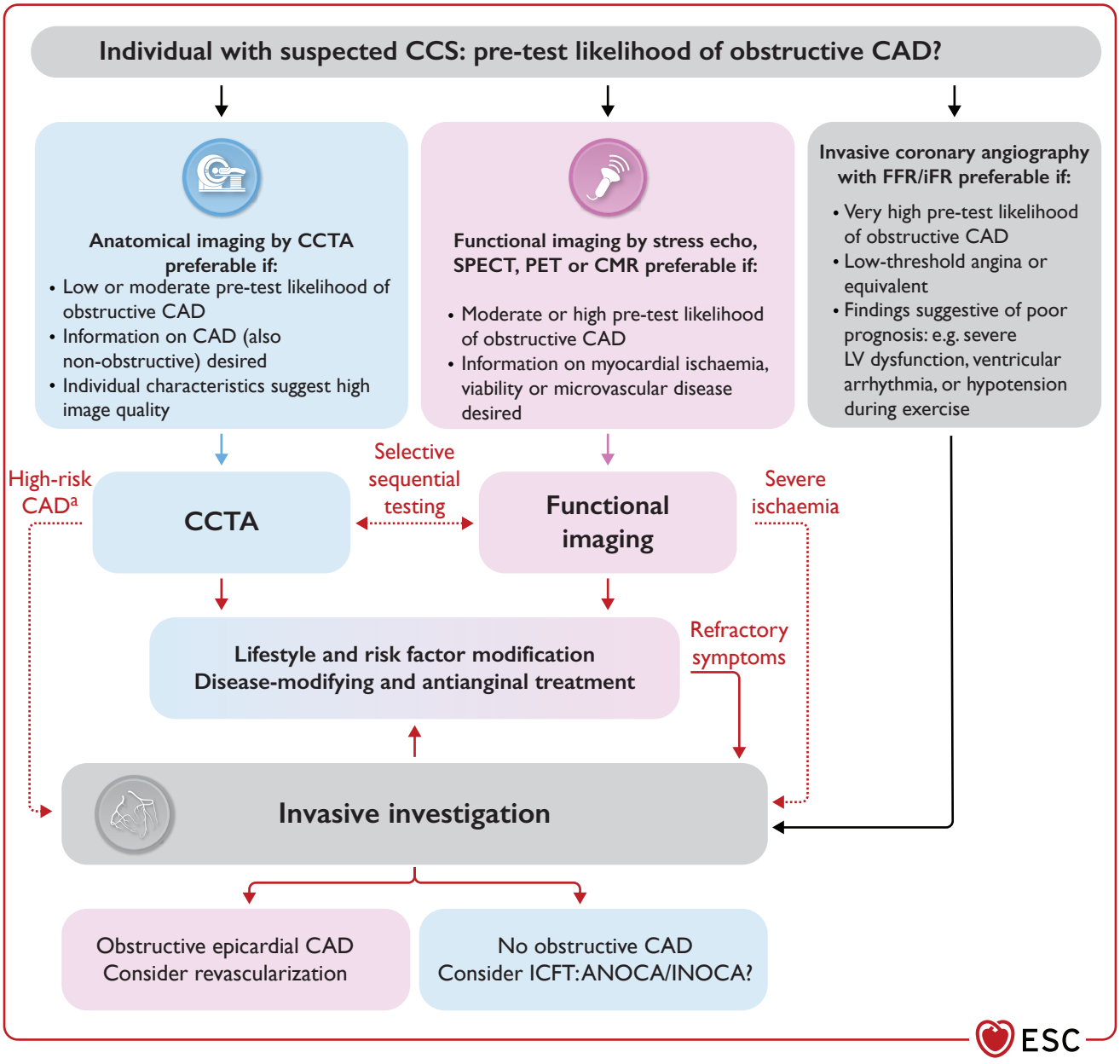

Figure 7 Initial management of symptomatic individuals with suspected chronic coronary syndrome. ANOCA, angina with non-obstructive coronary arteries; CAD, coronary artery disease; CCS, chronic coronary syndrome; CCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance; Echo, echocardiography; FFR, fractional flow reserve; ICFT, invasive coronary functional testing; iFR, instantaneous wave-free ratio; INOCA, ischaemia with non-obstructed coronary arteries; LV, left ventricular; PET, positron emission tomography; SPECT, single-photon emission computed tomography. Consider local availability and expertise, and individual characteristics when choosing non-invasive testing. *Table 6* offers tips for selecting the first-line test in people with suspected CCS. [a]High–risk CAD: obstructive CAD at high risk of adverse events by CCTA: ≥50% stenosis of the left main stem; three–vessel disease with severe stenoses (≥70% diameter stenosis); single- or two–vessel disease including the proximal LAD with severe stenoses. Consider functional imaging or invasive investigation.

Functional imaging should be selected as a first line test if information on myocardial ischaemia, viability, or microvascular disease is desired. Tests for detecting ischaemia have better rule-in power compared with CCTA and therefore should be selected if there is a moderate-high (>15-85%) likelihood of obstructive CAD. Moreover, functional imaging tests overcome the limitations of CCTA in certain groups (older patients with more extensive coronary calcifications, AF, and other situations with an irregular or fast heart rate, renal insufficiency, or iodinated contrast allergy), and avoid exposure to ionizing radiation in young individuals and in those suspected of ANOCA/INOCA (*Figure 7*).

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Table 6 Overview of non-invasive tests used for first-line testing in individuals with suspected chronic coronary syndrome

	Main imaging target(s) in CCS	Requirements	Limitations
Anatomical imaging			
CCTA	Atherosclerosis (obstructive and non-obstructive) in epicardial coronary arteries	Iodinated contrast Radiation Premedication: • Beta-blockers or ivabradine for heart rate control • Nitroglycerine for adequate vasodilation	Severely impaired kidney function[a] Documented allergy to iodinated contrast Tachyarrhythmia refractory to beta-blockade Irradiation (especially young women)
SPECT/CT **PET/CT**	Atherosclerosis coronary artery calcium score	Radiation	Irradiation (especially young women)
Functional imaging			
Stress Echo	LVEF and volumes		Poor Echo windows
	Wall motion abnormalities Myocardial perfusion Coronary velocity flow reserve	Performed with exercise, dobutamine and vasodilators Echo contrast to improve image quality and assess perfusion	Poor Echo windows Contraindications to stressor
CMR	LVEF and volumes		Non-CMR-compatible metal devices Severe claustrophobia
	MI (scar)	Paramagnetic contrast	Non-CMR-compatible metal devices Severe claustrophobia Haemodialysis
	Ischaemia/blood flow	Vasodilator stress + paramagnetic contrast	Non-CMR-compatible metal devices Severe claustrophobia Contraindications to stressor Haemodialysis
	Wall motion abnormalities	Inotropic stress (dobutamine)	Non-CMR-compatible metal devices Severe claustrophobia Contraindication to stressor
SPECT	LVEF and volumes Ischaemia/viability	Vasodilator or exercise stress Radioactive tracer	Contraindication to stressor Irradiation (especially young women)
PET	LVEF Ischaemia/blood flow Viability	Vasodilator stress Radioactive tracer (^{13}N-ammonia, ^{15}O-water, ^{82}Rb)	Contraindication to stressor Irradiation (especially young women)

CCS, chronic coronary syndrome; CCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance; CT, computed tomography; Echo, echocardiography; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PET, positron emission tomography; SPECT, single-photon emission computed tomography.
[a]Preventive measures are recommended for patients with eGFR <30 mL/min/1.73 m^2.[389]

The discussion about which modality to use as a first-line test has been heavily focused on the detection of obstructive epicardial stenoses, neglecting the relatively high prevalence of non-obstructive coronary disease and ANOCA/INOCA, especially in female patients. The current rationale behind choosing a first-line test should be to assess the anatomical severity and functional consequences of coronary disease, whether obstructive or not. In this regard, PET-CT should be more frequently considered and its availability increased as it combines calcium scoring with accurate operator-independent detection of myocardial ischaemia and CMD with a low irradiation dose.[45]

Individuals in the moderate likelihood group, except older men with all three CCS symptom characteristics, will have a likelihood of obstructive CAD around 20%. In these, anatomical and functional testing will each result in an intermediate positive predictive value with eventually many false positives, especially with CCTA easily overestimating stenosis severity. Sequential testing (i.e. functional testing after CCTA, or vice versa) will therefore be needed in many individuals to establish an accurate diagnosis of obstructive, ischaemia-inducing CAD (*Figure 8*). Sequential or combined anatomical and functional testing is also useful for the non-invasive diagnosis of ANOCA/INOCA.[41] Moreover, combined testing, e.g. combining CCTA and PET, may result in improved prognostication of CCS patients.[387]

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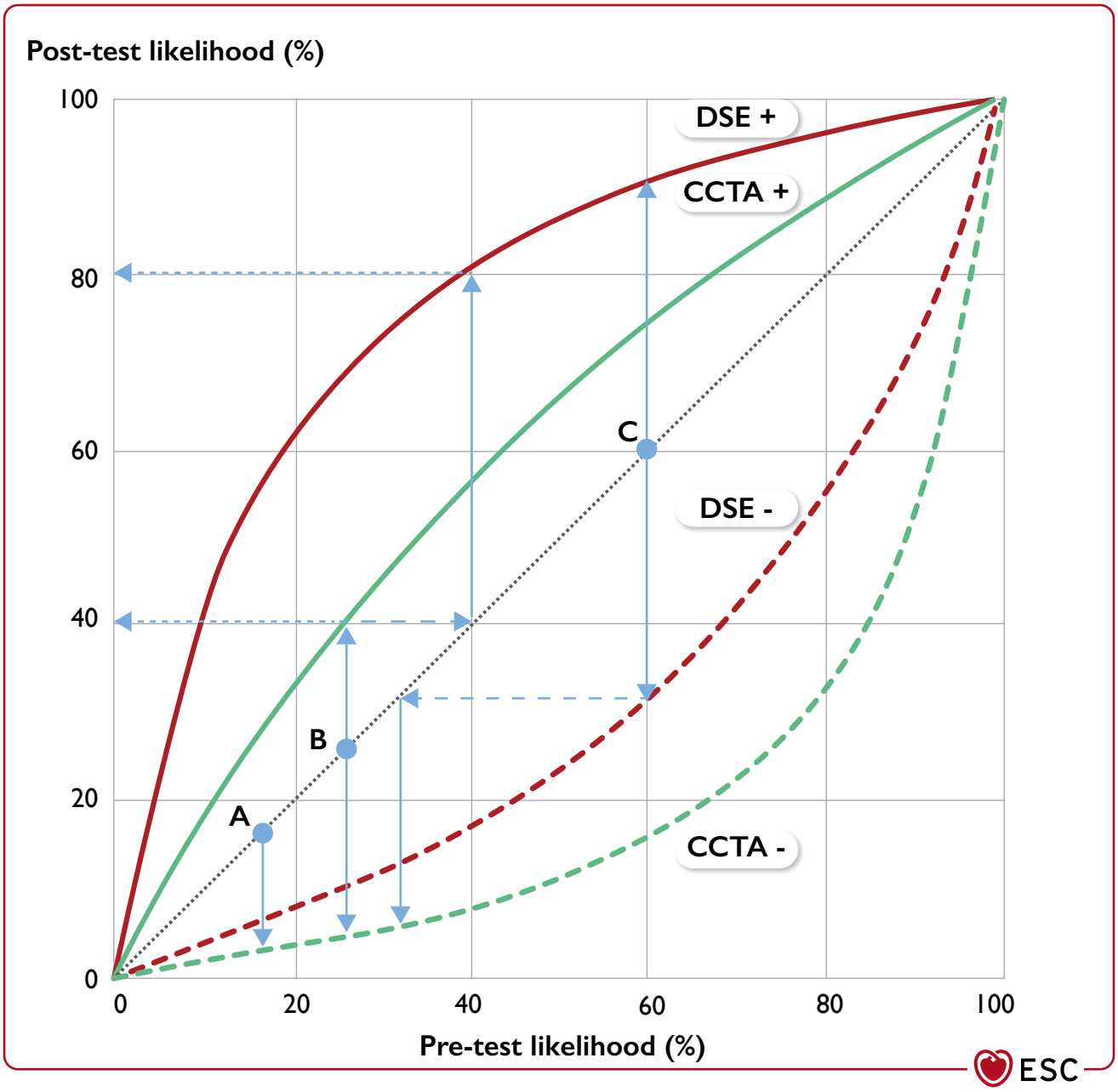

Figure 8 Ruling in and ruling out functionally significant obstructive coronary artery disease by sequential anatomical (coronary computed tomography angiography) and functional (dobutamine stress echocardiography) testing.[a] CAD, coronary artery disease; CCTA, coronary computed tomography angiography; DSE; dobutamine stress echocardiography; ECG, electrocardiogram; FFR, fractional flow reserve. The curves display the post-test likelihood of obstructive CAD for a positive (+) and a negative (–) test result for CCTA and DSE, as the pre-test likelihood of obstructive CAD increases. The post-test likelihoods were calculated using the likelihood ratios taken from recent meta-analyses.[148,388] [a]Based on invasive FFR measurement or diameter stenosis of ≥70%.

- A 70-year-old woman with four coronary risk factors and exertional dyspnoea has a pre-test likelihood of 16% (A). A normal CCTA almost completely rules out obstructive CAD with a very low negative post-test likelihood (2%).
- A 55-year-old man with two coronary risk factors and all three anginal symptom characteristics has a pre-test likelihood of 27% (B). An abnormal CCTA brings the post-test likelihood to 40%, insufficient to rule in obstructive CAD. Sequential testing with DSE performed after CCTA brings the post-test likelihood to 82%. A normal CCTA effectively rules out obstructive CAD.
- A 69-year-old man with four coronary risk factors and all three anginal symptom characteristics has an adjusted pre-test likelihood of 60% (C) (adjustment based on abnormalities on the resting ECG and on symptoms during exercise). A positive DSE alone has a high post-test likelihood (± 90%). A negative DSE is associated with a 32% post-test likelihood. Sequential testing by CCTA would allow ruling out obstructive CAD (<5% post-test likelihood).

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Recommendation Table 13 — Recommendations for selection of initial diagnostic tests in individuals with suspected chronic coronary syndrome (see also Evidence Table 13)

Recommendations	Class[a]	Level[b]
Selection of non-invasive testing		
It is recommended to select the initial non-invasive diagnostic test based on pre-test likelihood of obstructive CAD, other patient characteristics that influence the performance of non-invasive tests,[c] and local expertise and availability.[29,148]	I	C
In symptomatic patients in whom the pre-test likelihood of obstructive CAD by clinical assessment is >5%, CCTA or non-invasive functional imaging for myocardial ischaemia is recommended as the initial diagnostic test.[33,148,178,187,189,211,212,219,222,390]	I	B
To rule out obstructive CAD in individuals with low or moderate (>5%–50%) pre-test likelihood, CCTA is recommended as the preferred diagnostic modality.[29,148]	I	B
CCTA is recommended in individuals with low or moderate (>5%–50%) pre-test likelihood of obstructive CAD if functional imaging for myocardial ischaemia is not diagnostic.[391]	I	B
Functional imaging for myocardial ischaemia is recommended if CCTA has shown CAD of uncertain functional significance or is not diagnostic.[392–394]	I	B
In patients with a known intermediate coronary artery stenosis[d] in a proximal or mid coronary segment on CCTA, CT-based FFR may be considered.[395–401]	IIb	B
Subsequent invasive testing		
Invasive coronary angiography with the availability of invasive functional assessments is recommended to confirm or exclude the diagnosis of obstructive CAD or ANOCA/INOCA in individuals with an uncertain diagnosis on non-invasive testing.[36,49,308,384]	I	B

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ANOCA, angina with non-obstructive coronary arteries; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CT, computed tomography; FFR, fractional flow reserve; INOCA, ischaemia with non-obstructive coronary arteries.
[a]Class of recommendation.
[b]Level of evidence.
[c]Characteristics determining ability to exercise, likelihood of good image quality, expected radiation exposure, and risks or contraindications.
[d]Typically around 40%–90% by visual estimate.

After confirmation of diagnosis with the first line of testing, all patients should receive lifestyle and risk-factor modification recommendations, and disease-modifying and antianginal therapy should be prescribed. The ISCHEMIA trial (Initial Invasive or Conservative Strategy for Stable Coronary Disease)[47] showed that an early revascularization strategy did not yield a short-term survival benefit in patients without left main disease nor reduced LVEF and with moderate-severe ischaemia at non-invasive testing, suggesting that most such patients should initially be treated conservatively with optimized GDMT. Patients can be referred for ICA if CCTA detects a ≥50% stenosis of the left main stem, three-vessel or two-vessel disease including the proximal LAD artery with ≥70% stenosis, or if functional imaging shows moderate or severe ischaemia encompassing an extensive perfusion territory.

For patients with obstructive CAD and refractory symptoms despite optimized GDMT, a referral for ICA may be considered to improve symptoms through revascularization. Optimization of medical therapy by combining two or more antianginal drugs can safely be obtained over 6 weeks in almost all patients and should be awaited before referral to ICA.[402,403] It is worth noting that in the Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina (ORBITA) trial, PCI did not provide short-term advantages compared with GDMT in terms of reducing anginal frequency or physical limitations.[402] In the CLARIFY registry, anginal symptoms resolved in many CCS patients over time without requiring revascularization or changes in antianginal therapy.[404]

Combined anatomical and functional imaging before ICA facilitates its planning by orientating the invasive cardiologist to perform, in the same session, haemodynamic assessment of coronary stenoses and ICFT to detect microvascular disease or vasospasm in individuals suspected of ANOCA/INOCA, performing these tests in a single session rather than in staged procedures.

3.3.5. Adverse-event risk assessment

Chronic coronary syndromes can be complicated by cardiovascular death, ischaemic and haemorrhagic events, HF, arrhythmic events, the development of valvular heart disease, and other comorbidities, which are further discussed in the Supplementary data, available at *European Heart Journal* online. It is recommended that all patients with newly diagnosed obstructive CAD or myocardial ischaemia undergo an adverse-risk event assessment to identify those at high risk of adverse outcomes who could benefit from revascularization beyond symptom relief. Based on large registries and historical RCTs, a high event risk has been defined as a cardiac mortality rate of >3% per year, intermediate event risk as between ≥1% and ≤3% per year, and low event risk as <1% per year.[405]

Adverse-event risk stratification is usually based on the same clinical, non-invasive and invasive investigations used to diagnose obstructive CAD (see *Table 14*).

Clinical history, physical examination, 12-lead ECG and laboratory tests can provide important prognostic information. Assessment of risk factors such as advanced age, diabetes mellitus (DM), or renal failure allows the identification of patients at high risk of events.[406–408] Left ventricular function is the strongest predictor of long-term survival; a patient with an LVEF of <50% is already at high risk for all-cause and cardiovascular death.[409,410]

Although the diagnostic value of an exercise ECG is limited, the occurrence of ST-segment depression at a low workload combined with exertional symptoms (angina or dyspnoea), low exercise capacity, complex ventricular ectopy, or other arrhythmias and abnormal BP response are markers of a high risk of cardiac mortality.[411–414]

High plaque burden and coronary stenoses are well-known prognostic markers. The ISCHEMIA trial using a cut-off of 70% stenosis on CCTA[317] confirms the very old observations of the Coronary Artery Surgery Study[182] that the prognosis of obstructive CAD-related CCS is mainly determined by the number of >70% obstructed coronary arteries or by the presence of a left main stenosis (using for the latter a cut-off of >50% diameter stenosis on coronary angiography).[317] More recently, the classical paradigm that the severity of stenoses and the number of diseased vessels are the main determinants of prognosis has been challenged by *post hoc* analyses of the SCOT-HEART trial and other CCTA-based

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registries showing that plaque burden and presence of adverse plaque characteristics, especially low-attenuation plaque, are the strongest predictors of fatal and non-fatal MI above the classical risk factors, including stenosis severity.[210,415–417] These findings emphasize a major advantage of anatomical imaging by CCTA as an initial test in selected patients, allowing the assessment of severity and extent of obstructive CAD as well as coronary plaque characteristics.

Regarding the prognostic impact of inducible myocardial ischaemia by functional stress imaging, the evidence remains conflicting. While there are extensive data from large observational studies[315,418–425] consistently demonstrating a robust prognostic value conferred by the extent of inducible ischaemia as detected by functional imaging (e.g. ≥3/16 abnormal segments at stress echocardiography, ≥10% LV ischaemia at nuclear or magnetic resonance perfusion imaging, or decreased hyperaemic flow or flow reserve at quantitative PET imaging), *post hoc* analyses of the randomized COURAGE[426,427] and ISCHEMIA[317] trials showed that only CAD severity, but not ischaemia severity, was independently predictive of long-term mortality and MI risk. These discrepancies may be explained by selection and entry biases between registries and RCTs.[428] Registries typically report on all-comer populations with suspected CCS referred for diagnostic testing and/or revascularization, representing the real-life scenario. RCTs usually include only a very selected group of patients, and the external applicability of their findings is always open for debate. As COURAGE and ISCHEMIA selectively included only patients with functionally moderate or severe myocardial ischaemia but without any information on CAD anatomical severity, it becomes harder to demonstrate a prognostic effect of myocardial ischaemia, and the anatomical burden becomes the prominent prognostic factor. The PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial, which included patients more representative of an all-comer population, demonstrated that CCTA, mainly by detecting non-obstructive CAD, outperformed functional testing in predicting outcomes, emphasizing the prognostic significance of imaging coronary atherosclerosis beyond myocardial ischaemia.[208] However, adding the Framingham Risk Score to the functional test result improved its prognostic value, making the difference with anatomical testing insignificant. Both modalities are thus equivalent for detecting CCS symptoms and predicting outcomes when considering risk factors.

Besides imaging coronary atherosclerosis, the additional benefit of ICA is the ability to perform intracoronary pressure measurements. While FFR of ≤0.8 and iFR of ≤0.89 have been associated with a higher risk of vessel-related cardiovascular events, it is important to remember that a lower FFR/iFR reflects more profound ischaemia in the vessel territory and is associated with a progressive and proportional increase in risk.[318,319] A similar observation has been made with FFR-CT.[401] It has also been shown that for any given FFR value, a more proximal lesion is associated with more extensive ischaemia and an increased risk of a clinical event.[429] In addition, global FFR, summing the coronary pressure collected in each of the three main coronary vessel territories as a single patient-related index (normal value of global FFR = 1 + 1 + 1 = 3), can appreciate overall cardiovascular risk; patients with a borderline FFR but with a global FFR of <2.72 showed a significantly increased risk compared with higher global-FFR patients.[430,431] One of the main limitations of such a global integrative approach based on invasive coronary pressure is that it requires advancing a pressure wire in each of the three coronary arteries, which is not often performed[341] and is not recommended as a routine, based on the RIPCORD2[347] and FUTURE results.[346] Recent methods using 3-dimensional image reconstruction and computational fluid dynamics enable FFR estimation with CCTA[432] or with 'wire-less' invasive coronary angiography.[433,434] This allows a less invasive, easier and more accurate global FFR calculation, provided imaging is of sufficiently good quality.[369–371]

In summary, when assessing event risk, clinicians should choose an integrative approach, considering risk factors, comorbidities, LV dysfunction, the severity of myocardial ischaemia, the number of functionally significantly stenotic coronary arteries, and the coronary plaque burden and characteristics, as all of these are likely interrelated factors that affect overall prognosis.

Recommendation Table 14 — Recommendations for definition of high risk of adverse events (see also Evidence Table 14)

Recommendations	Class[a]	Level[b]
An initial stratification of risk of adverse events is recommended based on basic clinical assessment (e.g. age, ECG, anginal threshold, diabetes, CKD, LVEF).[406–408]	I	B
The use of one or more of the following test results is recommended to identify individuals at high risk of adverse events:[405] • exercise ECG: o Duke Treadmill Score < −10;[191] • stress SPECT or PET perfusion imaging: o area of ischaemia ≥10% of the LV myocardium;[287,315,422,423,435] • stress echocardiography: o ≥3 of 16 segments with stress-induced hypokinesia or akinesia;[435] • stress CMR: o ≥2 of 16 segments with stress perfusion defects or ≥3 dobutamine-induced dysfunctional segments;[435] • CCTA: o left main disease with ≥50% stenosis, three-vessel disease with ≥70 stenosis, or two-vessel disease with ≥70% stenosis, including the proximal LAD or[317] one-vessel disease of the proximal LAD with ≥70% stenosis and FFR-CT ≤0.8.	I	B
In individuals at high risk of adverse events (regardless of symptoms), ICA—complemented by invasive coronary pressure (FFR/iFR) when appropriate—is recommended, with the aim of refining risk stratification and improving symptoms and cardiovascular outcomes by revascularization.[318,319]	I	A

CCTA, coronary computed tomography angiography; CKD, chronic kidney disease; CMR, cardiac magnetic resonance; CT, computed tomography; ECG, electrocardiogram; FFR, fractional flow reserve; FFR-CT, CCTA-derived FFR; ICA, invasive coronary angiography; iFR, instantaneous wave-free ratio; LAD, left anterior descending; LV, left ventricular; LVEF, left ventricular ejection fraction; PET, positron emission tomography; SPECT, single-photon emission computed tomography.
[a]Class of recommendation.
[b]Level of evidence.

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3.4. STEP 4: Initial therapy

Initial therapy frequently starts during the diagnostic process. In individuals with a high suspicion of CCS, sublingual nitroglycerine is frequently prescribed to treat anginal pain symptoms. Rapid relief within 1 or 2

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min of chest discomfort after sublingual nitroglycerine increases the likelihood of CCS. Patients may be advised to refrain from strenuous physical activities before the diagnostic process is completed and should be instructed what to do if prolonged anginal chest pain indicative of acute MI arises.

Guideline-directed management and therapy are started during or after the diagnostic process is concluded. The main goals of treating CCS are to improve both QoL and life expectancy. This involves various interventions to reduce the risk of (i) cardiac mortality, (ii) non-fatal ischaemic events, (iii) progression of epicardial and/or microvascular chronic coronary disease, and (iv) symptoms and limitations caused by CCS. When deciding on treatment options, it is important to consider patient preferences, possible complications of procedures or medications, and healthcare costs. In shared decision-making with patients, clinicians should clearly explain that certain treatments can alleviate symptoms, while others can reduce the likelihood of ischaemic events.

4. Guideline-directed therapy

4.1. Patient education, lifestyle optimization for risk-factor control, and exercise therapy

4.1.1. Patient education

In CCS patients, education on risk factors and symptom management is associated with improvements in knowledge, self-care, and patient empowerment, and may improve health-related QoL.[436] In addition, education can facilitate long-term adherence to lifestyle interventions.[437,438] Educational programmes—either alone or as a core component of multidisciplinary care management programmes—promote patients' awareness of their condition and the rationale for lifestyle interventions. However, awareness of CVD risk factors through education alone might be insufficient for adoption of healthy behaviour.[439] Therefore, self-care programmes are needed to enable patients to have a major role in coping with their condition and accepting their prescribed treatment.[440,441] Elements in patient education include (modifiable) risk factors in relation to individual cardiovascular risk, since risk perception is an integral part of many major health behaviour theories, ultimately leading to modification of human habits.[441,442]

Information on benefits of risk-factor control on recurrence risk, disease progression, complications, and overall survival should be discussed. The format, time horizon, and outcome used for risk estimation influence patient perceptions and should be considered when designing risk communication tools.[443–445]

Lifelong education for patient-centred information and problem-based learning is superior to home-sent information in improving risk-factor control in the long term.[438,444] Refer to *Section 6.2.1* for further guidance on patient education.

4.1.2. Key lifestyle interventions for risk-factor control

Reducing CVD risk at the individual level begins with effective information on risk and anticipated risk reduction by treatment. Risk algorithms are available for use in clinical practice by means of interactive tools online. The use of the Smart risk score (U-prevent.com) is suggested by the European Association of Preventive Cardiology for risk estimation in patients with previous CVD.[446] Ideally, patients are made aware of their individual risks and the potential benefit of prevention treatments and then actively engaged in managing their disease. Treatment goals are communicated using a patient-centred approach (*Table 7*).

Table 7 Practical advice on lifestyle counselling and interventions

Topic	Recommendation and treatment goals in patients with established CCS
Lifestyle counselling	
Immunization	• Vaccination against influenza, pneumococcal disease and other widespread infections, e.g. COVID-19
Sleep quality	• Treat sleep-related breathing disorders
Sexual activity	• Males and females: low risk for stable patients who are not symptomatic at low-to-moderate activity levels • Males: PDE-5 inhibitors are generally safe, not to be taken in combination with nitrate medications because of risk of severe hypotension
Psychosocial aspects	• Avoid psychosocial stress • Treat depression and anxiety by psychological or pharmacological interventions
Environment/pollution	• Avoid passive smoking • Reduce environmental noise • Avoid exposure to air pollution
Lifestyle interventions for risk-factor control	
Smoking and substance abuse	• Use pharmacological and behavioural strategies to assist in smoking cessation • Avoid e-cigarettes • Abstain from substance abuse
Obesity and being overweight	• Obtain and maintain a healthy weight (BMI 18.5–25 kg/m^2) • Reduce weight through recommended energy intake and increased physical activity and through pharmacological/surgical interventions in selected patients
Hyperlipidaemia	• Ultimate LDL-C goal of <1.4 mmol/L (55 mg/dL) and a ≥50% reduction in LDL-C vs. baseline is recommended
Diabetes	• HbA1c < 7.0% (53 mmol/mol)
Arterial hypertension	• SBP 120–129 mmHg, provided the antihypertensive treatment is well tolerated
Diet and alcohol consumption	• Limit alcohol consumption to <100 g/week • Diet high in vegetables, fruit, and wholegrains (Mediterranean diet) • Limit saturated fat to <10% of total calorie intake
Physical activity and exercise	• 30–60 min moderate activity, >5 days/week • Reduce sedentary time and engage in at least light activity throughout the day

BMI, body mass index; CCS, chronic coronary syndrome; COVID-19, coronavirus disease 2019; HbA1c, glycated haemoglobin; LDL-C, low-density lipoprotein cholesterol; PDE-5, phosphodiesterase-5; SBP, systolic blood pressure.

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4.1.2.1. Smoking and substance abuse

Smoking cessation in CCS patients improves prognosis, with a reported 36% risk reduction of premature death in those who quit compared with those who continue to smoke.[447] Measures to promote smoking cessation include brief advice, counselling and behavioural interventions, and pharmacological therapy.[448,449] Patients should also avoid passive smoking.

Drug support to assist in smoking cessation should be considered in all smokers who are ready to undertake this action. Nicotine-replacement therapy, bupropion, or varenicline are effective,[450,451] and are not linked to an increase in MACE.[452]

The use of electronic cigarettes (e-cigarettes), as an alternative to conventional cigarettes, should be discouraged because they are not harm-free.[453] Newer devices deliver higher nicotine contents, and e-cigarettes emit other constituents, such as carbonyls, and fine and ultrafine particulates.[454] Evidence from several studies indicates that acute inhalation of e-cigarettes leads to negative changes in vascular endothelial function.[453,454] E-cigarettes should only be considered to aid tobacco cessation alongside a formal tobacco cessation programme.[453,455,456]

Various substances, including cocaine, opioids, and marihuana can have adverse effects on the cardiovascular system and have a potential for drug–drug interactions with cardiovascular medication.[457–459] Single-question screening for unhealthy drug use has been validated in primary care and can identify individuals requiring counselling on adverse cardiovascular effects.[460]

4.1.2.2. Weight management

In a population-based study, lifetime risk of incident CVD, and cardiovascular morbidity and mortality, were higher in those who were overweight or obese compared with those with a normal BMI (18.5–24.9 kg/m^2).[461]

Compared with normal BMI, among middle-aged men and women, competing hazard ratios (HR) for incident CVD were 1.21 [95% confidence interval (CI), 1.14–1.28] and 1.32 (95% CI, 1.24–1.40), respectively, for overweight (BMI of 25.0–29.9 kg/m^2), 1.67 (95% CI, 1.55–1.79) and 1.85 (95% CI, 1.72–1.99) for obesity (BMI of 30.0–39.9 kg/m^2), and 3.14 (95% CI, 2.48–3.97) and 2.53 (95% CI, 2.20–2.91) for morbid obesity (BMI of ≥40.0 kg/m^2). Obesity was associated with a shorter overall lifespan, and being overweight was associated with developing CVD at an earlier age.[461] In subjects with CAD, intentional weight loss is associated with a significantly lower risk of adverse clinical outcomes,[462] and has beneficial effects on risk-factor control and QoL.[463] Healthy diets with energy intake limited to the amount needed to obtain and maintain a healthy weight (BMI of 18.5–25 kg/m^2), and combined with increasing physical activity, are recommended for weight management.[16] If weight targets are not reached, pharmacological treatment with glucagon-like peptide-1 (GLP-1) receptor agonists may be considered for further weight reduction (*Section 4.3.4*). In patients without diabetes, the STEP8 trial showed a significant reduction in weight after 68 weeks with either semaglutide (mean weight change of −15.8%; 95% CI, −17.6% to −13.9%) or liraglutide (mean weight change of −6.4%; 95% CI, −8.2% to −4.6%) compared with placebo (−1.9%; 95% CI, −4.0% to 0.2%).[464] The double-blind, placebo-controlled Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity (SELECT) trial showed a significant reduction in the incidence of cardiovascular death, MI, or stroke (HR 0.80; 95% CI, 0.72–0.90) in patients with pre-existing CVD who were overweight or obese, but without diabetes, treated with weekly subcutaneous semaglutide.[465]

The SURMOUNT-1 (Efficacy and Safety of Tirzepatide Once Weekly in Participants Without Type 2 Diabetes Who Have Obesity or Are Overweight With Weight- Related Comorbidities: A Randomized, Double-Blind, Placebo-Controlled Trial) trial showed a dose-dependent weight-loss benefit (mean weight change of up to −20.9%; 95% CI, −21.8% to −19.9%) with tirzepatide, a combined glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist, compared with placebo in obese adults without diabetes over 72 weeks,[466] a dose effect that was confirmed in the SURMOUNT-2 trial.[467] Bariatric surgery in severe obesity appears to be a safe and effective intervention for further weight loss in CCS patients.[468]

Cardiac rehabilitation programmes should include weight-loss interventions to reach a healthy weight as a specific component. The incremental value of telehealth interventions and pharmacological interventions need full consideration in secondary prevention.[469]

4.1.2.3. Diet and alcohol

Dietary habits influence cardiovascular risk, mainly through risk factors such as lipids, BP, body weight, and DM. It is recommended to adopt a Mediterranean or similar diet to lower the risk of CVD, as described in the 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice.[16] If alcohol is consumed, it should be limited to <100 g/week or 15 g/day, since alcohol intake of >100 g/week is associated with higher all-cause and other CVD mortality in large individual-data meta-analyses.[470] A recent genetic analysis showed that the causal association between light-to-moderate levels of alcohol intake and lower cardiovascular risk is possibly mediated by confounding lifestyle factors, therefore questioning the previously observed cardioprotective role of light alcohol use.[471]

4.1.2.4. Mental health

Psychosocial stress, depression, and anxiety are associated with worse cardiovascular outcomes, and make it difficult for patients to make positive changes to their lifestyles or adhere to a therapeutic regimen. Therefore, assessment for psychosocial risk factors is recommended in secondary prevention.[16] Clinical trials have shown that psychological (e.g. counselling and/or cognitive behavioural therapy) and pharmacological interventions have a beneficial effect on depression, anxiety, and stress, with some evidence of a reduction in cardiac mortality and events compared with placebo (see *Section 6.1.2*).[472]

4.1.2.5. Physical activity and sedentary behaviour

Physical activity reduces the risk of many adverse health outcomes and risk factors in all ages and both sexes. There is an inverse relationship between moderate-to-vigorous physical activity and all-cause mortality, cardiovascular mortality, and atherosclerotic cardiovascular disease (ASCVD).[473] The reduction in risk continues across the full range of physical activity volumes, and the slope of risk decline is steepest for the least active individuals.[474] Adults are recommended to perform at least 150–300 min per week of moderate-intensity physical activity, or 75–150 min of vigorous-intensity physical activity, or an equivalent combination of both, spread throughout the week.[473] Additional benefits are gained with even more physical activity.[475] Practising physical activity should still be encouraged in individuals unable to meet the minimum. In sedentary individuals, a gradual increase in activity level is recommended.[476] Physical activity can be incorporated flexibly, either daily or limited to specific days. Activity patterns limited to 1–2 sessions per week but meeting recommended levels of physical activity have been shown to reduce all-cause mortality (HR 0.66; 95% CI, 0.62–0.72), CVD mortality (HR 0.60; 95% CI, 0.52–0.69), and cancer mortality (HR 0.83; 95% CI, 0.73–0.94) when compared with inactive participants.[477] Physical activity accumulated in bouts of even <10 min is associated with favourable outcomes, including mortality.[478]

High levels of time spent sedentary is associated with an increased risk for several major chronic diseases and mortality.[479] For physically

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inactive adults, light-intensity physical activity, even as little as 15 min a day, is likely to produce benefits.[479]

4.1.3. Exercise therapy

Exercise training, either alone or in the context of multidisciplinary, exercise-based cardiac rehabilitation, leads to reduction in hospitalizations, adverse cardiovascular events, mortality rates, and improved CVD risk profile in patients with ASCVD.[480–483] Therefore, exercise is a therapy that should be offered to every CCS patient in the setting of secondary disease prevention.[16]

Exercise training should be individually prescribed according to the FITT (frequency, intensity, time, type) model for aerobic and resistance training.[484]

For aerobic training (walking, jogging, cycling, swimming, etc.), an exercise frequency of at least 3 days/week, preferably 6–7 days/week, at moderate or moderate-to-high intensity is recommended. Relative intensity is determined based on an individual's maximum (peak) effort, e.g. percentage of cardiorespiratory fitness (%VO_2 max), percentage of maximum (peak) heart rate (%HRmax) or ventilatory thresholds (VT1 and VT2).[485] To date, there is insufficient evidence to promote high-intensity interval training over moderate-intensity continuous training; nevertheless, optimizing total energy expenditure (either by increasing intensity or total exercise volume) is related to greater favourable changes in cardiovascular risk and physical fitness.[486] Moderate-intensity continuous training is the most feasible and cost-effective aerobic training modality for patients with CCS. High-intensity interval training can be prescribed in selected patients for specific targets of intervention (e.g. to increase VO_2 peak).[485]

Resistance exercise in addition to aerobic training is associated with lower risks of total cardiovascular events and all-cause mortality.[16] The suggested prescription is one to three sets of 8–12 repetitions, at the intensity of 6%–80% of the individual's one-repetition maximum, at a frequency of at least 2 days per week, using a variety of 8–10 different exercises involving each major muscle group.[16,484]

Exercise is contraindicated in patients with refractory/unstable angina and other high-risk cardiovascular conditions (e.g. high-grade arrhythmias, decompensated HF, severe aortic dilatation, active thromboembolic disease). In non-cardiac unstable conditions (e.g. active infection, uncontrolled diabetes, end-stage cancer, chronic obstructive pulmonary disease exacerbation), exercise is contraindicated. Maintenance of the prescribed exercise regimen is crucial. According to a meta-regression analysis, no single exercise component predicts mortality outcomes, whereas the largest reductions in total and cardiovascular mortality were seen in post-cardiac rehabilitation patients with the highest adherence rate.[487] In addition, continuation of the exercise therapy (Phase III cardiac rehabilitation) is recommended as it will result in increased/maintained functional capacity, QoL, and physical activity levels.[488]

Sharing decision-making and offering a personalized prescription, based on the patient's preferences (self-selected training) and abilities (age, concomitant diseases, leisure and working habits, logistical restraints), is recommended to increase long-term adherence.[489] In addition, smartphone applications[490] and wearable activity trackers[491] may assist in long-term adherence to physical activity goals and exercise therapy (see *Section 6.2.1.3*).[492]

Home-based cardiac rehabilitation with or without telemonitoring may increase participation and be as effective as centre-based cardiac rehabilitation.[493] Telehealth interventions are more effective than no intervention and may also complement conventional cardiac rehabilitation.[494,495] Also, mobile device-based healthcare (mHealth) delivery through smartphones may be as effective as traditional centre-based cardiac rehabilitation, showing significant improvements in health-related QoL.[496]

Small, single-centre studies on exercise training in patients with INOCA show that it is feasible and improves cardiorespiratory function and QoL.[497] Larger trials are needed to determine the optimal rehabilitation protocols and define its long-term benefits.

Recommendation Table 15 — Recommendations for cardiovascular risk reduction, lifestyle changes, and exercise interventions in patients with established chronic coronary syndrome (see also Evidence Table 15)

Recommendations	Class[a]	Level[b]
An informed discussion on CVD risk and treatment benefits tailored to individual patient needs is recommended.[16]	I	C
Multidisciplinary behavioural approaches to help patients achieve healthy lifestyles, in addition to appropriate pharmacological management, are recommended.[484,498–503]	I	A
A multidisciplinary exercise-based programme to improve cardiovascular risk profile and reduce cardiovascular mortality is recommended.[480–482]	I	A
Aerobic physical activity of at least 150–300 min per week of moderate intensity or 75–150 min per week of vigorous intensity and reduction in sedentary time are recommended.[16,473,478,479]	I	B
Home-based cardiac rehabilitation and mobile health interventions should be considered to increase patients' long-term adherence to healthy behaviours, and to reduce hospitalizations or cardiac events.[480,493,494]	IIa	B

CVD, cardiovascular disease.
[a]Class of recommendation.
[b]Level of evidence.

4.2. Antianginal/anti-ischaemic medication

4.2.1. General strategy

In patients with CCS, antianginal medical therapy aims to control symptoms while ensuring acceptable tolerability and patient adherence. Several factors should be considered for the selection of antianginal medical therapy. First, there is no robust evidence from direct comparisons that some antianginal drugs are more effective than others for improving symptoms.[504,505] There have been no large randomized trials comparing head-to-head the historically first approved antianginal medications [i.e. beta-blockers or calcium channel blockers (CCBs)] vs. newer anti-ischaemic drugs (ivabradine, nicorandil, ranolazine, trimetazidine);[504,506] the latter have been tested in smaller trials assessing non-inferiority compared with beta-blockers[507] or CCBs,[508] or in a larger trial as add-on therapy with a background of beta-blockers and/or CCBs.[508,509] Moreover, there is no evidence that any antianginal medication may improve long-term cardiovascular outcomes, except beta-blockers if administered within 1 year after an acute MI.[510] Second, many patients require a combination of anti-ischaemic drugs to adequately control symptoms.[511] It remains unclear whether upfront combination therapy with two antianginal drugs is preferable to monotherapy, or which combinations of antianginal classes may be better

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than others for improving angina symptoms. Third, in any given patient, myocardial ischaemia and angina symptoms may be caused by various underlying pathophysiological mechanisms, alone or in combination;[6,512] these may include obstruction of epicardial coronary arteries, vasospasm, and endothelial/microvascular dysfunction. Based on their mechanisms of action, different classes of antianginal drugs may be preferable (as initial therapy or as part of combination therapy) for patients with myocardial ischaemia of predominantly obstructive, vasospastic, or microvascular origin.[513]

The current empirical paradigm for the selection of antianginal medical therapy has consisted of a hierarchical, stepwise approach including first-line (beta-blockers, CCBs) and second-line drugs (long-acting nitrates, nicorandil, ranolazine, ivabradine, trimetazidine).[1,514] This task force reinforces the concept that medical therapy for symptom control in CCS should be tailored to each patient's haemodynamic profile (BP, heart rate), comorbidities (particularly presence of HF), concomitant medications with potential drug interactions, and preferences, also taking into account the pathophysiological basis of myocardial ischaemia in each patient, as well as local availability of different drugs.[515,516] For many patients with CCS, initial drug therapy should include a beta-blocker and/or a CCB. Other antianginal drugs (long-acting nitrates, ivabradine, nicorandil, ranolazine, trimetazidine) can be added on top of a beta-blocker and/or a CCB, or as a part of initial combination therapy in appropriately selected patients (*Figure 9*).

Regardless of the initial strategy, response to initial antianginal therapy should be reassessed, and treatment should be adapted if adequate angina control is not achieved or if the initial treatment is poorly tolerated.

A review of the antianginal agents that can be used in the medical treatment of CCS can be found in the Supplementary data.

4.2.2. Beta blockers

Beta-blockers can be used for symptomatic relief of angina, or to improve prognosis in some patients with CCS. If used for antianginal purposes, the aim should be to lower resting heart rate to 55–60 beats per minute (b.p.m.).[517,518]

Beyond improving symptoms, the clinical benefit of beta-blockers in patients with CAD without prior MI and with normal LVEF is largely unknown in the absence of evidence from RCTs. The main findings of some observational studies addressing this issue are summarized in the Supplementary data.

The clinical benefit of beta-blockers in post-ACS patients with reduced LVEF is supported by solid evidence.[519–521] However, there are no large RCTs supporting the prescription of beta-blockers after uncomplicated ACS in patients with LVEF >40%.[522] The evidence provided by

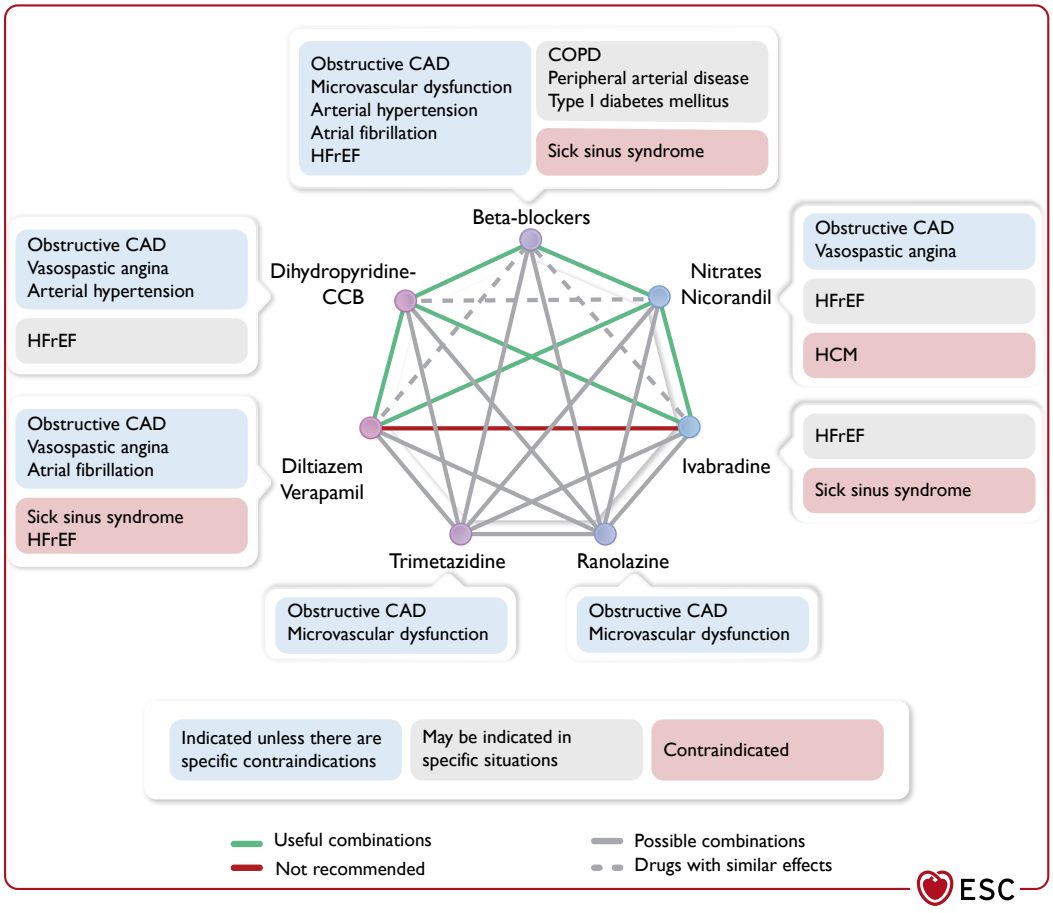

Figure 9 Possible combinations of antianginal drugs. CAD, coronary artery disease; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; HCM, hypertrophic cardiomyopathy; HFrEF, heart failure with reduced ejection fraction. The schematic shows useful combinations (green lines), combinations that are not recommended (red lines), possible combinations (solid blue lines), and drugs with similar effects (blue dashed lines), which can be combined in selected indications: HFrEF (ivabradine and beta-blocker), atrial fibrillation (diltiazem/verapamil and beta-blocker), vasospastic angina (dihydropyridine CCB and nitrates). Modified from Davies *et al.*[555].

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observational studies and meta-analyses is conflicting (some suggest an association between beta-blockers and better clinical outcomes, whereas others show a lack of association).[521,523–526] There have been only two open-label trials testing the efficacy of beta blockers in post-MI patients (NCT03278509 and NCT01155635), though both trials were underpowered to yield solid conclusions.[527] To further elucidate the benefit of beta-blockers in this clinical scenario, three European pragmatic, prospective, large-scale RCTs recruiting post-ACS patients with preserved LVEF to receive beta-blockers or control treatment are currently underway.[522,528–530]

The duration of beta-blocker therapy, in the long run, is a matter of debate, particularly in patients with prior MI and preserved LVEF.[531] Evidence from RCTs assessing beta-blockers rarely goes beyond a few years of follow-up, but patients are often given continuous treatment up to old age.[531] Observational data are also conflicting in this regard. One study has suggested that the clinical benefit of beta-blockers might be restricted to the first year after the index event, showing that their discontinuation at 1 year was not associated with higher 5-year mortality.[532] In contrast, a Swedish study starting the follow-up 1 year after the ACS episode has shown a lack of association between the use of beta-blockers and a composite of all-cause mortality, MI, unscheduled revascularization, or hospitalization for HF.[533] Another study has shown that the discontinuation of beta-blockers beyond 1 year after acute MI was associated with an increased risk of a composite of death or readmission for ACS, but not of all-cause mortality.[534] The impact of beta-blocker withdrawal 6–12 months after uncomplicated ACS in patients with LVEF ≥40% is being tested in two large-scale RCTs (NCT03498066, NCT04769362.[535]

Recommendation Table 16 — Recommendations for antianginal drugs in patients with chronic coronary syndrome (see also Evidence Table 16)

Recommendations	Class[a]	Level[b]
General strategy		
It is recommended to tailor the selection of antianginal drugs to the patient's characteristics, comorbidities, concomitant medications, treatment tolerability, and underlying pathophysiology of angina, also considering local drug availability and cost.	I	C
Selection of antianginal medication		
Short-acting nitrates are recommended for immediate relief of angina.[536,537]	I	B
Initial treatment with beta-blockers and/or CCBs to control heart rate and symptoms is recommended for most patients with CCS.[c] [518,538]	I	B
If anginal symptoms are not successfully controlled by initial treatment with a beta-blocker or a CCB alone, the combination of a beta-blocker and a DHP-CCB should be considered, unless contraindicated.[505,538,539]	IIa	B
Long-acting nitrates or ranolazine should be considered as add-on therapy in patients with inadequate control of symptoms while on treatment with beta-blockers and/or CCBs, or as part of initial treatment in properly selected patients.[d] [513,540]	IIa	B
When long-acting nitrates are prescribed, a nitrate-free or low-nitrate interval should be considered to reduce tolerance.[540]	IIa	B
Ivabradine should be considered as add-on antianginal therapy in patients with left ventricular systolic dysfunction (LVEF <40%) and inadequate control of symptoms, or as part of initial treatment in properly selected patients.[541,542]	IIa	B
Nicorandil or trimetazidine may be considered as add-on therapy in patients with inadequate control of symptoms while on treatment with beta-blockers and/or CCBs, or as part of initial treatment in properly selected patients.[543–550]	IIb	B
Ivabradine is not recommended as add-on therapy in patients with CCS, LVEF >40%, and no clinical heart failure.[509]	III	B
Combination of ivabradine with non-DHP-CCB or other strong CYP3A4 inhibitors is not recommended.[551]	III	B
Nitrates are not recommended in patients with hypertrophic cardiomyopathy or in co-administration with phosphodiesterase inhibitors.[552,553]	III	B

CCB, calcium channel blocker; CCS, chronic coronary syndrome; CYP3A4, cytochrome P450 3A4; DHP, dihydropyridine; DM, diabetes mellitus; LVEF, left ventricular ejection fraction.
[a]Class of recommendation.
[b]Level of evidence.
[c]These drugs may require caution or may be contraindicated in certain patients with low BP (beta-blockers and DHP-CCB), DM (beta-blockers), atrioventricular conduction disorders (beta-blockers and non-DHP-CCB), chronic obstructive pulmonary disease (non-cardioselective beta-blockers).
[d]Consideration for initial therapy: ivabradine, nicorandil, long-acting nitrates, ranolazine, or trimetazidine for patients with intolerance or contraindications to beta-blockers and/or CCBs; ranolazine and trimetazidine for patients with microvascular angina; nicorandil or nitrates for patients with coronary artery spasm. The drugs are listed in alphabetical order.

4.2.3. Combination therapy

The aim of antianginal medications is to ensure adequate relief of angina symptoms in patients with CCS, in part independently of their effect or lack of effect on MACE. Initiation of monotherapy, with subsequent escalation to a combination of antianginal drugs in the case of inadequate relief of symptoms, is a reasonable approach. In this context, the empirical approach of starting with a beta-blocker can be recommended in many patients with CCS, unless there are contraindications or other drugs are more suitable instead of beta-blockers (e.g. patients with low heart rate and/or BP). If a combination of antianginal drugs is required, the selection of the most appropriate drugs should be individualized and determined by the haemodynamic profile, comorbidities, and tolerability. The combination of a beta-blocker with a dihydropyridine CCB is appropriate for most patients, whereas the addition of other antianginal drugs (long-acting nitrates, ranolazine, nicorandil, trimetazidine, or ivabradine in patients with LV systolic dysfunction) can be considered when treatment with a beta-blocker and/or CCB is contraindicated or poorly tolerated, or when angina symptoms are inadequately controlled.

The following points should additionally be kept in mind: (i) beta-blockers are not indicated in the presence of sick sinus syndrome or

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atrioventricular conduction disorders,[554] and should be used with caution in patients with PAD and chronic obstructive pulmonary disease; (ii) CCBs require caution in patients with heart failure with reduced ejection fraction (HFrEF);[526] (iii) ivabradine should not be combined with non-dihydropyridine CCBs (verapamil or diltiazem); and (iv) ranolazine and trimetazidine are reasonable options as part of antianginal combination therapy in patients with low heart rate and/or BP.

4.3. Medical therapy for event prevention

Prevention of coronary ischaemic events is based on lowering the risk of coronary artery occlusion and consequent ACS. Medical event-preventing therapies include antithrombotic, lipid-lowering, anti-RAAS (renin–angiotensin–aldosterone system), anti-inflammatory, and metabolic-acting agents.

4.3.1. Antithrombotic drugs

The standard antithrombotic treatment of patients with epicardial atherosclerotic CAD is single antiplatelet therapy (SAPT), typically with aspirin. In patients with ACS or post-PCI, standard treatment is dual antiplatelet therapy (DAPT) with aspirin and an oral $P2Y_{12}$ inhibitor, for a duration of 12 months after ACS (with or without PCI)[65] or 6 months after CCS-PCI.[1,556] Thus, in ACS or CCS-PCI patients, DAPT is usually replaced by SAPT at some point. Several recent trials have investigated shortened DAPT durations and $P2Y_{12}$ inhibitor monotherapy post-PCI to reduce the risk of bleeding. On the other hand, in CCS patients with persistently high ischaemic risk and low bleeding risk, extended intensified antithrombotic therapy should be considered. Ultimately, the choice and duration of antithrombotic regimens largely depend on the delicate balance between each individual's ischaemic and bleeding risks.

The mechanisms of action of the most commonly used antithrombotic drugs in CCS patients are depicted in *Figure 10*.

4.3.1.1. Antiplatelet drugs

For details on antiplatelet drugs, please see Supplementary data, *Table S1*.

4.3.1.1.1. Aspirin monotherapy. Low-dose aspirin (75–100 mg once daily) is the traditional drug of choice in patients with CCS, with or without prior MI.[557,558] In an individual-patient data meta-analysis of secondary prevention trials (43 000 patient-years), aspirin vs. no aspirin significantly reduced the combined risk of non-fatal MI, non-fatal ischaemic stroke, or death from vascular causes [from 8.2% to 6.7% per year ($P < .0001$), with relative risk (RR) reductions of 31%, 22%, and 9%, respectively], translating into 15 fewer fatal and non-fatal serious vascular events for every 1000 patients treated for 1 year.[558] Aspirin allocation increased major gastrointestinal (GI) and extracranial bleeds, from 0.07% to 0.10% per year ($P < .0001$), with a non-significant increase in haemorrhagic stroke but reductions of about a fifth in total stroke (from 2.54% to 2.08% per year, $P = .002$) and in coronary events (from 5.3% to 4.3% per year, $P < .0001$).

Thus, for secondary prevention, the reduction of ischaemic events with aspirin outweighs serious bleeding events.[557,558] There is no evidence of different aspirin effects in women and men.[558,559] Daily aspirin doses of 75–100 mg seem to be as effective as higher doses for long-term treatments.[558–561]

4.3.1.1.2. Oral $P2Y_{12}$ inhibitor monotherapy.

4.3.1.1.2.1. Clopidogrel monotherapy. In addition to the cyclooxygenase-I pathway inhibited by aspirin, the platelet $P2Y_{12}$ receptor also plays a pivotal role in arterial thrombus formation and is the target for three oral platelet inhibitors: clopidogrel, prasugrel, and ticagrelor. The relative efficacy and safety of clopidogrel compared with aspirin for secondary prevention in CCS patients has been tested in multiple randomized trials that, taken together, have involved over 29 000 patient-years.[562,563]

In an overall population of 19 185 patients with either previous MI (within 35 days), stroke (within 6 months), or PAD, followed for a mean of 1.9 years, the CAPRIE trial (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events) demonstrated a small benefit in ischaemic events (RR reduction of 8.7%) with clopidogrel 75 mg/day vs. aspirin 325 mg/day.[564]

In the recent, open-label, South Korean, non-inferiority HOST-EXAM (Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis-EXtended Antiplatelet Monotherapy) trial, clopidogrel was compared with low-dose aspirin in 5530 patients after 6–18 months of uneventful DAPT post-PCI (72% initial ACS, 28% initial CCS).[565] Relative to aspirin, clopidogrel reduced the composite of all-cause death, non-fatal MI, readmission attributable to ACS, stroke, and BARC (Bleeding Academic Research Consortium) ≥3 bleeding from 7.7% to 5.7% at the end of the 2-year follow-up; the results were maintained at 5.8 years, in a *post hoc*, per-protocol, post-trial analysis.[566]

A very recent individual patient-level meta-analysis examined seven trials involving 24 325 patients (including recent ACS, post-CABG, or initial CCS patients) randomized to either aspirin monotherapy (12 147 patients) or $P2Y_{12}$ inhibitor monotherapy [clopidogrel in 7545 (62.0%), ticagrelor in 4633 (38.0%)] and followed for 6–36 months.[562] $P2Y_{12}$ inhibitors reduced the combined ischaemic outcome of cardiovascular death, MI, and stroke compared with aspirin (in doses of 100 or 325 mg daily), mainly through reduction of infarction. The risk of major bleeding was similar, whereas GI bleeding and haemorrhagic stroke occurred less frequently with a $P2Y_{12}$ inhibitor. The treatment effect was consistent across pre-specified subgroups (ACS or CCS) and type of $P2Y_{12}$ inhibitor.[562]

The above overall evidence supports clopidogrel monotherapy as an effective and safe alternative to aspirin monotherapy for long-term secondary prevention in patients with CCS.

4.3.1.1.2.2. Ticagrelor monotherapy. Since ticagrelor compared with clopidogrel is more effective and displays less variable platelet inhibition,[567,568] although with greater bleeding potential,[569] ticagrelor monotherapy has been compared with aspirin monotherapy for secondary prevention in CCS patients treated with PCI.

The RCT GLOBAL LEADERS trial [Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs. aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent (DES): a multicentre, open-label, randomized superiority trial][570] of 15 968 patients (53% with initial CCS) did not show superiority of ticagrelor monotherapy vs. standard of care in terms of survival or new Q-wave MI.[570] A pre-specified GLOBAL LEADERS ancillary analysis of independently adjudicated outcomes in 7585 patients reported non-inferiority for ischaemic events and no difference in BARC major bleeding between the two strategies.[571] A *post hoc* landmark analysis of the GLOBAL LEADERS trial, conducted in 11 121 uneventful patients at 1 year (53% CCS from trial onset, 47% transitioning to CCS from

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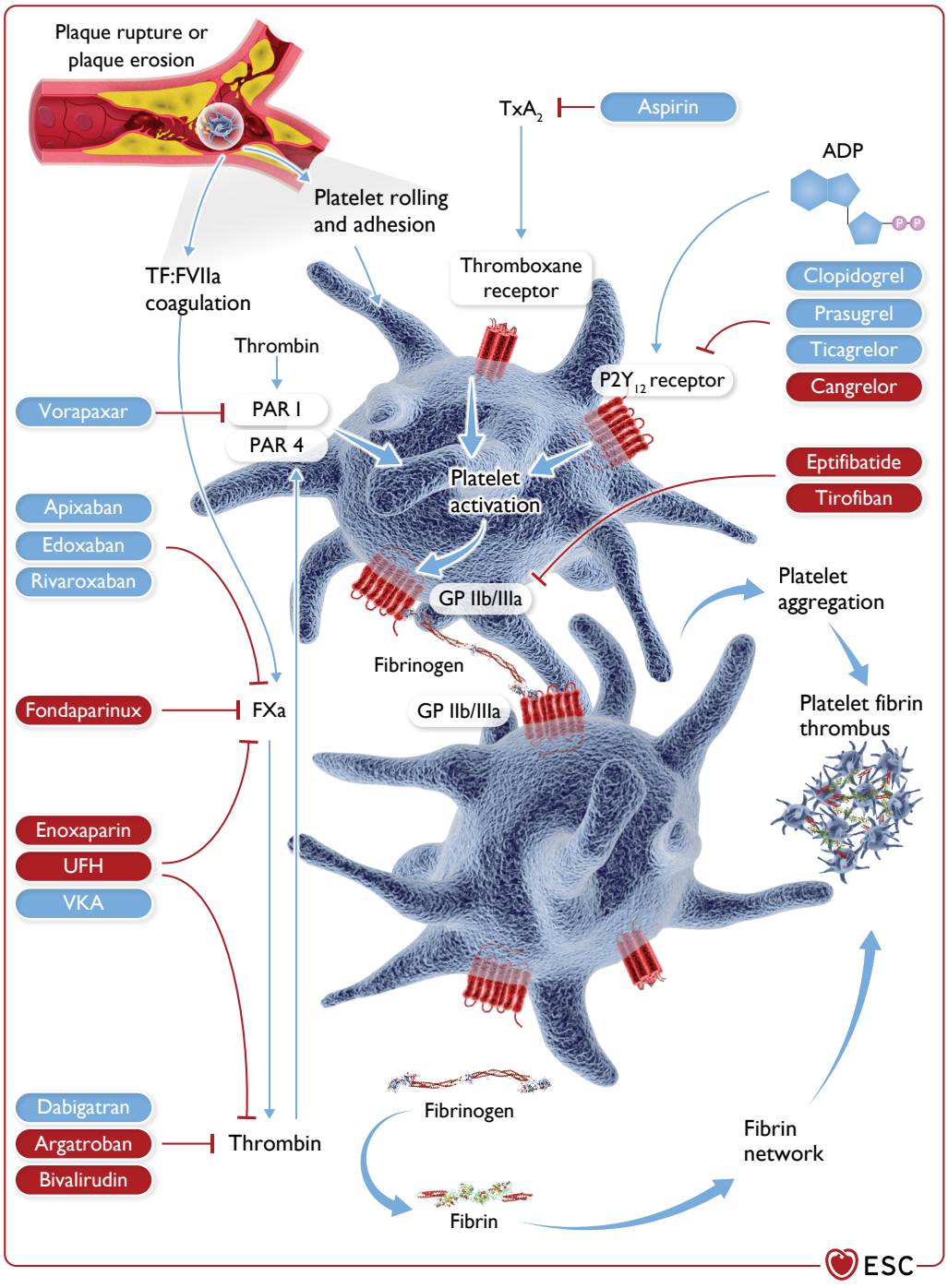

Figure 10 Antithrombotic drugs for chronic coronary syndromes: pharmacological targets. ADP, adenosine diphosphate; FVIIa, activated factor VII; FXa, activated factor X; GP, glycoprotein; PAR, protease-activated receptor; TF, tissue factor; TxA_2, thromboxane A2; UFH, unfractionated heparin; VKA, vitamin K antagonist. Orally administered drugs are shown on a blue background, parenterally administered ones on red. Aspirin prevents TxA2 formation by acetylating platelet cyclooxygenase-1.

ACS), showed reduced ischaemic events, but increased BARC 3 and 5 major bleeding, during ticagrelor monotherapy compared with aspirin monotherapy from 1 to 2 years after PCI.[572]

The double-blind, non-inferiority TWILIGHT trial, conducted in 7119 patients [35% CCS, 65% NSTE (non-ST-segment elevation)-ACS] undergoing high-risk PCI (defined as multivessel, stenting of >30 mm, thrombotic, two-stent bifurcation, left main, proximal LAD, or atherectomy-treated calcified lesions) and uneventfully receiving 3 months of ticagrelor-based DAPT after PCI, showed that ticagrelor monotherapy 90 mg b.i.d. (twice daily) compared with ticagrelor-based DAPT for an additional 12 months significantly reduced the primary endpoint of clinically relevant bleeds (BARC 2, 3, and 5, or BARC 3 and 5), with no significant increase in the composite of any death, MI, or stroke (3.9% in both groups).[573]

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The above trial data[570–573] and meta-analytical data[562,563,574] suggest that ticagrelor monotherapy may be an option for selected CCS or stabilized post-ACS patients treated with PCI. However, the overall evidence is weaker than for other recommended antithrombotic strategies. Moreover, the optimal timing and duration (longest tested duration 23 months) are unclear. Only the 90 mg b.i.d. regimen has been tested as monotherapy.[573,575] Data on prasugrel monotherapy for CCS patients are limited to a single-armed, open-label study with 3 months of follow-up.[576]

In summary, for long-term secondary prevention in CCS patients without an indication for oral anticoagulant (OAC), aspirin or, as an alternative, clopidogrel monotherapy are generally recommended. In selected patients at high ischaemic risk without high bleeding risk (HBR), ticagrelor monotherapy may be considered [at the time of writing not contemplated by the European Medicines Agency (EMA) (https://www.ema.europa.eu/en/medicines/human/EPAR/brilique)] with a lower level of evidence than for aspirin or clopidogrel (*Figure 11*). Details on the pharmacology of antiplatelet drugs[567,577–582] and on the randomized evidence (including trial limitations) can be found in the Supplementary data, *Table S1* and in the evidence tables.

4.3.1.1.3. Dual antiplatelet therapy post-percutaneous coronary intervention. After PCI for CCS, DAPT consisting of aspirin and clopidogrel is recommended to reduce the risk of stent thrombosis and MI compared with aspirin alone.[556] With few exceptions, there is no reason to replace clopidogrel with ticagrelor, based on the ALPHEUS (Assessment of Loading with the $P2Y_{12}$ Inhibitor Ticagrelor or Clopidogrel to Halt Ischemic Events in Patients Undergoing Elective Coronary Stenting) trial results demonstrating, in 1883 patients followed for 30 days, that ticagrelor did not significantly reduce PCI-related MI or major myocardial injury, while minor bleeding was significantly increased compared with clopidogrel.[583]

In the THEMIS trial (The Effect of Ticagrelor on Health Outcomes in diabEtes Mellitus patients Intervention Study) of 19 220 CCS patients aged ≥50 years, with type 2 DM and no previous MI or stroke (58% with prior PCI), ticagrelor plus low-dose aspirin marginally reduced ischaemic events compared with placebo plus aspirin at a median follow-up of 40 months, but increased major bleeding, including intracranial haemorrhage.[584]

A default DAPT duration of 6 months is recommended for CCS patients undergoing PCI.[556] However, multiple RCTs have investigated shorter DAPT durations (1 or 3 months) to decrease the risk of bleeding.[570,573,585–588] The combined evidence indeed shows a decrease in—mostly minor—bleeding, without an increase in ischaemic events, indicating that a shorter duration of DAPT of 1–3 months post-PCI may benefit CCS patients who are not at high ischaemic risk or who are at HBR.

This concept was tested in the MASTER-DAPT trial (Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation with an Abbreviated versus Standard DAPT Regimen), randomizing 4579 PCI patients (~50% CCS) with HBR, after 1-month uneventful DAPT, to immediate DAPT discontinuation or to DAPT continuation for at least 2 additional months.[587] After 335 days, the trial demonstrated that discontinuation was non-inferior for ischaemic events compared with standard duration of DAPT, but major and clinically relevant non-major bleeding was reduced.[587]

A meta-analysis, including 11 RCTs and 9006 patients (42% CCS) at HBR [defined by a PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual AntiPlatelet Therapy (PRECISE-DAPT) score of ≥25 or by Academic Research Consortium for High Bleeding Risk (ARC-HBR) criteria, listed in Supplementary data, *Table S2*][589–591] showed at 12 months of follow-up that an abbreviated DAPT of 1–3 months reduced both major bleeding and ischaemic events, as well as cardiovascular mortality, compared with standard DAPT, irrespective of CCS or ACS presentation.[591]

The overall data indicate that, in CCS patients with HBR, DAPT discontinuation 1–3 months after PCI is recommended, while in patients without HBR, DAPT duration may be reduced only in the absence of high ischaemic risk (*Figure 11*). For patients at high ischaemic risk without HBR, see below.

4.3.1.1.4. Extended intensified antithrombotic therapy. In patients at high ischaemic risk without HBR, there are three options for intensifying antithrombotic therapy to prevent ischaemic events, albeit at the cost of increased bleeding: (i) continue DAPT, consisting of aspirin and clopidogrel or of aspirin and prasugrel after PCI, based on the results of the DAPT Study;[592] (ii) add ticagrelor to aspirin in post-MI patients, based on the PEGASUS-TIMI (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin - Thrombolysis In Myocardial Infarction) 54 trial;[593] or (iii) add very low-dose rivaroxaban to aspirin in CCS patients, based on the COMPASS trial (Cardiovascular Outcomes for People Using Anticoagulant Strategies).[594]

The randomized DAPT Study demonstrated, in patients at 1-year post-PCI, that an additional 18 months of DAPT reduced ischaemic events compared with aspirin alone, but moderate and severe GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries) or BARC bleeding rates were higher, and all-cause death tended to be increased.[592] Of note, in the DAPT Study, first-generation DES were used with an increased risk of stent thrombosis.

The PEGASUS-TIMI 54 trial showed that in aspirin-treated patients with a history of MI 1–3 years previously and at least one high-risk characteristic (i.e. aged >65 years, DM, second MI, multivessel CAD, or CKD), ticagrelor (90 or 60 mg b.i.d.) vs. placebo reduced ischaemic events at 3 years, while it increased TIMI (Thrombolysis In Myocardial Infarction) major, but not fatal, bleeding.[593] The 60 mg dose was safer and better tolerated than the 90 mg dose[584,593] and therefore approved. The subgroups of patients with (compared with those without) DM, multivessel CAD, and PAD benefited more from ticagrelor.[595–597]

The COMPASS trial demonstrated that the combination of aspirin plus rivaroxaban 2.5 mg b.i.d., but not rivaroxaban 5.0 mg b.i.d. monotherapy, reduced ischaemic events, but increased modified-ISTH (International Society on Thrombosis and Haemostasis) major bleeding, compared with aspirin alone in patients with stable atherosclerotic disease (mostly CAD, with additional risk conditions if younger than 65 years).[594] There was no significant difference in intracranial or fatal bleeding between the two treatment arms, and death rates were lower in the aspirin plus rivaroxaban 2.5 mg b.i.d. group. Subgroups of patients with (compared with those without) DM, PAD, mild CKD, and active smoking habit benefited more from aspirin plus rivaroxaban.[594,598]

Patient eligibility for extended intensified antithrombotic therapy must be defined taking into account individual patient characteristics (see Supplementary data, *Table S2*), as well as study inclusion and exclusion criteria. The different options are described in *Table 8*.

In summary, in high ischaemic risk CCS patients without HBR, either aspirin plus ticagrelor 60 mg b.i.d. or aspirin plus rivaroxaban 2.5 mg b.i.d. should be considered, based on patient characteristics (*Figure 11*). DAPT prolongation with clopidogrel or prasugrel may also be an option, although the evidence for this choice suffers limitations. In patients with extended intensified antithrombotic therapy, re-evaluation of bleeding and ischaemic risk at regular intervals is essential. Randomized evidence beyond study follow-up times is unavailable.

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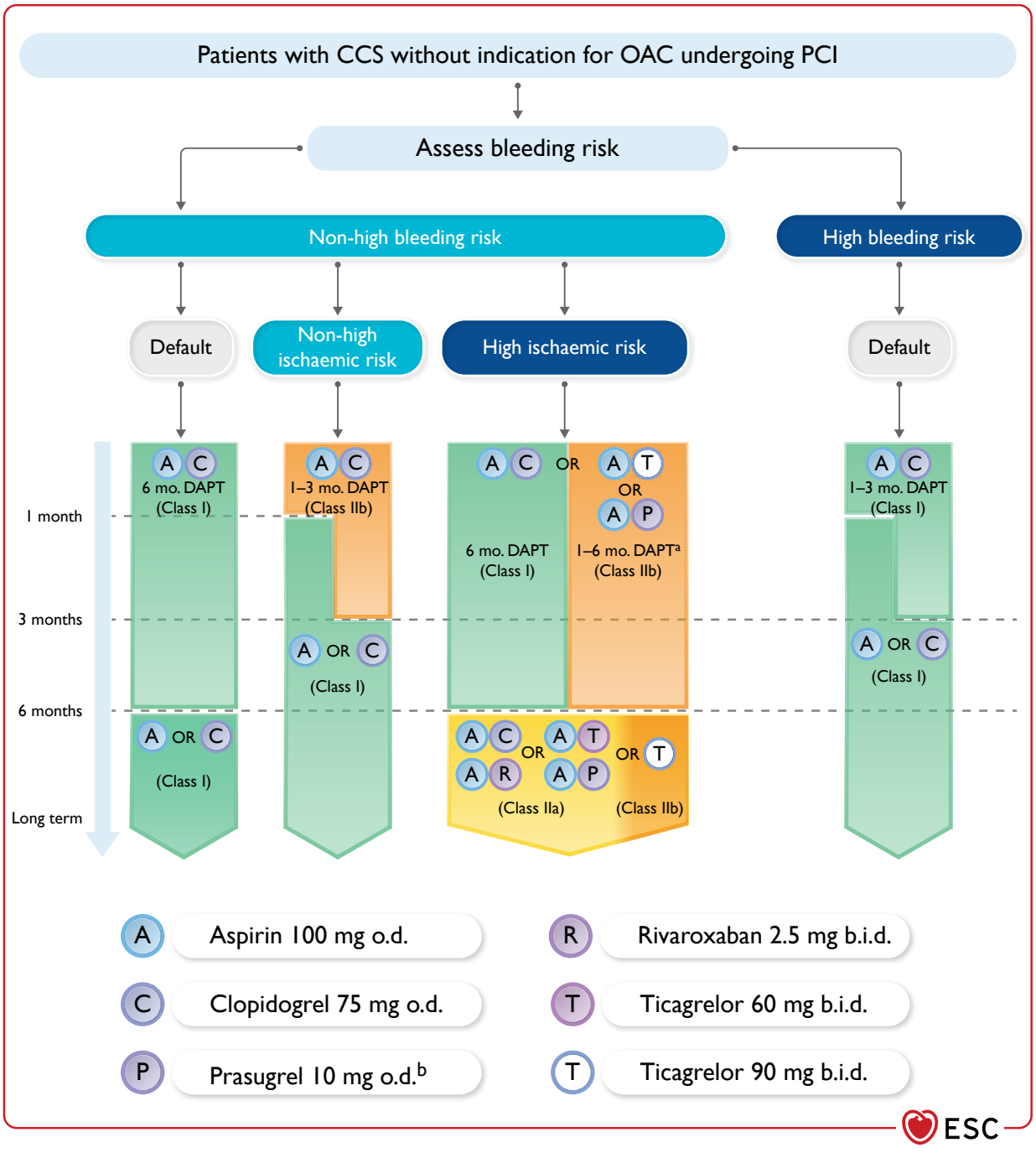

Figure 11 Antithrombotic treatment in chronic coronary syndrome patients undergoing percutaneous coronary intervention. ARC-HBR, Academic Research Consortium for High Bleeding Risk; b.i.d., bis in die (twice daily); CCS, chronic coronary syndrome; CYP2C19, cytochrome P450 2C19; DAPT, dual antiplatelet therapy; mo., months; OAC, oral anticoagulant; o.d., once daily; PCI, percutaneous coronary intervention; PRECISE-DAPT, PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy. [a]In CCS patients undergoing high-thrombotic risk stenting (e.g. complex left main stem, 2-stent bifurcation, suboptimal stenting result, prior stent thrombosis, previously known CYP2C19*2/*3 polymorphisms), prasugrel or ticagrelor (in addition to aspirin) may be considered instead of clopidogrel for the first month, and up to 3-6 months. [b]Prasugrel 5 mg o.d. for patients aged ≥75 years or with a body weight <60 kg. Bleeding risk criteria according to PRECISE-DAPT or ARC-HBR.

4.3.1.1.5. Genotype- and phenotype-guided dual antiplatelet therapy. There is high laboratory interindividual variability in patients treated with clopidogrel, with patients who carry a cytochrome P450 2C19 (CYP2C19) loss-of-function allele having less platelet inhibition and a higher risk of ischaemic events post-PCI compared with non-carriers.[599,600] In ST-segment elevation myocardial infarction (STEMI) patients, early de-escalation from aspirin plus ticagrelor or aspirin plus prasugrel to aspirin plus clopidogrel based on genotyping or platelet function testing was non-inferior for net adverse clinical events (ischaemic endpoints and bleeding combined) compared with routine

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Table 8 Options for extended intensified antithrombotic therapy

Drug	Dose	Clinical setting	NNT (ischaemic outcomes)	NNH (bleeding outcomes)
Co-administered with aspirin 100 mg o.d.				
Rivaroxaban (COMPASS trial; vs. placebo)	2.5 mg b.i.d.	Patients with CAD or symptomatic PAD at high risk of ischaemic events	77	84 (modified-ISTH major bleeding)
Co-administered with low-dose aspirin 75–162 mg o.d.				
Clopidogrel, (6505/9961 of DAPT trial; vs. placebo)	75 mg/day	Post MI in patients who have tolerated DAPT for 1 year (25% ACS, 22% previous MI)	63	105 (moderate and severe GUSTO bleeds, or BARC 2, 3, and 5 bleeds)
Prasugrel, (3456/9961 of DAPT trial; vs. placebo)	10 mg/day (5 mg/day if body weight <60 kg or age ≥75 years)	Post PCI for MI in patients who have tolerated DAPT for 1 year	63	105 (as above)
Ticagrelor (PEGASUS-TIMI 54; vs. placebo)	60/90 mg b.i.d.	Post-MI in patients who have tolerated DAPT for 1 year	84	81 (TIMI major bleeds)

ACS, acute coronary syndrome; BARC, Bleeding Academic Research Consortium; b.i.d., bis in die (twice daily); CAD, coronary artery disease; DAPT, dual antiplatelet therapy; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; ISTH, International Society on Thrombosis and Haemostasis; MI, myocardial infarction; NNH, number needed to cause a harmful event; NNT, number needed to treat to prevent an adverse event; o.d., once daily; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; TIMI, Thrombolysis In Myocardial Infarction. Drugs (in addition to aspirin 75–100 mg/day) for extended DAPT options are listed in alphabetical order. For definitions of highly/moderately increased ischaemic and bleeding risk see Supplementary data, *Tables S2 and S3*. NNT refers to the primary ischaemic endpoints and NNH refers to the key safety endpoints of the respective trials. NNT and NNH from the DAPT trial are pooled numbers for clopidogrel and prasugrel.

treatment with ticagrelor or prasugrel.[601,602] In patients with CCS, current evidence does not support the routine use of genotype or platelet function testing.[602–607] However, in patients undergoing high-risk PCI who are known carriers of a CYP2C19 loss-of-function allele, replacing aspirin plus clopidogrel with aspirin plus ticagrelor or prasugrel is a reasonable option.[600,607,608]

4.3.1.2. Anticoagulant therapy

4.3.1.2.1. Monotherapy with oral anticoagulant. Historical randomized data from patients with recent MI not undergoing PCI, followed for up to 4 years, showed that OAC monotherapy with a vitamin K antagonist (VKA) targeted to an international normalized ratio (INR) of about 3.0–4.0 was at least as effective as low-dose aspirin in preventing MACE, but with a significant increase in major bleeding.[609,610] Moreover, given the obsoletely high INR target and the cumbersome management, VKA has not gained popularity for secondary prevention in patients with CCS. Successful introduction of the direct oral anticoagulants (DOACs) for stroke prevention in AF and for prevention and treatment of venous thrombo-embolism (VTE) has renewed the interest in OAC for patients with CAD. The COMPASS trial in CCS and/or PAD patients at high ischaemic risk, however, reported no significant ischaemic benefit of rivaroxaban monotherapy 5 mg twice daily over aspirin alone, with a significantly higher incidence of modified-ISTH major bleeding, although not of fatal bleeding.[594]

Thus, in CCS patients without a concomitant long-term indication for OAC, OAC monotherapy with either VKA or rivaroxaban (the only DOAC currently tested in this context) is not recommended. OAC may be considered, however, when antiplatelet agents are not tolerated, if the risk of bleeding is not high,[594,611] or in CCS patients with a concomitant long-term indication for OAC (see below).

4.3.1.2.2. Combination of anticoagulant and antiplatelet therapy after percutaneous coronary intervention in chronic coronary syndrome patients with AF or other indication for oral anticoagulant. Approximately one in five patients with AF need to undergo PCI, with a theoretical indication for both OAC for stroke prevention (for which DOACs are preferred to VKA) and DAPT for stent thrombosis and MI prevention, leading to triple antithrombotic therapy.[612,613] The combination of an OAC plus DAPT, however, leads to an increased bleeding risk, and major bleeding is associated with earlier mortality and should therefore be avoided when possible.[614] In this setting, the results of five RCTs have shown that double compared with triple antithrombotic therapy reduced major or clinically relevant non-major bleeding, without a significant increase of ischaemic events, leading to the recommended use of double antithrombotic therapy (OAC plus $P2Y_{12}$ receptor inhibitor, mostly clopidogrel) after a 1–4 week period of triple antithrombotic therapy in CCS patients with AF undergoing PCI.[615–620]

The AUGUSTUS trial (Open-Label, 2 × 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban versus Vitamin K Antagonist and Aspirin versus Aspirin Placebo in Patients with AF and Acute Coronary Syndrome or Percutaneous Coronary Intervention) additionally demonstrated that the DOAC apixaban reduced major or clinically relevant non-major bleeding compared with VKA, independently of a double or triple antithrombotic regimen.[619] The AUGUSTUS trial and several meta-analyses demonstrated that aspirin compared with placebo reduced stent thrombosis events, which occurred mainly during the first 30 days after PCI and not thereafter, while increasing bleeding risk.[620–622]

Thus, based on the combined evidence, double antithrombotic therapy with a DOAC and clopidogrel for up to 12 months should be standard care for CCS patients with AF undergoing PCI, with additional aspirin only for a limited initial period (from during PCI up to a maximum of 30 days in patients at high ischaemic risk). In patients with the highest bleeding risk, clopidogrel discontinuation at 6 (or even 3) months post-PCI and continuation of OAC alone may be considered when ischaemic risk is not high [Class IIb/level of evidence (LOE) C]. Ticagrelor or prasugrel should generally not be used as part of triple antithrombotic therapy, while ticagrelor, and possibly prasugrel (although specific data are not available), may be considered as part of double

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antithrombotic therapy when there is a very high risk of stent thrombosis and a low bleeding risk.[619,623,624]

After a 6- to 12-month period of double antithrombotic therapy, in most AF-PCI CCS patients, OAC alone is preferred over continuation of double antithrombotic therapy.[625,626] An open-label randomized trial, conducted in 2236 Japanese AF patients who had undergone PCI (71% of patients) or CABG (11% of patients) >1 year before or had known CAD not requiring revascularization, compared rivaroxaban monotherapy (15 or 10 mg once daily based on creatinine clearance) with rivaroxaban plus SAPT (mostly aspirin).[627] At a median follow-up of 23 months, the occurrence of ISTH major bleeding and of all-cause deaths were each significantly lower with rivaroxaban monotherapy, whereas MACE occurrence did not differ significantly in the two treatment arms.[627]

Whether the above considerations remain valid when the indication for OAC is other than AF, e.g. mechanical heart valves (where DOACs are not indicated) or VTE, is uncertain given limited available evidence. In the absence of data regarding the efficacy for MACE prevention of rivaroxaban 10 mg once daily and apixaban 2.5 mg twice daily, which should be used for extended OAC after the first 6 months of therapeutic anticoagulation in patients with VTE,[628] it is recommended to resume full doses of these anticoagulants in case of concomitant CCS.

4.3.1.3. Coronary artery bypass grafting and antithrombotic therapy

Low-dose aspirin is recommended lifelong in patients undergoing CABG.[629,630] Aspirin should be continued until the day of CABG and restarted as soon as there is no concern over bleeding, possibly within 24 h of CABG.[631,632] In general, other antithrombotic drugs should be stopped at intervals related to their duration of action (prasugrel stopped ≥7 days before; clopidogrel ≥5 days before; ticagrelor ≥3 days before; and rivaroxaban, apixaban, edoxaban, and dabigatran 1–2 days before, depending on drug and renal function).[633,634] Although not consistent, there is evidence that DAPT with a $P2Y_{12}$ receptor inhibitor compared with aspirin monotherapy provides higher graft patency rates after CABG.[635,636,637] A meta-analysis of four RCTs, involving 1316 patients (with 3079 grafts) followed for 3 to 12 months after CABG, reported superior vein graft patency with ticagrelor-based DAPT vs. aspirin alone, but with increased rates of BARC 2–5 (but not BARC 3–5) bleeds, and no significant differences in cardiovascular death, or the composite of cardiovascular death, MI, and stroke, or the composite of all-cause death, MI, stroke, and revascularization.[635] Therefore, in patients undergoing CABG for CCS, DAPT is not routinely indicated; however, it may be considered in selected cases at increased risk of graft occlusion who are not at high bleeding risk (defined in Supplementary data, *Tables S2 and S3*).

Transient new-onset AF is common 2 to 3 days after CABG, occurring in approximately one-third of patients.[638] AF after CABG is associated with a higher stroke risk,[639] which is, however, lower than that with AF unrelated to surgery.[640] The impact of early OAC initiation on patient outcomes remains unclear.[641,642] In a Danish cohort study, early OAC initiation was associated with a lower risk of thrombo-embolic events,[641] while in a Swedish cohort study, OAC was associated with no reduction of thrombo-embolic complications but an increased risk of major bleeding.[642]

Decisions on OAC should consider thrombo-embolic and bleeding risks, timing, and duration of post-operative AF. Longer AF durations and delayed-onset post-CABG have higher risks. We refer to the 2024 ESC Guidelines for the management of AF regarding recommendations for OAC in this context. It is unknown whether, in such patients, the combination of aspirin and OAC may be more effective compared with OAC alone in preventing ischaemic events post-CABG.

4.3.1.4. Proton pump inhibitors

Antithrombotic therapy may provoke GI bleeding, especially in patients at increased risk, such as the elderly, those with a history of GI bleeding or peptic disease, high alcohol consumption, chronic use of steroids or non-steroidal anti-inflammatory drugs (NSAIDs), or receiving a combination of antithrombotic drugs.[643–645] In patients on various types of antithrombotic therapy, proton pump inhibitors may be effective in reducing the risk of GI bleeding, in particular from gastroduodenal lesions.[646–648] In general, gastric protection with proton pump inhibitors is recommended in patients at increased risk of GI bleeding for as long as any antithrombotic therapy is administered.[65,86] Because the proton pump inhibitors omeprazole and esomeprazole inhibit CYP2C19, when administered with clopidogrel, they reduce exposure to clopidogrel's active metabolite; while their use is discouraged in combination with clopidogrel, univocal effects of these combinations on the risk of ischaemic events or stent thrombosis have not been demonstrated (https://www.ema.europa.eu/en/medicines/human/EPAR/plavix).[643,646] Of note, proton pump inhibitors do not increase MACE vs. placebo in patients with CVD.[646]

Recommendation Table 17 — Recommendations for antithrombotic therapy in patients with chronic coronary syndrome (see also Evidence Table 17)

Recommendations	Class[a]	Level[b]
Long-term antithrombotic therapy in patients with chronic coronary syndrome and no clear indication for oral anticoagulation		
In CCS patients with a prior MI or remote PCI, aspirin 75–100 mg daily is recommended lifelong after an initial period of DAPT.[558,559]	I	A
In CCS patients with a prior MI or remote PCI, clopidogrel 75 mg daily is recommended as a safe and effective alternative to aspirin monotherapy.[562,564–566,649]	I	A
After CABG, aspirin 75–100 mg daily is recommended lifelong.[558,559,629]	I	A
In patients *without* prior MI or revascularization but with evidence of significant obstructive CAD, aspirin 75–100 mg daily is recommended lifelong.[557–559]	I	B
Adding a second antithrombotic agent to aspirin for extended long-term secondary prevention should be considered in patients at enhanced ischaemic risk[c] and without high bleeding risk[d] (options and definitions in *Table 8* and in the Supplementary data online, *Tables S2 and S3*).[592–594]	IIa	A
In CCS or stabilized post-ACS patients who underwent PCI and were initially treated with ticagrelor-based DAPT, who remain at high ischaemic risk and are not at high bleeding risk, ticagrelor monotherapy 90 mg b.i.d. may be considered as an alternative to dual or other single antiplatelet therapy.[563,570–573]	IIb	C

Continued

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Antithrombotic therapy post-percutaneous coronary intervention in patients with chronic coronary syndrome and no indication for oral anticoagulation		
In CCS patients with no indication for oral anticoagulation, DAPT consisting of aspirin 75–100 mg and clopidogrel 75 mg daily for up to 6 months is recommended as the default antithrombotic strategy after PCI-stenting.[650–654]	I	A
In patients at high bleeding risk[d] but not at high ischaemic risk,[c] it is recommended to discontinue DAPT 1–3 months after PCI and to continue with single antiplatelet therapy.[587,591]	I	A
Stopping DAPT after 1–3 months from PCI-stenting may be considered in patients who are not at high bleeding risk nor at high risk of ischaemic events.[588,655–657,c,d]	IIb	B
In CCS patients undergoing high-thrombotic risk stenting (e.g. complex left main stem, 2-stent bifurcation, suboptimal stenting result, prior stent thrombosis, previously known CYP2C19 *2/*3 polymorphisms), prasugrel or ticagrelor (in addition to aspirin) may be considered instead of clopidogrel, for the first month, and up to 3–6 months.	IIb	C
Long-term antithrombotic therapy in patients with chronic coronary syndrome and an indication for oral anticoagulation		
In CCS patients with a long-term indication for OAC, an AF therapeutic dose of VKA alone or, preferably, of DOAC alone (unless contraindicated) is recommended lifelong.[609,627]	I	B
Antithrombotic therapy post-percutaneous coronary intervention in chronic coronary syndrome patients with an indication for oral anticoagulation		
In patients with an indication for OAC who undergo PCI, initial low-dose aspirin once daily is recommended (loading dose when not on maintenance dose) in addition to OAC and clopidogrel.	I	C
In patients who are eligible for OAC, DOAC (unless contraindicated) is recommended in preference to VKA.[619,658]	I	A
After uncomplicated PCI in CCS patients with concomitant indication for OAC: • early cessation of aspirin (≤1 week); • followed by continuation of OAC and clopidogrel: o up to 6 months in patients not at high ischaemic risk;[c] or o up to 12 months in patients at high ischaemic risk;[c] • followed by OAC alone; is recommended.[616–619,622,627,659]	I	A
Continuation of aspirin up to 1 month after PCI, in addition to OAC and clopidogrel, should be considered in patients at high ischaemic risk[c] or with anatomical/procedural characteristics judged to outweigh the bleeding risk.[620–622,e]	IIa	B
When concerns about high bleeding risk prevail over concerns about stent thrombosis or ischaemic stroke: rivaroxaban 15 mg daily should be considered in preference to rivaroxaban 20 mg daily for the duration of concomitant antiplatelet therapy;[616]	IIa	B
dabigatran 110 mg twice daily should be considered in preference to dabigatran 150 mg twice daily for the duration of concomitant antiplatelet therapy.[617]	IIa	B
In patients with an indication for VKA in combination with single or dual antiplatelet therapy, targeting VKA intensity to an INR in the lower part of the recommended range and to a time in therapeutic range >70% should be considered.[615,660–663]	IIa	B
The use of ticagrelor or prasugrel is generally not recommended as part of triple antithrombotic therapy with aspirin and an OAC.	III	C
Antithrombotic therapy post-coronary artery bypass grafting		
It is recommended to initiate aspirin post-operatively as soon as there is no concern over bleeding.[629,630]	I	B
DAPT may be considered after CABG in selected patients at greater risk of graft occlusion[f] and at low risk of bleeding.[635]	IIb	B
Use of proton pump inhibitors		
A proton pump inhibitor is recommended in patients at increased risk of gastrointestinal bleeding for the duration of combined antithrombotic therapy (antiplatelet therapy and/or OAC).[646–648,664]	I	A
A proton pump inhibitor should be considered when a single antithrombotic (antiplatelet or anticoagulant) drug is used, considering the gastrointestinal bleeding risk of the individual patient.[646,665–668]	IIa	A

ACS, acute coronary syndrome; AF, atrial fibrillation; ARC-HBR, Academic Research Consortium for High Bleeding Risk; b.i.d., bis in die (twice daily); CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS, chronic coronary syndrome; CKD, chronic kidney disease; CYP2C19, cytochrome P450 2C19; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; INR, international normalized ratio; LAD, left anterior descending; MI, myocardial infarction; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; PRECISE-DAPT, PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual AntiPlatelet Therapy; VKA, vitamin K antagonist.

[a]Class of recommendation.

[b]Level of evidence.

[c]Enhanced thrombotic/ischaemic risk criteria for extended treatment with a second antithrombotic agent (Supplementary data, *Table S3*). Thrombotic risk encompasses (i) the risk of thrombosis occurring, and (ii) the risk of death should a thrombotic event occur, both of which relate to anatomical, procedural, and clinical characteristics. Thrombotic/ischaemic risk factors for CCS (that may also apply to CABG) patients include stenting of left main stem, proximal LAD, or last remaining patent artery; suboptimal stent deployment; stent length of >60 mm; diabetes mellitus; CKD; bifurcation with two stents implanted; treatment of chronic total occlusion; and previous stent thrombosis on adequate antithrombotic therapy.

[d]Bleeding-risk criteria according to PRECISE-DAPT or ARC-HBR (Supplementary data, *Table S2*).

[e]Anatomical/procedural thrombotic risk characteristics: stenting of left main, proximal LAD, or last remaining patent artery; suboptimal stent deployment; stent length of >60 mm; bifurcation with two stents implanted; treatment of chronic total occlusions.

[f]For example, stentectomy, endarterectomy, poor venous graft quality.

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4.3.2. Lipid-lowering drugs

Evidence from genetic, epidemiological, and randomized clinical studies has established the key causal role of LDL-C and other apo-B-containing lipoproteins in the development of atherosclerotic disease.[669] In patients with established ASCVD, lowering of LDL-C levels reduces the risk of recurrent MACE.[128,670,671] Elevated lipid levels should be managed according to the 2019 ESC/EAS Guidelines for the management of dyslipidaemias[64] and the 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice.[16]

Because patients with CCS are considered at very high cardiovascular risk, the treatment goal is to lower LDL-C levels to <1.4 mmol/L (<55 mg/dL) and achieve a reduction by at least 50% from baseline. For patients who experience a second vascular event within 2 years while taking maximum tolerated statin-based therapy, an even lower LDL-C goal of <1.0 mmol/L (40 mg/dL) may be considered.

In addition to exercise, diet, and weight control, which favourably affect blood lipid levels and are recommended for all patients with CCS (see *Section 5.1*), pharmacological treatment with a maximally tolerated dose of a potent statin is the first-line therapy recommended for all CCS patients.[128,670,671] In a landmark meta-analysis involving patients with and without ASCVD, statin treatment was shown to reduce the risk of major vascular events by 22%, all-cause mortality by 10%, and mortality due to coronary heart disease by 20% per 1.0 mmol/L of achieved reduction in LDL-C levels.[670] High-intensity statin treatment (i.e. atorvastatin ≥40 mg or rosuvastatin ≥20 mg daily) reduces LDL-C levels by 45%–50% on average, although interindividual variability exists.[672] Statins should not be given when pregnancy is planned, during pregnancy, or during the breastfeeding period.[64]

In many patients with CCS, statin therapy alone will not suffice to achieve the recommended LDL-C goals;[673] hence, a combination of lipid-lowering drug therapy is required. In a trial of patients with recent ACS, the combination of statin with ezetimibe resulted in additional reduction of LDL-C levels by 20%–25% compared with simvastatin monotherapy. This LDL-C reduction translated into a modest reduction of a composite endpoint involving fatal and non-fatal events (6.4% RR reduction, 2.0% absolute risk reduction).[674] Ezetimibe should be used as second-line therapy when the treatment goal is not achieved with maximally tolerated statin therapy, or as first-line therapy in the case of intolerance to any statin regimen. Proprotein convertase subtilisin/kexin type 9 inhibitors (alirocumab or evolocumab), administered subcutaneously every 2 or 4 weeks, lower LDL-C levels by 60% when added to statin therapy.[675] In cardiovascular outcomes trials, these monoclonal antibodies resulted in significant reduction of non-fatal cardiovascular events, with no impact on cardiovascular mortality.[675,676] Their favourable safety profile was recently confirmed for longer follow-up (median 5 years) in open-label extension studies of the outcomes trials.[677] The high cost of PCSK9 inhibitors is still a limitation for broader implementation.

Bempedoic acid is an oral cholesterol synthesis inhibitor that lowers LDL-C by approximately 18% in monotherapy and 38% when combined with ezetimibe.[678,679] In a recent cardiovascular outcomes trial including statin-intolerant patients, bempedoic acid significantly reduced MACE.[680] Inclisiran, a small interfering ribonucleic acid molecule, is administered subcutaneously every 3–6 months and reduces LDL-C by approximately 50% either in combination with statin or without statin therapy.[681] A cardiovascular outcomes trials for inclisiran is currently underway (ClinicalTrials.gov identifier: NCT03705234).

In patients scheduled to undergo elective PCI, pre-treatment with a high-dose statin in statin-naïve patients or loading with high-dose statin in statin-treated patients has been shown to reduce the risk of periprocedural events.[682] Routine pre-treatment or loading (in the context of pre-existing statin treatment) with a high-dose statin can be considered in patients with CCS undergoing PCI.

Recommendation Table 18 — Recommendations for lipid-lowering drugs in patients with chronic coronary syndrome (see also Evidence Table 18)

Recommendations	Class[a]	Level[b]
Lipid-lowering treatment with an LDL-C goal of <1.4 mmol/L (55 mg/dL) and a ≥50% reduction in LDL-C vs. baseline is recommended.[64,670,671]	I	A
A high-intensity statin up to the highest tolerated dose to reach the LDL-C goals is recommended for all patients with CCS.[670,671]	I	A
If a patient's goal is not achieved with the maximum tolerated dose of statin, combination with ezetimibe is recommended.[674]	I	B
For patients who are statin intolerant and do not achieve their goal on ezetimibe, combination with bempedoic acid is recommended.[680]	I	B
For patients who do not achieve their goal on a maximum tolerated dose of statin and ezetimibe, combination with a PCSK9 inhibitor is recommended.[675,676]	I	A
For patients who do not achieve their goal on a maximum tolerated dose of statin and ezetimibe, combination with bempedoic acid should be considered.	IIa	C
For patients with a recurrent atherothrombotic event (not necessarily of the same type as the first event) while taking maximally tolerated statin therapy, an LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered.[675,676]	IIb	B

CCS, chronic coronary syndrome; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9.
[a]Class of recommendation.
[b]Level of evidence.

4.3.3. Renin–angiotensin–aldosterone blockers/ angiotensin receptor neprilysin inhibitor

Modulation of the RAAS and the neprilysin inhibitor sacubitril in combination with a RAS blocker has proved beneficial in patients with HF post-MI and in patients with hypertension. In these clinical syndromes, RAAS inhibition has greatly improved morbidity and mortality. Angiotensin-converting enzyme inhibitors (ACE-Is) can reduce mortality, MI, stroke, and HF among patients with LV dysfunction,[683–685] previous vascular disease,[686–688] and high-risk DM.[689] These data bring strong evidence to recommend ACE-Is [or angiotensin receptor blockers (ARBs) in cases of intolerance] for the treatment of patients with CCS with co-existing hypertension, LVEF ≤40%, DM, or CKD, unless contraindicated (e.g. severe renal impairment, hyperkalaemia, etc.). In trials that include patients with mildly reduced and preserved LV function >40%, the effect of ACE-Is to reduce all-cause death, cardiovascular death, non-fatal MI, stroke, or HF in patients with atherosclerosis is not uniform.[686,687,690] A meta-analysis, including 24 trials and 61 961 patients, documented that, in CCS patients without HF, RAAS inhibitors reduced cardiovascular events and death only when compared

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with placebo, but not when compared with active control treatment.[691] For this reason ACE-I therapy in CCS patients without HF or high cardiovascular risk is not generally recommended, unless required to meet BP targets. However, a new observational study showed that ACE-I/ARB therapy was associated with significant long-term survival benefit in patients post-PCI for STEMI/non-ST-segment elevation myocardial infarction (NSTEMI). This survival benefit is apparent in patients with both preserved and reduced LV function. These findings provide contemporary evidence to support the use of these agents in coronary patients who underwent PCI for STEMI/NSTEMI, irrespective of their baseline LV function.[692]

Sacubitril/valsartan contains an ARB and a prodrug of neprilysin inhibitor, which inhibits the degradation of endogenous natriuretic peptides. In patients with LVEF ≤35% (of ischaemic aetiology in 60%), sacubitril/valsartan proved to reduce HF hospitalization and cardiovascular death compared with ACE-I.[693] Moreover, sacubitril/valsartan may decrease myocardial ischaemia because of its effect in reducing LV wall stress and improving coronary circulation. The risk of coronary events using sacubitril/valsartan compared with ACE-I was also significantly reduced on post-hoc analyses.[694]

4.3.4. Sodium–glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists

Sodium–glucose cotransporter 2 (SGLT2) inhibitors and GLP-1 receptor agonists were initially intended as glucose-lowering medications for patients with type 2 DM; however, a growing body of evidence has established that these drugs lower ASCVD risk and confer cardiovascular benefits beyond their glucose-lowering potential.[688,695–697] Among patients with DM, SGLT2 inhibitor use was associated with a reduced risk of MACE, especially in patients with established ASCVD.[698] The exact mechanism(s) by which SGLT2 inhibitors improve CVD outcomes remain largely unknown, but several hypotheses have been proposed.[695,696,699–702] The benefits of SGLT2 inhibitors may relate more to cardiorenal haemodynamic effects than to atherosclerosis[16] The cardiovascular benefits of GLP-1 receptor agonists is driven by reduced risk of ASCVD-related events.[703] Overall, the results of cardiovascular outcome trials of SGLT2 inhibitors and GLP-1 receptor agonists support their recommendation as first-line treatment for all patients with type 2 DM and ASCVD including CCS, independently of decisions about glycaemic management (*Recommendation Table 19*).

In patients with HF with reduced (HFrEF) or preserved EF (HFpEF), dapagliflozin and empagliflozin lowered the risk of worsening HF or cardiovascular death in the presence or absence of type 2 DM.[704–707] Recent results indicate benefits of SGLT2 inhibitors on hospitalization for HF and cardiovascular death in patients at high cardiovascular risk, irrespective of HF history.[708] Recommendations for the use of SGLT2 inhibitors in patients with diabetes and patients with HF are detailed in the 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes[86] and the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure[526] and its 2023 Focused Update. [709] Recommendations on the use of these medications in patients with HF are given in *Section 4.3.4* and *Recommendation Table 24*.

In patients with pre-existing CVD, the SELECT trial assessed the effect of weekly subcutaneous administration of the GLP-1 receptor agonist semaglutide at a dose of 2.4 mg on MACE reduction in overweight or obese adults without type 2 DM. The trial involved 17 604 patients with established CVD and a BMI ≥27 kg/m^2. Patients lost a mean of 9.4% of body weight over the first 2 years with semaglutide vs. 0.88% with placebo. The primary cardiovascular endpoint—a composite of death from cardiovascular causes, non-fatal MI, or non-fatal stroke—was reduced significantly, with an HR of 0.80 (95% CI, 0.72–0.90; $P < .001$).[465]

Recommendation Table 19 — Recommendations for sodium–glucose cotransporter 2 inhibitors and/or glucagon-like peptide-1 receptor agonists in patients with chronic coronary syndrome (see also Evidence Table 19)

Recommendations	Class[a]	Level[b]
CCS patients with type 2 diabetes		
SGLT2 inhibitors with proven CV benefit[c] are recommended in patients with T2DM and CCS to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication.[86,688,695,697,700]	I	A
GLP-1 receptor agonists with proven CV benefit[d] are recommended in patients with T2DM and CCS to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication.[710,711]	I	A
CCS patients without type 2 diabetes		
The GLP-1 receptor agonist semaglutide should be considered in overweight (BMI ≥27 kg/m^2) or obese CCS patients without diabetes to reduce CV mortality, MI, or stroke.[465]	IIa	B

BMI, body mass index; CCS, chronic coronary syndrome; CV, cardiovascular; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin; MI, myocardial infarction; SGLT2, sodium–glucose cotransporter 2; T2DM, type 2 diabetes mellitus.
[a]Class of recommendation.
[b]Level of evidence.
[c]Canaglifozin, dapagliflozin, empagliflozin, sotagliflozin (listed in alphabetical order).
[d]Dulaglutide, efpeglenatide, liraglutide, semaglutide (listed in alphabetical order).

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4.3.5. Anti-inflammatory agents for event prevention

Four large double-blind trials have compared the effects of anti-inflammatory agents vs. placebo in patients with atherothrombotic CAD. The Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS) tested three doses of the anti-interleukin-1-beta monoclonal antibody canakinumab against placebo in over 10 000 patients with previous MI and plasma C-reactive protein ≥2 mg/L.[712] The highest dose (300 mg every 3 months) reduced plasma interleukin-6 and C-reactive protein and the combined endpoint of cardiovascular death, non-fatal MI, and non-fatal stroke over a mean of 3.7 years: 3.90 vs. 4.50 events per 100 person-years (HR 0.86; 95% CI, 0.75–0.99; $P = .031$). The other doses did not provide favourable results. Despite efficacy, the drug was not developed further for this indication because of the risk of fatal infections and high costs.

Low-dose methotrexate (target dose 15–20 mg once weekly) did not reduce the composite of cardiovascular death, non-fatal MI, non-fatal stroke, or unstable angina-driven revascularization in 4786 patients with previous MI or multivessel coronary atherosclerosis and additional DM or metabolic syndrome.[713] The trial was stopped early (median 2.3 year follow-up) for futility.

The COLCOT (Colchicine Cardiovascular Outcomes Trial) tested low-dose colchicine (0.5 mg daily) vs. placebo in 4745 patients with recent MI (<30 days) regardless of C-reactive protein values.[714] During a median of 2.3 years, the composite of cardiovascular death, resuscitated

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cardiac arrest, non-fatal MI, non-fatal stroke, or unstable angina-driven revascularization occurred in 5.5% on colchicine vs. 7.1% on placebo (HR 0.77; 95% CI, 0.61–0.96; $P = .02$). Colchicine had favourable effects on each outcome component. All-cause mortality did not differ (43 vs. 44 events). Diarrhoea was reported in 9.7% vs. 8.9% (statistically non-significant); pneumonia, although not frequent, was recorded more often with colchicine than placebo (0.9% vs. 0.4%; $P = .03$).

The LODOCO2 trial (Low-Dose Colchicine 2) randomized 5500 patients with atherosclerotic CAD who had been stable for at least 6 months to low-dose colchicine (0.5 mg daily) or placebo for a median of 2.4 years.[715] The primary endpoint (cardiovascular death, spontaneous MI, ischaemic stroke, or ischaemia-driven revascularization) occurred in 6.8% on colchicine vs. 9.6% on placebo (HR 0.69; 95% CI, 0.57–0.83; $P < .001$). The main secondary endpoint (cardiovascular death, non-fatal MI, or non-fatal stroke) was reduced by 28% (4.2% on colchicine vs. 5.7% on placebo; HR 0.72; 95% CI, 0.57–0.92; $P = .007$). There were no significant differences in rates of pneumonia or GI disorders. The incidence of non-cardiovascular death was nominally higher, but not statistically significant (0.7 vs. 0.5 events per 100 person-years; HR 1.51; 95% CI, 0.99–2.31).

A recent meta-analysis including over 12 000 patients with atherothrombotic CAD[716] has estimated the treatment effects of colchicine vs. placebo for individual outcome components. Significantly lower risks were found for MI (RR, 0.76; 95% CI, 0.61–0.96), stroke (RR, 0.48; 95% CI, 0.30–0.77) and unstable angina-driven revascularization (RR, 0.61; 95% CI, 0.42–0.89), with no significant difference for cardiovascular death (RR, 0.73; 95% CI, 0.45–1.21), all-cause death (RR, 1.01; 95% CI, 0.71–1.43), or GI events (provided colchicine daily dose did not exceed 0.5 mg; RR, 1.02; 95% CI, 0.92–1.14).

Recommendation Table 20 — Recommendations for anti-inflammatory drugs in patients with chronic coronary syndrome (see also Evidence Table 20)

Recommendation	Class[a]	Level[b]
In CCS patients with atherosclerotic CAD, low-dose colchicine (0.5 mg daily) should be considered to reduce myocardial infarction, stroke, and need for revascularization.[714–716]	IIa	A

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CAD, coronary artery disease; CCS, chronic coronary syndrome.
[a]Class of recommendation.
[b]Level of evidence.

Recommendation Table 21 — Recommendations for angiotensin-converting enzyme inhibitors in patients with chronic coronary syndrome (see also Evidence Table 21)

Recommendations	Class[a]	Level[b]
In CCS patients, ACE-Is (or ARBs) are recommended in the presence of specific comorbidities, such as hypertension, diabetes, or heart failure.[683–685]	I	A
ACE-Is should be considered in CCS patients at very high risk of cardiovascular events.[686,687,690,691]	IIa	A

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ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCS, chronic coronary syndrome.
[a]Class of recommendation.
[b]Level of evidence.

4.4. Revascularization for chronic coronary syndromes

Invasive treatment of CAD with either CABG or PCI is historically described under the term revascularization. Although both procedures increase CFC[365,366] and prevent myocardial ischaemia during exercise or emotional stress, they do not heal coronary atherosclerosis. Revascularization by both modalities improves angina-related health status.[50,52,717] Randomized and meta-analytical evidence supports a survival benefit above medical therapy for CABG in patients with left main disease,[718–721] as well as three-vessel disease,[722] particularly in patients with LV dysfunction.[719,723,724] Most of this evidence was obtained prior to the introduction of disease-modifying therapies such as ACE-Is/ARBs and statins. Meta-analytical evidence suggests a potential benefit of PCI on cardiovascular survival,[55,725,726] which, similarly to CABG, appears to be related to the prevention of MI.[55,727] In general, among surgically eligible patients with multivessel disease, CABG is superior to PCI and to medical therapy, particularly in those with diabetes and higher coronary complexity.[727,728] Recent evidence has generated controversy on (i) the value of routine early revascularization compared with optimal medical therapy alone,[47,56,314,729] (ii) the value of PCI vs. CABG for complex CAD,[326,730] and (iii) the value of ischaemia testing for decision-making in revascularization.[315,317,726] At the same time, advances in interventional technologies and medications have expanded the application of PCI to more complex forms of CAD.[731]

4.4.1. Appropriate indication for myocardial revascularization

In CAD patients with moderate or severe inducible ischaemia but no left main disease nor LVEF of <35%, the largest-to-date ISCHEMIA trial, up to 5 years, did not show significant benefit of an initial invasive strategy over an initial conservative strategy for the primary endpoint of ischaemic cardiovascular events or death from any cause,[47] triggering discussion about the role of initial angiography followed by revascularization when feasible, in this type of CCS patients, once optimal medical therapy has been established. The CLARIFY registry found that many CCS patients with angina experience a resolution of symptoms over time, often without changes in treatment or revascularization, and experience good outcomes.[404] While these findings suggest that this type of CCS patients should initially receive conservative medical management, it is worth noting that patients who were randomly assigned to the invasive strategy in the ISCHEMIA trial experienced significantly lower rates of spontaneous MI and greater improvement in angina-related health status compared with those assigned to the conservative strategy.[47,50] Furthermore, the ORBITA 2 trial demonstrated that patients with stable angina, who were receiving minimal or no antianginal medication and had objective evidence of ischaemia, experienced a lower angina symptom score following PCI treatment compared with a placebo procedure, indicating a better health status with respect to angina.[52] Although initial conservative medical management of CCS patients is generally preferred, symptom improvement by revascularization should therefore not be neglected if patients remain symptomatic despite antianginal treatment.

After publication of the ISCHEMIA trial results, several meta-analyses have reported similar overall survival and inevitably higher rates of procedural MI with routine revascularization, while confirming consistently greater freedom from spontaneous MI, unstable angina, and anginal symptoms after revascularization compared with GDMT alone.[732–734] Of note, these meta-analyses showed some differences in methodology, in selected trials, and follow-up duration.

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Furthermore, the importance of 'any myocardial infarction' as an endpoint is complicated by a debate over the prognostic importance of procedural infarctions as well as how various MI definitions affect the prediction of long-term outcomes[735,736] A more recent meta-analysis of RCTs that included the longest available follow-up showed that adding revascularization to GDMT reduced cardiac mortality compared with GDMT alone. The cardiac survival benefit improved with the duration of follow-up and was linearly related to a lower rate of spontaneous MI.[55]

In ISCHEMIA, patients randomized to initial medical therapy alone had significantly more spontaneous MIs during the 5-year follow-up, which were associated with subsequent cardiovascular death.[737] An early invasive strategy was associated with lower long-term risks of cardiovascular events, mainly spontaneous MIs, compared with a conservative strategy, at the cost of a higher risk of procedural MIs.[738]

Extended follow-up of the ISCHEMIA trial population up to 7 years (ISCHEMIA-EXTEND) revealed a significant 2.2% absolute decrease in cardiovascular mortality (adjusted HR 0.78; 95% CI, 0.63–0.96) favouring the initial invasive strategy.[56] The benefit was most marked in patients with multivessel CAD (≥70% diameter stenosis on CCTA; adjusted HR 0.68; 95% CI, 0.48–0.97) but was offset by a significant 1.2% absolute increase in non-cardiac mortality, without a significant difference (absolute decrease of −0.7%) in all-cause mortality.[56] In a recent meta-analysis of 18 trials, on the other hand, non-cardiac mortality did not differ significantly by initial invasive or conservative strategy in CCS patients with preserved or slightly impaired LVEF.[739] In a *post hoc* analysis of the ISCHEMIA trial, CAD severity was associated with a higher risk of all-cause death, MI, and the primary endpoint of the trial.[317] This effect appeared to be most noticeable in patients with multivessel disease and/or proximal LAD stenosis (≥70% diameter stenosis on CCTA).

4.4.2. Additional considerations on reduced systolic left ventricular function: myocardial viability, revascularization, and its modality

Ischaemic cardiomyopathy is the leading cause of HFrEF, and new ischaemic events are the main drivers of worsening LV function, strongly impacting long-term survival.[740] Ischaemic HFrEF is characterized by irreversibly damaged and scarred myocardium alternating with 'viable' myocardium that may be dysfunctional owing to repetitive ischaemic episodes (stunning) or chronic hypoperfusion (hibernation).[741] According to classical concepts, revascularization combined with GDMT synergistically improves systolic LV function and overall prognosis in patients with ischaemic HFrEF by restoring sufficient perfusion to dysfunctional yet viable myocardial segments and preventing new ischaemic events.[742] However, it carries increased periprocedural risk, especially in patients with severe LV dysfunction (LVEF ≤ 35%). A meta-analysis of 26 observational studies, including 4119 patients, showed that CABG can be performed with acceptable operative mortality (5.4%; 95% CI, 4.5%–6.4%) and 5-year actuarial survival (75%) in patients with severe LV dysfunction (mean pre-operative EF of 24.7%).[743]

In the 1990s, observational studies reported improved survival after revascularization in patients with severe CAD, significant LV dysfunction, and evidence of myocardial viability on imaging tests.[744] The PARR-2 trial (PET and Recovery Following Revascularization) randomized 430 patients with suspected ischaemic cardiomyopathy to an F-18-fluorodeoxyglucose PET-assisted strategy or standard care. While there was a non-significant trend towards lower risk of cardiac events at 1 year with PET assistance,[745] the 5-year follow-up showed no overall reduction in cardiac events.[746] However, significant benefits were observed when adhering to PET recommendations (after excluding 25% protocol violations).[746] *Post hoc* analyses and substudies confirmed the positive outcomes of a PET-guided strategy.[747,748]

The Surgical Treatment for Ischemic Heart Failure (STICH) trial randomized 1212 patients with CAD without left main diseases eligible for CABG and LVEF ≤35% to receive either CABG and GDMT, or GDMT alone. The trial failed to achieve its primary endpoint of all-cause mortality at a median follow-up of 4 years (HR with CABG, 0.86; 95% CI, 0.72–1.04; $P = .12$).[53] However, at a median follow-up of 9.8 years, both all-cause and cardiovascular mortality were significantly reduced with CABG compared with GDMT alone (from 66.1% to 58.9%; HR 0.84; 95% CI, 0.73–0.97; $P = .02$; and from 49.3% to 40.5%; HR 0.79; 95% CI, 0.66–0.93; $P = .006$, respectively).[54] The reduction of cardiovascular mortality by CABG was greater in patients with three-vessel disease[54] and the reduction of all-cause mortality was greater in younger patients, in whom cardiovascular deaths accounted for a larger proportion of deaths vs. older patients ($P = .004$ for interaction).[749] Viability was assessed by SPECT, dobutamine echocardiography, or both in 50% of STICH patients (298 randomized to CABG and 303 randomized to GDMT alone).[750] There were no significant interactions between presence or absence of myocardial viability and improved LV function or long-term survival benefit for CABG above GDMT.[747,748,750]

There have been no RCTs directly comparing CABG and PCI in patients with ischaemic HF. A meta-analysis of 21 studies, mostly observational except three including STICH, published between 1983 and 2016, supported CABG and PCI on a background of GDMT in appropriate patients with multivessel disease and LV systolic dysfunction; revascularization with either CABG or PCI improved long-term survival compared with GDMT, but compared with PCI, CABG provided a survival benefit and a lower risk of MI or repeat revascularization, with a slightly higher incidence of stroke.[751]

PCI is increasingly used over CABG for treating patients with ischaemic HF and multivessel disease, as shown by two large registries.[752,753] While these registries suggest that CABG is associated with a lower risk of long-term all-cause and cardiovascular mortality and lower MACE compared with PCI in patients with CAD and LVEF ≤35%,[752,753] it is important to interpret these observational studies with great caution, given significant differences in baseline characteristics, including age, history of previous MI, severity of CAD, and completeness of revascularization.[754] For the comparison of CABG with PCI in managing ischaemic HF with severely impaired LV dysfunction and multivessel CAD, the results of ongoing trials (NCT05427370 and NCT05329285) are awaited.

The Percutaneous Revascularization for Ischemic Left Ventricular Dysfunction (REVIVED-BCIS2) trial randomized 700 patients with impaired LV function (EF ≤ 35%), extensive CAD amenable to PCI, and evidence of myocardial viability in at least four dysfunctional myocardial segments to a strategy of PCI plus GDMT or GDMT alone.[729] After a 3.4-year follow-up, PCI showed no significant reduction in the composite primary endpoint of all-cause death or HF rehospitalization (HR 0.99; 95% CI, 0.78–1.27; $P = .96$). Patients treated by PCI showed slight and temporary improvements in their symptoms and no incremental improvement of overall LV function compared with GDMT.

A pre-specified secondary analysis of REVIVED-BCIS2, conducted in 87% of patients, failed to establish significant correlations between viability extent (assessed by CMR or dobutamine stress echocardiography) and outcomes, thereby challenging the traditional concept of myocardial hibernation, which can be reversed by revascularization.[755] However, the analysis did find that larger amounts of non-viable myocardium were linked to an increased risk of the primary outcome,

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regardless of whether PCI was performed, suggesting that viability assessment may be useful for risk stratification.

The two main RCTs, STICH and REVIVED-BCIS2, differ in various aspects. The REVIVED-BCIS2 trial patients were, on average, 10 years older than those in the STICH trial, had a less frequent history of MI (50% vs. 78%) and were more likely to be angina-free at baseline (67% vs. 36%). REVIVED-BCIS2 included fewer patients with three-vessel disease (38% vs. 60%). Additionally, patients in REVIVED-BCIS2 received more modern HF therapy and were more commonly treated with an ICD/CRT (cardiac resynchronization therapy) (21%/53% vs. 2%/19%). Finally, the duration of follow-up was shorter compared with the STICH trials. All these factors may have contributed to the absence of any PCI effect on survival.

In conclusion, the heterogeneous designs of the above studies, the statistical underpower of subgroup analyses, the heterogeneous methods of viability assessments (e.g. based on metabolism, contractile reserve, or scar extent) and variable quantification (dichotomous vs. continuous) leave many open questions on how viability should be defined,[756] and when and why it should be assessed in ischaemic HFrEF patients. For instance, the classical binary definition of myocardial viability may benefit from more contemporary paradigms and from greater focus on anatomic alignment between viable myocardial regions and feasible revascularization of corresponding perfusing arteries.[741] Moreover, therapeutic aims should go beyond enhancing local and overall LV function to include safeguarding against new ischaemic events[727] and their ensuing possibly lethal arrhythmias. Therefore, an integrative approach, including highly specialized imaging, HF, arrhythmia, and revascularization specialists, is needed for optimal patient management and improved outcomes.

4.4.3. Additional considerations—complete vs. partial revascularization

Complete revascularization treating all vessels and lesions causing ischaemia is preferable to incomplete revascularization.[757] However, various factors may influence the implementation of complete revascularization, including clinical setting, comorbidities, anatomical and procedural features, advanced age, or frailty.[758,759] Furthermore, whether the focus of complete revascularization should be anatomical or functional is still unclear. In the PCI group of the SYNTAX (SYNergy Between PCI with TAXUS and Cardiac Surgery) trial, a higher residual SYNTAX score, indicating incomplete anatomical revascularization, was associated with a higher mortality rate.[760] However, the outcomes of anatomically incomplete but functionally complete revascularization by PCI were superior to those of anatomically complete revascularization.[49,308,761] Of note, recent studies suggest that significant levels of residual ischaemia can persist despite good angiographic results after complex coronary stenting.

Individual reports suggest that incomplete revascularization is associated with increased mortality compared with complete revascularization.[762] In addition, unintended incomplete revascularization appears to be a surrogate marker of anatomic complexity and comorbidities, predisposing to more rapid native CAD progression.[760,763] An important predictor of anatomical incomplete revascularization by PCI is the presence of chronic total occlusion. Randomized trials have shown improvements of angina and QoL with PCI for chronic total occlusion lesions,[764,765] but failed to show any reduction of mortality risk and MI rates.[764–767]

Among patients with high-risk multivessel CAD, incomplete anatomical revascularization is reported more frequently among those treated with PCI compared with those treated with CABG. The rate ranges from 32% to 56% for PCI and 30% to 37% for CABG.[759,762,768] However, interpreting these data is challenging due to several factors. Firstly, there is no uniform definition of complete revascularization.[769,770] Secondly, although completeness of revascularization with PCI can be evaluated immediately after the procedure, many patients require staged procedures to achieve complete revascularization. Thirdly, within the first year after CABG, 20% to 40% of patients may experience asymptomatic graft failure as determined by CCTA.[771–773] Therefore, selecting a revascularization modality cannot be based solely on completeness of revascularization but rather should be determined through shared decision-making and a risk–benefit assessment.

4.4.4. Assessment of clinical risk and anatomical complexity

While both CABG and PCI have shown continuous technical improvements and better clinical outcomes over time,[774,775] the potential benefit of revascularization must be carefully evaluated against the procedural risk. The Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) risk model has proved to be more effective than the EuroSCORE II risk model in predicting peri-operative mortality and complications in CABG patients due to its continuous calibration.[776] It has also shown satisfactory discrimination for all-cause death at 30 days in patients undergoing CABG, allowing differentiation of high (>8%) and intermediate (4% to 8%) from low (<4%) surgical mortality risk. Although primarily designed for surgical risk assessment, the STS-PROM score can also be used to evaluate the risk of revascularization through PCI in patients with multivessel disease, as recent studies[326] have shown similar mortality rates between PCI and CABG. However, in patients with left main coronary artery disease (LMCAD) participating in the EXCEL trial (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization), the STS risk models were effective in predicting outcomes for CABG but not for PCI regarding peri-operative mortality and renal failure.[777] Interestingly, the STS stroke risk model was more successful in predicting outcomes for PCI compared with CABG. More accurate risk prediction tools are needed to precisely estimate adverse events following LMCAD revascularization through both CABG and PCI. Other clinical factors, such as frailty or liver cirrhosis,[778,779] have been found to increase post-operative mortality and should be taken into consideration during the decision-making process.[780]

The SYNTAX score was prospectively developed as an angiographic stratification tool to quantify the complexity of coronary lesions in patients with left main coronary artery (LMCA) or multivessel CAD and aid clinicians in deciding the most appropriate revascularization procedure during Heart Team discussions.[781] However, there are limitations to the SYNTAX score. Firstly, it is a time-consuming score requiring a detailed angiographic evaluation of each lesion. Secondly, there is considerable inter-observer variability in its calculation, with a poor correlation between core lab and operator-calculated SYNTAX score being reported.[779] Thirdly, it is an anatomical score that quantifies obstruction but not plaque burden. Fourthly, it does not take physiological and clinical variables into account.[782] Machine learning may streamline this process, generating prognostic information that is superior to clinical risk scores[783] and relevant to clinical decision-making.

The SYNTAX II score was developed by combining clinical and anatomic features to better guide decision-making between CABG and PCI than the anatomical SYNTAX score.[784,785] Although the usefulness of the SYNTAX II score was demonstrated in several studies,[785–787] it

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overestimated 4-year all-cause mortality in the EXCEL trial.[788] The updated version, SYNTAX score II 2020, using the SYNTAX Extended Survival (SYNTAXES) data and external validation in the population of the FREEDOM, BEST, and PRECOMBAT trials,[789] showed modest discrimination for predicting 5-year MACE (c-index for PCI and CABG of 0.62 and 0.67, respectively) and acceptable discrimination for predicting 10-year mortality. Another validation study indicated that the score displayed acceptable discrimination for all-cause mortality at 5 years in a Japanese cohort with LMCAD and/or multivessel CAD,[787] but external validation in a prospective setting is lacking.[783]

The British Cardiovascular Intervention Society myocardial jeopardy score (BCIS-JS) is an alternative to the SYNTAX score, enabling the assessment of the severity and extent of CAD. It has been proven effective in predicting mortality after PCI and assessing the completeness of revascularization,[790] but it is not as commonly used as the SYNTAX score.

4.4.5. Choice of myocardial revascularization modality

Both myocardial revascularization modalities—PCI and CABG—can achieve excellent outcomes, although through different mechanisms, in appropriately selected patients when GDMT alone fails.

4.4.5.1. Patients with single- or two-vessel coronary artery disease

Randomized evidence and subgroup analyses of trials enrolling a broader spectrum of CAD patients showed similar performance of PCI and CABG in patients with one- or two-vessel CAD, with or without the involvement of the proximal LAD in terms of death, stroke, or MI.[791–797] In patients with complex LAD lesions, the need for late repeat revascularization is higher after PCI than CABG,[797] but CABG is a more invasive procedure with inherent risks, longer hospital stay and healing.[758]

4.4.5.2. Patients with unprotected left main coronary artery disease

Over the past two decades, several trials have compared PCI and CABG in patients with multivessel CAD, with or without unprotected LMCAD[326,728,730,798–801] (*Table 9*). The patients who were included in these trials had to meet the eligibility criteria for both CABG or PCI at an acceptable risk level, and their coronary anatomy had to allow complete revascularization through both procedures. However, due to the strict inclusion criteria, only a small percentage of eligible patients (ranging from 6% to 40%) were enrolled in these trials.[798,801] The strict inclusion criteria resulted in enrolling a relatively young population with a lower burden of comorbidities (mean age <66 years).[728,730,798,801]

Meta-analyses of RCTs have shown that the risk of death is similar for both CABG and PCI for LMCAD, even for patients with a high SYNTAX score, up to 5–10 years after the intervention. However, the risk of stroke is higher with CABG, while the risk of spontaneous MI is higher with PCI.[728,730,800,802–804] In the individual-patient data meta-analysis of four randomized trials,[730] mortality over 5 years was not statistically different between patients treated with PCI or with CABG [11.2% vs. 10.2%; HR 1.10 (95% CI, 0.91–1.32); $P = .33$; absolute risk difference of 0.9%]. A similar treatment effect was observed for 10-year mortality [22.4% vs. 20.4%; HR 1.10 (95% CI, 0.93–1.29); $P = .25$; absolute risk difference 2.0%]. Spontaneous MI was lower in the CABG arm [6.2% vs. 2.6%; HR 2.35 (95% CI, 1.71–3.23); $P < .0001$; absolute risk difference 3.5%], while the results of periprocedural MI differed according to whether the analysis used the protocol definition or the universal definition of MI (available for only two studies). Stroke was not statistically different overall [2.7% vs. 3.1%; HR 0.84 (95% CI, 0.59–1.21); $P = .36$; absolute risk difference of −0.4%]. However, in a pre-specified analysis of the first 12 months of follow-up, stroke was lower after PCI than after CABG [0.6% vs. 1.6%; HR 0.37 (95% CI, 0.19–0.69); $P = .002$; absolute risk difference of −1.0%].[782] Subgroup analysis based on the SYNTAX score and the number of additionally involved coronary vessels revealed no difference in all-cause mortality between CABG and PCI for SYNTAX score ≤32 or LMCA stenosis with 0/1 vessel disease. However, a trend for higher all-cause mortality was noted with PCI for SYNTAX score >32 (HR 1.30; 95% CI, 0.92–1.84) and/or LMCA stenosis with 2/3 vessel disease (HR 1.25; 95% CI, 0.97–1.60).[782] Of note, the LMCA stenosis involved distal bifurcation in 75% of the patients, and the absence of a bifurcation lesion had no impact on mortality.[730] True bifurcation left main lesions (defined as Medina type 1,1,1 or 0,1,1 both main vessel and side vessel >50% narrowed with reference diameters ≥2.75 mm),[805] which frequently require 2-stent techniques, have worse clinical outcomes than non-bifurcation lesions.[806–808] Despite excellent results after LMCA bifurcation stenting on angiography, 13% of patients still experience residual ischaemia in turn associated with higher long-term cardiovascular mortality.[809] Using intracoronary imaging guidance to optimize stent expansion and prevent side-branch jailing may improve outcomes after PCI of bifurcation LMCA lesions.[810]

Operator experience may significantly affect the outcomes after interventional procedures. A single-centre study from China found that operators with a higher volume of procedures performed (>15 per year) had better outcomes for unprotected LMCA PCI.[811] An analysis of the outcome data from the British Cardiovascular Intervention Society's national PCI database on 6724 patients who underwent PCI for unprotected LMCA between 2012 and 2014 revealed that the volume of procedures performed by the operator plays a significant role in determining the outcome after PCI of unprotected LMCA.[812] Although high-volume operators undertook PCIs on patients with greater comorbid burden and CAD complexity compared with low-volume operators, 12-month survival was lower in high-volume operators [odds ratio (OR) 0.54; 95% CI, 0.39–0.73]. A close association between operator volume and superior 12-month survival was observed ($P < .001$).

A 2022 Joint ESC/EACTS (European Association for Cardio-Thoracic Surgery) task force recently reviewed the 2018 guideline recommendations on the revascularization of LMCAD in low-risk surgical patients with suitable anatomy for PCI or CABG.[782] The review was mainly based on the recent individual-patient data meta-analysis[730] of the long-term outcomes after CABG or PCI for LMCAD from four randomized clinical trials that included 4394 patients between March 2005 and January 2015. The review confirmed that for stable CCS patients with left main stem disease requiring revascularization, both treatment options are clinically reasonable based on patient preference, expertise availability, and local operator volumes. It was proposed that revascularization with CABG be the recommended option, with suggested class I and LOE A, while PCI be overall recommended with a suggested class IIa and LOE A. The present guidelines confirm that, among patients suitable for both revascularization modalities, CABG is recommended as the overall preferred revascularization mode over PCI, given the lower risk of spontaneous MI and repeat revascularization.[730,782] The present guidelines also acknowledge that in patients with significant LMCA stenosis of low complexity (SYNTAX score ≤22), in whom PCI can provide equivalent completeness of revascularization to that of CABG, PCI is recommended as an alternative to CABG, given its lower invasiveness and non-inferior survival.[718,728,730,802,813]

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Table 9 Summary of trial-based evidence for the comparison of percutaneous coronary intervention and coronary artery bypass grafting in patients with left main coronary artery disease

Study	Study population	Primary endpoint	Follow-up	Findings
PRECOMBAT (non-inferiority)[814]	600 patients with newly diagnosed LMCAD who had stable angina, unstable angina, silent ischaemia, or non-ST-segment elevation MI	All-cause death, MI, stroke, or ischaemia-driven target vessel revascularization	2 years	1-year follow-up: 8.7% and 6.7% primary endpoints for PCI and CABG, respectively, absolute risk difference 2% (95% CI, –1.6% to 5.6%), $P = .01$ for non-inferiority 2-year follow-up: 12.2% and 8.1% primary endpoints for PCI and CABG, respectively, HR 1.50 (95% CI, 0.90–2.52), $P = .12$
PRECOMBAT (extended follow-up)[815]			5 years	17.5% and 14.3% primary endpoints for PCI and CABG, respectively, HR 1.27 (95% CI, 0.84–1.90), $P = .26$
PRECOMBAT (extended follow-up)[816]			11.3 years (median)	29.8% and 24.7% primary endpoints for PCI and CABG, respectively, HR 1.25 (95% CI, 0.93–1.69)
SYNTAX[817]	1800 patients with *de novo* three-vessel ($n = 1095$) and LMCAD ($n = 795$)	All-cause death, stroke, MI, and repeat revascularization	1 year	For the LMCAD group: 15.8% and 13.7% primary endpoints for PCI and CABG, respectively; $P = .44$
SYNTAX[818]			3 years	For the LMCAD group: 26.8% and 22.3%, primary endpoints for PCI and CABG, respectively; $P = .20$
SYNTAX[813]			5 years	For the LMCAD group: 36.9% and 31.0% primary endpoints for PCI and CABG, respectively, HR 1.25 (95% CI, 0.93–1.69), $P = .12$
SYNTAX (extended follow-up)[795]		All-cause death	10 years	For the LMCAD group: 27% and 28% primary endpoints for PCI and CABG, respectively, HR 0.92 (95% CI, 0.69–1.22)
NOBLE (non-inferiority hypothesis)[819]	1201 patients with LMCAD who had stable angina pectoris, unstable angina pectoris, or non-ST-segment elevation myocardial infarction	All-cause death, non-procedural MI, any repeat coronary revascularization, or stroke	3.1 years (mean)	28% and 18% primary endpoints for PCI and CABG, HR 1.51 (95% CI, 1.13–2.00), $P = .004$ for superiority
NOBLE (extended follow-up)[820]			4.9 years (median)	28% and 19% primary endpoints for PCI and CABG, HR 1.58 (95% CI, 1.24–2.01), $P < .001$ for superiority
EXCEL (non-inferiority hypothesis)[821]	1905 patients with LMCAD of low or intermediate anatomical complexity (SYNTAX score ≤ 32)	All-cause death, stroke, or MI	3 years (median)	15.4% and 14.7% primary endpoints for PCI and CABG, absolute risk difference 0.7% (upper 97.5% confidence limit: 4%), $P = .02$ for non-inferiority; HR 1.00 (95% CI, 0.79–1.26), $P = .98$ for superiority
EXCEL (extended follow-up)[822]			5 years	22.0% and 19.2% primary endpoints for PCI and CABG, absolute risk difference 2.8% (95% CI, −0.9 to 6.5), $P = .13$; OR 1.19 (95% CI, 0.95–1.50)

CABG, coronary artery bypass grafting; CI, confidence interval; HR, hazard ratio; LMCAD, left main coronary artery disease; MI, myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention.

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4.4.5.3. Patients with multivessel coronary artery disease

The SYNTAX and SYNTAXES randomized trials, comparing PCI and CABG for multivessel CAD with or without unprotected LMCAD, reported differences in terms of survival and freedom from cardiovascular events dependent on SYNTAX score.[795,798,823] The recently published 10-year follow-up results of the SYNTAX trial (SYNTAXES trial) reported similar all-cause death rates with both revascularization modalities,[795] while there was significantly higher mortality in patients with SYNTAX scores ≥33 who were randomized for PCI (HR 1.41; 95% CI, 1.05–1.89).[795] A significant 5-year mortality gap between PCI and CABG has been reported among patients with complex multivessel CAD in the presence of DM (15.7% after PCI vs. 10.7% after CABG; HR 1.44; 95% CI, 1.20–1.77; $P = .0001$).[728]

In the FREEDOM trial (Strategies for Multivessel Revascularization in Patients with Diabetes), 1900 patients with diabetes and multivessel disease without LMCAD were randomized to CABG vs. PCI (using first-generation DES). Long-term results at a median follow-up duration of 3.8 years [interquartile range (IQR) 2.5–4.9 years] showed higher all-cause mortality in the PCI group vs. CABG group (24.3% vs. 18.3%; $P = .01$).[801] Out of all the centres that participated in the study, only 25 agreed to participate in the FREEDOM extended follow-up, and therefore, only 49.6% of patients in the study were followed up for up to 8 years thus limiting statistical power. The all-cause mortality rate among the FREEDOM follow-up patients was not significantly different between those who underwent PCI and CABG procedures (23.7% vs. 18.7%; HR 1.32; 95% CI, 0.97–1.79; $P = .076$). In multivariable analysis, a significant interaction emerged between patient age and long-term survival benefit of CABG surgery. Patients younger than the median age at study entry (63.3 years) preferentially derived benefit from CABG; mortality among patients ≤63.3 years old was 20.7% (PCI) vs. 10.2% (CABG); mortality among patients >63.3 years old was 26.3% vs. 27.6% ($P = .01$ for interaction).[824]

4.4.5.4. Impact of coronary pressure guidance on multivessel coronary artery disease patients undergoing percutaneous coronary intervention

Consistently higher rates of repeat revascularizations following PCI compared with CABG have been shown in clinical trials involving multivessel CAD patients, with significant impacts on outcomes.[825] With the use of modern DESs, the rate of repeat revascularization after PCI has declined.[725,795,802,820] FFR guidance during PCI leads to lower revascularization rates compared with angiography-guided PCI, with fewer stents placed in the FFR group.[826]

In the FAME 3 trial, 1500 patients with three-vessel CAD not involving the LMCA were randomly assigned to PCI with second-generation DESs (durable polymer zotarolimus-eluting stents) guided by FFR, or to CABG.[326] At 1-year follow-up, the incidence of the composite primary endpoint, MACCE [major adverse cardiac (death from any cause, MI, stroke, or repeat revascularization) or cerebrovascular events], was 10.6% among patients assigned to FFR-guided PCI and 6.9% among patients assigned to CABG surgery (HR 1.5; 95% CI, 1.1–2.2), findings that were not consistent with non-inferiority ($P = .35$ for non-inferiority).[326] At 3-year follow-up, there still was a significantly higher rate of MACCE for PCI than for CABG (18.6% vs. 12.5%; HR 1.5; 95% CI, 1.2–2.0; $P = .002$), consistent with the 1-year follow-up results. However, there was no difference in the incidence of the composite of death, MI, or stroke after FFR-guided PCI compared with CABG (12.0% vs. 9.2%; HR 1.3; 95% CI, 0.98–1.83; $P = .07$). The rates of death (4.1% vs. 3.9%; HR 1.0; 95% CI, 0.6–1.7; $P = .88$) and stroke (1.6% vs. 2.0%; HR 0.8; 95% CI, 0.4–1.7; $P = .56$) were not different, while MI again occurred more frequently after PCI (7.0% vs. 4.2%; HR 1.7; 95% CI, 1.1–2.7; $P = .02$).[827] Repeat revascularization was also more frequent after PCI (11.1% vs. 5.9%; HR 1.9; 95% CI, 1.3–2.7; $P = .001$). Of note, after both PCI and CABG, event rates were lower (about half for mortality) than in the SYNTAX cohort of patients with three-vessel CAD. There was a narrower difference for MI rates between the two modalities, probably owing to procedural advances with PCI and CABG and improvements in GDMT. In patients with less complex CAD (SYNTAX score ≤22), outcomes were as favourable as after CABG.

4.4.5.5. Virtual percutaneous coronary intervention: combination of coronary pressure mapping with coronary anatomy for percutaneous coronary intervention planning

There is increasing evidence on the impact of post-PCI FFR/iFR/QFR on outcomes after PCI.[828–833] A quarter of these patients have residual ischaemia (FFR < 0.80 or iFR ≤ 0.89) after angiographically successful PCI, with circa 80% of cases attributable to focal lesions not identified by angiography alone.[830] One randomized trial reported that post-PCI iFR/FFR can be improved by additional intracoronary intervention, including post-dilatation or additional stent implantation, but remains ≤0.80 in 18% of cases.[829] Preliminary results demonstrate that the combination of invasive coronary pressure mapping by iFR pullback or QFR mapping superimposed on the anatomical information of ICA accurately predict the post-PCI coronary pressure for any combination of stent location and stent length, as part of a 'virtual PCI' approach,[348,834] and allows modification of the procedural planning in about 30% of cases.[835] The AQVA (Angio-based Quantitative Flow Ratio Virtual PCI Versus Conventional Angio-guided PCI in the Achievement of an Optimal Post-PCI QFR) trial ($n = 300$) demonstrated that a strategy of QFR/ICA-based virtual PCI was associated with a higher rate of post-PCI QFR ≥0.90 compared with angiography-based PCI (93.4% vs. 84.9%, $P = .009$).[836] The DEFINE GPS trial (NCT04451044) is currently investigating the clinical benefit of pre-procedural coronary pressure mapping with iFR pullback and 'virtual PCI' to clarify this issue further and improve post-PCI clinical outcomes.

Virtual PCI can be conducted by combining anatomical information from CCTA with that of FFR-CT. FFR-CT/CCTA-based virtual PCI has two theoretical advantages over ICA-based virtual PCI: (i) it does not require invasive investigation, and (ii) it provides information on vessel wall/plaque composition.[837] FFR-CT/CCTA-based virtual PCI has been shown to accurately predict post-PCI FFR[838] and to modify PCI procedural planning in 31% of lesions and 45% of patients.[839] The Precise Procedural and PCI Plan (P4) trial (NCT05253677) is currently investigating the clinical benefit of iFR-based virtual PCI to clarify this issue further and improve post-PCI clinical outcomes.

4.4.5.6. Impact of intracoronary imaging guidance on multivessel coronary artery disease patients undergoing percutaneous coronary intervention

Three large randomized trials have recently investigated the clinical benefit of intracoronary imaging during 'complex' PCI. One trial, RENOVATE-COMPLEX PCI,[840] mainly investigated the benefit of IVUS (74% IVUS, 26% OCT), while the two others, OCTOBER[810] and ILUMIEN IV,[841] investigated the benefit of OCT. Importantly, while OCTOBER (true bifurcation lesions) and RENOVATE-COMPLEX PCI (including true bifurcation lesions, long lesions,

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chronic total occlusion lesions) focused on 'anatomically' complex lesions, ILUMIEN IV made the choice to define 'complexity' by the clinical context (DM and STEMI/NSTEMI) and/or by the anatomical characteristics of the lesions.

In RENOVATE-COMPLEX PCI, intravascular imaging-guided PCI led to a lower risk of a composite of death from a cardiac cause, target vessel-related MI, or clinically driven target-vessel revascularization than angiography-guided PCI by 2 years (7.7% vs. 12.3%; HR 0.64; 95% CI, 0.45–0.89; $P = .008$).[840]

In OCTOBER, OCT-guided PCI led to a lower risk of a composite of death from a cardiac cause, target-lesion MI, or ischaemia-driven target-lesion revascularization than angiography-guided PCI by 2 years (10.1% vs. 14.1%; HR 0.70; 95% CI, 0.50–0.98; $P = .035$).[810] In ILUMIEN IV, OCT-guided PCI failed to decrease the rate of the primary efficacy endpoint of target-vessel failure, defined as death from cardiac causes, target-vessel MI, or ischaemia-driven target-vessel revascularization (7.4% vs. 8.2%; HR 0.90; 95% CI, 0.67–1.19; $P = .45$), while the incidence of definite/probable stent thrombosis was significantly reduced by OCT guidance vs. angiography guidance (0.5% vs. 1.4%; HR 0.36; 95% CI, 0.14–0.91; $P = .02$).[841]

4.4.5.7. Hybrid revascularization in multivessel coronary artery disease patients

Arterial grafting with left internal mammary artery (LIMA) to the LAD system and multiple arterial grafting reduces the risk of graft occlusion, thus increasing the longevity of revascularization efficacy after CABG.[842,843] Hybrid revascularization of multivessel CAD with minimally invasive direct coronary artery bypass (MIDCAB)-LAD plus PCI of the remaining arteries may represent an alternative option. Hybrid off-pump revascularization seems a suitable option for patients at moderate-to-high risk for surgery by avoiding the use of cardiopulmonary bypass. Despite this attractive concept, the frequency of hybrid revascularizations remains extremely modest, with about 0.1% of surgical revascularizations.[844] Few data are available comparing hybrid revascularization vs. conventional CABG or PCI. Large registry data report higher rates of bleeding, renal failure, MI, and HF with hybrid revascularization compared with PCI alone,[844] while a very small randomized trial reported similar clinical outcomes at long-term follow-up.[845] It seems challenging to perform larger RCTs to investigate this question. The recent National Heart, Lung, and Blood Institute-funded Hybrid Trial (Hybrid Coronary Revascularization Trial; NCT03089398) was prematurely discontinued due to slow enrolment, with only 200 patients in 5 years.

4.4.6. Patient–physician shared decision-making to perform and select revascularization modality

Shared decision-making between patients and healthcare professionals, based on patient-centred care, is considered a paramount process in defining the appropriate therapeutic pathway. Essential aspects of shared decision-making are: a complete and accurate explanation of the disease; presentation and description of therapeutic options; discussion of potential risks, benefits, and impact on QoL for each procedure; considering patient preferences and goals; and carefully explaining each step of the post-procedural course and follow-up. Poor shared decision-making is associated with worse physical and mental outcomes, lower adherence to therapy, and an increased number of emergency department visits.[846–848] Shared decision-making and family meetings involving relatives increase patient trust in the physicians, with greater adherence to therapeutic decisions. Shared decision-making and patient medical education, considering the patient's characteristics, mental status, cultural beliefs, and educational level, are therefore associated with increased patient knowledge and better QoL and with lower levels of anxiety and depression.[849–851]

Using lay language and discussion with patients and relatives of short-term procedure-related and long-term risks and benefits—such as survival, relief of angina, QoL, the potential need for late reintervention, the need for prevention measures, and uncertainties associated with different treatment strategies—are of great importance. Although current recommendations are primarily based on the ability of treatments to reduce adverse events, including improved survival, there is growing interest in PROMs.[852] Patients are not only interested in knowing how recommended treatment impacts prognosis but also their QoL in the way they perceive it.[853] The patient's right to decline the treatment option recommended by the Heart Team must be respected. Patient refusal of a recommended treatment should be acknowledged in a written document after the patient has received the necessary information. In this case, the Heart Team may offer the patient an alternative treatment option.

The multidisciplinary Heart Team, on site or with partner institutions (Hub-Spoke institutions)—comprising clinical or non-invasive cardiologists, cardiac surgeons and interventional cardiologists, as well as anaesthetists or other specialists and healthcare professionals, if deemed necessary—should provide a balanced multidisciplinary decision-making process.

Transparency in informed consent is critical, particularly when treatment options are debated. Complex cases, such as patients with CAD of high anatomic complexity and significant non-cardiac comorbidities, should be discussed in the Heart Team, taking into consideration other characteristics not always included in traditional databases, such as frailty. Heart Team/guideline discordance is common in complex CAD patients undergoing revascularization, especially in elderly patients, those with complex coronary disease, and those treated at centres without cardiac surgery service. These patients have a higher risk of mid-term mortality.[854]

In all cases, it is necessary to allow sufficient time to assess all available information and clearly explain and discuss the findings with each patient. The rationale for a decision and consensus on the optimal revascularization treatment should be documented on the patient's chart. While the Heart Team decision is mainly driven by long-term survival benefits with a certain modality of revascularization, patient's preferences must be respected.[853,855,856]

4.4.7. Institutional protocols, clinical pathways, and quality of care

Institutional protocols, developed by the Heart Team and aligned with the current guidelines, should delineate specific anatomical and functional criteria of disease complexity and specific clinical subsets of patient' risk for cardiac surgery or intervention that may or may not be treated *ad hoc*. These protocols should be incorporated into clinical pathways, with regular meetings to assess the applied indications for myocardial revascularization and monitor the safety and effectiveness of the procedures, ensuring the quality of delivered patient care. Collaborative protocols are necessary when cardiac surgery isn't available on site, and remote Heart Team meetings should be established.

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Recommendation Table 22 — Recommendations for revascularization in patients with chronic coronary syndrome (see also Evidence Table 22)

Recommendations	Class[a]	Level[b]
Informed and shared decisions		
It is recommended that patients scheduled for percutaneous or surgical revascularization receive complete information about the benefits, risks, therapeutic consequences, and alternatives to revascularization, as part of shared clinical decision-making.[847,848,857]	I	C
For complex clinical cases, to define the optimal treatment strategy, in particular when CABG and PCI hold the same level of recommendation, a Heart Team discussion is recommended, including representatives from interventional cardiology, cardiac surgery, non-interventional cardiology, and other specialties if indicated, aimed at selecting the most appropriate treatment to improve patient outcomes and quality of life.	I	C
It is recommended to communicate the proposal of the Heart Team in a balanced way using language that the patient can understand.	I	C
It is recommended that the decision for revascularization and its modality be patient-centred, considering patient preferences, health literacy, cultural circumstances, and social support.[849–851]	I	C
It is recommended that the Heart Team (on site or with a partner institution) develop institutional protocols to implement the appropriate revascularization strategy in accordance with current guidelines.[855,856,858]	I	C
Revascularization to improve outcomes		
In chronic coronary syndrome patients with left ventricular ejection fraction >35%		
In CCS patients with LVEF >35%, myocardial revascularization is recommended, in addition to guideline-directed medical therapy, for patients with functionally significant left main stem stenosis to improve survival.[718,719,859,860]	I	A
In CCS patients with LVEF >35%, myocardial revascularization is recommended, in addition to guideline-directed medical therapy, for patients with functionally significant three-vessel disease to improve long-term survival and to reduce long-term cardiovascular mortality and the risk of spontaneous myocardial infarction.[55,56,317,732–734]	I	A
In CCS patients with LVEF >35%, myocardial revascularization is recommended, in addition to guideline-directed medical therapy, for patients with functionally significant single- or two-vessel disease involving the proximal LAD, to reduce long-term cardiovascular mortality and the risk of spontaneous myocardial infarction.[55,56,317,719,732–734]	I	B
In chronic coronary syndrome patients with left ventricular ejection fraction ≤35%		
In CCS patients with LVEF ≤35%, it is recommended to choose between revascularization or medical therapy alone, after careful evaluation, preferably by the Heart Team, of coronary anatomy, correlation between coronary artery disease and LV dysfunction, comorbidities, life expectancy, individual risk-to-benefit ratio, and patient perspectives.	I	C
In surgically eligible CCS patients with multivessel CAD and LVEF ≤35%, myocardial revascularization with CABG is recommended over medical therapy alone to improve long-term survival.[53,54,749,861]	I	B
In selected CCS patients with functionally significant MVD and LVEF ≤35% who are at high surgical risk or not operable, PCI may be considered as an alternative to CABG.[526,729]	IIb	B
Revascularization to improve symptoms		
In CCS patients with persistent angina or anginal equivalent, despite guideline-directed medical treatment, myocardial revascularization of functionally significant obstructive CAD is recommended to improve symptoms.[50,321,402,732,734,757]	I	A
Assessment of procedural risks and post-procedural outcomes		
In patients with complex CAD in whom revascularization is being considered, it is recommended to assess procedural risks and post-procedural outcomes to guide shared clinical decision-making.	I	C
Calculation of the STS score is recommended to estimate in-hospital morbidity and 30-day mortality after CABG.[777,862–864]	I	B
In patients with multivessel obstructive CAD, calculation of the SYNTAX score is recommended to assess the anatomical complexity of disease.[786,865]	I	B
Intracoronary imaging guidance by IVUS or OCT is recommended when performing PCI on anatomically complex lesions, in particular left main stem, true bifurcations, and long lesions.[866,337,810,840,841]	I	A
Intracoronary pressure measurement (FFR or iFR) or computation (QFR) :		
• is recommended to guide lesion selection for intervention in patients with multivessel disease; [308,826,866,867]	I	A
• should be considered at the end of the procedure to identify patients at high risk of persistent angina and subsequent clinical events;[828,830,831,868]	IIa	B
• may be considered at the end of the procedure to identify lesions potentially amenable to treatment with additional PCI.[350,829,831]	IIb	B

Continued

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Choice of revascularization modality		
It is recommended that physicians select the most appropriate revascularization modality based on patient profile,[c] coronary anatomy,[d] procedural factors,[e] LVEF, preferences, and outcome expectations.[719,725,728,792–795,801,816,820,822,859,869]	I	C

CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS, chronic coronary syndrome; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; IVUS, intravascular ultrasound; LAD, left anterior descending; LV, left ventricular; LVEF, left ventricular ejection fraction; MVD, multivessel disease; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; QFR, quantitative flow ratio; STS, Society of Thoracic Surgeons; SYNTAX, SYNergy Between PCI with TAXUS and Cardiac Surgery.
[a]Class of recommendation.
[b]Level of evidence.
[c]Age, frailty, cognitive status, diabetes, and any other comorbidities.
[d]Multivessel disease with/out left main stem involvement, high anatomical complexity, and likelihood of revascularization completeness.
[e]Local expertise and outcomes, surgical and interventional risk.

Recommendation Table 23 — Recommendations for mode of revascularization in patients with chronic coronary syndrome (see also Evidence Table 23)

Anatomically and clinically based recommendations for revascularization in CCS	Class[a]	Level[b]
Left main disease		
In CCS patients at low surgical risk[c] with significant left main coronary stenosis, CABG:		
• is recommended over medical therapy alone to improve survival;[719]	I	A
• is recommended as the overall preferred revascularization mode over PCI, given the lower risk of spontaneous myocardial infarction and repeat revascularization.[728,730,782]	I	A
In CCS patients with significant left main coronary stenosis of low complexity (SYNTAX score ≤22), in whom PCI can provide equivalent completeness of revascularization to that of CABG, PCI is recommended as an alternative to CABG, given its lower invasiveness and non-inferior survival. [718,728,730,802,813]	I	A
In CCS patients with significant left main coronary stenosis of intermediate complexity (SYNTAX score 23–32), in whom PCI can provide equivalent completeness of revascularization to that of CABG, PCI should be considered, given its lower invasiveness and non-inferior survival.[718,728,730,802,805,809,813,820,822]	IIa	A
Left main with multivessel disease[d]		
In CCS patients at low surgical risk with suitable anatomy, CABG is recommended over medical therapy alone to improve survival.[718,719,870]	I	A
In CCS patients at high surgical risk, PCI may be considered over medical therapy alone.[728,813]	IIb	B
Multivessel disease[d] and diabetes		
In CCS patients with significant multivessel disease and diabetes, with insufficient response to guideline-directed medical therapy, CABG is recommended over medical therapy alone and over PCI to improve symptoms and outcomes.[801,824,871–874]	I	A
In CCS patients at very high surgical risk, PCI should be considered over medical therapy alone to reduce symptoms and adverse outcomes.[55,874]	IIa	B
Three-vessel disease, without diabetes		
In CCS patients with significant three-vessel disease, preserved LVEF, no diabetes, and insufficient response to guideline-directed medical therapy, CABG is recommended over medical therapy alone to improve symptoms, survival, and other outcomes.[719,722,875]	I	A
In CCS patients with preserved LVEF, no diabetes, insufficient response to guideline-directed medical therapy, and significant three-vessel disease of low-to-intermediate anatomic complexity in whom PCI can provide similar completeness of revascularization to that of CABG, PCI is recommended, given its lower invasiveness, and generally non-inferior survival.[326,728,795,798,876]	I	A
Single- or double-vessel disease involving the proximal LAD		
In CCS patients with significant single- or double-vessel disease involving the proximal LAD and insufficient response to guideline-directed medical therapy, CABG or PCI is recommended over medical therapy alone to improve symptoms and outcomes.[52,321,719,791,792]	I	A
In CCS patients with complex significant single- or double-vessel disease involving the proximal LAD, less amenable to PCI, and insufficient response to guideline-directed medical therapy, CABG is recommended to improve symptoms and reduce revascularization rates.[877–879]	I	B
Single- or double-vessel disease not involving the proximal LAD		
In symptomatic CCS patients with significant single- or double-vessel disease not involving the proximal LAD and with insufficient response to guideline-directed medical therapy, PCI is recommended to improve symptoms.[50,321,732]	I	B
In symptomatic CCS patients with significant single- or double-vessel disease not involving the proximal LAD and with insufficient response to guideline-directed medical therapy, not amenable to revascularization by PCI, CABG may be considered to improve symptoms.	IIb	C

CABG, coronary artery bypass grafting; CCS, chronic coronary syndrome; LAD, left anterior descending; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; SYNTAX, SYNergy Between PCI with TAXUS and Cardiac Surgery.
[a]Class of recommendation.
[b]Level of evidence.
[c]For example: absence of previous cardiac surgery, or severe morbidities, or frailty, or immobility precluding CABG.
[d]Multivessel disease is defined as the involvement of at least two main coronary arteries.

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5. Optimal assessment and treatment of specific groups

5.1. Coronary artery disease and heart failure

About half of acute and chronic HF patients have an ischaemic aetiology.[880,881] Over the last decades, the proportion of ischaemic HFrEF has decreased while that of HFpEF, defined according to the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure,[526] has increased.[882] The evaluation of inducible ischaemia is important in patients with HF, given the high prevalence of CAD.[883–885] Moreover, patients with HFpEF may present MVA due to CMD.[886] Indeed, CMD was observed in up to 75% of patients with HFpEF and was associated with worse diastolic relaxation velocities, as well as higher filling pressures, and an increased risk of adverse events.[883–885,887–890] Clinical assessment alone may under-estimate the proportion of patients with obstructive or non-obstructive CAD, which can be found in up to 81% of HFpEF patients.[887] Under-estimation of obstructive CAD leads to failure in identifying those patients who may benefit from revascularization. Conversely, in ANOCA patients with preserved LV function, a CFR of <2 was independently associated with diastolic dysfunction and future MACE, especially HFpEF events.[891] This suggests that CMD and myocardial stiffness may contribute to HFpEF pathophysiology.[892] In HFpEF patients, functional imaging should, therefore, be considered to detect CMD and epicardial CAD.

Exercise or pharmacological stress echocardiography can be used for the assessment of inducible ischaemia and can also help in the differential diagnosis of HFpEF.[893,894] Stress SPECT or PET can also be used for the detection of inducible ischaemia. Non-invasive stress testing can be difficult in patients with HF because of possible exercise intolerance. CCTA is recommended in patients with HF with a low-to-intermediate pre-test likelihood of obstructive CAD and those with equivocal non-invasive stress tests, provided there is no contraindication to contrast administration.[894–898] In HFpEF patients, perfusion PET should be considered for the detection of CMD.[891] In patients with HFrEF and moderate-to-severe inducible myocardial ischaemia, surgical revascularization improved long-term survival.[54,315] The results of the REVIVED-BCIS2 trial seem to contradict these findings, as PCI did not reduce mortality or HF hospitalization in patients with severe LV systolic dysfunction (LVEF ≤ 35%) receiving optimal medical therapy.[729] The same trial also revealed that viability testing did not offer any prognostic benefit.[755] The role of myocardial revascularization and viability testing is further addressed in *Section 4.4.2*.

In HF patients with anginal (or equivalent) symptoms, despite optimized GDMT, CCTA or ICA is recommended to confirm the diagnosis of obstructive CAD and its severity.

Over the past three decades, several landmark clinical trials have provided robust evidence on the prognostic benefit of pharmacological therapies in patients with HFrEF. In these patients, four drug classes [ACE-Is or angiotensin receptor neprilysin inhibitors (ARNIs),[891] beta-blockers, mineralocorticoid receptor antagonists (MRAs), and SGLT2 inhibitors] are recommended for outcome improvement regardless of HF aetiology and comorbidities, including CAD.[526]

In patients with HFrEF, an ARB is recommended in patients who do not tolerate ACE-Is or ARNIs. Also, ivabradine should be considered in addition to the four pillars. It can be used as an alternative to beta-blockers, when contraindicated or not tolerated, or as additional antianginal therapy in patients with sinus rhythm and heart rate of >70 b.p.m.[899] Other antianginal drugs (e.g. amlodipine, felodipine, nicorandil, trimetazidine, ranolazine, and nitrates) are effective for improving symptoms in patients with HFrEF.[546,900–902] Diltiazem and verapamil increase HF-related events in patients with HFrEF and are contraindicated.[526] In patients with LVEF ≤35% of ischaemic aetiology, an ICD is strongly recommended for primary prevention; in those with LVEF ≤35% and QRS >130 ms, CRT needs to be considered.[526] Further details regarding the management of patients with HFrEF are reported in the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure.[526]

In patients with HFpEF, in addition to diuretics for treating congestion, SGLT2 inhibitors are now recommended for outcome improvement.[709] Additionally, beta-blockers, long-acting nitrates, CCBs, ivabradine, ranolazine, trimetazidine, nicorandil, and their combinations should be considered in patients with HFpEF and CAD for angina relief, but without foreseen benefits on HF and coronary endpoints. Low-dose rivaroxaban may be considered in patients with CAD and HF, LVEF of >40%, and sinus rhythm when at high risk of stroke and with low haemorrhagic risk.[526,903,904]

Evidence and recommendations for myocardial revascularization in patients with HF are reported in *Section 4.4.2*. Notably, patients with advanced HF may be candidates for LV assistance devices and/or heart transplantation.[526]

During of high-risk PCI for complex CAD[905] in patients with HFrEF, mechanical cardiac support, such as the microaxial flow pump, may minimize the risk of severe complications and provide haemodynamic stability, facilitating the achievement of complete revascularization.[906,907]

Recommendation Table 24 — Recommendations for management of chronic coronary syndrome patients with chronic heart failure (see also Evidence Table 24)

Recommendations	Class[a]	Level[b]
Managing CCS in heart failure patients		
In HF patients with LVEF ≤35% in whom obstructive CAD is suspected, ICA is recommended with a view towards improving prognosis by CABG, taking into account the risk-to-benefit ratio of the procedures.[54,729,749,908]	I	B
In HF patients with LVEF >35% and suspected CCS with low or moderate (>5%–50%) pre-test likelihood of obstructive CAD, CCTA or functional imaging is recommended.[887]	I	C
In HF patients with LVEF >35% and suspected CCS with very high (>85%) pre-test likelihood of obstructive CAD, ICA (with FFR, iFR, or QFR when needed) is recommended.[887]	I	C

Continued

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In patients with HFpEF with persistent angina or equivalent symptoms and normal or non-obstructive epicardial coronary arteries, PET or CMR perfusion or invasive coronary functional testing should be considered to detect or rule out coronary microvascular dysfunction.[883–885,887–889]	IIa	B
In selected patients with HFrEF undergoing high-risk PCI for complex CAD, the use of a microaxial flow pump may be considered in experienced centres.[905–907]	IIb	C
Managing heart failure in CCS patients		
It is recommended that CCS patients with HF be enrolled in a multidisciplinary HF management programme to reduce the risk of HF hospitalization and to improve survival.[526,909–911]	I	A
An ACE-I, an MRA, an SGLT2 inhibitor (dapagliflozin or empagliflozin), and, in stable conditions, a beta-blocker are recommended for CCS patients with HFrEF to reduce the risk of HF hospitalization and death.[526,704,705,912,913]	I	A
An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with Heart Failure with mildly reduced Ejection Fraction (HFmrEF) or HFpEF to reduce the risk of HF hospitalization or cardiovascular death.[706,707]	I	A
An ARB is recommended in symptomatic patients with CCS and HFrEF unable to tolerate an ACE-I or ARNI to reduce the risk of HF hospitalization and cardiovascular death.[914]	I	B
Sacubitril/valsartan is recommended as a replacement for an ACE-I or ARB in CCS patients with HFrEF to reduce the risk of HF hospitalization and of cardiovascular and all-cause death.[693]	I	B
Diuretics are recommended in CCS patients with HF and signs and/or symptoms of congestion to alleviate symptoms, improve exercise capacity, and reduce HF hospitalizations.[915]	I	B
An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA class II–III) of ischaemic aetiology (unless they have had an MI in the prior 40 days), and an LVEF ≤35% despite ≥3 months of optimized medical treatment, provided they are expected to survive substantially longer than 1 year with good functional status.[526,916]	I	A
An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients who have recovered from a ventricular arrhythmia causing haemodynamic instability, and who are expected to survive for >1 year with good functional status, in the absence of reversible causes or unless the ventricular arrhythmia has occurred <48 h after an MI. [917–920]	I	A
CRT is recommended for CCS patients with symptomatic HF, sinus rhythm, LVEF ≤35% despite GDMT, and a QRS duration ≥150 ms with an LBBB QRS morphology to improve symptoms and survival and to reduce morbidity.[526,921,922]	I	A
CRT rather than right ventricular pacing is recommended for patients with HFrEF regardless of NYHA class or QRS width who have an indication for ventricular pacing for high-degree AV block in order to reduce morbidity. This includes patients with AF. [923–925]	I	A

ACE-I, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; AV, atrioventricular; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS, chronic coronary syndrome; CCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance; CRT, cardiac resynchronization therapy; FFR, fractional flow reserve; GDMT, guideline-directed medical therapy; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICA, invasive coronary angiography; ICD, implantable cardioverter defibrillator; iFR, instantaneous wave-free ratio; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PET, positron emission tomography; SGLT2, sodium–glucose cotransporter 2.
[a]Class of recommendation.
[b]Level of evidence.

5.2. Angina/ischaemia with non-obstructive coronary arteries

5.2.1. Definition

A large proportion of patients undergoing coronary angiography because of angina do not have obstructive epicardial coronary arteries (ANOCA). In these patients, the prevalence of demonstrable ischaemia (INOCA) varies, depending on the stress test performed, between 10% and 30% (*Figure 12*).[926–928] Angina/ischaemia with non-obstructive coronary arteries is more frequent among women (approximately 50% to 70%) than in men (30% to 50%) referred for ICA.[7,929] The mismatch between blood supply and myocardial oxygen demands leading to angina and ischaemia in ANOCA/INOCA may be caused by CMD and/or epicardial coronary artery spasm.[36] However, these conditions are rarely correctly diagnosed, and, therefore, no tailored therapy is prescribed for these patients. As a consequence, these patients continue to experience recurrent angina with poor QoL, leading to repeated hospitalizations, unnecessary repeat coronary angiography, and adverse cardiovascular outcomes in the short and long term.[36]

5.2.2. Angina/ischaemia with non-obstructive coronary arteries endotypes

Invasive functional coronary testing using Ach and adenosine in individuals suspected of CCS and with non-obstructive coronary arteries enables the differentiation of the following endotypes: (i) endothelial dysfunction; (ii) impaired vasodilation (low coronary flow reserve and/or high microvascular resistance); (iii) epicardial vasospastic angina; (iv) microvascular vasospastic angina; (v) endotype combinations; (vi) equivocal response, i.e. angina without fulfilling any endotype criteria.[37,38] The prevalence of ANOCA and INOCA in relation to the presence of the endotypes is shown in *Figure 12*. Angina with non-obstructive coronary arteries occurs in up to 70% of the patients undergoing ICA, of whom 25% have documented ischaemia (INOCA). Among the patients who are tested with Ach, 80% show endothelial dysfunction, 60% have MVA/VSA, and 50% have an impaired CFR and/or high microvascular resistance.[38,927,930,931] This emphasizes the importance of testing not only patients with INOCA but also all patients with ANOCA to determine the final endotype so that appropriate treatment can be initiated.

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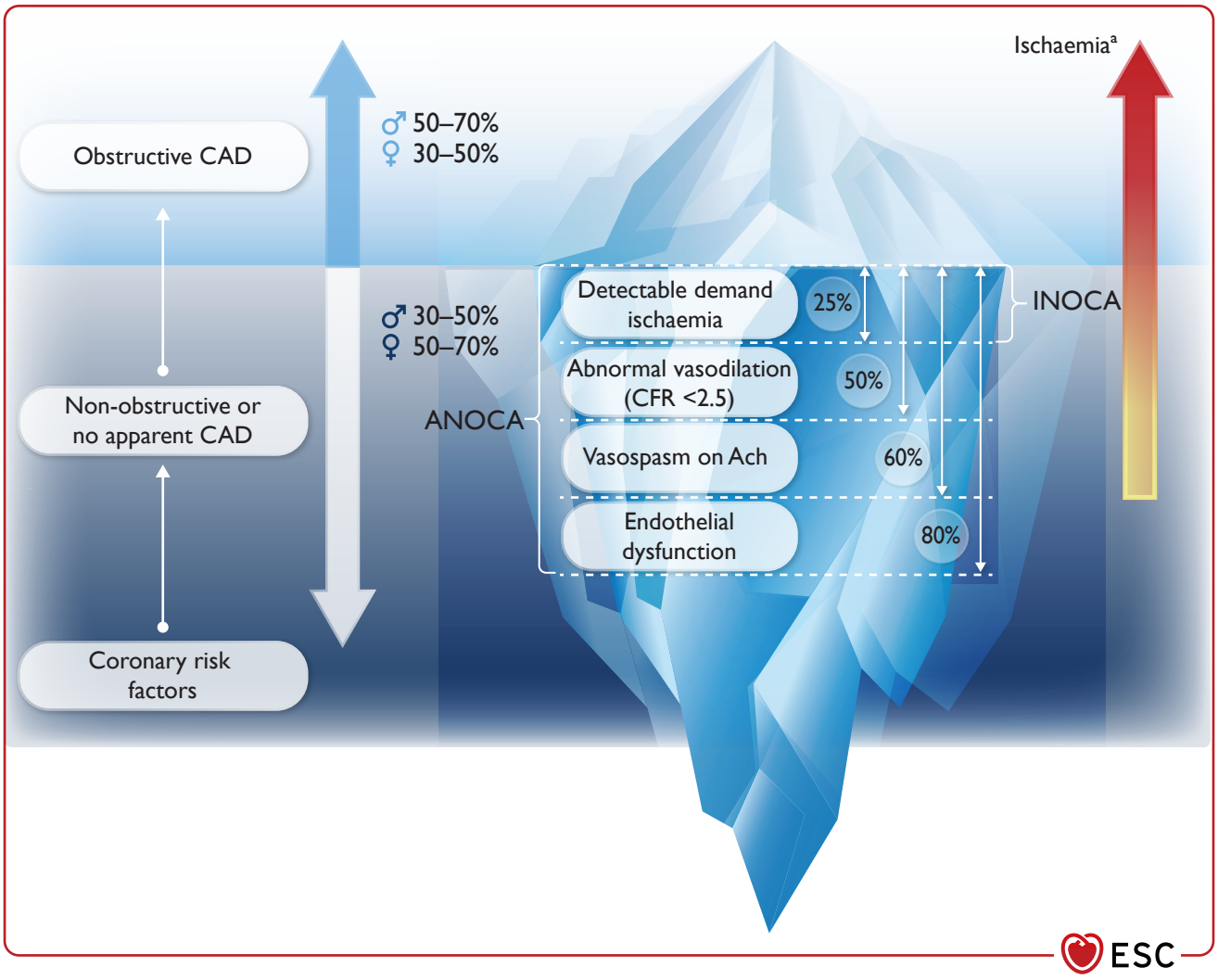

Figure 12 Prevalence of disease characteristics in patients with ANOCA/INOCA referred for invasive coronary functional testing. Ach, acetylcholine; ANOCA, angina with non-obstructive coronary arteries; CFR, coronary flow reserve; i.c., intracoronary; INOCA, ischaemia with non-obstructive coronary arteries. In the ILIAS (Inclusive Invasive Physiological Assessment in Angina Syndromes) registry,[927] ANOCA is present in up to 70% of patients referred for invasive coronary angiography and functional testing. Endothelial dysfunction is present in 80% and an acetylcholine test is positive in 60% of these patients. An impaired CFR (≤2.5), measured by i.c. Doppler guidewires, is present in 50%, while ischaemia (INOCA) is documented by non-invasive functional testing in only 25% of ANOCA patients. The prevalence of coronary vasospasm can vary in different studies depending on dose of acetylcholine and test protocol. [a]Prevalence of ischaemia by non-invasive functional testing increases from non-obstructive to obstructive CAD.

5.2.2.1. Microvascular angina

Microvascular angina is the clinical manifestation of myocardial ischaemia caused by structural or functional changes in the coronary microvasculature (leading to impaired CFR and/or reduced microcirculatory conductance) and/or abnormal vasoconstriction of coronary arterioles (causing dynamic arteriolar obstruction).[932,933] Both vascular dysfunction mechanisms may co-exist and contribute to MVA.

The prevalence of MVA was 26% in a study of patients with non-obstructive CAD who had a CFVR below 2 when assessed by transthoracic Doppler echocardiography.[934] Studies assessing CMD invasively or by PET with different cut-offs have found that 39% to 54% had CMD.[935,936] The threshold for CMD varies between studies and depending on the techniques used (PET, CMR, thermodilution, or Doppler); the threshold is a CFR of <2.0–2.5.[36,39] A thermodilution CFR of <2.0 has low sensitivity for identifying CMD, but using the same threshold as for Doppler (<2.5) results in reasonable diagnostic accuracy.[937]

Smoking, age, diabetes, hypertension, and dyslipidaemia are associated with CMD.[934,935,938] Other studies have shown that diabetes was uncommon among patients with angina and non-obstructive CAD, while hypertension and dyslipidaemia were relatively more prevalent.[939,940] Inflammatory conditions such as systemic lupus erythematosus (SLE) and rheumatoid arthritis appear to be associated with MVA and are not infrequently encountered in patients with angina.[941] Inflammatory diseases occur more often in women after menopause than in men, which may contribute to the sex differences in MVA.[942–944] Last, but not least, there is increasing evidence that psychosocial stress is involved in coronary vasomotor disorders.[945,946]

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5.2.2.2. Epicardial vasospastic angina

Vasospastic angina is the clinical manifestation of myocardial ischaemia caused by abnormal vasoconstriction of one or more epicardial coronary arteries leading to a dynamic coronary obstruction. Standardized diagnostic criteria for VSA have been defined.[73] Microvascular angina and epicardial VSA can co-exist, which is associated with a worse prognosis.[947] Concomitant endothelial dysfunction is prevalent in most patients with INOCA with inducible coronary artery spasm and/or impaired adenosine-mediated vasodilation.[38,948]

The Japanese population has a higher prevalence of coronary vasospasm than Western populations. In addition, the frequencies of multiple coronary spasms (≥2 spastic arteries) by provocative testing in Japanese (24.3%) and Taiwanese populations (19.3%) are markedly higher than those in Caucasians (7.5%).[949–951]

5.2.3. Clinical presentations

Angina/ischaemia with non-obstructive coronary arteries is associated with a wide variation in its clinical presentation, and symptom burden may vary over time. Failure to diagnose epicardial obstructive CAD in a patient with documented ischaemia should stimulate a subsequent search pathway to elucidate ANOCA/INOCA endotypes.

5.2.4. Short- and long-term prognosis

Symptoms of angina/ischaemia with non-obstructive coronary arteries are associated with adverse physical, mental, and social health.[952] Angina/ischaemia with non-obstructive coronary arteries is associated with poor QoL, higher risk of disability, and a higher incidence of adverse events, including mortality, morbidity, healthcare costs, recurrent hospital readmissions and repeat coronary angiograms.[300,953–958] The incidence of all-cause death and non-fatal MI in patients with non-obstructive atherosclerosis was higher than in those with angiographically normal epicardial vessels.[298,959–961] Proven myocardial ischaemia by stress echocardiography or nuclear imaging was associated with a higher incidence of events compared with ischaemia detected by exercise electrocardiographic stress testing.[958] There is a two- to four-fold higher risk of adverse cardiovascular outcomes in patients with MVA diagnosed by PET or transthoracic echocardiography and a two-fold higher risk in patients with epicardial endothelial-dependent dysfunction.[300,962] Microvascular angina due to impaired CFR was associated with increased major adverse cardiac events and target-vessel failure rates over a 5-year follow-up period.[931] Vasospastic angina is associated with major adverse events, including sudden cardiac death, acute MI, and syncope.[963] In a group of ANOCA/INOCA patients, abnormal non-invasive testing did not allow the identification of patients with a higher risk of long-term cardiovascular events. However, adding intracoronary physiological assessment to non-invasive information allowed the identification of patient subgroups with up to a four-fold difference in long-term cardiovascular events.[357]

5.2.5. Diagnosis

The presence of myocardial ischaemia on functional imaging without obstructive CAD on CCTA or ICA should always raise the clinical suspicion of ANOCA/INOCA. The diagnosis of ANOCA/INOCA is exclusively based on invasive functional evaluation of the coronary microcirculation, given that no technique allows direct visualization of the coronary microcirculation *in vivo* in humans. Several non-invasive and invasive tests have been established to assess the coronary microvascular function (*Figure 13*).[6,41,964,965]

5.2.5.1. Non-invasive diagnosis

Non-invasive tests (stress echocardiography, PET, perfusion CCTA, and CMR) allow diagnosing ANOCA/INOCA by measuring the CFR.[41] These techniques have an excellent negative predictive value, but the positive predictive value is an issue for most, as obstructive CAD needs to be ruled out before the diagnosis of CMD can be made. Only hybrid techniques such as CCTA with perfusion and PET-CT offer combined imaging of the epicardial coronary arteries and functional testing of the coronary microcirculation in a single test.[6,964]

5.2.5.2. Invasive coronary functional testing

Invasive coronary functional testing consists of a comprehensive evaluation of the coronary circulation in a single procedure by combining angiography, direct invasive assessment of the coronary haemodynamics by intracoronary pressure and flow measurement either by thermodilution (bolus/continuous) or Doppler techniques, and pharmacological vasomotor testing. Recently, a standardized protocol has been proposed.[36]

5.2.5.2.1. Basic coronary functional testing. Intracoronary pressure and flow measurements allow assessment of the haemodynamic significance of focal or diffuse coronary lesions by measuring FFR or iFR (see *Section 3.3.3.2*) and of microcirculatory function by measuring CFR and IMR, HMR, or MRR[361,961] (see *Section 3.3.3.3*). Coronary microvascular dysfunction is characterized by decreased CFR and increased microvascular vascular resistance (IMR, HMR, MRR). Decreased CFR can be due to structural or functional microvascular dysfunction.[926,966] Functional CMD is characterized by increased resting flow linked to enhanced nitric oxide synthase (NOS) activity, whereas patients with structural CMD have endothelial dysfunction, leading to a reduced increase of coronary blood flow during exercise.[926,966]

A Doppler-derived CFR of <2.5 in non-obstructive CAD indicates an abnormal microcirculatory response corresponding to a thermodilution-derived CFR of <2.5.[361,926,937,961] Of note, in assessing coronary microvascular function, continuous thermodilution showed significantly less variability than bolus thermodilution on repeated measurements.[382] An increased IMR (≥25) indicates microvascular dysfunction.[380,381] For the Doppler-derived HMR, a value of >2.5 mmHg/cm/s indicates augmented microvascular resistance.[42] Recently, MRR has been considered abnormal for values <2.7.[364,967] Doppler flow analysis allows assessment of the flow-recovery time after Ach administration as a sign of myocardial ischaemia, which is helpful in the diagnosis of patients with equivocal test results.[968]

5.2.5.2.2. Coronary vasomotor testing. Epicardial and microvascular endothelium-dependent vasodilation and vasospasm are tested by intracoronary bolus administration or graded infusion of Ach, first at a low dose/grade to assess endothelial dysfunction at the microvascular or epicardial level, and after that at a higher dose/grade to eventually induce microvascular or/and epicardial coronary vasospasm. The LAD artery is usually preferred as the pre-specified target vessel reflecting its subtended myocardial mass and coronary dominance. The left circumflex coronary artery is also tested if Ach is administered in the LMCA. Additional studies in the right coronary artery may be appropriate if the initial tests are negative and clinical suspicion is high. As Ach exerts a cholinergic effect on the atrioventricular node, significant bradycardia may ensue if infused especially in the right coronary artery or a dominant left circumflex coronary artery. Bradycardia can be prevented by selective infusion in the LAD, prophylactic ventricular pacing, or reduction of the concentration infused or of the injected dose. If necessary, the

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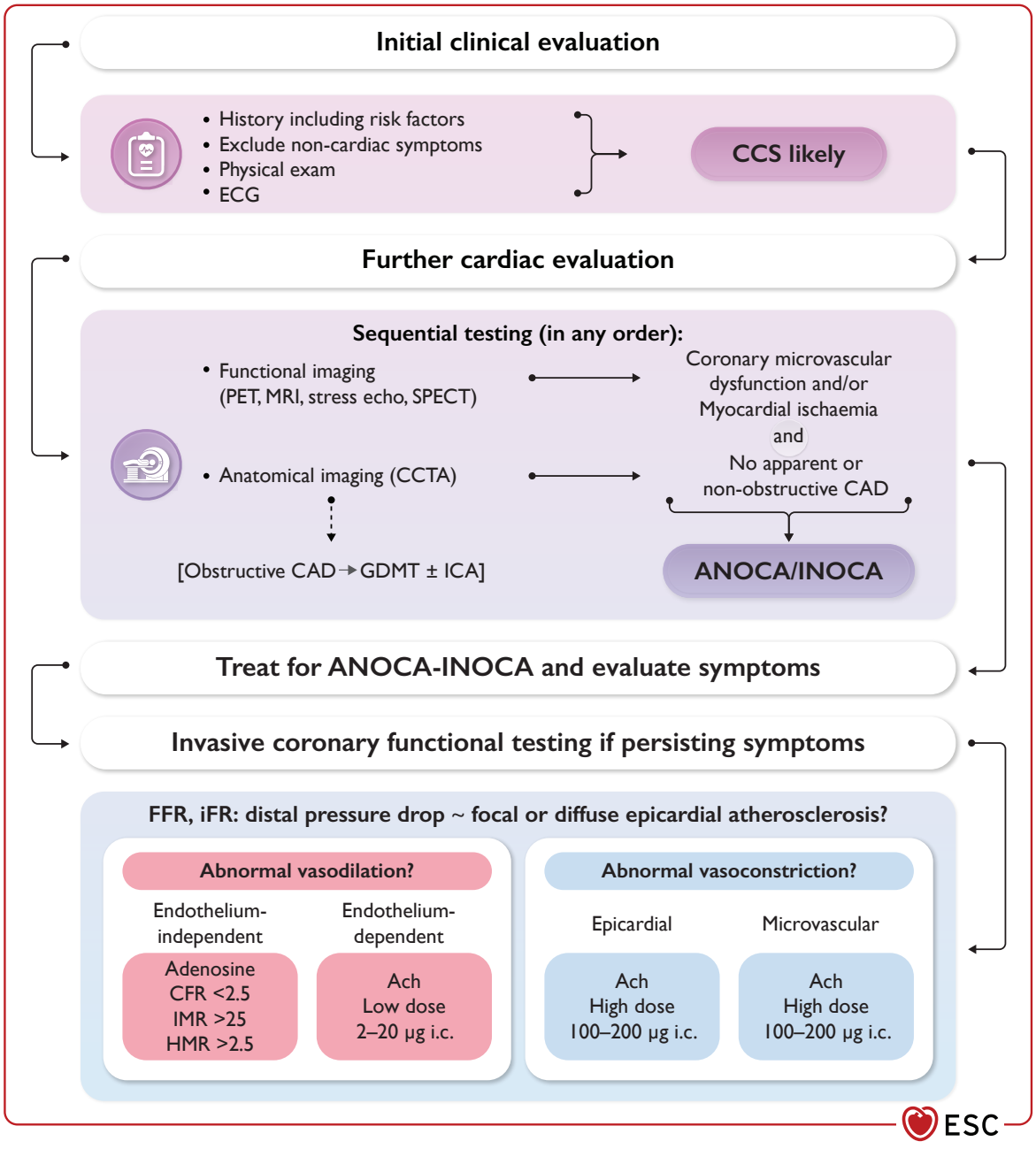

Figure 13 Diagnostic algorithm for patients with angina/ischaemia with non-obstructive coronary arteries. Ach, acetylcholine; ANOCA, angina with non-obstructive coronary arteries; CAD, coronary artery disease; CCS, chronic coronary syndrome; CCTA, coronary computed tomography angiography; CFR, coronary flow reserve; ECG, electrocardiogram; echo, echocardiography; FFR, fractional flow reserve; GDMT, guideline-directed medical therapy; HMR, hyperaemic myocardial velocity resistance; i.c., intracoronary; ICA, invasive coronary angiography; iFR, instantaneous-wave free ratio; IMR, index of microcirculatory resistance; INOCA, ischaemia with non-obstructive coronary arteries; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

bradycardia effect of Ach can be antagonized by atropine. The effect of Ach is short in contrast to the prolonged effect of ergonovine, which was previously used for the provocation of coronary vasospasm.[969] The diagnosis of MVA and VSA due to microvascular or macrovascular vasospasm is made according to established criteria.[41,73,932] The test is considered positive for macrovascular spasm if symptoms occur, accompanied by ischaemic ECG changes and an angiographic ≥90% reduction of the coronary lumen. If the lumen reduction is <90%, the diagnosis of microvascular spasm is made. The vasospastic effect of Ach is rapidly transient and can, if needed, be reversed by intracoronary administration of nitroglycerine, which also allows assessment of endothelium-independent epicardial coronary vasodilation. The safety

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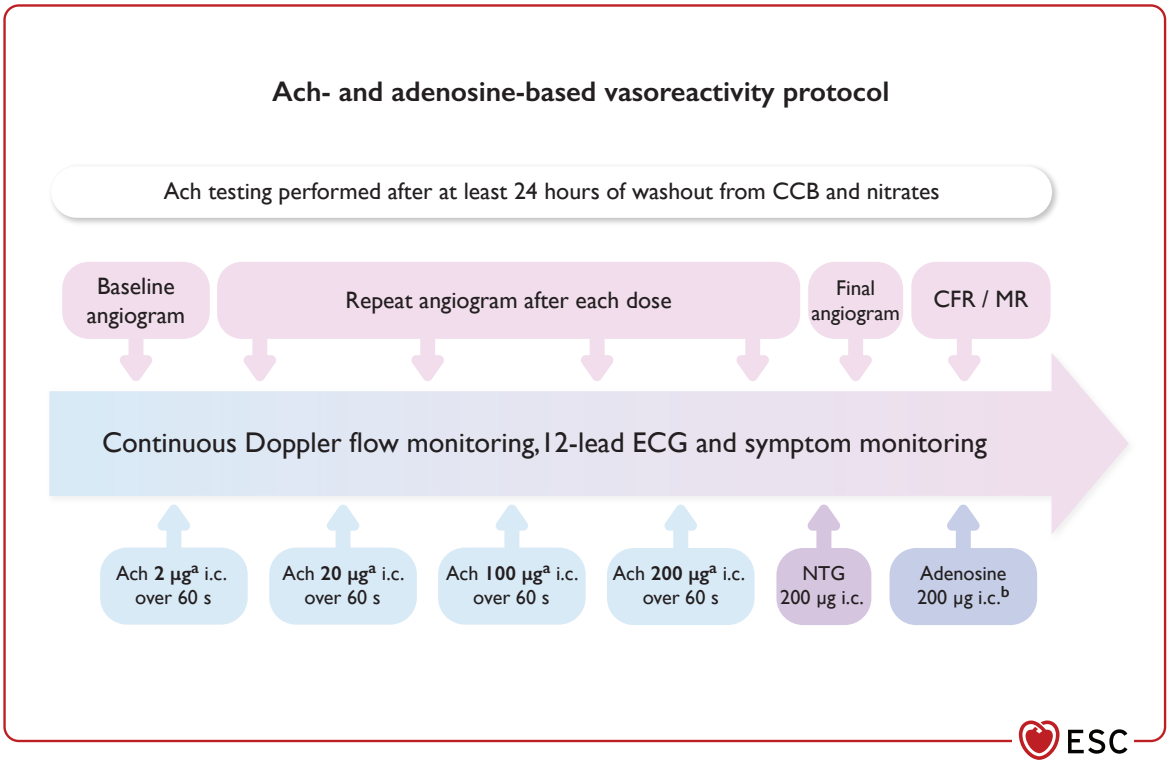

Figure 14 Spasm provocation and functional testing protocol. Ach, acetylcholine; CCB, calcium channel blocker; CFR, coronary flow reserve; ECG, electrocardiogram; i.c., intracoronary; i.v., intravenous; MR, microvascular resistance; NTG, nitroglycerine. i.c. bolus injections of Ach over 60s to assess: (i) endothelial-dependent vasodilation using low-dose Ach (2–20 µg), and (ii) endothelial dysfunction and vasoconstriction using high-dose Ach (100–200 µg). This is followed by i.c. administration of nitroglycerine (200 µg) to revert vasospasm. Endothelial-independent vasodilation is assessed by i.c. adenosine (200 µg) or i.v. infusion to determine CFR and IMR. Coronary flow can be continuously monitored if i.c. Doppler guidewires are used. [a]The incremental administration of Ach is stopped whenever a coronary vasospasm is induced. [b]i.v. adenosine can also be used.

of coronary vasospasm provocation testing with increasing intracoronary Ach boluses of up to a maximum of 200 µg has been repeatedly reported.[37,970,971] In a small study, testing coronary vasospasm using this algorithm was also safe in patients with a recent ACS.[972]

At the end of the procedure, microcirculatory vasomotor response to i.v. administration of the endothelium-independent vasodilator adenosine[973] is assessed and CFR, IMR, HMR, or MRR are measured. In patients with contraindications to the use of adenosine, papaverine can be used[974] but precautionary measures need to be taken given the risk of inducing polymorphic ventricular tachycardia.[975,976]

Different protocols have been applied in clinical practice. *Figure 14* shows an example of a standardized and stepwise algorithm for ICFT that may be adopted in the cardiac catheterization laboratory for diagnosing vasospasm. Informed consent should be obtained, mentioning unlicensed, parenteral use of Ach, and administration performed by an experienced interventional cardiologist.

5.2.6. Management of angina/ischaemia with non-obstructive coronary arteries

Management should be patient-centred with a patient-oriented multidisciplinary care approach.[977] *Figure 15* provides an algorithm for the therapeutic management of ANOCA/INOCA. In all patients with established ANOCA/INOCA due to the frequent presence of coronary atherosclerosis and endothelial dysfunction, tailored counselling on lifestyle factors is warranted to address risk factors, reduce symptoms, and improve QoL and prognosis. Management of traditional CVD risk factors, hypertension, dyslipidaemia, smoking, and diabetes should be as per clinical practice guidelines recommendations.

Treatment of anginal symptoms in patients with ANOCA/INOCA is challenging as the patients represent a heterogeneous group and randomized trials are lacking. A small study showed that a stratified antianginal therapy algorithm based on coronary functional testing resulted in improved angina symptoms and QoL compared with a control group treated with standard therapy.[978] In patients with MVA and reduced CFR and/or increased IMR (which may reflect arteriolar remodelling), beta-blockers, CCBs, ranolazine, and ACE-Is are used.[979] In these patients, anti-ischaemic therapy with amlodipine or ranolazine resulted in a significant improvement in exercise time.[980] In patients with either epicardial or microvascular spasm following Ach testing, calcium antagonists should be considered as first-line therapy. In patients with severe VSA, it may be necessary to administer unusually high dosages of calcium antagonist (2 × 200 mg diltiazem daily or higher up to 960 mg daily) or even a combination of non-dihydropyridine (such as diltiazem) with dihydropyridine calcium blockers (such as amlodipine). Of note, a small study using either oral diltiazem or placebo up to 360 mg/day in CMD for 6 weeks did not substantially improve symptoms or QoL, but diltiazem therapy did reduce the prevalence of epicardial spasm.[981] Nicorandil, a combinatorial vasodilator agent acting via nitrate- and potassium-channel activation, may be an effective alternative, although side effects are frequent.[982] First-line therapy can also be combined

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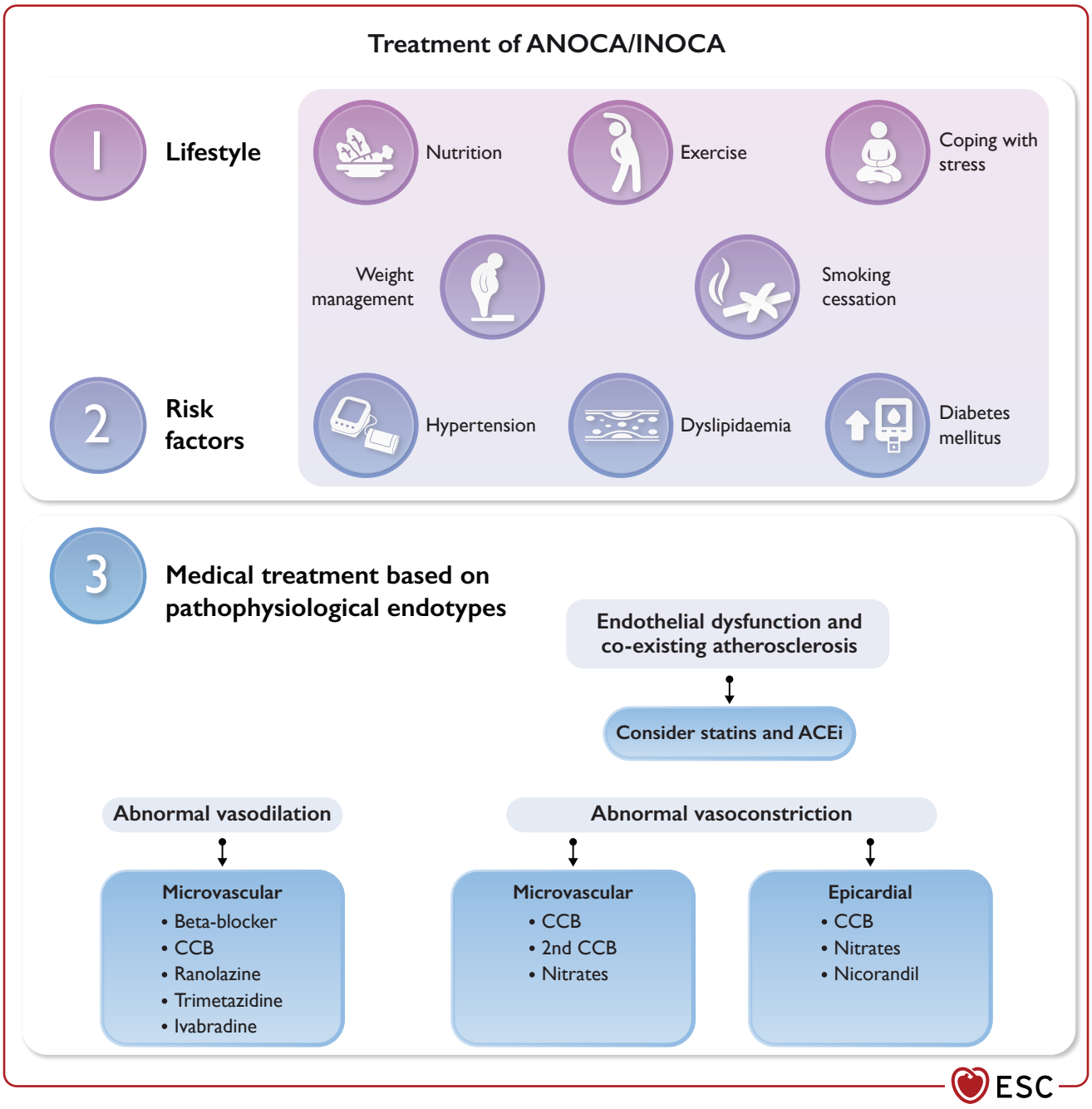

Figure 15 Treatment of angina/ischaemia with non-obstructive coronary arteries. ACE-I, angiotensin-converting enzyme inhibitor; ANOCA, angina with non-obstructive coronary arteries; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; INOCA, ischaemia with non-obstructive coronary arteries. Treatment of ANOCA/INOCA patients includes lifestyle modification, management of cardiovascular risk factors, and antianginal treatment according to underlying endotypes. Note: endotypes frequently overlap, requiring combined medical therapy.

with ranolazine, an antianginal agent that improves myocyte relaxation and ventricular compliance by decreasing sodium and calcium overload.[983] Spinal cord stimulation is an option for patients who remain refractory after medical therapy.[984]

There are currently several studies evaluating therapies specific to ANOCA/INOCA. The Women's IschemiA Trial to Reduce Events in Non-ObstRuctIve CORonary Artery Disease (WARRIOR, NCT03417388) is currently enrolling subjects in a multicentre, prospective, randomized, blinded outcome evaluation to assess intensive statin and ACE-I/ARB therapy (ischaemia-intensive medical therapy) vs. usual care on MACE in symptomatic women with ANOCA. The Precision Medicine with Zibotentan in Microvascular Angina (PRIZE) trial holds future promise (NCT04097314). Zibotentan is an oral, endothelin A receptor antagonist that may provide benefit by opposing the reported vasoconstrictor response of coronary microvessels to endothelin.

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Recommendation Table 25 — Recommendations for diagnosis and management of patients with angina/ischaemia with non-obstructive coronary arteries (see also Evidence Table 25)

Recommendations	Class[a]	Level[b]
Diagnosis of ANOCA/INOCA endotypes		
In persistently symptomatic patients despite medical treatment with suspected ANOCA/INOCA (i.e. anginal symptoms with normal coronary arteries or non-obstructive lesions at non-invasive imaging, or intermediate stenoses with normal FFR/iFR at coronary arteriography) and poor quality of life, invasive coronary functional testing is recommended to identify potentially treatable endotypes and to improve symptoms and quality of life, considering patient choices and preferences.[36,37,298,930,939,985]	I	B
In persistently symptomatic patients with documented or suspected ANOCA/INOCA, transthoracic Doppler of the LAD, stress echocardiography, CMR, and PET may be considered for the non-invasive assessment of coronary/myocardial flow reserve.[44,231,233–235,300,986,987]	IIb	B
Diagnostic tests for vasospastic angina		
In individuals with suspected vasospastic angina, a resting 12-lead ECG recording during angina is recommended.	I	C
In patients with suspected vasospastic angina and repetitive episodes of rest angina associated with ST-segment changes that resolve with nitrates and/or calcium antagonists, invasive coronary functional testing is recommended to confirm the diagnosis and to determine the severity of underlying atherosclerotic disease.	I	C
In individuals with suspected vasospastic angina and frequent symptoms, ambulatory ST-segment monitoring should be considered to identify ST-segment deviation during angina.[192–194]	IIa	B
Management of ANOCA/INOCA		
In symptomatic patients with ANOCA/INOCA, medical therapy based on coronary functional test results should be considered to improve symptoms and quality of life.[298,977]	IIa	A
For the management of endothelial dysfunction, ACE-I should be considered for symptom control.[988]	IIa	B
For the management of microvascular angina associated with reduced coronary/myocardial blood flow reserve, antianginal medications aiming at preventing demand myocardial ischaemia should be considered for symptom control.[989,990]	IIa	B
For the treatment of isolated vasospastic angina		
Calcium channel blockers are recommended to control symptoms and to prevent ischaemia and potentially fatal complications.[991–996]	I	A
Nitrates should be considered to prevent recurrent episodes.[993,997,998]	IIa	B
For the treatment of overlapping endotypes		
In patients with evidence of overlapping endotypes, combination therapy with nitrates, calcium channel blockers, and other vasodilators may be considered.[999,1000]	IIb	B

Continued

ACE-I, angiotensin-converting enzyme inhibitor; ANOCA, angina with non-obstructive coronary arteries; CMR, cardiac magnetic resonance; ECG, electrocardiogram; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; INOCA, ischaemia with non-obstructive coronary arteries; LAD, left anterior descending; PET, positron emission tomography.
[a]Class of recommendation.
[b]Level of evidence.

5.3. Other specific patient groups

5.3.1. Older adults

Between 2015 and 2050, the proportion of the world's population aged >60 years is set to nearly double to 22%. Ageing predisposes patients to a high incidence and prevalence of CAD, in both men and women. Typically, in the context of CVD, older patients are defined as those ≥75 years of age;[1] it should be noted, however, that such age cut-offs are relatively arbitrary, and biological age influences this threshold in clinical practice. Clinical characteristics of the older adult population are heterogeneous, with frailty, comorbidity, cognitive function, and health-related QoL playing important roles in guiding clinical care and as predictors of adverse outcomes.[1001–1005] Older patients often present with symptoms other than angina, which may delay the diagnosis of CCS.[1004]

Ageing is often accompanied by both comorbidities and frailty, and consequently leads to potentially excessive polypharmacy.[531] In making treatment decisions, clinicians should take into account the limited external validity of RCTs for older adults.[36] Older people are often underrepresented in RCTs as a consequence of exclusion criteria and under-recruitment,[531,1006,1007] though they have been shown to have a higher underlying risk for cardiovascular outcomes.[1008] The treatment of CCS in older adults is complicated by a higher vulnerability to complications for both conservative and invasive strategies, such as bleeding, renal failure, and neurological impairments, all of which require special attention. The use of DES, compared with bare-metal stents, in combination with a short duration of DAPT, is associated with significant safety and efficacy benefits in older adults.[1009] Frailty is of utmost importance in the clinical decision-making.[1010]

5.3.2. Sex differences in chronic coronary syndromes

Ischaemic heart disease is the leading cause of mortality for women, yet they have been historically underrepresented in RCTs.[1011–1013] Differences in symptom presentation, in the accuracy of diagnostic tests for obstructive CAD, and other factors that lead to differential triage, evaluation, or early treatment of women with myocardial ischaemia

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compared with men could contribute to unfavourable outcomes. There are also risk factors that are unique to women.[1014,1015] Not only premature menopause,[1016] but also hypertensive disorders of pregnancy, pre-term delivery, gestational diabetes, small-for-gestational-age delivery, placental abruption, and pregnancy loss are predictors of subsequent CVD.[1017] Also, the association between low socioeconomic status and increased cardiovascular risk seems stronger in women.[1018] In addition, higher levels of residential segregation are associated with incident CVD and obesity among black women.[1019]

Women are less likely to be referred for diagnostic testing and are under-treated for essential secondary prevention therapies.[1020] Compared with men, women have a shorter survival after PCI[1021] and CABG.[1022] In a large-scale, individual-patient data pooled analysis of contemporary PCI trials with early and new-generation DES, women had a higher risk of MACE and ischaemia-driven target-lesion revascularization compared with men at 5 years following PCI.[1021] However, the excess risk after PCI among women can be primarily explained by a greater burden of cardiovascular risk factors and comorbid conditions.[1023] Nevertheless, in a population undergoing contemporary PCI, women and men had similar risks of death or new Q-wave MI at 2 years, but women faced a higher risk of bleeding and haemorrhagic stroke compared with men.[1024]

Women with signs and symptoms suggestive of cardiac ischaemia should be investigated carefully. The same guideline-recommended cardiovascular preventive therapy should be provided to women and men.[1025] Hormone replacement therapy in post-menopausal women does not reduce the risk of ischaemic myocardial disease[1015] and it may come at the cost of other health risks,[1026] which should be discussed with the patient.

5.3.3. High bleeding-risk patients

An HBR is increasingly present in many CCS patients referred for coronary revascularization. The ARC-HBR consortium provided a consistent definition of HBR for patients undergoing PCI. Patients are considered at HBR if at least one major or two minor criteria are met.[590] In the context of PCI in HBR patients, short duration of DAPT (1–3 months) and PCI with a DES was beneficial in many recent studies.[1009,1027–1032]

5.3.4. Inflammatory rheumatic diseases

Patients with inflammatory rheumatic diseases have an increased risk of CVD compared with the general population.[1033,1034] Accumulating evidence has shown elevated cardiovascular morbidity and mortality in other rheumatic and musculoskeletal diseases, including gout, vasculitis, systemic sclerosis, myositis, mixed connective tissue disease, Sjögren syndrome, SLE, and the antiphospholipid syndrome.[1035–1044]

Some of these patient categories have two- to three-fold higher prevalences of asymptomatic ASCVD compared with the general population,[1045–1051] which is linked to ASCVD outcomes.[1049,1052–1054] Thus, identification of ASCVD such as carotid artery plaque(s) may be considered in ASCVD and CAD risk evaluation.[1050,1055–1057]

In patients with inflammatory rheumatic diseases and CCS, CVD preventive medications such as lipid-lowering medications and antihypertensive treatment should be used as in the general population.[1058–1062]

5.3.5. Hypertension

Blood pressure lowering has been associated with favourable cardiovascular outcomes in patients regardless of the presence of CAD.[1063] Due to concerns of a possible J-curve relationship between achieved BP and cardiovascular outcomes in patients with CAD, previous guidelines did not recommend a target BP of <120/70 mmHg. In line with the 2024 ESC Hypertension Guidelines[1064], the present guidelines recommend that treated systolic BP values in most CCS patients be targeted to 120–129 mmHg, provided the treatment is well tolerated. In cases where on-treatment systolic BP is at or below target (120–129 mmHg) but diastolic BP is not at target (≥80 mmHg), intensifying BP-lowering treatment to achieve an on-treatment diastolic BP of 70–79 mmHg may be considered to reduce CVD risk.[1065] More lenient targets (e.g. 140/90 mmHg) can be considered in older patients (≥85 years of age) or patients with pre-treatment symptomatic orthostatic hypotension. In hypertensive patients with a history of MI, beta-blockers and RAS blockers are first-line treatments. In patients with symptomatic angina, beta-blockers and/or CCBs can be useful.[1065]

5.3.6. Atrial fibrillation

Diagnostic assessment of CAD (CCTA and non-invasive tests) may be difficult in AF with a high ventricular rate. In patients with CAD and AF, rhythm or rate control strategies may help improve symptoms of myocardial ischaemia. Amiodarone or dronedarone are drugs of choice for rhythm control, as an alternative to catheter ablation, in patients with CAD and AF. Sotalol may also be considered. Beta-blockers, diltiazem, verapamil, or digoxin can be used for rate control depending on the LVEF.[613] After PCI, combined anticoagulant and antiplatelet therapies are needed. Recommendations on post-PCI antithrombotic therapy in patients with AF and indication for OAC are detailed in *Section 4.3.1.2.2* and *Recommendation Table 17*.[613,621,659] Surgical ablation of AF during isolated CABG seems to be safe and effective in improving long-term outcomes.[1066] Concomitant surgical closure of the left atrial appendage is recommended as an adjunct to oral anticoagulation in patients with AF undergoing cardiac surgery (e.g. CABG) to prevent ischaemic stroke and thrombo-embolism (see the ESC 2024 Guidelines for the management of Atrial Fibrillation).[1067]

5.3.7. Valvular heart disease

In patients with valvular heart disease with a risk for associated CAD who require surgery or in whom a decision of a percutaneous or surgical approach is still pending, ICA or CCTA is recommended to determine the need for coronary revascularization.[1068] Evidence of CAD in patients with valvular heart disease can drive to a surgical instead of a percutaneous treatment of valvular heart disease. Invasive coronary angiography is recommended in patients with secondary mitral regurgitation as this condition is frequently due to ischaemic LV dysfunction.[1068] Routine stress testing to detect CAD associated with severe symptomatic valvular heart disease is not recommended because of low diagnostic value and potential risk. The usefulness of FFR or iFR in patients with valvular heart disease is not well established, and caution is warranted in interpreting these measurements, especially in the presence of aortic stenosis.[1068] Beta-blockers need to be used with caution in patients with aortic valve disease. Coronary artery bypass grafting is recommended in patients with a primary indication for aortic/mitral/tricuspid valve surgery and significant coronary stenosis. Percutaneous coronary intervention should be considered in patients with a primary indication of transcatheter aortic valve implantation or transcatheter mitral valve intervention and coronary artery diameter stenosis of >70% in proximal segments.[1068]

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5.3.8. Chronic kidney disease

Chronic kidney disease increases the risk of CAD progression and is associated with high mortality rates due to cardiovascular causes.[1069,1070] Patients with CKD have a higher burden of atherosclerosis and more advanced plaque features.[1070] Despite the higher prevalence of disease, non-invasive diagnostic testing is often less accurate, and guidance related to the use of pharmacological and interventional therapy is limited due to inconsistent definitions of CKD and underrepresentation of CKD patients in clinical trials.[1070–1072]

Careful assessment of the risk-to-benefit ratio is needed in patients with CKD before considering ICA, CCTA, or non-invasive tests requiring nephrotoxic agents.[1073] Pre-existing CKD is the primary patient-related risk factor for the development of acute kidney injury (AKI), whereas DM increases the susceptibility to develop AKI. The most important measures to prevent AKI are using the lowest necessary total dose of low-osmolality or iso-osmolality contrast medium and sufficient pre- and post-hydration.[1073]

CKD raises the risks associated with both CABG and PCI.[316] The ISCHEMIA-CKD trial included patients with advanced CKD [estimated glomerular filtration rate (eGFR) of <30 mL/min/1.73 m^2 or dialysis] and CCS with moderate or severe myocardial ischaemia detected by stress test. An invasive strategy of ICA and PCI was not superior to conservative management in reducing the primary endpoint of death or non-fatal MI.[1074]

In a propensity score-matched analysis involving 5920 CKD patients (2960 pairs), PCI utilizing second-generation DES displayed a reduced risk of death, stroke, and repeat revascularization at 30 days when compared with CABG.[1075] However, PCI was associated with a higher risk of repeat revascularization over the long term. Conversely, among patients on dialysis, the findings favoured CABG over PCI. Additionally, a meta-analysis of 11 registries revealed lower rates of death, MI, and repeat revascularization with CABG in contrast to PCI among patients with eGFR of <60 mL/min/1.73 m^2.[1076] Nevertheless, there is a notable absence of large RCTs comparing revascularization modalities among CKD patients.

5.3.9. Cancer

Several cancer treatments are associated with an increased risk of CCS. Spontaneous bleeding in ACS and CCS patients has been associated with subsequent cancer diagnosis.[1077] A prompt evaluation of bleeding may be useful to enable an early detection of cancer. The management of CCS is similar in patients with and without cancer. However, decisions regarding coronary revascularization should be undertaken by a multidisciplinary team. The approach should be individualized and based on life expectancy, additional comorbidities such as thrombocytopaenia, increased thrombosis, or bleeding risk, and potential interactions between drugs used in CCS management and anticancer therapy.[1078,1079]

5.3.10. Optimal treatment of patients with human immunodeficiency virus

Patients with human immunodeficiency virus (HIV) have longer life expectancy than before due to effective antiretroviral therapy (ART), but are twice as likely to develop CVD compared with the general population.[1080] The long-term CVD outcomes in patients with HIV may change, given the relatively recent epidemiological transition of HIV to a chronic disease. Dyslipidaemia is a common condition in patients with HIV, whether treated or untreated with ART.[1081] The treatment of dyslipidaemia in patients with HIV includes both non-pharmacological and pharmacological options. Special attention to the impact of polypharmacy, drug interactions between ART and lipid-lowering medications, and close monitoring for adverse events is critical to successfully managing dyslipidaemia and risk of CVD in patients with HIV. Hepatic cytochrome P450 3A4 (CYP3A4) metabolizes many statins; many ARTs are also metabolized by CYP3A4 and, thus, may have interactions with statins. Simvastatin and lovastatin are contraindicated with protease inhibitors; atorvastatin has less of a CYP3A4 interaction; pravastatin, fluvastatin, pitavastatin and rosuvastatin are not or minimally metabolized through CYP3A4.[1082,1083] Ezetimibe has no interactions with CYP3A4 or ART.[1081]

A clinical trial investigating the impact of PCSK9 inhibitor therapy on lipids, inflammatory markers, and subclinical ASCVD (including non-calcified plaque and arterial inflammation) in HIV is currently being conducted [EPIC-HIV study (Effect of PCSK9 Inhibition on Cardiovascular Risk in Treated HIV Infection), NCT03207945]. Future studies are needed to evaluate the impact of PCSK9 inhibition on clinical events in HIV.

5.3.11. Socially and geographically diverse groups

A lower socioeconomic status has implications of increased CVD mortality[1084] and poorer CVD risk factor profiles.[1085] A multicohort study of 1.7 million adults followed up for any cause of death for an average of 13 years found that low socioeconomic status was associated with a 2.1-year reduction in life expectancy between the ages 40 and 85 years.[1086] Education level, occupation, household income, health, disability, and living conditions also contribute to socioeconomic status. There were different rates of decline in mortality from CVD in Europe between the most and the least deprived.[1087] It has been proposed that on this basis, CVD could become a disease prevalently of the lower socioeconomic groups by the mid-2020s.[1088]

Black patients with diabetes have a higher hospitalization burden with a concomitant disparity in comorbid presentation and outcome compared with other patients with diabetes.[1089] South Asian ethnicity, even after adjustment for traditional risk factors, is associated with an increased risk of coronary heart disease outcomes. This risk was greater than other studied racial/ethnic groups and second only to diabetes in coronary heart disease risk prediction.[1090]

Within a large prospective study, South Asian individuals had a substantially higher risk of ASCVD than individuals of European ancestry.[1091] South Asians have a more diffuse pattern with multivessel involvement. However, less is known about other morphological characteristics, such as atherosclerotic plaque composition and coronary diameter in South Asian populations. Despite a similar coronary calcification burden, higher non-calcified plaque contribution, elevated thrombosis, and inflammatory markers likely contribute to the disease pattern. Although the current evidence on the role of coronary vessel size remains inconsistent, smaller diameters in South Asians could play a potential role in the higher disease prevalence.[1092] Individuals of South Asian descent have a high prevalence of CYP2C19 loss-of-function alleles (poor metabolizers: 13% vs. 2.4% in European populations),[1093] which are associated with reduced efficacy of clopidogrel.

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Recommendation Table 26 — Recommendations for older, female, high bleeding risk, comorbid, and socially/geographically diverse patients (see also Evidence Table 26)

Recommendations	Class[a]	Level[b]
Older adults		
In older adults (≥75 years), particular attention to drug side effects, intolerance, drug–drug interactions, overdosing, and procedural complications is recommended.	I	C
In older, as in younger, individuals, diagnostic and revascularization decisions based on symptoms, extent of ischaemia, frailty, life expectancy, comorbidities, and patient preferences are recommended.	I	C
Sex		
Similar guideline-directed cardiovascular preventive therapy is recommended in women and men.	I	C
Systemic post-menopausal hormone therapy is not recommended in women with CCS, given the lack of cardiovascular benefit and an increased risk of thrombo-embolic complications.[1026,1094,1095]	III	A
High bleeding risk		
Bleeding risk assessment is recommended using the PRECISE-DAPT score, the qualitative ARC-HBR tool or other, validated methods.[589,590]	I	B
HIV		
Attention to interaction between antiretroviral treatment and statins is recommended in patients with HIV.[1096]	I	B
Socioeconomic, geographical, and under-investigated groups		
Continued targeted efforts are recommended: • to increase delivery of safe and effective cardiac care to all CCS patients, especially those of lower socioeconomic classes; and • to enhance inclusion in future clinical trials of geographical, social, or other groups that are currently underrepresented.	I	C

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ARC-HBR, Academic Research Consortium for High Bleeding Risk; CCS, chronic coronary syndrome; HIV, human immunodeficiency virus; PRECISE-DAPT, PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual AntiPlatelet Therapy.
[a]Class of recommendation.
[b]Level of evidence.

5.4. Screening for coronary artery disease in asymptomatic individuals

Presence of asymptomatic atherosclerotic CAD is common in the general population.[1097–1100] In the Swedish Cardiopulmonary Bioimage Study, CCTA was performed in randomly selected individuals from the general population.[1097] In the 25 182 individuals without known CAD, atherosclerotic plaque was present in 42% of participants. Plaque was more common in older individuals and in males (males 50–54 vs. 60–64 years old: 41% vs. 69%, and females 50–54 vs. 60–64 years old: 19% vs. 40%). Obstructive coronary stenosis was present in 5% of participants. In the PESA study (Progression of Early Subclinical Atherosclerosis), 63% of asymptomatic middle-aged participants had subclinical atherosclerosis,[157] although most of them were categorized as low-risk individuals by several risk scores.[142]

The risk of adverse events in asymptomatic subjects can be estimated using the European risk-estimation system [Systematic Coronary Risk Estimation 2 (SCORE2)], described in the 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice.[16,1101] Systematic screening of risk factors cannot be strongly recommended in the general population as it did not affect CVD outcomes.[1102] However, when patients are seen for other reasons, opportunistic screening is effective at increasing detection rates of CVD risk factors, such as high BP or lipids. Hence, opportunistic screening is recommended, although its beneficial effect on clinical outcomes remains uncertain.[1103]

Information on CAC can be used to guide risk-factor management, and initiate lipid-lowering and antithrombotic treatment in patients with estimated future risk around treatment decision thresholds.[1104] To date, two randomized screening studies have indicated that statin therapy impacts outcomes when guided by CACS in younger patients with high CACS.[1105,1106] Coronary artery calcium score could potentially guide not only risk-factor management but also primary prophylaxis with aspirin, but randomized studies are lacking.[1107] Importantly, opportunistic screening of the burden of calcified atherosclerotic CAD can be accurately accessed with non-ECG-gated chest CT performed for other reasons.[17,1108] Reporting the visual interpretation of the coronary plaque burden according to a simple score with four categories (none, mild, moderate, severe) is recommended.[1108–1110] However, there is no current evidence to support further diagnostic imaging in asymptomatic individuals on the basis of presence of calcified plaque alone.

Carotid ultrasound,[1111] aortic pulse wave velocity, arterial augmentation index, and ankle–brachial index are other modalities to improve the prediction of future CVD events. However, evidence is less extensive for these modalities compared with CACS.

Recommendation Table 27 — Recommendations for screening for coronary artery disease in asymptomatic individuals (see also Evidence Table 27)

Recommendations	Class[a]	Level[b]
Opportunistic screening of healthy individuals for cardiovascular risk factors and to estimate the risk of future cardiovascular events using scoring systems, e.g. SCORE2 and SCORE-OP, is recommended to detect individuals at high risk and guide treatment decisions.[16,1101,1112]	I	C
When coronary artery calcification findings are available from previous chest CT scans, using these findings to enhance risk stratification and guide treatment of modifiable risk factors should be considered.[17,1108–1110]	IIa	C
CACS may be considered to improve risk classification around treatment decision thresholds.[1104–1106]	IIb	C
An ultrasound of the carotid arteries may be considered as an alternative when CACS is unavailable or not feasible to detect atherosclerotic disease and to improve risk classification around treatment decision thresholds.[1111]	IIb	B

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CACS, coronary artery calcium scoring; CT, computed tomography; SCORE2, Systematic Coronary Risk Estimation 2; SCORE-OP, Systematic Coronary Risk Estimation 2–Older Persons.
[a]Class of recommendation.
[b]Level of evidence.

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6. Long-term follow-up and care

6.1. Voice of the patient

A diagnosis of CCS can have an impact on self-identity, lifestyle, employment, and cause anxiety, depression, and burdensome treatment. Patients are experts in their own conditions, and their voices and preferences are integral to decisions about treatment. Health outcomes improve with better patient involvement, and *shared decision-making* is central to future patient care.[1113]

6.1.1. Communication

Communication is essential to support patients' understanding, adherence, and engagement in decision-making.[1114] Good communication requires providing information at an appropriate level, active listening, assessing patient understanding, and determining patient perspectives and priorities. A meta-analysis summarizing a total of 127 studies of communication training concluded that patients were 19% more likely to be non-adherent when physicians had poor communication, and 12% more likely to be non-adherent when their physicians had not received communication training.[1115] Communication and shared decision-making can be particularly challenging when patients have comorbidities, low health literacy, language differences, cognitive impairment, depression, or anxiety, and when evidence for treatment is less robust.

Patient reported outcome measures can be useful to improve assessment and communication of symptoms, function, and QoL, and can highlight problems that may not have been previously discussed. Under- and overestimation of symptoms can lead to a lack of or inappropriate treatment.[1116,1117] The routine use of PROMs in clinical practice is hampered by the challenge of interpretation of scores and their integration into routine clinical processes.[1116]

Although quality of communication can be improved through training, meta-analyses have not found evidence of significant impact on outcomes such as physical or mental health, satisfaction, QoL, or specific risk factors in patients with cancer, diabetes, and hypertension.[1115,1118,1119] Structured tools and a flexible range of resources (including videos, workbooks, and health-literacy materials) that provide individualized information and decision aids can be adjuncts to better communication and shared decision-making.[443] A systematic review of 17 RCTs of tools to support decision-making in severe illness concluded that they improved patient knowledge and readiness to make decisions.[1120]

Communicating the risk of future CVD events and how risk can be lowered through lifestyle and medications is best presented using visual or imaging approaches, natural frequencies rather than percentages, and positive framing (focusing on risk-reduction benefits).[1121–1125] Relative risk reduction is more persuasive than either absolute risk reduction or the number needed to treat.[1122] The use of risk prediction estimates may have an impact on individuals' health when their information (i.e. predicted risk stratification) changes individuals' behaviour, self-management decisions, and even treatment decisions.[446] This enables patients to gain insights into their cardiovascular prognosis and to empower them to take part in the decision-making process.[1126] This approach may increase self-motivation for therapy adherence and lifestyle changes, including changes in nutrition, physical activity, relaxation training, weight management, and participation in smoking cessation programmes for resistant smokers.[446] Previous unsuccessful attempts to change to a healthy lifestyle or take guideline-recommended treatment can be addressed to set realistic goals.[446]

Communication should be clear regarding symptoms, even if not cardiac. Patients with CCS experiencing non-cardiac chest pain experience uncertainty about the cause and actions to take. A multidisciplinary approach and evaluation of non-cardiac aetiology with an appropriate referral are advocated to ensure that appropriate treatment is initiated.[1127,1128]

6.1.2. Depression and anxiety

Depression is common (15%–20% prevalence) in CVD, and associated with poor adherence and worse outcomes, including MACE and premature death.[1129] Coronary microvascular dysfunction (prevalent in INOCA) is linked with psychological stress and depression.[946] Unfortunately, depression and psychological stress are often unrecognized due to a lack of systematic screening using validated tools.[1129] For anxiety, a recent meta-analysis involving 16 studies reported a prevalence in post-MI between 5.5% and 58%, and a 27% greater risk of poor clinical outcomes in anxious patients compared with those without anxiety.[1130] In contrast, in a 15-year follow-up of 1109 patients with CCS moderate anxiety did not increase the risk of cardiovascular events compared with low anxiety levels. Patients on a high but decreasing anxiety trajectory had an HR of 1.72 (95% CI, 1.11–2.68) for cardiovascular events.[1131] Treatment of psychosocial factors, depression, and anxiety with pharmacotherapy, psychotherapy, and/or exercise can improve symptoms and QoL in some patients, and there is some evidence for improvement in cardiac outcomes.[472,1132–1134] Stepped care (initial therapy based on patient preferences) and a combination of therapies may be more efficacious.[1129,1135] First-line treatment with selective serotonin reuptake inhibitors (recommended in CCS) or non-pharmacological interventions and a multidisciplinary collaborative approach are recommended.[1129]

6.2. Adherence and persistence

Earlier analyses reported that adherence to long-term therapies in chronic conditions in Western countries averaged 50% and was lower in developing countries.[1136] Pooled prevalence of non-adherence from a recent meta-analysis of eight studies ($n = 3904$ patients with multimorbidity) was 42.63% (95% CI, 34%–51%).[1137] Data from the ESC-EORP EUROASPIRE V registry indicate that many CCS patients still have unhealthy lifestyles in terms of smoking, diet, and sedentary behaviour.[1138] Poor adherence and persistence (duration of time in which medications and healthy behaviours are continued) have a profound effect on effective management, patient safety, and outcomes. The World Health Organization (WHO) advocates training in adherence for healthcare professionals, a multidisciplinary approach, support rather than blame, tailored interventions based on illness-related demands for each patient, and viewing adherence as a dynamic process.[1136]

The five dimensions of adherence are patient, disease, provider, therapy, and healthcare system (*Figure 16*).[1139] Therefore, identifying patients at risk of non-adherence, addressing all five dimensions, developing a multidisciplinary pathway to support *sustained* adherence, and a follow-up strategy are essential steps.[1139]

6.2.1. Adherence to healthy lifestyle behaviours

Different strategies may help improve long-term adherence to a healthy lifestyle (*Figure 17*).

6.2.1.1. Why behavioural changes are difficult

Making changes to unhealthy lifestyles and controlling risk factors can be a daunting task as these are usually longstanding habits and patterns

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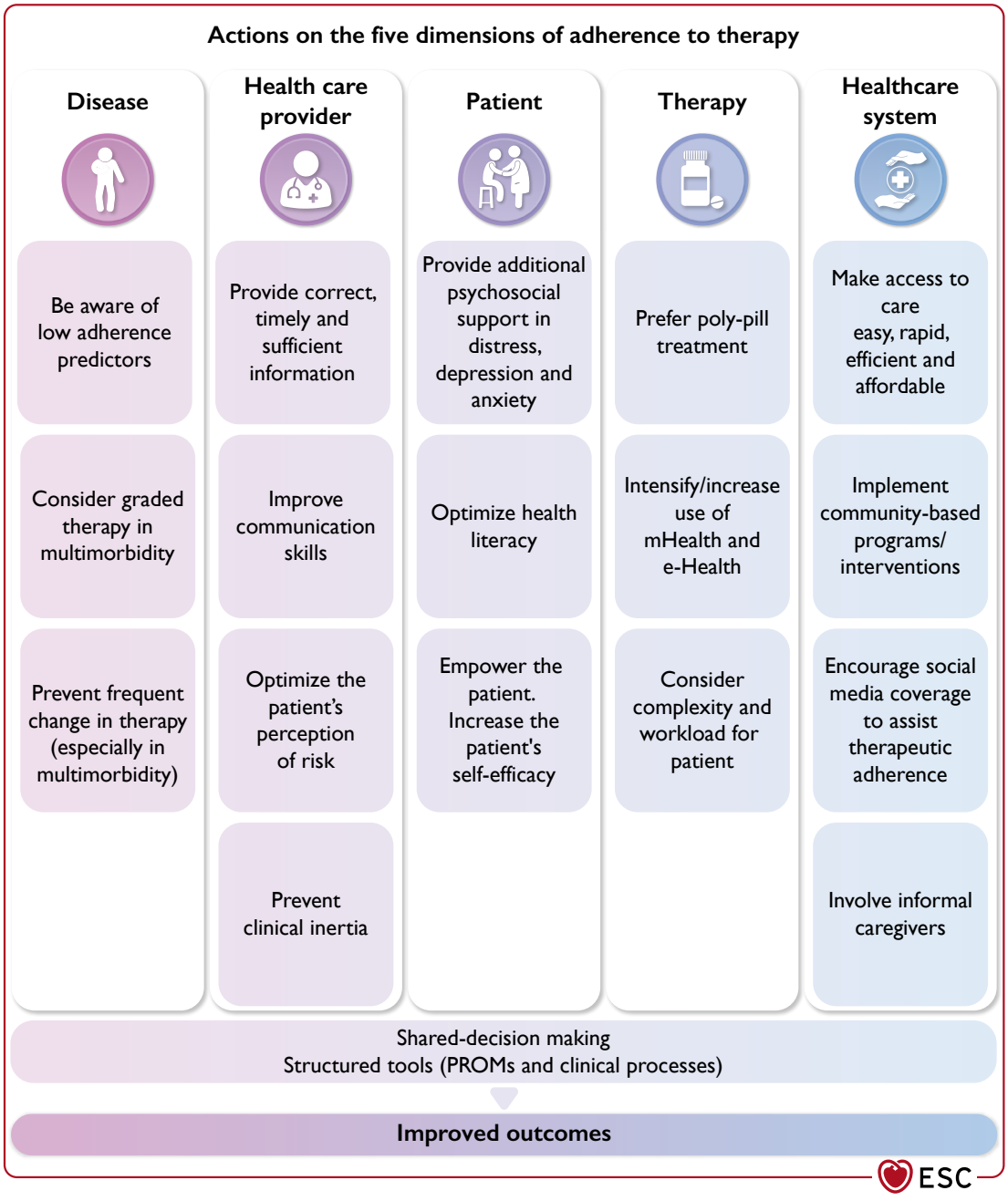

Figure 16 Actions on the five dimensions of adherence to therapy. e-Health, healthcare services provided electronically; mHealth, mobile device-based healthcare; PROMs, patient-reported outcome measures. Adapted from Pedretti *et al.*[1139].

of behaviour. Habits and environmental cues primarily govern behaviours, so education and information alone are seldom enough.[1140] Factors such as psychological state and low health literacy (associated with depression and worse behavioural risk factors) also impact the ability to make changes.[1141,1142]

6.2.1.2. How to change behaviour and support healthy lifestyles

A multidisciplinary approach and behavioural counselling can improve adherence. A systematic review and meta-analysis of 12 RCTs of nurse-led patient-centred interventions for secondary prevention found greater adherence to smoking cessation and physical activity, and better control of total cholesterol (with medication titration), but no improvements in dietary habits, BP, blood glucose, or survival.[1143] A systematic review of behavioural counselling found that medium- to high-contact counselling resulted in 20% lower risk of CVD events, lower BP, and decreased LDL-C and adiposity in adults with CVD risk factors.[1144] Incorporating cardiovascular visual images into risk-factor discussions is effective in reducing subsequent 10-year risk assessment and individual risk factors.[445]

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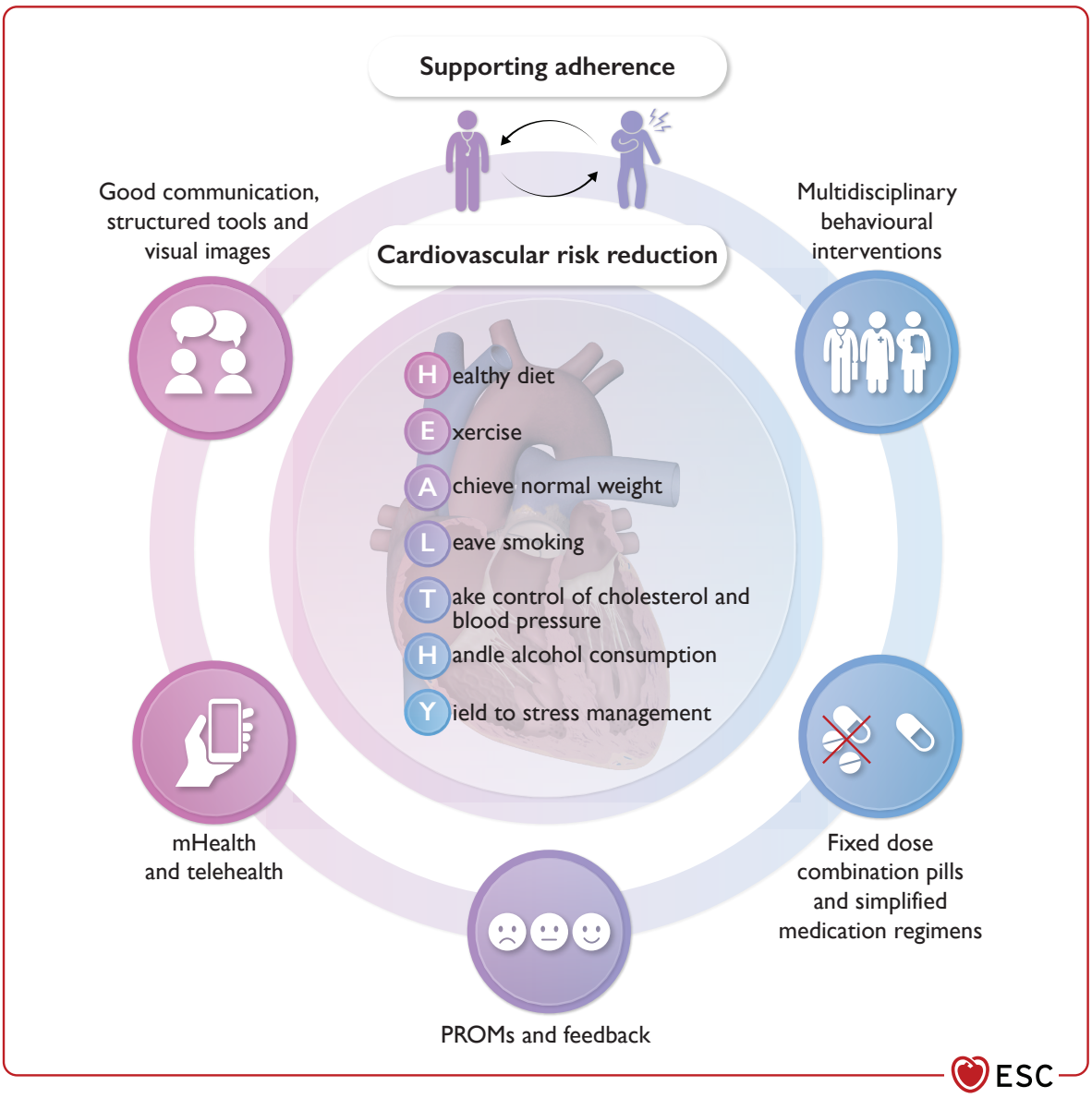

Figure 17 Strategies for long-term adherence to a healthy lifestyle. mHealth, mobile device-based healthcare; PROMs, patient-reported outcome measures.

Lifestyle changes also impact relatives, partners, and friends, so they should be involved in patient support.[1139] Physical activity can be incorporated flexibly, either daily, or limited to specific days. Activity patterns limited to 1–2 sessions per week but meeting recommended levels of physical activity have been shown to reduce or postpone all-cause, CVD, and cancer mortality risk.[477] Importantly, maintaining changed behaviour over time is a challenge. Some trials have shown an impact of lifestyle intervention on cardiovascular health and behavioural metrics, which became attenuated in the long term as the intensity of the intervention declined.[1145]

6.2.1.3. Digital and mHealth

Behavioural change and habit formation can be facilitated through technology such as wearable devices, the internet, and smartphones. In 27 studies including 5165 patients with CAD or cerebrovascular disease, text messaging and smartphone apps resulted in a greater ability to reach BP targets and exercise goals, less anxiety, and increased awareness of diet and exercise compared with control.[1146] Nevertheless, there was no significant difference in smoking cessation, LDL-C, and hospital readmissions.[1146] Digital interventions mainly stimulate healthy behavioural factors but are less effective in reducing unhealthy behavioural factors (smoking, alcohol intake, sedentary behaviour, and unhealthy diet) and clinical outcomes.[1146,1147]

The use of wearable devices has significantly increased physical activity and decreased waist circumference, systolic BP, and LDL-C among individuals with chronic conditions including CVD.[491] Younger age has been associated with a higher increase in physical activity, and CVD has been associated with a lower increase. Wearable activity trackers have shown effectiveness, but the effect was greater when

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combined with other behaviour-change strategies.[491] A systematic review of CCS patients that used activity trackers combined with feedback by healthcare professionals (most also giving lifestyle education) showed a significant increase in peak VO_2 in studies using an accelerometer (but not a pedometer) compared with non-users. The overall effect across studies reduced MACE and improved QoL.[1148] Similarly, smartphone and tablet computer apps have been shown to increase physical activity (minutes per week or steps per day) among people with CVD (1543 participants, most of them with CCS). This effect was largest in small studies focused on physical activity only, participants ≥60 years old, and duration of up to 3 months.[1149] Adherence to the apps was 20% to 85% and tended to wane over time. Of note, the implementation of digital and mHealth should not be at odds with a less digital-oriented care for those unfamiliar with new technologies (e.g. elderly people).

6.2.1.4. How to assess adherence

Addressing lifestyle behaviour and medication adherence in a non-judgemental way at clinical encounters is important to identify barriers and offer tailored solutions to promote healthier actions. The encounter can be useful to review patient self-monitoring records (digital or written), accelerometer data, and diaries, or validated questionnaires on physical activity.

6.2.2. Adherence to medical therapy

Guideline-directed medications are key to the effective management of CCS and prevention of subsequent cardiovascular events, but dependent on patient adherence and persistence with treatment. Despite robust evidence of benefits in terms of mortality and morbidity,[1150] adherence remains suboptimal.[1151] Although adherence is usually higher in RCTs, approximately 28% of CCS patients in the ISCHEMIA trial were non-adherent to prescribed medications at baseline.[1152] Non-adherence was associated with significantly worse health status regardless of randomization to the conservative or invasive strategy.[1152] Medication adherence can be intentional or unintentional, and can be adversely affected by polypharmacy, complex drug regimens, high cost, and side effects.

6.2.2.1. Strategies to improve medication adherence

Improving adherence to medications has proved challenging.[1153] One systematic review and meta-analysis (771 studies to 2015) found that interventions that were behaviourally focused, e.g. linking medication-taking to existing habits, were more effective than those that were cognitively focused.[1154] A systematic review of 17 trials of adherence for secondary CVD prevention found that a short message service, a fixed-dose combination pill, and a community health worker-based intervention (one trial each) increased adherence compared with usual care.[1155] Behavioural and mixed behavioural/educational interventions improved adherence in older adults with multiple medications (low-quality evidence), with little evidence for educational-only interventions.[1156] Drug reminder packaging—i.e. incorporating the date and time for the medication to be taken in a package (pre-filled containers)—can act as a prompt, with some evidence that it increases pills taken and improves diastolic BP and HbA1c levels.[1157] Treating depression is important, as depression was associated with reduced adequate and optimal adherence to recommended medications 12 months post-PCI in an analysis of 124 443 patients.[1158] Simplifying medication regimens using fixed-dose polypills has been shown to increase adherence.[1159–1162] The SECURE trial demonstrated that patients 6 months post-MI randomized to a polypill containing aspirin, ramipril, and atorvastatin had significantly lower MACE and were more likely to have high adherence at 6 and 24 months compared with the usual care group.[1163]

6.2.2.2. mHealth strategies for medication adherence

A review of mobile phone text messaging found promising, if limited, evidence that such messaging could improve medication adherence up to 12 months after acute coronary events.[1164] Similarly, another review of 24 studies of text messages and/or apps found robust evidence for adherence to pharmacological therapy.[1146] A pilot trial of 135 non-adherent patients with hypertension and/or diabetes randomized patients to a highly tailored digital intervention (text messages and interactive voice response) or usual care for 12 weeks. Medication adherence was significantly improved in the intervention group, along with improvements in systolic BP and HbA1c, compared with the control group.[1165]

Recommendation Table 28 — Recommendations for adherence to medical therapy and lifestyle changes (see also Evidence Table 28)

Recommendations	Class[a]	Level[b]
Mobile health interventions (e.g. using text messages, apps, wearable devices) are recommended to improve patient adherence to healthy lifestyles and medical therapy.[491,1148,1149,1154,1156,1164]	I	A
Behavioural interventions are recommended to improve adherence.[491,1140,1144]	I	B
Simplifying medication regimens (e.g. using fixed-dose drug combinations) is recommended to increase patient adherence to medications.[1139,1163,1166]	I	B
Multiprofessional and family involvement is recommended to promote adherence, in addition to patient education and involvement.[1139]	I	C

[a]Class of recommendation.
[b]Level of evidence.

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6.3. Diagnosis of disease progression

Long-term follow-up of patients with CCS who have either established CAD (prior acute MI, revascularization, known CAD) or non-obstructive CAD includes surveillance for disease progression. However, current literature is sparse regarding mode, frequency, and duration. Follow-up of patients is based on their clinical condition, which includes cardiovascular risk factors, residual symptoms, cardiac complications [such as post-infarction LV remodelling and dysfunction, associated mitral regurgitation (mostly functional), known HF, significant arrhythmias], and non-cardiac comorbidities like PAD, stroke, and renal dysfunction.

The main goal of follow-up is to determine the patient's risk of developing new cardiac events through risk stratification and to identify symptoms suggestive of CAD progression. A second goal is

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to promptly diagnose and manage extracoronary complications, such as the onset of HF, arrhythmias, and valvular dysfunction. Additionally, during long-term follow-up, antianginal and disease-modifying medication should be optimized and adjusted based on the development of comorbidities. The potential benefits vs. bleeding risks of antithrombotic drugs should be considered and evaluated over time.

Although assessing the anginal status is traditionally considered the cornerstone of clinical follow-up, it is worth noting that angina resolves in 40% of CCS patients at 1 year with further annual decreases, most often without revascularization or adaptation of antianginal therapy.[404] In contrast to patients with resolving symptoms, those with persistent or recurrent angina are at higher risk of cardiovascular death or MI.[404] The worse prognosis of persisting angina, however, was only observed in patients with a previous MI.[408]

6.3.1. Risk factors for recurrent coronary artery disease events

Patients with established ASCVD are at high risk of recurrent events and different risk factors have been identified. The REACH registry demonstrated that, in addition to the traditional risk factors, the burden of disease, lack of treatment, and geographical location are all related to an increased risk of cardiovascular morbidity and mortality in CCS patients and validated a risk score that allows estimation of the risk for MACE.[1167] Using data from stabilized CCS patients from 27 European countries included in the EUROASPIRE IV and V surveys, a new risk model with an online risk calculator to predict recurrent CVD events in patients under the age of 75 years was developed and externally validated in the SWEDEHEART registry.[1168,1169] This model indicated that the risk of recurrent MACE is mainly driven by comorbidities including diabetes, renal insufficiency, and dyslipidaemia, but also symptoms of depression and anxiety. A study of patients with established CAD from the UK Biobank confirmed the value of classical risk factors, lifestyle, and sociodemographic factors in predicting recurrent MACE.[1170] In addition, it was found that high genetic predisposition to CAD, low HDL-C, and younger age at first ACS event most strongly predicted the recurrence risk. A polygenic risk score, when added to the Framingham score, improved predictions of events in a large population in the USA.[1171] Although the prediction of recurrent MACE has been refined, it must be emphasized that the predictive power of the different risk factors is weak and that a significant part of recurrent MACE in CCS patients remains unexplained. Furthermore, the models do not incorporate information on LV function, HF, concomitant valvular disease, atherosclerotic disease burden in other vascular beds, or the severity of existing CAD.[1172] While risk factors for recurrent cardiac events have been established, no clinical studies have tested predefined clinical pathways for long-term follow-up of various types of CCS patients. As a result, the long-term clinical follow-up of CCS patients is primarily empirical, based on good clinical judgement, and on the same criteria used in the initial diagnostic process to define high risk of adverse events (*Section 3.3.5* and *Figure 18*).

6.3.2. Organization of long-term follow-up

When scheduling long-term follow-up for CCS patients with recurring or worsening angina, it is important to consider factors such as patient type, the presence of risk factors, availability of diagnostic techniques, and cost-effectiveness following regional or national healthcare policies. Different CCS phenotypes may develop or recur during long-term follow-up, altering the follow-up needed over time. The intervals and examination methods during long-term follow-up may vary based on the CCS phenotype, coronary atherosclerotic burden, presence of CMD, and severity of ischaemic LV dysfunction.

A stepwise approach based on risk assessment can be followed, like that applied for diagnosing and treating individuals with suspected CCS.

Step 1: This involves an annual clinical evaluation, by a general practitioner or a cardiologist, encompassing symptom evaluation, medication review, physical examination, a resting 12-lead ECG, and blood tests for lipid profile, renal function, glycaemic status, and full blood count. The ECG should be scrutinized for heart rate, rhythm, evidence of silent ischaemia/infarction, and evaluation of PR, QRS, and QT intervals. Any new symptoms suggestive of ACS, especially with ECG changes, warrant adherence to the 2023 ESC Guidelines for the management of patients with acute coronary syndromes. [65] Current medical therapy and lifestyle measures for risk-factor control can be maintained or optimized for asymptomatic patients.

Step 2: If CCS patients develop new or worsening angina or HF symptoms, arrhythmias or ECG changes, further cardiac evaluation is crucial, especially if symptoms persist despite optimized GDMT. Recurrent CAD event risk should be assessed based on symptoms, progression of risk factors, and resting ECG changes. Echocardiography may be performed to assess LV function, cardiac dimensions, and valvular abnormalities. Exercise ECG testing may be considered to confirm symptoms and evaluate functional capacity if it alters patient management. However, routine functional testing is not recommended for asymptomatic post-PCI patients, as it has not been shown to improve outcomes compared with standard care after 2 years.[1173]

Step 3: CCS patients with persistent symptoms at low exercise levels despite optimized GDMT or unexpectedly reduced LV function, especially with regional contraction abnormalities, need further cardiac testing to detect the progression of CAD and assess the event risk.

For patients with known non-obstructive CAD, CCTA can help detect new obstructive stenoses, evaluate atherosclerotic disease progression, and identify high-risk plaque features, while functional imaging is reasonable for detecting myocardial ischaemia and guiding further management. In patients with ANOCA/INOCA and stratified medical therapy, CCTA can be useful to detect new or progressing CAD.

For patients with obstructive CAD or previous cardiac events, non-invasive functional imaging is the preferred method to detect and quantify myocardial ischaemia and/or scar. However, in patients with severely limiting angina and known severe ischaemia on functional testing or high-risk CAD on CCTA, direct referral to ICA for revascularization is preferred due to the very high risk of recurrent CAD events. Although CCTA can detect CABG graft patency and exclude in-stent restenosis (ISR) in broad lumen arteries, functional imaging is preferred for assessing patients with prior revascularization because of the high frequency of extensive CAD in these patients.[1174–1176]

Step 4: In all patients with recurrent or worsening anginal symptoms, lifestyle modifications, risk-factor management, and GDMT should be intensified before considering further interventions. For patients with significant inducible myocardial ischaemia or high-risk CAD, and persistent anginal symptoms despite lifestyle modifications and intensified GDMT, repeat coronary revascularization may be necessary to alleviate symptoms and improve prognosis. For patients with prior CABG experiencing stable symptoms, it's important to optimize GDMT whenever possible. If frequent angina persists despite GDMT optimization, ICA or CCTA can assist in guiding treatment decisions.[1177–1179] When symptoms are uncertain, functional testing may help clarify the presence and extent of myocardial ischaemia.

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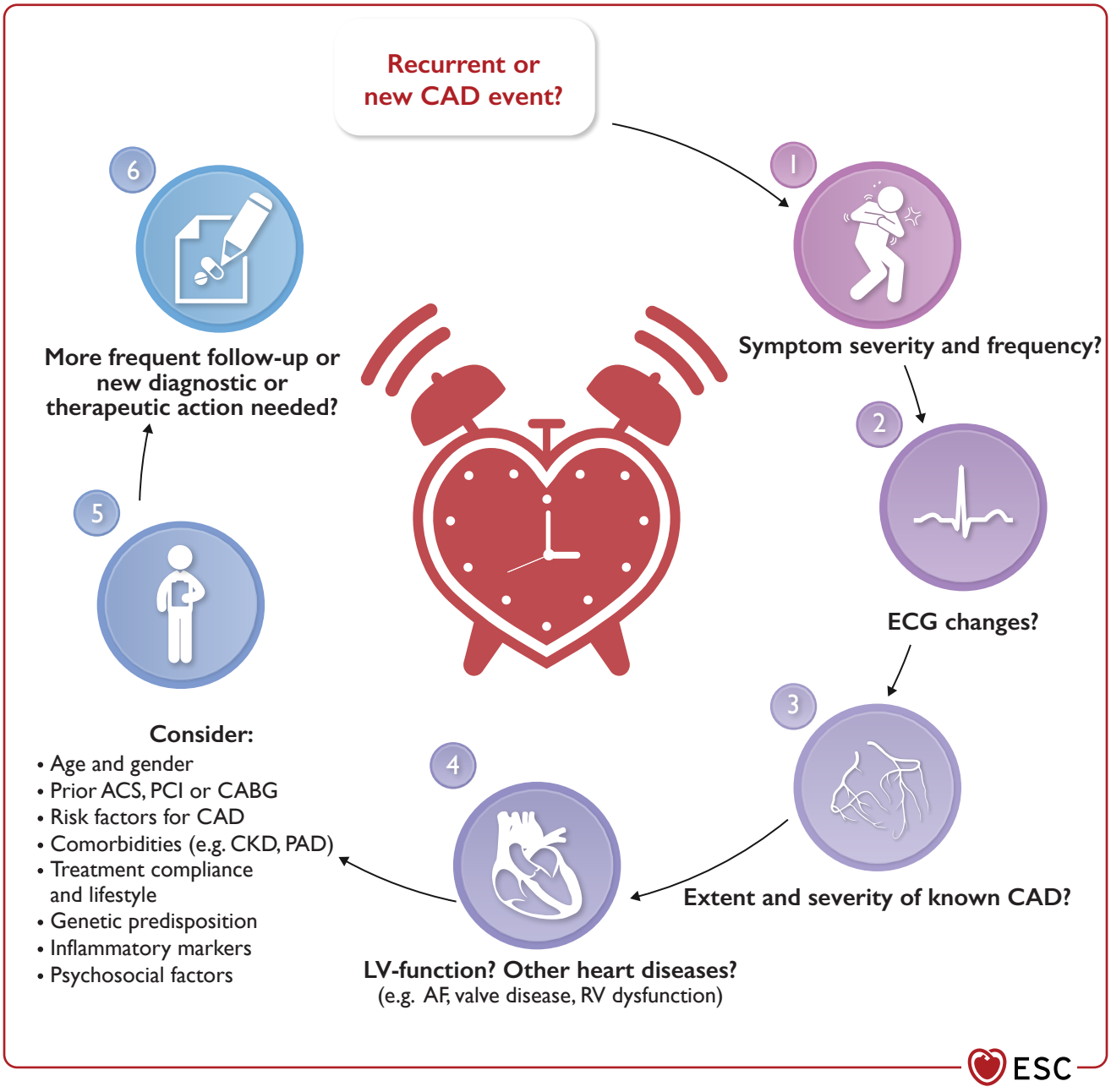

Figure 18 Approach for the follow-up of patients with established chronic coronary syndrome. ACS, acute coronary syndrome; AF, atrial fibrillation; CABG, coronary aortic bypass grafting; CAD, coronary artery disease; CCS, chronic coronary syndrome; CKD, chronic kidney disease; ECG, electrocardiogram; LV, left ventricle; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; RV, right ventricle.

6.3.3. Non-invasive diagnostic testing

All non-invasive diagnostic testing, including CCTA, stress SPECT, or PET myocardial perfusion imaging, stress echocardiography, and stress CMR have been shown to provide prognostic information in patients with established CAD.[296,1180,1181] Anatomical imaging with CCTA has the advantage of providing information on left main disease and graft patency. Stress imaging provides information on the degree of ischaemia, which helps guide an appropriate management plan. For example, symptomatic patients with moderate-to-severe myocardial ischaemia despite GDMT will usually undergo additional revascularization. In patients with known ANOCA/INOCA, non-invasive imaging with stress SPECT or PET myocardial perfusion imaging, stress CMR, or stress echocardiography remain first-line investigations, although the diagnostic yield may be low;[927] however, the current standard remains invasive coronary functional testing.

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Recommendation Table 29 — Recommendations for diagnosis of disease progression in patients with established chronic coronary syndrome (see also Evidence Table 29)

Recommendations	Class[a]	Level[b]
Asymptomatic patients with established chronic coronary syndromes		
Regardless of symptoms, periodic visits (e.g. annual) to a general practitioner or cardiovascular healthcare professional are recommended to evaluate cardiovascular risk factor control and to assess changes in risk status, disease status, and comorbidities that may require lifestyle, medical, or procedural interventions.	I	C
Symptomatic patients with established chronic coronary syndromes		
Reassessment of CAD status is recommended in patients with deteriorating LV systolic function that cannot be attributed to a reversible cause (e.g. longstanding tachycardia or myocarditis).	I	C
Risk stratification is recommended in patients with new or worsening symptoms, preferably using stress imaging.	I	C
In patients with symptoms refractory to medical treatment or at high risk of adverse events, invasive coronary angiography (with FFR/iFR when necessary) is recommended for risk stratification and for possible revascularization aimed at improving symptoms and prognosis.	I	C
In CCS patients with symptoms refractory to medical treatment, and who have had previous coronary revascularization, CCTA should be considered to evaluate bypass graft or stent patency (for stents ≥3 mm).[1174–1176]	IIa	B

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CAD, coronary artery disease; CCS, chronic coronary syndrome; CCTA, coronary computed tomography angiography; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; LV, left ventricular; QFR, quantitative flow ratio.
[a]Class of recommendation.
[b]Level of evidence.

6.4. Treatment of myocardial revascularization failure

One in five revascularized patients needs a repeat revascularization within the first 5 years after myocardial revascularization, with higher risk after PCI compared with CABG.[1182] Revascularization failure can manifest either shortly after the initial procedure (within 30 days) or later on, and recurring symptoms may result from either restenosis of the treated coronary segment or the failure of bypass grafts,[772] alongside the progression of underlying native CAD.[1183,1184] Published evidence regarding diagnosis and management of myocardial revascularization failure has been summarized in the 2020 EAPCI (European Association of Percutaneous Cardiovascular Interventions) Expert Consensus Paper.[1182]

6.4.1. Percutaneous coronary intervention failure

Stent thrombosis and ISR are the most frequent reasons for PCI failure. Stent thrombosis occurs infrequently and is multifactorial. Anatomical and mechanical factors, as well as lack of adherence or hyporesponsiveness to antiplatelet treatment, are frequently the reasons behind this.[1182,1185] The majority of patients with stent thrombosis present with ACS and should be treated according to the 2023 ESC Guidelines for the management of patients with acute coronary syndromes.[65] Urgent ICA to confirm diagnosis and treatment is indicated. After restoration of coronary flow, intracoronary imaging to identify mechanical failure should be performed. Repeated DES implantation is indicated in case of stent fracture or collapse and residual edge dissections, while high-pressure non-compliant balloon dilation is indicated in case of stent under-expansion or malapposition.

In-stent restenosis results as a response to vessel wall injury (neointimal hyperplasia) or neoatherosclerosis in the stented segment of the coronary artery. Although significantly less frequent than after bare-metal stent implantation, the incidence of clinical in-DES restenosis is up to 10% within the first 10 years after DES implantation[1182] and remains the most frequent cause of PCI failure. The clinical presentation of ISR is mostly CCS, with 20% ACS, and the remaining asymptomatic. The indication to treat ISR is like that for native CAD. Radiological stent enhancement and intracoronary imaging are encouraged to determine the ISR mechanism. PCI treatment of ISR should be focused on the stenotic segment. Lesion preparation (ultra-high pressure balloon dilation, intravascular lithotripsy, rotation atherectomy) and correction of mechanical issues are required.[1182] Thereafter, drug-coated balloon angioplasty or DES implantation is necessary.[1186,1187] Drug-eluting balloon angioplasty and repeat stenting with DES were equally effective and safe in treating bare-metal ISR, but drug-coated balloon angioplasty was less effective than repeat paclitaxel DES implantation in treating DES ISR.[1186] However, at 10-year follow-up there was no difference in clinical endpoints between drug-coated balloon angioplasty and DES implantation, whereas both were more effective than balloon angioplasty in preventing target-lesion revascularization.[1187] Everolimus DES was associated with better long-term outcomes than drug-coated balloons.[1188]

6.4.2. Managing graft failure after coronary artery bypass grafting

A variety of reasons have the potential to adversely affect bypass graft patency.[1189] These include technical (quality of graft material, surgical precision) and pathophysiological aspects (competitive flow, activity of the coagulation system, disease progression, etc.). Technical aspects and competitive flow are thought to influence early graft failure, while disease progression and graft degeneration affect long-term patency.[1182,1189]

The majority of graft occlusions are clinically silent.[1189] If symptoms occur, prompt diagnostic workup (including ECG, assessment of biomarkers, and possibly repeat coronary angiography) is warranted to limit or prevent potential damage from graft occlusion.[316] Acute CABG graft failure (<1 month after surgery) is observed in approximately 12% of grafts mostly due to technical problems.[1190] Late failure of saphenous vein grafts occurs in up to 50% at 10 years, with vein graft occlusion rates in up to 27% within 1 year after surgery.[771,1191]

The decision for optimal treatment (conservative, CABG revision/redo CABG or PCI of the native vessel or of the failed graft) should be made individually considering haemodynamic stability, technical

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reasons for graft failure, and ability to treat native CAD. PCI is the first choice over redo CABG for late graft failure, with PCI of the native vessel rather than PCI of the graft.[772,1182,1192,1193]

If re-operation is required, the surgical risk is generally increased.[1182,1192] If acute re-operation is required, acute ischaemia is generally present, and adhesions and the presence of patent grafts increase the complexity of the procedure. It is, therefore, important to weigh this risk against the expected benefit. Since a patent left internal thoracic artery (LITA) to the LAD confers the largest part of CABG prognostic potential,[1189,1194] redo CABG is primarily recommended in patients with indications for CABG and occluded LITA or if the LITA was not used during the first operation.[772]

Recommendation Table 30 — Recommendations for treatment of revascularization failure (see also Evidence Table 30)

Recommendations	Class[a]	Level[b]
DES is recommended over drug-coated balloons for treatment of in-DES restenosis.[1186–1188]	I	A
LIMA is indicated as the conduit of choice for redo CABG in patients in whom the LIMA was not used previously.[1195]	I	B
Redo CABG should be considered for patients without a patent LIMA graft to the LAD.[842,1192,1196]	IIa	B
PCI of the bypassed native artery should be considered over PCI of the bypass graft.[1197]	IIa	B

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CABG, coronary artery bypass grafting; DES, drug-eluting stent; LAD, left anterior descending; LIMA, left internal mammary artery; PCI, percutaneous coronary intervention.
[a]Class of recommendation.
[b]Level of evidence.

6.5. Recurrent or refractory angina/ischaemia

An ageing population and an increased survival rate in patients with CAD due to improvements in anti-ischaemic medical therapy and coronary revascularization have led to a growing number of patients with severe and diffuse CAD not amenable to further revascularization procedures. Despite the use of antianginal drugs and/or PCI or CABG, the proportion of patients with CAD who have daily or weekly angina ranges from 2% to 24%.[555]

Refractory angina is defined as long-lasting symptoms (for >3 months) due to established reversible ischaemia: (i) in the presence of obstructive CAD, which cannot be controlled by escalating medical therapy with additional antianginal drugs, bypass grafting, or PCI including recanalization of chronic total coronary occlusion; or (ii) due to ANOCA/INOCA. In the case of ANOCA/INOCA, further investigations are required to define the different endotypes (*Section 4.4.2*) and appropriate treatment (*Section 6.3*) before diagnosing refractory angina.[36]

The QoL of patients with refractory angina is poor, with frequent hospitalization and a high level of resource utilization.[555] Once conventional anti-ischaemic targets have been exhausted, novel therapies can be ranked by mechanism of action, promotion of collateral growth, transmural redistribution of blood flow, and neuromodulation of the cardiac pain syndrome.

Considering the chronic nature of the disease and according to risk–benefit assessments, among the currently available options, the most promising and easily implementable in everyday clinical practice are enhanced external counterpulsation and the coronary sinus reducer device,[555] after all medical therapy and mechanical revascularization options have been exhausted (see *Sections 4.2* and *4.4*). Enhanced external counterpulsation has been shown to ameliorate refractory angina in several trials.[1198]

The coronary sinus reducer consists of controlled coronary sinus narrowing with the implantation of a large stainless-steel device to increase coronary sinus pressure and improve perfusion in the LAD territory.[1199] In a recent meta-analysis including eight registries and one RCT, in a total of 846 patients with refractory angina, use of a coronary sinus reducer led to improvement of ≥1 CCS class in 76% (95% CI, 73%–80%) of patients and an improvement of ≥2 CCS class in 40% (95% CI, 35%–46%) of patients.[1200] The Coronary Sinus Reducer Objective Impact on Symptoms, MRI Ischaemia and Microvascular Resistance (ORBITA-COSMIC) trial, a small proof-of-concept RCT, found no evidence that implantation of a coronary sinus reducer improved transmural myocardial perfusion, but it was associated with improved angina symptoms compared with placebo.[1201]

There are several ongoing RCTs evaluating the use of coronary sinus reducer in ANOCA/INOCA, such as COronary SInus Reducer for the Treatment of Refractory Microvascular Angina (COSIMA; NCT04606459), and the Efficacy of the COronary SInus Reducer in Patients with Refractory Angina II (COSIRA-II; NCT05102019).

A variety of new pharmacological approaches is becoming available and includes angiogenetic therapies with vascular endothelial growth factors and fibroblast growth factors, as well as stem cell therapy with intramyocardial delivery of $CD34^+$ cells.[1202,1203] However, further RCTs are needed to validate the feasibility of such therapeutic strategies.

To date, the main limitations of reported experiences with all novel therapeutic options regard the small number of treated patients and the duration of follow-up. Larger sham-controlled RCTs are required to define the role of each treatment modality for specific subgroups, and ultimately to aim at the best possible personalized treatment algorithm, based on aetiology stratification, and escalation of available therapeutic modalities.

Recommendation Table 31 — Recommendations for recurrent or refractory angina/ischaemia (see also Evidence Table 31)

Recommendations	Class[a]	Level[b]
In patients with refractory angina leading to poor quality of life and with documented or suspected ANOCA/INOCA, invasive coronary functional testing is recommended to define ANOCA/INOCA endotypes and appropriate treatment, considering patient choices and preferences.[36,37,298,930,939,985]	I	B
In patients with debilitating angina and obstructive CAD refractory to optimal medical and revascularization strategies, a reducer device for coronary sinus constriction may be considered to improve symptoms, in experienced centres.[1199–1201,1204]	IIb	B

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ANOCA, angina with non-obstructive coronary arteries; CAD, coronary artery disease; INOCA, ischaemia with non-obstructive coronary arteries.
[a]Class of recommendation.
[b]Level of evidence.

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6.6. Treatment of disease complications

Patients with CCS who develop LV dysfunction may experience advanced HF, malignant arrhythmias and secondary valvular heart disease (i.e. mitral and tricuspid regurgitation).

Prior MI and ischaemic aetiology are negative prognostic markers in patients with advanced HF,[1205] as well as in those with secondary mitral regurgitation.[1206] Specific treatments need to be considered in these patients regardless of HF aetiology (i.e. ischaemic).[526] Advanced HF treatments include: high diuretic doses; a combination of diuretics and renal replacement therapy to treat congestion; inotropic and vasopressor agents to reduce hypoperfusion; and mechanical circulatory support in selected patients with severe symptoms or exercise intolerance, despite optimal medical therapies, and without right ventricular dysfunction. Heart transplantation is recommended for patients with advanced HF, refractory to medical/device therapy, and who do not have absolute contraindications. Early evaluation for mechanical circulatory supports or heart transplantation is currently suggested also in patients with mild symptoms [i.e. New York Heart Association (NYHA) class II] and high-risk profile (i.e. LVEF of <20%, recurrent HF events, hypotension, intolerance to medical therapy, worsening organ failure, ventricular arrhythmias/ICD shock).[526]

An ICD is recommended in patients with ischaemic cardiomyopathy and LVEF of <35% or who have recovered from ventricular arrhythmias.[526] Frequent, symptomatic ventricular arrhythmias in ICD recipients should be treated medically with either beta-blockers or amiodarone. In patients with CCS who develop ventricular fibrillation or polymorphic ventricular tachycardia, assessment for myocardial ischaemia should be performed without delay. In patients with CAD in whom sustained monomorphic ventricular tachycardia recurs while on amiodarone treatment, catheter ablation is recommended over the escalation of antiarrhythmic drugs.[1207] Percutaneous treatment of secondary mitral regurgitation in patients with advanced HF may be considered to improve symptoms.[526] Treatment of secondary tricuspid regurgitation in advanced stages of disease was, until recently, supported by limited evidence.[1208] Percutaneous tricuspid transcatheter edge-to-edge repair was found to reduce significantly severe tricuspid regurgitation and was associated with improvements in QoL at 1 year.[1209]

7. Key messages

- Symptoms of myocardial ischaemia due to obstructive atherosclerotic CAD overlap with those of CMD or vasospasm.
- Similar guideline-directed cardiovascular preventive therapy is recommended in women and men in spite of the sex differences in the clinical presentation.
- Inclusion of risk factors to classic pre-test likelihood models of obstructive atherosclerotic CAD improves the identification of patients with very low (≤5%) pre-test likelihood of obstructive CAD in whom deferral of diagnostic testing should be considered.
- CACS is a reliable 'simple' test to modify the pre-test likelihood of atherosclerotic obstructive CAD.
- First-line diagnostic testing of suspected CCS should be done by non-invasive anatomic or functional imaging.
- Selection of the initial non-invasive diagnostic test should be based on the pre-test likelihood of obstructive CAD, other patient characteristics that influence the performance of non-invasive tests, and local expertise and availability.
- CCTA is preferred to rule out obstructive CAD and detect non-obstructive CAD.
- Functional imaging is preferred to correlate symptoms to myocardial ischaemia, estimate myocardial viability, and guide decisions on coronary revascularization.
- PET is preferred for absolute MBF measurements, but CMR perfusion studies may offer an alternative.
- Selective second-line cardiac imaging with functional testing in patients with abnormal CCTA and CCTA after abnormal functional testing may improve patient selection for ICA.
- ICA is recommended to diagnose obstructive CAD in individuals with a very high pre- or post-test likelihood of disease, severe symptoms refractory to GDMT, angina at a low level of exercise, and/or high event risk.
- When ICA is indicated, it is recommended to evaluate the functional severity of 'intermediate' stenoses by invasive functional testing (FFR, iFR) before revascularization.
- Computed FFR based on the 3D reconstruction of ICA is emerging as a valuable alternative to wire-based coronary pressure to evaluate the functional severity of 'intermediate' stenoses.
- The use of imaging guidance is now recommended when performing complex PCI.
- A single antiplatelet agent, aspirin or clopidogrel, is generally recommended long term in CCS patients with obstructive atherosclerotic CAD.
- For high thrombotic-risk CCS patients, long-term therapy with two antithrombotic agents is reasonable, as long as bleeding risk is not high.
- For CCS patients with sinus rhythm, DAPT is recommended at the time of PCI and for 1 to 6 month(s), according to high or low bleeding risk, respectively.
- For CCS patients requiring OAC and undergoing PCI, OAC and DAPT (aspirin and clopidogrel) for 1 to 4 weeks, followed by OAC and clopidogrel for up to 6 months in patients not at high ischaemic risk and up to 12 months in patients at high ischaemic risk, followed by OAC alone should be considered.
- In CCS patients with functionally significant multivessel CAD, current evidence indicates benefit of myocardial revascularization over GDMT alone for symptom improvement, prevention of spontaneous MI, and reduction of cardiovascular mortality at long follow-up.
- Among CCS patients with normal LV function and no significant left main or proximal LAD lesions, current evidence indicates that myocardial revascularization over GDMT alone does not prolong overall survival.
- Among CCS patients with reduced LV function and ischaemic cardiomyopathy, current evidence indicates that surgical revascularization compared with GDMT alone prolongs overall survival at very long follow-up.
- Among patients with complex multivessel CAD without LMCAD, particularly in the presence of diabetes, who are clinically and anatomically suitable for both revascularization modalities, current evidence indicates longer overall survival after CABG than PCI.
- Among patients who are clinically and anatomically suitable for both revascularization modalities, a greater need for repeat revascularization after PCI than surgery, independently of multivessel CAD anatomical severity, has been consistently reported with current surgical and stent technology.
- Lifestyle and risk-factor modification combined with disease-modifying and antianginal medications are cornerstones in the management of CCS.

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- Shared decision-making between patients and healthcare professionals, based on patient-centred care, is paramount in defining the appropriate therapeutic pathway for CCS patients. Patient education is key to improve risk-factor control in the long term.
- The relatively high prevalence of ANOCA/INOCA and its associated MACE rate warrants improvement in the diagnosis and treatment of affected patients.
- Persistently symptomatic patients with suspected ANOCA/INOCA who do not respond to GDMT should undergo invasive coronary functional testing to determine underlying endotypes.
- Characterization of endotypes is important to guide appropriate medical therapy for ANOCA/INOCA patients.
- Research on effective methods to support specific healthy lifestyle behaviours, and sustain medication and healthy lifestyle adherence over time, is needed.
- More research is needed on improving the implementation of health-promoting policies and practices in the workplace setting.

8. Gaps in evidence

- It remains unclear if screening for subclinical obstructive CAD in the general population is useful.[1106,1210] Further large-scale studies are needed to investigate the prognostic benefit of screening and treating asymptomatic CCS in the general population, preferably involving different geographical regions. Optimal screening options remain to be determined for specific groups at high risk (e.g. asymptomatic individuals with diagnosed diabetes for longer than 10 years).
- Most studies assessing diagnostic strategies in individuals with symptoms suspected of CCS were performed in populations with a moderate (>15%–50%) pre-test clinical likelihood of obstructive CAD. Further studies are needed to determine the optimal and most cost-effective diagnostic strategy in individuals with a low (>5%–15%) pre-test clinical likelihood of obstructive CAD.
- The current diagnosis of ANOCA/INOCA and its different endotypes is mainly determined by invasive coronary functional testing.[36] Further research is needed to refine and assess non-invasive diagnostic imaging modalities for CMD. Currently available and new non-invasive imaging modalities should be calibrated against invasive testing, allowing the use of their measurements interchangeably.
- The role of antithrombotic therapy in CCS patients with ANOCA/INOCA remains to be established.
- Because of how evidence has accrued over time, there is no clear evidence about the existence of first- and second-line antianginal therapy. It is unclear whether long-acting nitrates, ranolazine, nicorandil, ivabradine, trimetazidine, or any of their combinations improve anginal symptoms more than beta-blockers or CCBs.
- The optimal type and duration of DAPT is still uncertain in some subsets of patients (e.g. patients with prior revascularization who might benefit from shorter or longer DAPT strategies).
- The long-term benefit of beta-blocker therapy in post-MI patients without reduced EF remains to be elucidated.
- In view of the reported positive impact of low-dose colchicine in patients with CCS in reducing MI, stroke, and revascularization, future studies should identify whether certain patient subgroups (e.g. those with elevated biomarker levels) might derive even greater clinical benefit from this treatment.
- A *post hoc* analysis of ISCHEMIA detected a graded association between the severity of obstructive CAD assessed by CCTA and all-cause mortality and acute MI during follow-up.[317] There is a need for randomized data comparing contemporary medical treatment against early revascularization plus medical therapy in subsets of patients with an increased risk for death or MI as determined by the *post hoc* analysis. Moreover, because the benefit of an invasive strategy with respect to cardiac mortality was shown in a meta-analysis of chronologically heterogeneous trials, including several conducted more than two decades ago, the impact of early revascularization plus GDMT vs. contemporary GDMT on all-cause and cardiac mortality in patients with CCS should ideally be tested in a well-designed, adequately powered randomized trial.
- Some meta-analyses have reported a reduction in cardiac mortality without a reduction in all-cause mortality. There is a need to clarify the impact of revascularization in CCS patients on cardiovascular and non-cardiovascular mortality.
- Complete revascularization of multivessel CAD by PCI can be achieved as a single procedure (index PCI) or as staged PCI. In the setting of CCS, the value of staged PCI and the optimal interval between interventions needs to be evaluated.
- Whether CABG surgery and PCI are comparable among patients with ischaemic cardiomyopathy and HFrEF in the modern era of HF treatment needs to be evaluated.
- Various imaging techniques, such as low-dose DSE, CMR, and PET/CT, can identify hibernating myocardium with the potential for functional recovery after revascularization.[1211] Further randomized trials with contemporary, well-defined modalities and strict adherence to protocol are needed to clarify the clinical benefits (if any) of viability testing.
- Residual ischaemia post-PCI, as determined by FFR/iFR, reflects remaining atherosclerotic lesions and/or suboptimal PCI results, but also persistent or worsening microvascular dysfunction. Whether post-PCI FFR/iFR is a 'modifiable' risk factor remains to be proved.
- Among patients suitable for off-pump CABG with complex multivessel CAD but no LMCAD, the impact of hybrid revascularization on outcomes, including peri-operative complications other than MACE, needs more extensive investigation. Data on the optimal time interval between MIDCAB-LIMA and PCI are lacking.
- Whether the decision process based on a multidisciplinary Heart Team leads to better outcomes than standard institutional practice remains to be investigated.
- The medical therapy of ANOCA/INOCA is largely empirical. Therefore, prospective randomized clinical trials are needed to determine the efficacy of antianginal treatments in improving symptoms and outcomes for the different endotypes.
- Research on effective methods to support healthy lifestyle behaviours, and sustain medication and healthy lifestyle adherence over time, is needed. In addition, more research is needed on improving the implementation of health-promoting policies and practices in the workplace setting.
- There is a need for further evidence on the effectiveness of neuromodulation, spinal cord stimulation, therapeutic angiogenesis, and coronary sinus occlusion in patients who suffer from refractory angina, despite guideline-directed medical treatment and revascularization.

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9. 'What to do' and 'What not to do' messages from the guidelines

Table 10 lists all Class I and Class III recommendations from the text alongside their level of evidence.

Table 10 'What to do' and 'What not to do'

Recommendations	Class[a]	Level[b]
Recommendations for history taking, risk factor assessment, and resting electrocardiogram in individuals with suspected chronic coronary syndrome		
In individuals reporting symptoms of suspected myocardial ischaemic origin, a detailed assessment of cardiovascular risk factors, medical history, and symptom characteristics (including onset, duration, type, location, triggers, relieving factors, time of day) is recommended.	I	C
If clinical or ECG assessment suggests ACS rather than CCS, immediate referral to the emergency department and/or repeated measurement of blood troponin, preferably using high-sensitivity or ultrasensitive assays, to rule out acute myocardial injury is recommended.	I	B
A resting 12-lead ECG is recommended in all individuals reporting chest pain (unless an obvious non-cardiac cause is identified), particularly during, or immediately after, an episode suggestive of myocardial ischaemia.	I	C
Using ST-segment deviations during supraventricular tachyarrhythmias, particularly during re-entrant atrioventricular tachycardias, per se, as reliable evidence of obstructive CAD, is not recommended.	III	B
Recommendations for basic biochemistry in the initial diagnostic management of individuals with suspected chronic coronary syndrome		
The following blood tests are recommended in all individuals to refine risk stratification, diagnose comorbidities, and guide treatment:		
• lipid profile including LDL-C;	I	A
• full blood count (including haemoglobin);	I	B
• creatinine with estimation of renal function;	I	B
• glycaemic status with HbA1c and/or fasting plasma glucose.	I	B
In patients with suspected CCS, it is recommended to assess thyroid function at least once.	I	B
Recommendations for estimating, adjusting and reclassifying the likelihood of obstructive atherosclerotic coronary artery disease in the initial diagnostic management of individuals with suspected chronic coronary syndrome		
It is recommended to estimate the pre-test likelihood of obstructive epicardial CAD using the Risk Factor-weighted Clinical Likelihood model.	I	B
It is recommended to use additional clinical data (e.g. examination of peripheral arteries, resting ECG, resting echocardiography, presence of vascular calcifications on previously performed imaging tests) to adjust the estimate yielded by the Risk Factor-weighted Clinical Likelihood model.	I	C
Recommendations for resting transthoracic ultrasound and cardiac magnetic resonance imaging in the initial diagnostic management of individuals with suspected chronic coronary syndrome		
A resting transthoracic echocardiogram is recommended: • to measure LVEF, volumes and diastolic function; • identify regional wall motion abnormalities; • identify non-coronary cardiac disease (e.g. hypertrophy, cardiomyopathy, valve disease, pericardial effusion); • assess right ventricular function and estimate systolic pulmonary artery pressure; to refine risk stratification and guide treatment.	I	B
Recommendations for the use of exercise ECG in the initial diagnostic management of individuals with suspected chronic coronary syndrome		
Exercise ECG is recommended in selected patients for the assessment of exercise tolerance, symptoms, arrhythmias, BP response, and event risk.	I	C
Exercise ECG is not recommended for diagnostic purposes in patients with ≥0.1 mV ST-segment depression on resting ECG, left bundle branch block or who are being treated with digitalis.	III	C
In individuals with a low or moderate (>5–50%) pre-test likelihood of obstructive CAD, an exercise ECG is not recommended to rule out CAD if CCTA or functional imaging tests are available.	III	C
Recommendations for ambulatory ECG monitoring in the initial diagnostic management of individuals with suspected chronic coronary syndrome		
Ambulatory ECG monitoring is recommended in subjects with chest pain and suspected arrhythmias.	I	C

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Recommendations for non-invasive anatomical imaging tests in the initial diagnostic management of individuals with suspected chronic coronary syndrome—coronary computed tomography angiography, if available, and supported by local expertise		
In individuals with suspected CCS and low or moderate (>5%–50%) pre-test likelihood of obstructive CAD, CCTA is recommended to diagnose obstructive CAD and to estimate the risk of MACE.	I	A
CCTA is recommended in individuals with low or moderate (>5%–50%) pre-test likelihood to refine diagnosis if another non-invasive test is non-diagnostic.	I	B
CCTA is not recommended in patients with severe renal failure (eGFR <30 mL/min/1.73 m^2), decompensated heart failure, extensive coronary calcification, fast irregular heart rate, severe obesity, inability to cooperate with breath-hold commands, or any other conditions that can make obtaining good imaging quality unlikely.	III	C
Recommendations for non-invasive tests in the initial diagnostic management of individuals with suspected chronic coronary syndrome—stress echocardiography, if available, and supported by local expertise		
In individuals with suspected CCS and moderate or high (>15%–85%) pre-test likelihood of obstructive CAD, stress echocardiography is recommended to diagnose myocardial ischaemia and to estimate the risk of MACE.	I	B
During stress echocardiography, when two or more contiguous myocardial segments are not visualized, it is recommended to use commercially available intravenous ultrasound contrast agents (microbubbles) to improve diagnostic accuracy.	I	B
During stress echocardiography, myocardial perfusion using commercially available intravenous ultrasound contrast agents (microbubbles) is recommended to improve diagnostic accuracy and to refine risk stratification beyond wall motion.	I	B
Recommendations for non-invasive functional myocardial imaging tests in the initial diagnostic management of individuals with suspected chronic coronary syndrome—resting and stress single-photon emission computed tomography/positron emission tomography—cardiac magnetic resonance imaging, if available, and supported by local expertise		
In individuals with suspected CCS and moderate or high (>15%–85%) pre-test likelihood of obstructive CAD, stress SPECT or, preferably, PET myocardial perfusion imaging is recommended to: • diagnose and quantify myocardial ischaemia and/or scar; • estimate the risk of MACE; • quantify myocardial blood flow (PET).	I	B
In patients selected for PET or SPECT myocardial perfusion imaging, it is recommended to measure CACS from unenhanced chest CT imaging (used for attenuation correction) to improve detection of both non-obstructive and obstructive CAD.	I	B
In individuals with suspected CCS and moderate or high (>15%–85%) pre-test likelihood of obstructive CAD, CMR perfusion imaging is recommended to diagnose and quantify myocardial ischaemia and/or scar and estimate the risk of MACE.	I	B
Recommendations for invasive coronary angiography in individuals with suspected obstructive coronary artery disease		
When ICA is indicated, radial artery access is recommended as the preferred access site.	I	A
When ICA is indicated, it is recommended to have coronary pressure assessment available and to use it to evaluate the functional severity of intermediate non-left main stem stenoses prior to revascularization.	I	A
Invasive coronary angiography is recommended to diagnose CAD in individuals with a very high (>85%) clinical likelihood of disease, severe symptoms refractory to guideline-directed medical therapy, angina at a low level of exercise, and/or high event risk.	I	C
In individuals with de novo symptoms highly suggestive of obstructive CAD that occur at a low level of exercise, ICA with a view towards revascularization is recommended as first diagnostic test after clinical assessment by a cardiologist.	I	C
Recommendations for functional assessment of epicardial artery stenosis severity during invasive coronary angiography to guide revascularization		
During ICA, selective assessment of functional severity of intermediate diameter stenoses is recommended to guide the decision to revascularize, using the following tools:		
• FFR/iFR (significant ≤0.8 or ≤0.89, respectively);	I	A
• QFR (significant ≤0.8).	I	B
Systematic and routine wire-based coronary pressure assessment of all coronary vessels is not recommended.	III	A
Recommendations for selection of initial diagnostic tests in individuals with suspected chronic coronary syndrome		
It is recommended to select the initial non-invasive diagnostic test based on pre-test likelihood of obstructive CAD, other patient characteristics that influence the performance of non-invasive tests, and local expertise and availability.	I	C
In symptomatic patients in whom the pre-test likelihood of obstructive CAD by clinical assessment is >5%, CCTA or non-invasive functional imaging for myocardial ischaemia is recommended as the initial diagnostic test.	I	B
To rule out obstructive CAD in individuals with low or moderate (>5%–50%) pre-test likelihood, CCTA is recommended as the preferred diagnostic modality.	I	B
CCTA is recommended in individuals with low or moderate (>5%–50%) pre-test likelihood if functional imaging for myocardial ischaemia is not diagnostic.	I	B

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Functional imaging for myocardial ischaemia is recommended if CCTA has shown CAD of uncertain functional significance or is not diagnostic.	I	B
Invasive coronary angiography with the availability of invasive functional assessments is recommended to confirm or exclude the diagnosis of obstructive CAD or ANOCA/INOCA in individuals with an uncertain diagnosis on non-invasive testing.	I	B
Recommendations for definition of high risk of adverse events		
An initial stratification of risk of adverse events is recommended based on basic clinical assessment (e.g. age, ECG, anginal threshold, diabetes, CKD, LVEF).	I	B
The use of one or more of the following test results is recommended to identify individuals at high risk of adverse events: • Exercise ECG: o Duke Treadmill Score < −10; • stress SPECT or PET perfusion imaging: o Area of ischaemia ≥10% of the LV myocardium; • Stress echocardiography: o ≥3 of 16 segments with stress-induced hypokinesia or akinesia; • stress CMR: o ≥2 of 16 segments with stress perfusion defects or ≥3 dobutamine-induced dysfunctional segments; • CCTA: o left main disease with ≥50% stenosis, three-vessel disease with ≥70 stenosis, or two-vessel disease with ≥70% stenosis, including the proximal LAD or one-vessel disease of the proximal LAD with ≥70% stenosis and FFR-CT ≤0.8.	I	B
In individuals at high risk of adverse events (regardless of symptoms), ICA—complemented by invasive functional measures (FFR/iFR) when appropriate—is recommended, with the aim of refining risk stratification and improving symptoms and cardiovascular outcomes by revascularization.	I	A
Recommendations for cardiovascular risk reduction, lifestyle changes, and exercise interventions in patients with established chronic coronary syndrome		
An informed discussion on CVD risk and treatment benefits tailored to individual patient needs is recommended.	I	C
Multidisciplinary behavioural approaches to help patients achieve healthy lifestyles, in addition to appropriate pharmacological management, are recommended.	I	A
A multidisciplinary exercise-based programme to improve cardiovascular risk profile and reduce cardiovascular mortality is recommended.	I	A
Aerobic physical activity of at least 150–300 min per week of moderate intensity or 75–150 min per week of vigorous intensity and reduction in sedentary time are recommended.	I	B
Recommendations for antianginal drugs in patients with chronic coronary syndrome		
It is recommended to tailor the selection of antianginal drugs to the patient's characteristics, comorbidities, concomitant medications, treatment tolerability, and underlying pathophysiology of angina, also considering local drug availability and cost.	I	C
Short-acting nitrates are recommended for immediate relief of angina.	I	B
Initial treatment with beta-blockers and/or CCBs to control heart rate and symptoms is recommended for most patients with CCS.	I	B
Ivabradine is not recommended as add-on therapy in patients with CCS, LVEF >40%, and no clinical heart failure.	III	B
Combination of ivabradine with non-DHP-CCB or other strong CYP3A4 inhibitors is not recommended.	III	B
Nitrates are not recommended in patients with hypertrophic cardiomyopathy or in co-administration with phosphodiesterase inhibitors.	III	B
Recommendations for antithrombotic therapy in patients with chronic coronary syndrome		
In CCS patients with a prior MI or remote PCI, aspirin 75–100 mg daily is recommended lifelong after an initial period of DAPT.	I	A
In CCS patients with a prior MI or remote PCI, clopidogrel 75 mg daily is recommended as a safe and effective alternative to aspirin monotherapy.	I	A
After CABG, aspirin 75–100 mg daily is recommended lifelong.	I	A
In patients *without* prior MI or revascularization but with evidence of significant obstructive CAD, aspirin 75–100 mg daily is recommended lifelong.	I	B
In CCS patients with no indication for oral anticoagulation, DAPT consisting of aspirin 75–100 mg and clopidogrel 75 mg daily for up to 6 months is recommended as the default antithrombotic strategy after PCI-stenting.	I	A
In patients at high bleeding risk, but not at high ischaemic risk, it is recommended to discontinue DAPT 1–3 months after PCI and to continue with single antiplatelet therapy.	I	A
In CCS patients with a long-term indication for OAC, an AF therapeutic dose of VKA alone or, preferably, of DOAC alone (unless contraindicated) is recommended lifelong.	I	B
In patients with an indication for OAC who undergo PCI, initial low-dose aspirin once daily is recommended (loading dose when not on maintenance dose) in addition to OAC and clopidogrel.	I	C

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In patients who are eligible for OAC, DOAC (unless contraindicated) is recommended in preference to VKA.	I	A
After uncomplicated PCI in CCS patients with concomitant indication for OAC: • early cessation of aspirin (≤1 week); • followed by continuation of OAC and clopidogrel: o up to 6 months in patients not at high ischaemic risk; or o up to 12 months in patients at high ischaemic risk; • followed by OAC alone; is recommended.	I	A
The use of ticagrelor or prasugrel is generally not recommended as part of triple antithrombotic therapy with aspirin and an OAC.	III	C
It is recommended to initiate aspirin post-operatively as soon as there is no concern over bleeding.	I	B
A proton pump inhibitor is recommended in patients at increased risk of gastrointestinal bleeding for the duration of combined antithrombotic therapy (antiplatelet therapy and/or OAC).	I	A
Recommendations for lipid-lowering drugs in patients with chronic coronary syndrome		
Lipid-lowering treatment with an LDL-C goal of <1.4 mmol/L (55 mg/dL) and a ≥50% reduction in LDL-C vs. baseline is recommended.	I	A
A high-intensity statin up to the highest tolerated dose to reach the LDL-C goals is recommended for all patients with CCS.	I	A
If a patient's goal is not achieved with the maximum tolerated dose of statin, combination with ezetimibe is recommended.	I	B
For patients who are statin intolerant and do not achieve their goal on ezetimibe, combination with bempedoic acid is recommended.	I	B
For patients who do not achieve their goal on a maximum tolerated dose of statin and ezetimibe, combination with a PCSK9 inhibitor is recommended.	I	A
Recommendations for sodium–glucose cotransporter 2 inhibitors and/or glucagon-like peptide-1 receptor agonists in patients with chronic coronary syndrome		
CCS patients with type 2 diabetes		
SGLT2 inhibitors with proven CV benefit are recommended in patients with T2DM and CCS to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication.	I	A
GLP-1 receptor agonists with proven CV benefit are recommended in patients with T2DM and CCS to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication.	I	A
Recommendations for angiotensin-converting enzyme inhibitors in patients with chronic coronary syndrome		
In CCS patients, ACE-Is (or ARBs) are recommended in the presence of specific comorbidities, such as hypertension, diabetes, or heart failure.	I	A
Recommendations for revascularization in patients with chronic coronary syndrome		
It is recommended that patients scheduled for percutaneous or surgical revascularization receive complete information about the benefits, risks, therapeutic consequences, and alternatives to revascularization, as part of shared clinical decision-making.	I	C
For complex clinical cases, to define the optimal treatment strategy, in particular when CABG and PCI hold the same level of recommendation, a Heart Team discussion is recommended, including representatives from interventional cardiology, cardiac surgery, non-interventional cardiology, and other specialties if indicated, aimed at selecting the most appropriate treatment to improve patient outcomes and quality of life.	I	C
It is recommended to communicate the proposal of the Heart Team in a very balanced way and in a language that the patient can understand.	I	C
It is recommended that the decision for revascularization and its modality be patient-centred, considering patient preferences, health literacy, cultural circumstances, and social support.	I	C
It is recommended that the Heart Team (on site or with a partner institution) develop institutional protocols to implement the appropriate revascularization strategy in accordance with current guidelines.	I	C
In CCS patients with LVEF >35%, myocardial revascularization is recommended, in addition to guideline-directed medical therapy, for patients with functionally significant left main stem stenosis to improve survival.	I	A
In CCS patients with LVEF >35%, myocardial revascularization is recommended, in addition to guideline-directed medical therapy, for patients with functionally significant three-vessel disease to improve long-term survival and to reduce long-term cardiovascular mortality and the risk of spontaneous myocardial infarction.	I	A
In CCS patients with LVEF >35%, myocardial revascularization is recommended, in addition to guideline-directed medical therapy, for patients with functionally significant single- or two-vessel disease involving the proximal LAD, to reduce long-term cardiovascular mortality and the risk of spontaneous myocardial infarction.	I	B
In CCS patients with LVEF ≤35%, it is recommended to choose between revascularization or medical therapy alone, after careful evaluation, preferably by the Heart Team, of coronary anatomy, correlation between coronary artery disease and LV dysfunction, comorbidities, life expectancy, individual risk-to-benefit ratio, and patient perspectives.	I	C

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In surgically eligible CCS patients with multivessel CAD and LVEF ≤35%, myocardial revascularization with CABG is recommended over medical therapy alone to improve long-term survival.	I	B
In CCS patients with persistent angina or anginal equivalent, despite guideline-directed medical treatment, myocardial revascularization of functionally significant obstructive CAD is recommended to improve symptoms.	I	A
In patients with complex CAD in whom revascularization is being considered, it is recommended to assess procedural risks and post-procedural outcomes to guide shared clinical decision-making.	I	C
Calculation of the STS score is recommended to estimate in-hospital morbidity and 30-day mortality after CABG.	I	B
In patients with multivessel obstructive CAD, calculation of the SYNTAX score is recommended to assess the anatomical complexity of disease.	I	B
Intracoronary imaging guidance by IVUS or OCT is recommended when performing PCI on anatomically complex lesions, in particular left main stem, true bifurcations, and long lesions.	I	A
Intracoronary pressure measurement (FFR or iFR) or computation (QFR) is recommended to guide lesion selection for intervention in patients with multivessel disease.	I	A
It is recommended that physicians select the most appropriate revascularization modality based on patient profile, coronary anatomy, procedural factors, LVEF, preferences, and outcome expectations.	I	C
Recommendations for mode of revascularization in patients with chronic coronary syndrome		
Left main disease		
In CCS patients at low surgical risk with significant left main coronary stenosis, CABG: • is recommended over medical therapy alone to improve survival	I	A
• is recommended as the overall preferred revascularization mode over PCI, given the lower risk of spontaneous myocardial infarction and repeat revascularization	I	A
In CCS patients with significant left main coronary stenosis of low complexity (SYNTAX score ≤22), in whom PCI can provide equivalent completeness of revascularization to that of CABG, PCI is recommended as an alternative to CABG, given its lower invasiveness and non-inferior survival.	I	A
Left main with multivessel disease		
In CCS patients at low surgical risk with suitable anatomy, CABG is recommended over medical therapy alone to improve survival.	I	A
Multivessel disease and diabetes		
In CCS patients with significant multivessel disease and diabetes, with insufficient response to guideline-directed medical therapy, CABG is recommended over medical therapy alone and over PCI to improve symptoms and outcomes.	I	A
Three-vessel disease, without diabetes		
In CCS patients with significant three-vessel disease, preserved LVEF, no diabetes, and insufficient response to guideline-directed medical therapy, CABG is recommended over medical therapy alone to improve symptoms, survival, and other outcomes.	I	A
In CCS patients with preserved LVEF, no diabetes, insufficient response to guideline-directed medical therapy, and significant three-vessel disease of low-to-intermediate anatomic complexity in whom PCI can provide similar completeness of revascularization to that of CABG, PCI is recommended, given its lower invasiveness, and generally non-inferior survival.	I	A
Single- or double-vessel disease involving the proximal LAD		
In CCS patients with significant single- or double-vessel disease involving the proximal LAD and insufficient response to guideline-directed medical therapy, CABG or PCI is recommended over medical therapy alone to improve symptoms and outcomes.	I	A
In CCS patients with complex significant single- or double-vessel disease involving the proximal LAD, less amenable to PCI, and insufficient response to guideline-directed medical therapy, CABG is recommended over PCI to improve symptoms and reduce revascularization rates.	I	B
Single- or double-vessel disease not involving the proximal LAD		
In symptomatic CCS patients with single- or double-vessel disease not involving the proximal LAD and with insufficient response to guideline-directed medical therapy, PCI is recommended to improve symptoms.	I	B
Recommendations for management of chronic coronary syndrome patients with chronic heart failure		
Managing CCS in heart failure patients		
In HF patients with LVEF ≤35% in whom obstructive CAD is suspected, ICA is recommended with a view towards improving prognosis by CABG, taking into account the risk-to-benefit ratio of the procedures.	I	B
In HF patients with LVEF >35% and suspected CCS with low or moderate (>5%–50%) pre-test likelihood of obstructive CAD, CCTA or functional imaging is recommended.	I	C
In HF patients with LVEF >35% and suspected CCS with very high (>85%) pre-test likelihood of obstructive CAD, ICA (with FFR, iFR, or QFR when needed) is recommended.	I	C

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Managing heart failure in CCS patients		
It is recommended that CCS patients with HF be enrolled in a multidisciplinary HF management programme to reduce the risk of HF hospitalization and to improve survival.	I	A
An ACE-I, an MRA, an SGLT2 inhibitor (dapagliflozin or empagliflozin), and, in stable conditions, a beta-blocker are recommended for CCS patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HF with mildly reduced ejection fraction (HFmrEF) or HFpEF to reduce the risk of HF hospitalization or cardiovascular death.	I	A
An ARB is recommended in symptomatic patients with CCS and HFrEF unable to tolerate an ACE-I or ARNI to reduce the risk of HF hospitalization and cardiovascular death.	I	B
Sacubitril/valsartan is recommended as a replacement for an ACE-I or ARB in CCS patients with HFrEF to reduce the risk of HF hospitalization and death.	I	B
Diuretics are recommended in CCS patients with HF and signs and/or symptoms of congestion to alleviate symptoms, improve exercise capacity, and reduce HF hospitalizations.	I	B
An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA class II–III) of ischaemic aetiology (unless they have had an MI in the prior 40 days), and an LVEF ≤35% despite ≥3 months of optimized GDMT, provided they are expected to survive substantially longer than 1 year with good functional status.	I	A
An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients who have recovered from a ventricular arrhythmia causing haemodynamic instability, and who are expected to survive for >1 year with good functional status, in the absence of reversible causes or unless the ventricular arrhythmia has occurred <48 h after an MI.	I	A
CRT is recommended for CCS patients with symptomatic HF, sinus rhythm, LVEF ≤35% despite GDMT, and a QRS duration ≥150 ms with an LBBB QRS morphology to improve symptoms and survival and to reduce morbidity.	I	A
CRT rather than right ventricular pacing is recommended for patients with HFrEF regardless of NYHA class or QRS width who have an indication for ventricular pacing for high-degree AV block in order to reduce morbidity. This includes patients with AF.	I	A
Recommendations for diagnosis and management of patients with angina with non-obstructive coronary arteries/ischaemia with non-obstructive coronary arteries		
In persistently symptomatic patients despite medical treatment with suspected ANOCA/INOCA (i.e. anginal symptoms with normal coronary arteries or non-obstructive lesions at non-invasive imaging, or intermediate stenoses with normal FFR/iFR at coronary arteriography) and poor quality of life, invasive coronary functional testing is recommended to identify potentially treatable endotypes and to improve symptoms and quality of life, considering patient choices and preferences.	I	B
In individuals with suspected vasospastic angina, a resting 12-lead ECG recording during angina is recommended.	I	C
In patients with suspected vasospastic angina and repetitive episodes of rest angina associated with ST-segment changes that resolve with nitrates and/or calcium antagonists, invasive functional angiography is recommended to confirm the diagnosis and to determine the severity of underlying atherosclerotic disease.	I	C
For the treatment of isolated vasospastic angina: • calcium channel blockers are recommended to control symptoms and to prevent ischaemia and potentially fatal complications.	I	A
Recommendations for older, female, high bleeding risk, comorbid, and socially/geographically diverse patients		
In older adults (≥75 years), particular attention to drug side effects, intolerance, drug–drug interactions, overdosing, and procedural complications is recommended.	I	C
In older, as in younger, individuals, diagnostic and revascularization decisions based on symptoms, extent of ischaemia, frailty, life expectancy, comorbidities, and patient preferences are recommended.	I	C
Similar guideline-directed cardiovascular preventive therapy is recommended in women and men.	I	C
Systemic post-menopausal hormone therapy is not recommended in women with CCS, given the lack of cardiovascular benefit and an increased risk of thrombo-embolic complications.	III	A
Bleeding risk assessment is recommended using the PRECISE-DAPT score, the qualitative ARC-HBR tool or other, validated method.	I	B
Attention to interaction between antiretroviral treatment and statins is recommended in patients with HIV.	I	B
Continued targeted efforts are recommended: • to increase delivery of safe and effective cardiac care to all CCS patients, especially those of lower socioeconomic classes; and • to enhance inclusion in future clinical trials of geographical, social, or other groups that are currently underrepresented.	I	C
Recommendations for screening for coronary artery disease in asymptomatic individuals		
Opportunistic screening of healthy individuals for cardiovascular risk factors and to estimate the risk of future cardiovascular events using scoring systems, e.g. SCORE2 and SCORE-OP, is recommended to detect individuals at high risk and guide treatment decisions.	I	C

Continued

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Recommendations for adherence to medical therapy and lifestyle changes		
Mobile health interventions (e.g. using text messages, apps, wearable devices) are recommended to improve patient adherence to healthy lifestyles and medical therapy.	I	A
Behavioural interventions are recommended to improve adherence.	I	B
Simplifying medication regimens (e.g. using fixed-dose drug combinations) is recommended to increase patient adherence to medications.	I	B
Multiprofessional and family involvement is recommended to promote adherence, in addition to patient education and involvement.	I	C
Recommendations for diagnosis of disease progression in patients with established chronic coronary syndrome		
Regardless of symptoms, periodic visits (e.g. annual) to a general practitioner or cardiovascular healthcare professional are recommended to evaluate cardiovascular risk factor control and to assess changes in risk status, disease status, and comorbidities that may require lifestyle, medical, or procedural interventions.	I	C
Reassessment of CAD status is recommended in patients with deteriorating LV systolic function that cannot be attributed to a reversible cause (e.g. longstanding tachycardia or myocarditis).	I	C
Risk stratification is recommended in patients with new or worsening symptoms, preferably using stress imaging.	I	C
In patients with symptoms refractory to medical treatment or at high risk of adverse events, invasive coronary angiography (with FFR/iFR when necessary) is recommended for risk stratification and for possible revascularization aimed at improving symptoms and prognosis.	I	C
Recommendations for treatment of revascularization failure		
DES is recommended over drug-coated balloons for treatment of in-DES restenosis.	I	A
LIMA is indicated as the conduit of choice for redo CABG in patients in whom the LIMA was not used previously.	I	B
Recommendations for recurrent or refractory angina/ischaemia		
In patients with refractory angina leading to poor quality of life and with documented or suspected ANOCA/INOCA, invasive coronary function testing is recommended to define ANOCA/INOCA endotypes and appropriate treatment, considering patient choices and preferences.	I	B

ACE-I, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; AF, atrial fibrillation; ANOCA, angina with non-obstructive coronary arteries; ARB, angiotensin receptor blocker; ARC-HBR, Academic Research Consortium for High Bleeding; ARNI, angiotensin receptor neprilysin inhibitor; AV, atrioventricular; BP, blood pressure; CABG, coronary artery bypass grafting; CACS, coronary artery calcium score; CAD, coronary artery disease; CCB, calcium channel blocker; CCS, chronic coronary syndrome; CCTA, coronary computed tomography angiography; CKD, chronic kidney disease; CMR, cardiac magnetic resonance; CRT, cardiac resynchronization therapy; CT, computed tomography; CV, cardiovascular; CVD, cardiovascular disease; CYP3A4, cytochrome P450 3A4; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; DHP, dihydropyridine; DOAC, direct oral anticoagulant; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; FFR, fractional flow reserve; FFR-CT, coronary computed tomography angiography-derived fractional flow reserve; GDMT, guideline-directed medical therapy; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HIV, human immunodeficiency virus; ICA, invasive coronary angiography; ICD, implantable cardioverter defibrillator; iFR, instantaneous wave-free ratio; INOCA, ischaemia with non-obstructive coronary arteries; IVUS, intravascular ultrasound; LAD, left anterior descending; LBBB, left bundle branch block; LDL-C, low-density lipoprotein cholesterol; LIMA, left internal mammary artery; LV, left ventricular; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; OAC, oral anticoagulant; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; PCSK9, proprotein convertase subtilisin/kexin type 9; PET, positron emission tomography; PRECISE-DAPT, PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual AntiPlatelet Therapy; QFR, quantitative flow ratio; SCORE2, Systematic Coronary Risk Estimation 2; SCORE-OP, Systematic Coronary Risk Estimation 2–Older Persons; SGLT2, sodium–glucose cotransporter 2; SPECT, single-photon emission computed tomography; STS, Society of Thoracic Surgeons; SYNTAX, SYNergy Between PCI with TAXUS and Cardiac Surgery; T2DM, type 2 diabetes mellitus; VKA, vitamin K antagonist.
[a]Class of recommendation.
[b]Level of evidence.

10. Evidence tables

Evidence tables are available at *European Heart Journal* online.

11. Data availability statement

No new data were generated or analysed in support of this research.

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13. Appendix

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[¶]*Professor Jean-Philippe Collet sadly passed away during the development of these guidelines. Professor Collet's contribution to these guidelines was, as always, highly valued.*

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Washington State Health Care Authority

Noninvasive Cardiac Imaging for Coronary Artery Disease – Re-review

FINAL Evidence Report

October 19, 2021

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This technology assessment report is based on research conducted by a contracted technology assessment center, with updates as contracted by the Washington State Health Care Authority. This report is an independent assessment of the technology question(s) described based on accepted methodological principles. The findings and conclusions contained herein are those of the investigators and authors who are responsible for the content. These findings and conclusions may not necessarily represent the views of the HCA/Agency and thus, no statement in this report shall be construed as an official position or policy of the HCA/Agency.

The information in this assessment is intended to assist health care decision makers, clinicians, patients and policy makers in making sound evidence-based decisions that may improve the quality and cost-effectiveness of health care services. Information in this report is not a substitute for sound clinical judgment. Those making decisions regarding the provision of health care services should consider this report in a manner similar to any other medical reference, integrating the information with all other pertinent information to make decisions within the context of individual patient circumstances and resource availability.

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Executive Summary

Introduction

Clinical

Coronary artery disease (CAD), also referred to as coronary heart disease (CHD) or ischemic heart disease (IHD), is a leading cause of death for both men and women in the United States and is the most common form of cardiovascular disease. The public health and economic burdens of CAD are substantial. Atherosclerosis is the most common underlying cause of CAD and is the result of plaque buildup on artery walls. The buildup of plaque may partially or completely block blood flow (and hence oxygen and nutrient flow) in the coronary arteries via two primary mechanisms: 1) progressive narrowing of the vessel lumen and (2) thrombotic occlusion of the artery wherein the hard surface of the plaque tears away exposing inner fatty prothrombotic and platelet activating components at the site creating enlargement of the obstruction. The resulting decrease in blood flow may be chronic or acute. It may restrict blood supply to the myocardium and impair ability to supply oxygenated blood either at rest or during exertion. Atherosclerotic plaque occurs commonly and is asymptomatic for years and most people with plaque will never develop clinical coronary artery disease. Chest pain (angina) is the most common symptom of obstructive CAD and is the first presenting symptom in most patients. Plaque distribution, presence of collateral circulation and degree of vessel narrowing are factors which may influence symptom development and clinical impact of CAD, however, symptoms do **not** always correlate with lesion severity. Ischemia and impaired function may be present in the absence of observed obstruction.[57]

Diagnosis of CAD

Accurate and early assessment of patients with symptomatic CAD is important for risk stratification and initiation of appropriate treatments to reduce morbidity and mortality. Noninvasive techniques used to diagnose CAD fall into two general categories, those that evaluate the anatomical aspects of vessel occlusion and those that evaluate the functional impact of occlusion on cardiac function. Each has strengths and limitations. Noninvasive anatomic tests provide information on location and extent of blockage and include coronary CT angiography (CCTA) and cardiac magnetic resonance imaging (CMRI). Functional tests allow assessment of whether symptoms are correlated with narrowing leading to ischemic areas and generally include exercise (treadmill) electrocardiography (ECG), exercise/pharmacologic stress echocardiography, exercise/pharmacologic cardiac nuclear imaging with single-photon emission computed tomography (SPECT) or pharmacologic stress with positron emission tomography (PET). There has been recent interest in use of pharmacologic stress as part of computed tomography (CT) and magnetic resonance imaging (MRI) and in determining fractional flow reserve (FFR) with CT. The choice of testing is dependent on a variety of patient and other factors, particularly in patients with stable CAD. The patient's pre-test probability of CAD, test accuracy and the likelihood that test results would change management and lead to better outcomes important considerations. The effectiveness of non-invasive imaging tests is influenced by patient pretest probability/underlying disease prevalence which impacts test performance for measures that are influenced by disease prevalence. For any test, in patients with low pre-test probability of CAD, the number of potential false positive results necessitating further follow-up needs to be weighed against the potential for accurate

detection of CAD. In some included RCTs, the frequency of MI and death was low, reflecting the low pre-test probability in these trials. In these instances, the benefit of testing may be unclear. Clinical decision-making regarding choice of test(s) needs to also include consideration of the potential for additional/downstream testing, availability of other tests, cumulative radiation exposure and how results will inform appropriate management strategies and lead to improved outcomes while avoiding risks of testing such as additional radiation, false positives, and incidental findings.

Exercise electrocardiogram treadmill testing (ETT) and the imaging tests CTTA, stress nuclear imaging and stress echocardiography have become established as diagnostic tests for CAD. The focus of this HTA will be on the imaging tests and will not include ETT as an intervention. This review does not include evaluation of MRI (including stress MRI). As established testing modalities, the focus will be on evaluating their impact on clinical decision making for directing management that leads to improved patient outcomes.

Policy context/Reason for selection

CCTA and stress nuclear imaging were reviewed in 2008 and 2013 respectively. They are being re-reviewed in 2021 due to newly available published evidence. Stress echocardiography was not previously reviewed.

Objectives

The aim of this report is to evaluate the clinical impact, safety and cost-effectiveness of the three primary noninvasive imaging methods of diagnosing CAD, namely CCTA, stress nuclear imaging and stress echocardiography. In addition, adjuncts to CCTA including FFR and CT perfusion imaging were included. This review updates the 2008 CCTA HTA and 2013 nuclear imaging HTA and adds evaluation of stress echocardiography.

Contextual Questions

Three cardiac imaging modalities for diagnosis of CAD in symptomatic patients will be evaluated: CCTA, stress nuclear imaging, and stress echocardiography. Prior to addressing research questions related to the impact of cardiac imaging on clinical outcomes ***the diagnostic accuracy (validity)*** of these modalities compared with invasive coronary angiography (the usual reference standard) will be briefly summarized for context. Diagnostic accuracy parameters include sensitivity and specificity and prognostic value (positive and negative predictive values). Inter- and intra-rater reliability (reproducibility) will be described. Information for the contextual questions will be summarized using citations captured in the formal search for this HTA.

Key Questions and Scope

The following Key Questions focus on ***the impact on clinical outcomes*** for the use of CCTA, stress nuclear imaging, and stress echocardiography to diagnose CAD **in patients with known or suspected CAD who are *symptomatic.***

1. What is the comparative effectiveness of noninvasive cardiac anatomic or functional imaging modalities (CCTA, stress nuclear imaging, stress echocardiography) in leading to improved clinical outcomes (e.g., MI, mortality)?
2. What is the comparative effectiveness of noninvasive cardiac anatomic or functional imaging modalities (CCTA, stress nuclear imaging, stress echocardiography) with respect to clinical decision-making including additional testing and treatments?
3. What is the comparative effectiveness of noninvasive cardiac anatomic or functional imaging modalities (CCTA, stress nuclear imaging, stress echocardiography) with regard to harms or adverse events which may result directly from testing or additional, downstream testing?
4. Does effectiveness (in terms of clinical outcomes) or safety differ in special populations (e.g., women, those with comorbidities, the elderly) from noninvasive cardiac anatomic or functional imaging (CCTA, stress nuclear imaging, stress echocardiography)?
5. What is the cost-effectiveness of CCTA, stress nuclear imaging and stress echocardiography for clinical outcomes?

PICOTS/Scope:

Study Component	Inclusion	Exclusion
Patients	Adult patients (≥18 years of age) with symptoms of suspected (previously undiagnosed) CAD who present with • Stable (nonemergent) typical or atypical symptoms suspicious for CAD (e.g., chest pain, chest tightness, chest burning, shoulder pain, palpitations, jaw pain, or non-chest pain symptoms, such as dyspnea or worsening effort tolerance) • Suspected acute coronary syndrome (ACS) in emergency departments. Symptomatic adults with known/established CAD including those who have had prior MI and/or revascularization. For all questions, data on special populations and circumstances including the following will be evaluated: • Women • Patients with atypical symptoms • Elderly patients • Patients with comorbidities (including renal insufficiency, DM), LBBB)	• Asymptomatic patients • Patients presenting for evaluation of cardiac pathologies other than CAD (e.g., congenital abnormalities, valvular disease, evaluation of cardiomyopathy etiology, CHF) • Patients with STEMI
Intervention	• Coronary CT Angiography (including use of FFR) and CT perfusion imaging (pharmacologic stress) with 64 slice or higher CT • Stress nuclear imaging (including PET, SPECT) • Stress echocardiography	• CACS • Screening • Novel uses of any of these tests • MRI/MRA • Comparisons of technical performance parameters or variations of a testing modality (e.g., comparison different CT techniques) • Outdated equipment or

Study Component	Inclusion	Exclusion
		methods
Comparator(s)	• No testing • Usual care* • Comparison of the above interventions with each other • Invasive coronary angiography	
Outcomes	Clinical health outcomes (PRIMARY) • MI, cardiac death, all-cause mortality Clinical decision making • Referral for treatment • Referral for additional testing Harms, risks and consequences of testing (initial testing and subsequent testing) • Harms of testing (e.g., adverse events related to contrast agents, medication for pharmacologic stress testing), vascular complications (e.g. stroke) • Risks and consequences of testing (radiation exposure, psychological consequences of diagnosis, ramifications of additional testing, other†) Economic: Incremental cost-effectiveness or similar outcome	• Intermediate outcomes
Timing	• Emergent or non-emergent • Any point in the diagnostic workup	• None
Setting(s)	• Emergency department • Non-emergent settings	• None
Studies	• Focus will be on studies with the least potential for bias. Focus will start with RCT evidence; in the absence of RCTs, high quality comparative observational studies that control for potential confounding will be considered. Observational studies will primarily be considered for test-related harms. • Studies published in English in peer-reviewed journals, technology assessments or publicly available FDA reports. • Full (comparative) economic studies • Studies published after 2000 (except for stress echocardiography)	• Non-comparative studies • Modeling studies for prediction • Prognostic studies • Costing studies • Studies evaluating the incremental benefit of adding a test to another. • Studies published prior to 2000 (except for stress echocardiography)

CACS = coronary artery calcium scoring; CAD = coronary artery disease; CHF = congestive heart failure; CT = computed tomography; DM = diabetes mellitus; FFR = fractional flow reserve; LBBB = left bundle branch block; RCT = randomized controlled trials; MI = myocardial infarction; PET = positron emission tomography; SPECT = single photon emission computed tomography; STEMI = ST-segment elevation myocardial infarction.

*Usual care typically includes no treatment/nothing if low pretest probability, "watchful waiting", or medical treatment if high pretest probability.

†Other may include impact on patients such as days lost from work, procedures cancelled (waiting for tests), vacations cancelled, etc.

Methods

The scope of this report and final key questions were refined based on input from clinical experts. Clinical expert input was sought to confirm critical outcomes on which to focus. Draft Key Questions and PICOTS scope were published on the HCA website for public comment. None were received. Public

comments as well as those from clinical experts and peer-reviewers were considered for finalization of this report.

The 2008 review of CCTA focused on diagnostic accuracy and only one RCT measured the impact of CCTA on patient outcomes. Since 2008, many RCTs comparing CCTA with functional testing have been published and use of CCTA clinically has become more mature. In recent years, the technologies and their application have evolved and matured. Therefore, this HTA focuses on the clinical impact of CCTA. The key questions for 2013 review of cardiac nuclear imaging differed from this review evaluation and the prior review included screening of asymptomatic patients. This HTA focuses on the clinical impact of stress nuclear imaging (SPECT and PET). Given that stress echocardiography is an established modality for evaluating cardiac function, based on clinical input it is included in this HTA.

A formal, structured systematic search of the peer-reviewed literature was performed across multiple databases including PubMed to identify relevant peer reviewed literature as well as other sources (e.g., ECRI Guideline Trust) to identify pertinent clinical guidelines and previously performed assessments (Appendix B). For the systematic review portion of the report, studies were selected for inclusion based on pre-specified criteria detailed in the full report. All records were screened by two independent reviewers. Selection criteria included a focus on studies with the least potential for bias that were written in English and published in the peer-reviewed literature. Included studies reporting on primary outcomes of interest were critically appraised independently by two reviewers evaluating the methodological quality, study limitations and potential for bias based on study design as well as factors which may bias studies using defined templates and pre-specified criteria. Assessment of RCTs followed appropriate criteria based on methods described in *the Cochrane Handbook for Systematic Reviews of Interventions* [19,58] and guidance from the Agency for Healthcare Research and Quality (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[5] In keeping with the AHRQ methods and the 2016 report on non-invasive imaging for CAD,[129] each study was given a final rating of "good", "fair", or "poor" quality based on the degree to which valid methods for patient selection, inclusion, allocation to treatment were used as well as the comparability of intervention groups, attrition and use of appropriate means for controlling bias. These are more described in detail in the full report. Systematic reviews were evaluated using AMSTAR-2 and economic studies Economic studies were evaluated according to The Quality of Health Economic Studies (QHES) instrument developed by Ofman et. al.[104]

An overall Strength of Evidence (SOE) combines the appraisal of study limitations with consideration of the number of studies and the consistency across them, directness and precision of the findings to describe an overall confidence regarding the stability of estimates as further research is available. The SOE was assessed by two researchers following the principles for adapting GRADE (Grades of Recommendation Assessment, Development and Evaluation)[48,51,52] as outlined by the Agency for Healthcare Research and Quality (AHRQ).[5] The strength of evidence was based on the highest quality evidence available for the primary outcomes. Briefly, bodies of evidence consisting of RCTs were initially considered as High strength of evidence. The strength of evidence could be downgraded based on the limitations (i.e., risk of bias, consistency of effect, directness of outcome, precision of effect estimate, and reporting/publication bias). When assessing the SOE for studies performing subgroup analysis, we also considered whether the subgroup analysis was preplanned (*a priori*) and whether a test for homogeneity or interaction was done. The final strength of evidence was assigned an overall grade of high, moderate, low, or insufficient, which are defined as follows:

- High - Very confident that effect size estimates lie close to the true effect for this outcome; there are few or no deficiencies in the body of evidence; we believe the findings are stable.
- Moderate – Moderately confident that effect size estimates lie close to the true effect for this outcome; some deficiencies in the body of evidence; we believe the findings are likely to be stable but some doubt remains.
- Low – Limited confidence that effect size estimates lie close to the true effect for this outcome; major or numerous deficiencies in the body of evidence; we believe that additional evidence is needed before concluding that findings are stable or that the estimate is close to the true effect.
- Insufficient – We have no evidence, are unable to estimate an effect or have no confidence in the effect estimate for this outcome or the body of evidence has unacceptable efficiencies precluding judgment. If no evidence was identified, this was stated as such.

Methods for quantitative analysis are described in the full report. Briefly, meta-analyses were conducted using profile likelihood methods to get more precise effect estimates and focused on the primary outcomes. To determine the appropriateness of meta-analysis, we considered clinical and methodological diversity and assessed statistical heterogeneity. Sensitivity analyses were conducted excluding poor-quality studies, outlying data and related to clinical heterogeneity.

Results

To answer the key questions, from 15,443 unique citations retrieved from systematic searches, 295 were reviewed at full text and 81 studies across 112 publications were retained. The bulk of the new trials evaluated CCTA. A total of 36 studies (in 66 publications) (35 RCTs and 1 prospective comparative cohort)[3,9,17,18,23-25,27,28,42-44,50,54,59,60,62,68,73,76-79,81-84,86-89,92,94,99-102,107,108,111,117,121,123-125,131,132,135-137,139,140,142] comprised the primary evidence base for Key Questions 1–4 and an additional 31 studies (2 SRs and 29 nonrandomized observational studies)[2,7,8,10-12,16,22,30-32,34,37,38,40,46,63,64,66,67,72,90,91,95-97,103,110,112,116,128] provided supplemental data on safety (Key Question 3; see Appendix Tables O23-O25 for details). For cost-effectiveness (Key Question 5), 14 studies across 15 publications (3 systematic reviews and 11 formal economic analyses) were included.[6,13,14,41,50,61,65,74,85,93,114,115,134,138,143] Most trials were considered fair (17 RCTs) with 11 considered good and seven considered poor quality. In addition, 14 studies/reports that provided data for the contextual questions are described below.

Although we sought studies in the three symptomatic populations of interest (i.e., patients with unknown but suspected CAD, those with known/established CAD and those with suspected ACS), only 1 trial was specifically in patients with known CAD.[109] Populations in 13 trials[17,25,28,47,68,89,94,119,121,123,127,132,142] and one prospective comparative cohort[29] were predominately (≥80%) those with unknown/suspected CAD presenting to in an outpatient setting and are described as stable outpatients in the results. Five trials enrolled a mixed population of known and suspected CAD.[24,62,98,120,126] Sixteen trials were in patients presenting acutely to the ED or similar setting with suspected ACS (unstable angina or NSTEMI).[18,23,43,44,54,59,76,78,80,82,83,92,99,102,111,137] Studies in patients with STEMI were excluded. There was heterogeneity across trials regarding how pre-test risk was determined and reported. As described by authors, most populations were low to intermediate risk of CAD. Table 24 of the full report provides additional information on the pretest risk for included studies. Given this heterogeneity it was not possible to stratify results by this variable. Appendix M provides information as reported by trial authors, and patient and study characteristics can be found in Appendix Q.

Below is a summary of the key findings for this report.

An overview of results from the contextual question will be presented first followed by results for the key questions.

Contextual questions

Overall, evidence on diagnostic accuracy was available from 5 government related reports[1,55,105,106,129] and 9 systematic reviews [4,45,53,71,113,130,144] published in the peer review literature. The quality of systematic reviews was assessed; they varied with regard to whether and how individual accuracy studies were evaluated for risk of bias. Additional detail is found in the full report and Appendix L. Most studies focused on patients with stable symptoms with either suspect (not diagnosed) CAD or known CAD. The following tables summarize the general range for diagnostic accuracy parameters for each of the tests across populations and from government sources (see full report) using ICA as a referent and assuming 50% stenosis on ICA. Notes on risk of bias are included in the table. In addition, tables across populations and all sources identified are presented. Although ICA is commonly considered the gold standard for identifying CAD, there are well known limitations regarding variability, reliability, and image distortion in its use.[69,122] There have been many technological advances to ICA in the past decades that have addressed many of the limitations. Some limitations related to interpretation of ICA remain as is true of all tests included in this HTA.

ICA is an anatomic test, so accuracy for anatomic tests such as CCTA may differ from functional tests such as stress nuclear imaging or stress echocardiography when compared with ICA; a strict correspondence between ICA and functional tests is not expected.

The full report contains additional detail for accuracy parameters by population. No studies focusing on specific subpopulations were identified. Differential accuracy based on specific populations was not assessed in any of the studies identified.

Summaries from government systematic reviews including the 2008 and 2013 [redacted] HTAs: **diagnostic accuracy of imaging tests compared with invasive coronary angiography (ICA threshold ≥50% stenosis unless otherwise noted)**

Author, year	Risk of Bias	Sensitivity	Specificity	PPV	NPV	LR +	LR -	CAD prevalence
Coronary Computed Tomography Angiography								
2016 AHRQ (Low radiation) *	ROB assessment varied by SR	100%	89%	93%	99%	9.2	0.00	58%
NICE 2016	25 studies; no serious ROB	96%	79%	84%†	97%†	4.57†	0.05†	NR
[redacted] 2008	34 studies; 9 rated good, rest as fair	98%	82%	89%†	97%†	5.44†	0.02†	59%
Nuclear Stress Testing (SPECT)								
2016 AHRQ REPORT	ROB assessment varied by SR	83% to 85%	77% to 85%	79% to 85%	79% to 85%	3.56 to 5.13	0.18 to 0.22	50%

Author, year	Risk of Bias	Sensitivity	Specificity	PPV	NPV	LR +	LR -	CAD prevalence
NICE 2016	11 studies, ROB serious or very serious in 55%	81%	78%	88%	65%	3.68	0.24	NR
[redacted] 2013 (SPECT vs. FFR via ICA)	4 studies; ROB high in 25% of QUADAS domains	66% to 90%	50% to 100%	73% to 81%	58% to 91%	1.32 to 9.00*	0.10 to 0.68*	NR
Nuclear Stress Testing (PET)								
2016 AHRQ REPORT	ROB assessment varied by SR	82% to 90%	86% to 88%	93% to 96%	53% to 84%	5.57 to 5.88	0.11 to 0.21	63% to 80%
NICE 2016	1 study, no serious ROB	91%	86%	87%*	90%*	6.50*	0.10*	NR
[redacted]2013 (SPECT vs. FFR via ICA)	2 studies; ROB high in 30% of QUADAS domains;	76% to 95%	83% to 91%	76% to 86%	83% to 97%	4.47 to 10.56*	0.05 to 0.29*	NR
Stress Echocardiography								
2016 AHRQ REPORT	ROB assessment varied by SR	84% to 87%	72% to 77%	85% to 89%	69% to 73%	3.08 to 3.65	0.18 to 0.21	66% to 68%
NICE 2016 Wall motion, vasodilators	5 studies, no serious ROB	77%	76%	93%*	97%*	3.21*	0.30*	NR
NICE 2016 Wall motion, HR modifiers	8 studies, no serious ROB	76%	80%	88%	62%	3.80	0.30	NR

AHRQ = Agency for Healthcare Research and Quality; CAD = coronary artery disease; [redacted] Review; HR = heart rate; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; NICE = National Institute for Health and Care Excellence; NPV = negative predictive value; NR = not reported; PPV = positive predictive value; SR= systematic review.
* All included studies used prospective electrocardiography gating for CT; uses much lower radiation doses than other techniques.
† Calculated from other values the authors provide.

Summary of diagnostic accuracy across all sources (see full report)

	CCTA	SPECT	PET	Stress Echo
Sensitivity	93.4% to 100%	76% to 87%	90% to 91%	64% to 90%
Specificity	72% to 92%	70% to 92%	82% to 91%	72% to 96%
PPV	47% to 93%	32% to 95%	78% to 96%	72% to 98%
NPV	89% to 100%	47% to 97%	53% to 94%	36% to 97%
LR+	3.43 to 12.50	2.88 to 10.48	4.97 to 8.89	3.08 to 18.67
LR-	0.00 to 2.64	0.18 to 2.33	0.10 to 0.21	0.13 to 2.95
CAD prevalence ranges	24.2% to 75.5%	14.1% to 86%	36.5% to 80%	35.1% to 90.8%

CAD = coronary artery disease; CCTA = coronary computed tomography angiography; ; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; NPV = negative predictive value; PET = positron emission tomography; PPV = positive predictive value; SPECT = single-photon emission computed tomography; Stress Echo = stress echocardiography.

Summary of diagnostic accuracy across all sources (see full report), continued.

	FFRct	CT perfusion
Sensitivity	84% to 91%	54% to 66%
Specificity	55% to 84%	98% to 100%
PPV	58% to 100%	96% to 100%
NPV	0% to 90%	66% to 100%
LR+	2.02 to 3.70	33.00 to 54.00
LR-	0.16 to 0.23	0.45 to 0.47
CAD prevalence ranges	32% to 100%	NR

CAD = coronary artery disease; CT = computed tomography; FFRct = CT with fraction flow reserve; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; NPV = negative predictive value; PPV = positive predictive value.

Intraobserver reliability for CCTA was reported in three studies.[75,118,141] Between observer reliability was investigated in six studies.[15,49,59,75,118,141] Intraobserver reliability was investigated in two studies[20,39] for FFRct but no studies were found on interobserver agreement. CT perfusion was only investigated in one study.[21] Risk of bias for reliability studies is described in the full report.

For SPECT one intraobserver[33] and two interobserver[21,33] studies were identified ((k=0.96 and k=0.91 to 0.95) and one study[141] investigating PET was identified. Reliability studies on stress echocardiography included both exercise and dobutamine for inducing stress and included, three intraobserver[33,36,56] studies and five studies[33,35,36,45,56,70] in inter-rater reliability. Findings from these studies are summarized below.

- Intraobserver reliability in CCTA ranged from substantial agreement to almost perfect agreement (k=0.72 to 0.96), while interobserver reliability ranged from moderate to almost perfect agreement (k=0.58 to 0.94). In FFRct, intraobserver reliability ranged from fair to almost perfect agreement (k=0.40 to 0.94), but no studies were found for interobserver reliability. Likewise, only interobserver reliability was studied in CT perfusion and found substantial to almost perfect agreement (k=0.72 to 0.86).
- SPECT studies found almost perfect agreement for both intra- and interobserver agreement (k=0.96, k=0.91 to 0.95). Likewise, PET studies also saw almost perfect agreement for bother intra- and interobserver reliability (k=0.94, k=0.82).
- Intraobserver agreement studies in stress echocardiography found almost perfect agreement (k=0.81 to 0.90), while studies on interobserver agreement found moderate to almost perfect agreement (k=0.56 to 0.87).

Key Questions Results

Key Questions results are organized by testing modality for Key Questions 1 through 4 on the efficacy and safety of CCTA, stress nuclear testing (SPECT, PET) and stress echocardiography respectively. Key Question 5 is summarized separately.

The Key findings are summarized here. The bulk of the evidence identified for this report compared CCTA with functional testing. Therefore, results for will be summarized separately for Key Questions 1 through 4. Key findings for CCTA compared with ICA, and for CCTA plus FFRct, SPECT, PET and stress

echo will then be presented by outcomes for KQ 1 through 3. No studies of differential effectiveness or safety were identified for these tests. No studies of CT perfusion meeting the inclusion criteria were identified.

Please note that the Strength of Evidence (SOE) tables for KQ 1 through 4 are found section 10 and are not repeated here. Formal SOE across economic studies is not assessed.

CCTA versus functional testing

Figure A provides a summary of findings for key questions 1 and 2.

Key Question 1: Comparative effectiveness on clinical outcomes

There were 17 RCTs comparing CCTA with functional testing, six RCTs[28,68,89,94,123,132] in stable patients with suspected CAD and 11 RCTs (12 publications)[18,23,43,44,54,59,60,76,81,83,111,137] in patients with suspected ACS that reported primary clinical outcomes. Functional testing included imaging tests (stress nuclear, stress echocardiography and ETT. Given the limitations of ETT as a functional test, sensitivity analyses comparing CCTA with functional imaging tests only were conducted. There was no statistical interaction between the patient populations for any outcome.

Across studies that include stable patients with suspected CAD and patients with suspected ACS presenting to an emergency department or similar setting:

- There is no clear difference in the frequency of MI between CCTA and functional imaging tests (SOE Moderate).
    - Three smaller RCTs, one in stable patients and two in those with suspected ACS, reported no MI in either testing arm.
    - CCTA was associated with lower MI risk compared with functional testing based on pooled estimates across the 14 remaining RCTs (pooled RR 0.70, 95% CI 0.56 to 0.89, I^2=0%),[18,23,28,43,54,59,60,81,83,89,111,123,132,137], however, the RD (0.4, 95% CI 0.1 to 0.8 per 100 patients) was small. The association was no longer clearly significant following exclusion of one RCT (SCOT-HEART) in stable patients with suspected CAD in which 85% of all patients had ETT in addition to CCTA (13 RCTs, pooled RR 0.75, 95% CI 0.57 to 0.99, I^2=0) or when CCTA was compared with functional *imaging* only (11 RCTs, pooled RR 0.74, 95% CI 0.55 to 0.98) This pattern was seen across RCTs of stable patients when the one trial was excluded. Across 10 RCTs in patients with suspected ACS, there was no difference in the frequency of MI between CCTA and functional testing at any time.
- There was no association between CCTA and reduction in all-cause mortality compared with functional testing (SOE Moderate).
    - Six RCTs reported no mortality in either testing arm (one RCT in stable patients, five RCTs in suspected ACS patients).
    - There was no difference in all-cause mortality between CCTA and functional testing across the remaining 11 RCTs (pooled RR 0.99, 95% CI 0.40 to 2.68, I^2=0%). There was also no difference in all-cause mortality when the populations were considered separately.
- Cardiac death was rare in both patient populations, with six total cardiac deaths reported in patients receiving CCTA and 13 reported in patients receiving functional testing (SOE Insufficient).

- It is possible that smaller trials in particular may have been underpowered to detect differences in MI, all-cause mortality, and cardiac death between CCTA and functional testing given that many trials enrolled patients with low or low to intermediate pre-test risk.

Key Question 2: Clinical decision making

The majority of RCTs comparing CCTA with functional testing which reported one or more of the following outcomes in either stable patients with suspected CAD or patients presenting emergently with suspected ACS: Referral for ICA (19 RCTs, N=22,335), any additional noninvasive testing (17 RCTs, N=11,595), referral for any revascularization (19 RCTs, N=23,124) and referral for PCI specifically (12 RCTs, N=18,960). There was no statistical interaction between the patient populations for any outcome.

Summary of results across populations

Across studies that include stable patients with suspected CAD and patients with suspected ACS presenting to an emergency department or similar setting:

- **ICA referral:** CCTA was associated with more frequent ICA referral compared with functional testing (19 RCTs, 14.4 vs. 12 per 100 patients, pooled RR 1.25, 95% CI 1.09 to 1.47, I^2=67%, RD 2.7, 95% CI 1 to 4 per 100, I^2=59%) (SOE Moderate).
    - **In stable outpatients**, ICA referral was more frequent following CCTA, but the association bordered the null and there was substantial heterogeneity. However, exclusion of SCOT-HEART increased the effect size and strengthen the association between CCTA and ICA referral compared with functional testing and substantially reduced the heterogeneity (4 RCTS pooled, RR 1.57, 95% CI 1.21 to 1.65, I^2=0%, RD 4.1, 95% CI 3.0 to 5.2 per 100 patients).
    - **In patients with suspected ACS**, ICA referral (cumulative) was also more frequent following CCTA compared with functional testing but was less than the frequency seen in stable outpatients. Referral for ICA was highest at the index evaluation.
- **Referral for any additional noninvasive testing** was not different between CCTA and functional testing groups across populations (17 RCTs, 7.2 versus 7.6 per 100, pooled RR 0.82, 95% CI 0.53 to 1.28, I^2=83%) (SOE Low) or when populations were considered individually. Type of additional testing was inconsistently reported but appears to be primarily stress imaging.
- **Revascularization:** CCTA was associated with more frequent revascularization (9.5 per 100 patients) compared with functional testing (7.1 per 100 patients): 19 RCTs, pooled RR 1.52, 95% CI 1.26 to 1.90, I^2=66%, RD 2.4, 95% CI 1.4 to 3.3 per 100) (SOE Moderate). Again, this was also true when the populations were considered individually.
- **PCI for revascularization:** CCTA was associate with higher frequency of PCI as a revascularization procedure compared with functional testing (12 RCTs, 8.2 vs. 6.0 per 100 patients, pooled RR 1.63, 95% CI 1.22 to 2.35, I^2=74%, RD 2.4, 95% CI 1.3 to 3.6 per 100 patients) across populations (SOE Moderate).
    - In stable outpatients with suspected CAD, PCI was more common with CCTA, but the association failed to reach statistical significance (pooler RR 1.16, 95% CI 0.96 to 2.99).
    - In patients with suspected ACS the association between CCTA and PCI was seen at index testing but there was no difference between CCTA and functional testing at 1 to 6.5 months or ≥12 months.
- **Hospitalization**:

- **In stable outpatients t**here was no difference in hospitalization between CCTA and functional testing across four RCTs (SOE Moderate).
- **In patients with suspected ACS**,
  - At index testing, across comparators with CCTA there is substantial heterogeneity and results are mixed. While four RCTs comparing CCTA with any functional test suggest that hospitalization is less common with CCTA, large studies of CCTA vs echo and SPECT suggest that hospitalization may be more with CCTA (SOE Insufficient).
  - There was no difference in hospitalization between CCTA and functional testing across studies, regardless of comparator, at 1 to 6.5 months after index testing (9 RCTs, 3.0 vs. 3.9 per 100 patients, pooled RR 0.76, 95% CI 0.49 to 1.1, I^2=18%)[18,23,43,44,59,81,83,92,99] (SOE High). Similarly, there was no difference between testing arms at ≥12 months (6 RCTs 14.9 vs. 17.4 per 100 patients, pooled RR 0.90, 95% CI 0.77 to 1.03, I^2=0%).[54,60,76,78,81,137] (SOE High).

- **Subsequent ED visits:** In patients with suspected ACS there was no difference in emergency department visits after index testing between CCTA and functional testing across studies, regardless of comparator, at 1 to 6.5 months (7 RCTs, pooled RR 0.84, 95% CI 0.66 to 1.06, I^2=0%)[23,43,44,59,83,92,99] or at ≥12 months (5 RCTs, pooled RR 1.06, 95% CI 0.93 to 1.56, I^2=16%)[54,60,76,78,111] (SOE High for both time frames).
- **Medication**: CCTA was not consistently associated with initiation of, discontinuation of or changes in medications and results for many mediations were mixed. Evidence is insufficient to draw firm conclusions about the impact of testing on medication use (SOE Insufficient).

Figure A. Summary of CCTA vs. any functional test, KQ 1 and 2 results

Outcome	All patients	ED/similar setting	Stable outpatients
Key Question 1: Clinical outcomes			
MI	ϴ* Moderate SOE (14; N=21,661)	ϴ (10; N=5,977)	ϴ* (4; N=15,684)
All-cause death	ϴ **Moderate** SOE (11; N=18,935)	ϴ (7; N=4,001)	ϴ (4; N=14,934)
Cardiac death	Insufficient evidence	Insufficient evidence	Insufficient evidence
Key Question 2: Decision-making			
ICA	↑† Moderate SOE (19; N=22,335)	↑ (14; N=7,227)	ϴ† (4; N=15,107)
Any additional NIT	ϴ **Low** SOE (17; N=11,595)	ϴ (13; N=6,491)	ϴ (4; N=5,104)

Any revascularization	↑ Moderate SOE (19; N=23,124)	↑ (13; N=7,014)	↑ (19; N=16,110)
Hospitalization	Data not pooled	Index visit: Insufficient evidence ϴ High SOE 1–6.5 mos. (9; N=5,144) ≥12 mos. (6; N=3,624)	Any timepoint: ϴ Moderate SOE (4; N=14,810)
Subsequent ED visit	NR	ϴ High SOE 1–6.5 mos. (7; N=4,294) ≥12 mos. (5; N=2,855)	NR
Medication change	Insufficient evidence	Insufficient evidence	Insufficient evidence

ϴ = no difference between groups, ↓ = decreased risk with CCTA, ↑ = increased risk with CCTA
ED = emergency department; ICA = invasive coronary angiography; MI = myocardial infarction; mos. = months; NIT = noninvasive testing; NR = not reported; SOE = strength of evidence
*Excluding SCOT-HEART results not clearly statistically significant; similar results when studies comparing to ETT were excluded
†Exclusion of SCOT-HEART increased the effect size and strengthened the association between CCTA and ICA referral compared with functional testing and substantially reduced the heterogeneity

Key Question 3: Safety

Adverse events

- Major or serious test-related adverse events/harms are rare for all modalities. Complications reported across studies were minor. For stress testing most reported symptoms are expected responses to the pharmacologic agents used.
- No major complications were observed across 3 RCTS at time of index test or within 24 hours. (SOE Low) The largest RCT in stable outpatients also reported no test-related hospitalization in the CCTA arm and 0.1% (5/4837) in the functional testing arm[28] (SOE low).
- Minor complications at time of index test or within 24 hours was <4% across treatment arms across five RCTs in stable outpatients and five RCTs in patients with suspected ACS. Two other trials in patients with suspected ACS reported on a broader range of minor complications, one finding that 24% of patients in each testing arm[78] experienced them and the other that 14% of CCTA patients and 6.4% experienced minor complications (1 RCT, RR 2.16, 95% CI 1.12 to 4.14)[76] (SOE Low).
    - Contrast-related events related to CCTA occurred in ≤3% of patients at time of index testing as reported in six RCTs[18,23,28,59,68,87,123,140] and one case series. Transient creatinine elevation not requiring dialysis were reported in two trials as 0.2%[59] and 1%[23] (SOE Low) and a third RCT[18] reported that no contrast-induced nephropathy occurred (SOE Insufficient). Mild contrast reaction occurred in 0.5% to 2.1% of patients across six RCTs (SOE Low).
    - CCTA was associated with lower risk of chest pain, shortness of breath, or palpitations at the time of index testing compared with stress SPECT (1 RCT, 0.5% vs. 16% RR 0.03, 95%

CI 0.004 to 0.24, p<0.001) and stress echo (1 RCT, 0% vs. 3%, p=0.03)[76] in patients with suspected ACS (SOE Low). The symptoms are likely consistent with inducing cardiac stress with pharmacologic agents. One large RCT in stable outpatients reported much lower risk of symptoms related to nuclear stress testing (0.1%) and events related to dipyridamole or adenosine (0.2%) (SOE Low).

- Arrythmias occurred in ≤ 0.2% in all testing arm across testing arms (SOE Insufficient).

Radiation exposure

- **Radiation from index tests**: Across six RCTs comparing CCTA specifically with SPECT radiation exposure at index tended to be lower with CCTA (SOE Low). Five RCTs reported that CCTA was associated with a lower effective radiation dose for the index test; the sixth trial reported that CCTA was associated with slightly higher radiation (estimated difference 1.8 mSv). Rough estimates of difference between tests ranged from approximately 1.30 mSv to 11.9mSv. Stress echocardiography and ETT do not involve ionizing radiation (SOE Low).
- **Cumulative radiation**: Across nine RCTs, results are somewhat mixed, but suggest that cumulative radiation may be higher when CCTA is the initial test (SOE Low). Good- or fair-quality RCTs[23,28,59,76,82,99] found that CCTA was associated with higher cumulative radiation compared with functional testing with rough estimates of differences ranging from 1.9 mSv to 9.0 mSv in these trials. It is unclear from included RCTs what tests (e.g., SPECT, ICA) or procedures (e.g., PCI) were included in the estimates. Stress echocardiography does not involve ionizing radiation. It is unclear if some of the differences between arms would impact clinical decision making. CCTA was associated with lower cumulative radiation versus SPECT in two RCTs (estimated range 6 mSv to 15 mSv)[68,78] and no statistical difference between CCTA and SPECT was reported in a third smaller poor-quality RCT.[94]

Incidental Findings

Incidental findings are common with CCTA (28% to 44%) across included RCTs, systematic reviews and nonrandomized studies with pulmonary findings being most common. The proportions that were considered "potentially significant" "clinically significant" or "required follow-up" ranged from 4.9% to 16% (SOE Low).

Key Question 4. Differential effectiveness and safety

To evaluate differential efficacy and safety (heterogeneity of effect, interaction), we focused on RCTs as they have the least potential for bias and confounding thus allowing for causal inference. Further, only RCTs that formally tested for interaction between subgroups were reported for Key Question 4.

Three large RCTs comparing CCTA with functional testing reported tests for interaction between subgroups on efficacy and/or safety outcomes.[3,84,86,100,107,108,117,124,125,135,136] Only one of these pre-specified subgroup analyses and consider this in sample size determinations.[28,84,86,107,108,124,125] All performed multiple analyses for multiple outcomes, including multiple composite outcomes. None of the RCTs specified all outcomes evaluated. None specified hypotheses to be tested or expected direction.

- **Clinical outcomes**: Only one RCT[3,123] reported on the primary clinical outcomes of interest for this HTA. At a median of 3.2 years, the effect of CCTA did not appear to vary based on anginal classification (non-anginal chest pain, possible anginal chest pain) for MI (SOE Low), all-cause mortality (SOE Insufficient) or death due to CAD (SOE Insufficient). As many of these outcomes

appear to be rare, it is possible that this trial was not sufficiently powered to effectively evaluate interaction. The factors, outcomes and hypothesized direction do not appear to have been specified a priori.

- **Downstream testing:** One RCT in patients with suspected ACS found no significant variation in use of downstream testing with CCTA based on sex or race at either the index visit, or 28 day follow up. Downstream testing did vary by diabetes status; more downstream testing occurred with CCTA in patients with diabetes at index visit and by 28-day follow-up (interaction p-values 0.001 and 0.002 respectively). The factors, outcomes and hypothesized direction do not appear to have been specified a priori in this fair-quality trial (SOE Low).
- **ICA referral:** Across two RCTs, one in stable outpatients[124,125] and the other in patients with suspected ACS[136] the effect of CCTA versus functional testing on ICA referral did not vary by diabetes status. (SOE Low) Similarly, there was no effect modification in the trial in patients with suspected ACS by sex or race at index visit or by 28-day follow-up (SOE Low).
- **Revascularization**: Across two RCTs, one in stable outpatients[124,125] and the other in patients with suspected ACS[136] the effect of CCTA versus functional testing on revascularization did not vary by diabetes status (SOE Low). The effect of CCTA versus functional testing on revascularization was not modified by either sex (1 RCT) [136] or angina classification (1 RCT)[3] (SOE Insufficient).
- **Radiation exposure:** In stable outpatients, CTTA cumulative radiation may vary based on baseline heart rate. Patients with ≥75 beats-per-minute may have higher cumulative radiation with CCTA compared with functional testing. Tests for interaction by age, sex and BMI were not significant (SOE Insufficient). In patients with suspected ACS, there was insufficient evidence to confidently make conclusions about how radiation dose may vary by sex, diabetes status or race for CCTA versus functional testing index testing or within 28 days (SOE Insufficient).

CCTA versus ICA

Two RCTs (N=1,971 randomized), compared CCTA as an index diagnostic test versus direct referral to ICA in patients with suspected CAD (known CAD was an exclusion criteria). One good-quality trial included patients with atypical chest pain who had a mix of stable/chronic (treated on an outpatient basis) and acute (hospitalized) presentation.[25] One fair-quality trial included stable patients at primarily intermediate pre-test risk who were treated on an outpatient basis.[17]

- There was no difference in the risk of all-cause mortality or MI in CCTA versus ICA group at 12 and a median 40 months across one good- and one fair-quality RCT (SOE Low for both). Cardiac mortality was rare (SOE Insufficient).
- Compared with direct referral to ICA, CCTA was associated with a reduced risk of ICA without obstructive CAD (2 RCTs, N=1,019; 22 versus 65 per 100 patients; pooled RR 0.32, 95% CI 0.18 to 0.51, I^2=0%; pooled RD –48.0%, 95% CI –67.0% to –29.2%, I^2=73%) (SOE Moderate) and any revascularization (2 RCTs, N=1,832; 13 vs. 18 per 100 patients; pooled RR 0.71, 95% CI 0.55 to 0.96, I^2=0%; pooled RD –5.0%, 95% CI –8.0% to –2.0%, I^2=0%) (SOE Moderate) to include PCI but not CABG procedures, but an increased risk of additional downstream noninvasive testing (1 fair-quality RCT, N=1,503; 53 vs. 27 per 100 patients; RR 1.96, 95% CI 1.71 to 2.25; RD 26.0%, 95% CI 21.1% to 30.7%) (SOE Moderate). This latter trial found no difference between tests in the risk of cardiac hospitalization (4 vs. 4 per 100 patients) over 12 months (SOE Moderate).

- No major complications were reported in one good-quality trial and only one major complication was reported in the second fair-quality trial, major bleeding, which occurred in two patients (0.4%) in the ICA group; one patient (0.1%) required transfusion (SOE Low).

CCTA with FFR versus any noninvasive testing and versus ICA

One prospective comparative observational study was identified that enrolled patients into two simultaneous cohorts based on the planned test (per their physician) prior to enrollment: noninvasive test cohort (CCTA with FFR vs. any NIT; N=204) and (CCTA with FFR vs. direct referral to ICA; N=380).[26,29] The decision to send patients for noninvasive or invasive testing prior to enrollment was made by the patients' physicians; it is unclear what criteria were used to make this decision, though it is assumed that those patients who were being sent directly to ICA were higher risk than those being sent for noninvasive testing resulting is some selection bias.

Key Questions 1 and 2

CCTA with FFR vs. any NIT (planned NIT cohort)

- There was no difference between groups in any outcome over 12 months (SOE Insufficient for all outcomes).
- One MI occurred in the any noninvasive test group (0 vs. 1 per 100 patients). There were no deaths or hospitalizations with urgent revascularization in either group. Given that these are rare events, the study may not have been sufficiently powered to detect a difference.
- Risk of ICA was 21 vs. 16 per 100 patients; of ICA without obstructive CAD was 13 vs. 6 per 100 patients (at 3 months); and of any revascularization was 10 vs. 7 per 100 patients, respectively.

CCTA with FFR vs. ICA (planned ICA cohort)

- There were no differences between groups over 12 months in the risk of MI (1 vs. 1 per 100 patients), all-cause death (0 vs. 1 per 100 patients) or hospitalization with urgent revascularization (1 vs. 0 per 100 patients). Given that these are rare events, the study may not have been sufficiently powered to detect a difference (SOE Insufficient).
- Compared with direct referral to ICA, patients who underwent CCTA with FFR were referred to ICA significantly less often (51 vs. 100 per 100 patients; RR 0.51, 95% CI 0.45 to 0.59) and importantly, there were no events in the 61% of CCTA with FFR patients in whom ICA was cancelled in the planned ICA cohort. The risk of ICA without obstructive CAD was also significantly reduced following CCTA with FFR (39 vs. 100 per 100 patients; RR 0.39, 95% CI 0.33 to 0.47) (SOE Insufficient).
- There was no difference between groups in the risk of any revascularization (SOE Insufficient).

Key Question 3, Safety

- There was one mild contrast reaction from CCTA testing; no other information was provided (SOE Insufficient).
- Patients who received CCTA with FFR had significantly greater cumulative radiation exposure over 12 months compared to those who received any noninvasive test (planned noninvasive test cohort): 9.6 vs. 6.4 mSv, MD 3.1 (95% CI, 0.6 to 5.7); there was no difference for CCTA with FFR versus direct referral to ICA (planned ICA cohort) (SOE Low).

SPECT versus Stress Echocardiography and versus Exercise ECG

Key Questions 1 and 2, Efficacy

Four trials (1 good- and 3 fair-quality, N=1960) comparing SPECT with stress echocardiography (2 RCTs; 1 in stable, 1 in acute patients with suspected or known CAD)[120,126,133] and with exercise ECG (2 RCTs in stable, suspected CAD patients)[119,127] were identified. Given that the results across the four trials comparing SPECT with stress echocardiography and exercise ECG showed similar results in general, they are summarized together in the bullet points below.

- There was no difference in the risk of MI (SOE Insufficient), all-cause mortality (SOE low) or cardiac mortality (SOE Insufficient) between SPECT and stress echocardiography (2 trials) or exercise ECG (2 trials) across four trials (N=1,908) with varying populations and follow-up periods. The absolute risk was <2 per 100 patients across all testing arms for all outcomes over follow-up periods ranging from 1 to 24 months. Given that these are rare events, trials may not have been sufficiently powered to detect a difference.
- There was no difference in the risk of ICA (4 trials, N=1,908) (SOE Low) or additional noninvasive testing (N=3 trials, N=1,679) (SOE Insufficient) for SPECT versus stress echocardiography or exercise ECG across all four trials over follow-up periods ranging from 1 to 24 months, however, there was substantial heterogeneity. Individually, only the trials comparing SPECT versus exercise ECG reported statistically significant differences which favored SPECT for both ICA (1 trial) and additional noninvasive testing (2 trials); however, for the latter, the estimates across trials were inconsistent and imprecise. Differences in testing protocols, patient populations and/or pretest risk, and follow-up periods may have played a role in these findings.
- There was no difference in the risk of revascularization (4 trials, N=1,908) (SOE Moderate) or hospitalization (3 RCTs, N=1,451) (SOE Low) between SPECT and stress echocardiography or exercise ECG, or ED visits in 1 trial (N=229) of SPECT vs. echocardiography through 24 months of follow-up (SOE Low).

SPECT versus Clinical Assessment Alone and versus NICE Guideline-Directed Care

Key Questions 1 and 2, Efficacy

Two trials, one fair-quality trial (N=1,508)[80] comparing SPECT versus clinical assessment alone in acute patients with suspected ACS presenting to the ED and one good-quality trial (N=721)[47] comparing SPECT with NICE guideline-directed care in stable outpatients with suspected CAD, were identified. Given that the results across the two trials comparing SPECT with clinical assessment alone and with NICE guideline-directed care showed similar results in general, they are summarized together in the bullet points below.

- There was insufficient evidence to draw conclusions regarding the risk of MI and all-cause mortality in one RCT (SPECT vs. NICE guideline-directed care) with a median follow-up of 16 months and cardiac death across both RCTs (follow-up range, 1 to median 16 months). The absolute risk was ≤1.3 per 100 patients across both test arms in both trials for all outcomes. Given that these are rare events, the trials may not have been sufficiently powered to detect a difference (SOE Insufficient for all).
- SPECT was associated with a decreased risk of ICA across both trials (10.2 vs. 21.1 per 100, pooled RR 0.49, 95% CI 0.26 to 0.95, I^2=85%; pooled RD –11.1%, 95% CI –14.4% to –7.8%) (SOE

Low); the association was stronger in the trial comparing SPECT versus NICE guideline-directed care, likely due the direct referral to ICA of patients with high pretest risk per the NICE guideline algorithm, and could account for much of the heterogeneity in the pooled estimate. SPECT was also associated with a decreased risk of ICA showing no obstructive CAD (1 RCT, SPECT vs. clinical assessment alone: 21.9 vs. 39.3 per 100 patients; RR 0.56, 95% CI 0.32 to 0.96; RD –17.4%, 95% CI –33.3% to –1.4%) and unnecessary ICA (1 RCT, SPECT vs. NICE guideline-directed care: 7.1 vs. 28.8 per 100 patients; RR 0.25, 95% CI 0.17 to 0.36; RD –21.7%, 95% CI –27.9% to –15.5%) (SOE: Low for both).

- There was no difference between SPECT and clinical assessment alone or NICE guideline-directed care in the risk of any revascularization (2 RCTs, 5.9 vs. 7.0 per 100 patients; RR 0.85, 95% CI 0.57 to 1.28, I^2=0%) (SOE Low).
- SPECT was associated with decreased risk of additional downstream NIT over 12 months (12.1 vs. 68.3 per 100 patients; RR 0.18, 95% CI 0.15 to 0.21; RD –56.2%, 95% CI –60.7% to –51.7%) and hospitalization at the index visit (10.2 vs. 18.5 per 100 patients; RR 0.55, 95% CI 0.42 to 0.71; RD –8.3%, 95% CI –12.2% to –4.4%) compared with clinical assessment alone in one trial (SOE Low for both).

SPECT versus ICA

Key Questions 1 and 2, Efficacy

One good-quality trial (N=446)[126,133] comparing SPECT with ICA in stable outpatients with a mix of known and suspected CAD referred for outpatient angiography was identified.

- There was insufficient evidence to draw conclusions regarding the risk of MI, all-cause mortality and cardiac mortality between groups. Over 18 months, the absolute risk was ≤2 per 100 patients across both test arms for all outcomes; at 72 months, the absolute risk of all-cause mortality was 3 per 100 patients. Given that these are rare events, the trial may not have been sufficiently powered to detect a difference (SOE Insufficient).
- Compared with ICA, SPECT was associated with a decreased risk of additional downstream NIT (0.4 vs. 3.6 per 100 patients; RR 0.12, 95% CI 0.02 to 0.98; RD –3.2%, 95% CI –5.8% to –0.6%; timing unclear) and any revascularization after the index visit through 36 months (43.8 vs. 53.2 per 100 patients; RR 0.82, 95% CI 0.68 to 0.99; RD –9.4%, 95% CI –18.6% to –0.2%). There was no difference in the risk of any hospitalization for chest pain (SOE: Low for all).

Safety of SPECT (Key Question 3)

- Test-related complications appear to be rare following SPECT in one good-quality trial[47] (SOE Low).
- Data from one fair-quality trial was insufficient to draw conclusions regarding radiation exposure.[127] Mean exposure following SPECT was 14 mSv; exercise ECG does not use radiation.
- Adverse events from stress agents are relatively common and ranged from 2% to 13% of patients (5% to 37% of events) for dipyridamole and from 4% to 53% for regadenoson; the most common events included headache, dyspnea, GI upset/nausea and dizziness or lightheadedness (SOE Low). Most were minor and transient and are likely expected with use of pharmacologic cardiac stress.

Stress Echocardiography versus Exercise ECG

Key Questions 1 and 2, Efficacy

Five trials (1 good-, 1 fair- and 3 poor-quality) comparing stress echocardiography with exercise ECG, two (N=543) in stable patients with suspected CAD treated on an outpatient basis[50,121,142] and three (N=854) in patients with acute symptoms presenting to the ED or hospital.[24,62,102]

- There was insufficient evidence to draw conclusions regarding the risk of MI, all-cause mortality and cardiac mortality following stress echocardiography versus exercise ECG across the five trials. The absolute risks of MI and all-cause mortality across four trials were 1.3 vs. 0.9 and 0.6 vs. 0.9 per 100 patients, respectively, across follow-up periods ranging from 2 to 36 months. The absolute risk of cardiac mortality in one RCT was 0.5 vs. 0 at 36 months. Given that these are rare events, the trial may not have been sufficiently powered to detect a difference (SOE Insufficient for all).
- In stable patients with suspected CAD, stress echocardiography was associated with a reduced risk of ICA (1 good-quality RCT; 6.3 vs. 13.4 per 100 patients; RR 0.47, 95% CI 0.24 to 0.90; RD –7.1%, 95% CI –13.0 to –1.2%) (SOE Low) and additional downstream NIT (2 RCTs, 1 good and 1 poor quality; 5.8 vs. 42.7 per 100 patients; pooled RR 0.15, 95% CI 0.06 to 0.28, I^2=0%; pooled RD –31.6 (95% CI –49.3% to –14.0%, I^2=84%) (SOE Low) compared with exercise ECG over 28 to 36 months. Across the three trials in acute patients with a mix of known or suspected CAD, there was no difference between groups in either outcome, though one fair-quality trial tended to favor echocardiography for ICA (lower risk); heterogeneity was high possibly due to differences in populations, pretest risk and follow-up times (SOE Low for ICA; SOE Insufficient for additional NIT).
- Across trials in both stable (1 RCT) and acute patients (3 RCTs) with varying pretest risks of CAD, there were no differences between testing arms in the risk of revascularization (4 RCTs, 1 good, 2 fair and 1 poor quality) or (re)hospitalization (3 RCTs, 1 good, 1 fair and 1 poor quality) over follow-up periods ranging from 2 to 36 months (SOE Moderate for both).

Stress Echocardiography versus Standard Care

Key Questions 1 and 2, Efficacy

Data from one small, poor-quality trial (N=201)[102] in acute patients with suspected ACS are insufficient to draw conclusions regarding the risk of MI, all-cause or cardiac mortality, ICA, additional downstream NIT, any revascularization and rehospitalization for acute chest pain following stress echocardiography versus standard care.

- No MIs and no deaths were reported in either test arm. Stress echocardiography resulted in fewer referrals for ICA and additional NITs, and fewer rehospitalizations for acute chest pain, but no difference in revascularization rates (SOE Insufficient).

Stress Echocardiography versus ICA

Key Questions 1 and 2, Efficacy

One good-quality trial (N=448)[126,133] comparing stress echocardiography with ICA in stable outpatients with a mix of known and suspected CAD was identified.

- There was insufficient evidence to draw conclusions regarding the risk of MI, all-cause mortality and cardiac mortality between groups. Over 18 months, the absolute risk was <3 per 100 patients across both test arms for all outcomes; at 72 months, the absolute risk of all-cause mortality was 4.9 vs. 3.2 per 100 patients. Given that these are rare events, the trial may not have been sufficiently powered to detect a difference (SOE Insufficient).
- There were no differences between stress echocardiography and ICA in the risk of additional downstream NIT (SOE Insufficient), any revascularization and hospitalization for chest pain (SOE: Low for both).

Safety of Stress Echocardiography (Key Question 3)

- Data from one poor-quality trial is insufficient to draw conclusions regarding test-related complications.[102]
- Across 11 case-series,[10,22,38,46,64,90,95,103,110,112,128] the risk of major or life-threatening adverse events (e.g., death, MI, unstable angina, cerebrovascular accident, acute pulmonary edema) as a result of pharmacologic stress agents appears to be low: for dobutamine, ≤0.1% across all outcomes, and for dipyridamole and adenosine no major adverse events were reported. Minor transient events (e.g., arrhythmias, chest pain, headache, dyspnea, nausea/vomiting) were not uncommon (SOE low for all); most reported symptoms are expected responses to the pharmacologic agents used.
- Definite or suspected contrast related adverse events and allergic reactions appear to be rare (≤2% across all studies/outcomes) (SOE Low).

PET vs. SPECT

Two trials comparing PET versus SPECT, one in stable patients with a mixed of suspected or known CAD (N=210)[98] and one in stable patients with known CAD presenting with new or worsening symptoms (N=322),[109] were identified. Across both trials, there were no difference between test groups in any of the reported outcomes.

- There was insufficient evidence from one good-quality trial in patients with known CAD and new or worsening symptoms to draw firm conclusions regarding MI and all-cause mortality. The absolute risks of MI and all-cause mortality were ≤1 per 100 patients across both the PET and SPECT arms over 12 months (SOE Insufficient). There was no difference in the risk of ICA (29 vs. 28 per 100 patients); of diagnostic failure, defined as unnecessary ICA or additional confirmatory noninvasive testing within 2 months (2.0 vs. 2.5 per 100 patients); of any revascularization (16 vs. 15 per 100 patients); and of escalation in antianginal therapy (26 vs. 23 per 100 patients) (SOE Low for all).
- The only outcome reported by the older, poor-quality trial evaluating a mixed population of suspected and known CAD was cardiac mortality (absolute risk 3 vs. 4 in 100 patients over a mean 9 months) (SOE Insufficient).
- Neither trial reported on test safety or on differential effectiveness or safety.

Key Question 5: Cost-effectiveness of testing

Economic studies identified for inclusion primarily compared combinations of testing strategies involving CCTA, stress nuclear imaging (primarily SPECT), stress echocardiography, exercise ECG treadmill testing and invasive coronary angiography, with only few directly comparing one specific test to another. Only

[redacted]. A total of three systematic reviews[134,138,143] and 11 primary studies were included. Eight of the studies (in nine publications) were in stable outpatients with suspected CAD,[6,13,14,50,61,65,74,85,93] and three were in patients with suspected ACS.[41,114,115] Of these, two studies in stable outpatients[65,93] and three studies in patients with suspected ACS were conducted in the United States.[41,114,115] Industry funding was noted and/or author ties to related industries were described in three studies.[41,65,93] Full economic studies of diagnostic testing are complex, challenging to perform and challenging to interpret. A variety of assumptions and estimates from diverse sources (which may vary in quality) provide input into any economic model and impact the results of that model. These are discussed in the full report.

Most economic models described in the systematic reviews and the primary studies compared testing strategies (i.e., different scenarios for index test and subsequent sequential tests) not individual tests, making it difficult to draw definitive conclusions for specific tests. The results below attempt to focus on findings for specific tests. Variation across studies in data sources, estimation of model parameters, clinical pathways for test sequencing and decision making leading to additional testing and/or treatment make comparison across studies challenging. Evidence was mixed for demonstrating a definitive cost-effective diagnostic approach.

- Results across studies (including systematic reviews) were somewhat mixed.
- Cost-effectiveness and ICERs varied based on testing sequencing, pre-test likelihood of CAD, assumed accuracy of tests across populations. These key drivers were also identified in the prior HTAs.
- In stable outpatients with suspected CAD
    - The U.S. studies generally found CCTA to be the dominant initial testing strategy against comparators/other strategies, which included ICA and functional tests. FFRct in addition to CCTA was consider cost-effective in one industry-funded study.
    - Stress echocardiography and SPECT were found to be cost-effective compared to ICA.
    - Two systematic reviews suggest that stress echo or nuclear stress testing may be more cost effective than comparators in some settings depending on patient prior probability of CAD and prevalence of CAD. Stress echo may be more cost-effective than SPECT in patients with low to intermediate probability.
- In patients presenting with suspected ACS in an emergency setting
    - CCTA was compared with standard of care (variably defined), ETT, expert consensus based on ACC/AHA guidelines and “do nothing” strategies. CCTA was the dominant or cost-effective approach in most all comparisons.
    - In one poor-quality review of seven studies in patients with acute chest pain, stress nuclear testing was cost-effective versus traditional strategies involving ECG. However, authors note that stress nuclear testing in the acute setting may not often used in ‘real life’, due to logistical challenges.
- Common limitations across studies include
    - The assumption that ICA has 100% sensitivity and specificity.
    - Extrapolation of data to lifetime time horizon particularly when RCT data is only

available for approximately 2 years for many of the studies. Results from short-term time horizons may differ from those seen at longer term.
  - Lack of or insufficient modeling of indeterminate tests, false positive and false negative results, test accuracy based on sequencing of tests, potential adverse events and follow-up of incidental findings.
  - Some modeled strategies (e.g., some "do nothing" strategies) may not be consistent with clinical practice. Modeling of appropriate "no test" strategies was not done.
  - Models assume the availability of all tests and competence in performing and interpreting them across clinical settings.
  - Lack of information on the potential impact of radiation exposure for index and downstream testing.

Discussion

Regarding the pathophysiology of CAD and ischemia, several factors are important to consider. First, identification and degree of obstruction do not always correlate to patient symptoms, the presence or degree of ischemia or the functional impact. In addition, ischemia may be present in the absence of obstruction and would not be identified by anatomic testing.

The bulk of new evidence for this report is from RCTs comparing CCTA with functional tests.

- There is no clear difference between CCTA and functional imaging tests (i.e., stress nuclear testing, stress echocardiography) regarding impact on improving clinical outcomes (MI, all-cause mortality) in stable outpatients with suspected CAD or in patients with suspected ACS presenting to the ED or similar settings. It should be remembered that evidence of the impact of testing on clinical outcomes is indirect.
- CCTA was associated with higher frequency of ICA referral and use of PCI for revascularization compared with functional imaging. From the evidence available, it is not clear to what extent patients referred for these were considered at high risk for MI requiring revascularization. While increased ICA/PCI use may lead to fewer symptoms, related increased resource utilization and radiation exposure should be considered. No differences in the use of additional noninvasive testing between CCTA and functional tests were identified.
- Risk of serious test-related adverse events was very low across all imaging tests.
- While radiation exposure at time of index testing tended to be lower in CCTA recipients compared with SPECT (stress echo does not involve ionizing radiation), the evidence suggests that cumulative radiation may be higher with CCTA as an initial test. The extent to which this is influenced by additional non-invasive testing and/or ICA and PCI referral is unclear across included RCTs.
- Incidental findings requiring follow-up in patients receiving CCTA are common and require additional resources.
- Definitive conclusions regarding cost-effectiveness of any of the noninvasive imaging tests are not possible in large part due to substantial heterogeneity across economic studies regarding testing strategies and test sequencing.
- There was insufficient evidence for the use of FFRct in conjunction with CTTA.

The applicability of the evidence and findings reported here may be limited by the following factors.

- There was substantial heterogeneity across studies regarding patients, their pre-test risks of CAD (and how this was determined) and CAD risk factors, equipment used, testing protocols and study methods.
- Pretest CAD risk described in this HTA was as reported by study authors and included a variety of methods. Stratification by pre-test risk was not considered to be feasible given this heterogeneity.
- Stress echocardiography and SPECT are established modalities for diagnosis of CAD.
    - Fewer trials of these modalities were identified; most were older than CCTA trials and reflect older research methods and reporting standards. Included RCTs do not reflect state of the art equipment or techniques, whereas studies of CCTA involve more state-of the-equipment and methods.
    - Given that these are more established modalities, there has been less impetus and funding for RCTs and high-quality prospective observational studies than for evaluation of CCTA.
    - It is possible that more advanced techniques related to stress echocardiography using contrast for left ventricular opacification or myocardial perfusion imaging or quantitative methods for PET may have been used in included RCTs but were not assessed as separate advances.
- Substantial expertise is required to perform and interpret all diagnostic imaging tests for CAD. Across included studies, the level of expertise for all imaging tests was high. This level of expertise may not translate to all clinical settings. Similarly, the availability of updated equipment may also vary across settings. These factors need to be considered when weighing options for the “best test” for a given patient.

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1 Appraisal

1.1 Background and Rationale

1.1.1 Policy Context

CCTA and stress nuclear imaging were originally reviewed in 2008 and 2013 respectively. They are being re-reviewed in 2021 due to newly available published evidence. In addition, stress echocardiography is being reviewed (not previously reviewed by HTAP).

1.1.2 Objectives

The aim of this report is to evaluate the clinical impact (i.e., patient outcomes and patient management), safety and cost-effectiveness of the three primary noninvasive diagnostic tests for CAD, namely CCTA , stress nuclear imaging and stress echocardiography as well as FFR based on CT and CT perfusion (CTP) imaging. This review updates the 2008 CCTA HTA and 2013 nuclear imaging HTA and adds evaluation of stress echocardiography. Information on diagnostic accuracy (validity) for these modalities was summarized for context only given the clinical maturity of these imaging modalities. Coronary artery calcium scoring (CACS) as a diagnostic test was excluded as it is not a standalone diagnostic test; further, it was not chosen for re-review by the Health Care Authority. Use of CT (including CACS), CCTA, nuclear imaging and stress echocardiography for ***screening*** for CAD in ***asymptomatic*** individuals was excluded.

1.2 Contextual Questions

Prior to addressing research questions related to the impact of cardiac imaging on clinical outcomes ***the diagnostic accuracy (validity)*** of these modalities compared with invasive coronary angiography (the usual reference standard) will be briefly summarized for context, given the clinical maturity of these imaging modalities.

In patients with **known or suspected CAD who are *symptomatic***:

1. What is the diagnostic accuracy of *CCTA* for anatomical confirmation of obstructive CAD? Is there evidence of differential test accuracy for specific subpopulations (e.g., women, patients with comorbidities, the elderly)?

2. What is the diagnostic accuracy of *CCTA with determination of fractional flow reserve (FFR)* for the diagnosis of CAD? Is there evidence of differential test accuracy for specific subpopulations (e.g., women, patients with comorbidities, the elderly)?

3. What is the diagnostic accuracy of *stress CCTA* for the diagnosis of CAD? Is there evidence of differential test accuracy for specific subpopulations (e.g., women, patients with comorbidities, the elderly)?

4. What is the diagnostic accuracy of *stress nuclear imaging*? Is there evidence of differential test accuracy for specific subpopulations (e.g., women, patients with comorbidities, the elderly)?

5. What is the diagnostic accuracy of *stress echocardiography*? Is there evidence of differential test accuracy for specific subpopulations (e.g., women, patients with comorbidities, the elderly)?

1.3 Research Key Questions

The following Key Questions focus on ***the impact on clinical outcomes*** for the use of CCTA, stress nuclear imaging, and stress echocardiography to diagnose CAD **in patients with known or suspected CAD who are *symptomatic.***

1. What is the comparative effectiveness of noninvasive cardiac anatomic or functional imaging modalities (CCTA, stress nuclear imaging, stress echocardiography) in leading to improved *clinical outcomes* (e.g., MI, mortality)?

2. What is the comparative effectiveness of noninvasive cardiac anatomic or functional imaging modalities (CCTA, stress nuclear imaging, stress echocardiography) with respect to *clinical decision-making* including additional testing and treatments?

3. What is the comparative effectiveness of noninvasive cardiac anatomic or functional imaging modalities (CCTA, stress nuclear imaging, stress echocardiography) with regard to *harms or adverse events* which may result directly from testing or additional, downstream testing?

4. Does effectiveness (in terms of clinical outcomes) or safety of noninvasive cardiac anatomic or functional imaging (CCTA, stress nuclear imaging, stress echocardiography) differ in *special populations* (e.g., women, those with comorbidities, the elderly)?

5. What is the *cost-effectiveness* of noninvasive cardiac anatomic or functional imaging modalities (CCTA, stress nuclear imaging, stress echocardiography) for clinical outcomes?

1.4 Key Considerations Highlighted by Clinical Experts: Cardiac Imaging for CAD (symptomatic patients with suspected or known CAD)

1.4.1 Interventions

The use and complexity of noninvasive cardiac imaging has expanded substantially in the past three decades. Despite numerous advances in the technical performance of various cardiac imaging modalities, the precise role(s) of some of these tests and when to use them remains unclear. There is lack of consensus and some controversy across the clinical community with regard to the optimal noninvasive imaging approach(es) for evaluating patients with symptoms of ischemic heart disease, particularly in patients with low to intermediate pre-test risk for CAD.[221] Some clinicians suggest that

there is overuse of such imaging and note that inappropriate cardiac stress tests in particular costs the U.S. health care system as much as one half a billion dollars each year and expose patients to unnecessary radiation.[206] In contrast, some clinicians suggest that imaging tests may assist with risk stratification and initiation of appropriate medical therapy. Many clinicians question whether noninvasive imaging is necessary at all, in patients who are at very low, low or even intermediate risk of CAD. In these populations, a large number of false positive tests are generally seen which may lead to additional testing and clinical evaluation and/or initiation of unnecessary or inappropriate treatment. In addition, many clinicians cite lack of evidence that testing in these populations leads to better clinical outcomes such as myocardial infarction. In general, appropriate use criteria indicate that imaging tests in populations with low pretest CAD probability presenting with non-acute chest pain, interpretable ECG and ability to exercise are rarely appropriate or use may be uncertain.[259]

In addition to the question of whether *any* testing is needed in patients with low to intermediate CAD risk, there continues to be controversy regarding whether anatomic tests such as CCTA or functional tests such as stress ECG, stress echocardiography or stress nuclear imaging should be the initial test for evaluating patients for suspected or known CAD or those with suspected ACS. While anatomic tests allow for visualization of coronary artery obstruction, the presence of obstruction does not always correspond to patient symptoms and does not provide information on the impact of the obstruction on myocardial function. Acute MI frequently occurs in patients without prior obstructive plaque.[206] Stress testing provides information on the functional impact of obstruction on the myocardium when hemodynamically significant stenosis is present but does not provide direct visualization of plaque (obstructive or not).[206] CCTA is the primary noninvasive imaging test that is used to specifically evaluate coronary anatomy. The primary functional *imaging* tests used to diagnose CAD are stress echocardiography and stress nuclear imaging via SPECT and less commonly, PET.

The choice of which test(s) to use for the evaluation of CAD is a function of historical practice, institutional availability, local expertise to perform and interpret exams and reimbursement. Each test has its proponents, pros and cons. All require substantial expertise for performance and interpretation; thus, the accuracy of the test will vary according to technical and reader expertise.

Stress ECG (exercise treadmill testing, ETT) has been used for decades to evaluate possible ischemic heart disease due to coronary artery obstruction and remains a common initial functional test in many settings. It has the advantages of being widely available, portable, relatively easy and quick to perform and interpret and is inexpensive. Changes on the electrical signals identified with ECG however, may not be apparent unless there is substantial ischemia (or infarction) due to obstruction of the coronary arteries and does it not provide visualization of the heart. None-the-less it is often the first test considered and may be standard of care in many settings. It is one of the functional comparators described in studies of CCTA, nuclear stress testing and stress echocardiography included in this report.

Stress echocardiography has also been used for decades to image and evaluate changes in wall motion due to myocardial ischemia (or infarction) induced when stress via exercise or pharmacologic agents is applied, thus providing functional assessment of impact of obstruction on cardiac function and anatomy. Changes in wall motion are seen earlier in a patient's clinical course if ischemia is present compared with electrical changes. Echocardiography may also provide valuable information regarding the integrity of

various cardiac structures (e.g., papillary muscle and related valve function) that may have been impacted by CAD. Stress echocardiography is widely available, portable, and relative to other imaging modalities for CAD, relatively inexpensive and does not involve ionizing radiation. Stress echo may be difficult to perform and interpret in obese patients or those with pulmonary disease. It is operator dependent and requires substantial expertise for comprehensive, accurate interpretation.

Nuclear stress testing via SPECT or PET, (often collectively referred to as myocardial perfusion imaging) also provide functional information via evaluation of cardiac wall motion and function. Both require the use of radioactive tracers in addition to pharmacologic stress agents and involve specialized equipment which may not be readily available in smaller clinical settings. SPECT is most commonly used.

PET is less commonly used largely due to its availability outside of larger institutions coupled with equipment reliability and maintenance issues. Both require expertise for comprehensive, accurate interpretation.

CCTA is used to evaluate coronary artery anatomy and visually estimate the amount of coronary artery obstruction. Its use has become more common in the past 15 to 20 years as the technology has advanced, including use of methods for reducing radiation exposure. Advantages include CCTA's ability to rapidly visualize coronary obstruction and presence of plaque in the vessels. As with SPECT and PET, CCTA involves radiation exposure and requires specialized equipment. In addition to potential concerns regarding radiation exposure, particularly if contrast is used, image artifacts in patients with substantial coronary artery calcium may render images uninterpretable. A certain level of expertise is required for interpretation.

Although a number of RCTs comparing CCTA with functional testing have been conducted in the past decade in particular, as previously mentioned, there is lack of consensus and some controversy across the clinical community with regard to the optimal noninvasive imaging approach(es) for evaluating patients with symptoms of ischemic heart disease, particularly in patients with low to intermediate pre-test risk for CAD.[221] This may be part due to somewhat conflicting results across trials on the impact of CCTA compared with functional testing on clinical outcomes, referral for ICA, diagnosis of new CAD and impact on treatment decisions. Proponents of the CCTA approach cite reduced myocardial infarctions and the ability to introduce preventative medical therapy as the advantages of it.[154] In particular, many feel that the predictive values of CCTA can reduce unnecessary downstream testing.[154] However, the 2017 meta-analysis referenced above found that CCTA leads to an increase in downstream invasive procedures. This systematic review and meta-analysis of trials published through 2017, found that CCTA, when compared to functional stress testing, may reduce the incidence of myocardial infarction but had no significant impact on death or cardiac hospitalization.[73] One included trial, the SCOT-HEART was the main driver for the reduction in myocardial infarctions.[215] In this trial, 85% of patients in the CCTA arm received functional stress testing. When it was removed from the analysis, the difference in myocardial infarctions was no longer significant. The same review found that CCTA increases rates of invasive coronary angiography and coronary revascularization, as well as new coronary artery disease diagnoses and new prescriptions for aspirin and statin medications compared with functional testing.

One primary disadvantage of CCTA is that it does not provide functional information on the impact of the hemodynamic significance of obstruction. Clinicians may therefore also order one of the functional tests previously described for further clinical decision making, including the need for referral to ICA. Recently, studies have evaluated the use of FFR derived from CCCT data (FFRct) and CT perfusion (CTP), which uses pharmacologic stress during CT to evaluate the hemodynamic impact of obstruction to complement anatomic visualization. These adjuncts to CCTA are not widely used currently and their role in routine evaluation of CAD is not established. Limited clinical studies of these have evaluated the incremental value of adding them to CCTA and have been conducted in highly specialized settings. Overall, both FFRct and CTP have showed better accuracy than CCTA alone but have low overall positive predictive value[46]; accuracy is impacted by CAD prevalence and pre-test probability. With regard to FFRct, only one device/analysis method, the HeartFlow is currently commercially available and FDA approved (510K) for use. It uses CTTA imaging data that are transferred to HeartFlow, Inc. a sole vendor, for analysis. This may limit the utility of this technology. Concerns regarding the diagnostic accuracy of FFRct (including the number of false positives), potential higher use of ICA when used as a substitute for planned noninvasive cardiovascular testing and limited evidence of clinical utility or impact on clinical outcomes have been noted in a recent review.[100] In addition, concerns regarding timely reporting of results in an acute care setting have been raised. A recent study evaluating a strategy of CCTA with selective FFRct in stable outpatients reported no difference in cost or clinical outcomes compared with standard care.[44] (This study did not meet the inclusion criteria for this HTA.) Anecdotally, it may be used in low-risk patients, particularly women, who many clinicians feel should not be tested. This may be of concern as middle-aged women may be at higher risk of radiation induced cancers.

CT myocardial perfusion imaging evaluates the impact of epicardial and microvascular disease on myocardial blood flow. There are limitations to its use including the need for extra time to prepare for and perform stress imaging in addition to the CT anatomic imaging, timing the use of pharmacologic stressors as well as additional contrast and radiation exposure that are involved.

1.4.2 Costs

Stress ECG is the least costly of the primary tests that are used to evaluate symptomatic patients for CAD. With regard to noninvasive imaging, the least expensive is stress echocardiography. CCTA is slightly less expensive than SPECT. In addition to costs related to primary testing, the costs of any additional downstream testing needed to follow-up inconclusive tests, false positives, incidental findings and treatments need to be considered. The choice of test is also influenced by reimbursement.

1.4.3 Patient considerations

The value of doing a test is related to the pre-test likelihood of disease and the extent to which a test helps confirm or rule out a given diagnosis. The pre-test likelihood of CAD is largely based on sex, age, type of chest pain as well as other symptoms and factors. This is important when considering use of a diagnostic test and in comparing the results of studies validating diagnostic tests. Predictive values are influenced by the pre-test probability of disease. Cardiac imaging in patients who are asymptomatic is

not routinely done or considered appropriate by many clinicians, evidence-based clinical guidelines and recent USPSTF evaluations and guidelines.

Evaluation of patient pre-test CAD probability has traditionally been based on the work of Diamond and Forrester[55], however a wide variety of other methods have been used and proposed. The HEART ((History, Electrocardiogram, Age, Risk factors, Troponin) methods is frequently used in emergency departments to triage patients presenting with acute chest pain or suspicion of acute coronary syndrome and determine next steps for testing and care.[16,219]

CCTA and nuclear stress testing are noninvasive imaging tests, they do, however, expose the patient to ionizing radiation. Given the cumulative nature of radiation exposure, consideration of patient age, habitus, and other factors need to be weighed in considering the types and sequences of tests. For CCTA since scanning includes not only the coronary arteries but surrounding structures as well, potential abnormalities in structures other than the coronary arteries with CCTA and heart might be observed, and further evaluation may be required. The costs and implications of incidental findings should be considered.

A recent CADTH rapid report on patient and caregiver perspectives on advanced cardiac imaging suggest that patient-provider communication needs to extend beyond the general benefits and risks of scanning to include information about the processes and pathways of attending the scan, why they are undergoing such imaging, why it is important and what they can expect from the process.[231]

1.4.4 Professional considerations

The primary goal of doing testing is to provide information on the need (or lack thereof) for initiating appropriate treatment. In many instances, guideline directed medical therapy and lifestyle change recommendations serve as the primary recommendations in patients with low to intermediate risk of CAD. Recent studies suggest that for patients at low to intermediate risk, results may be similar for guideline directed medical therapy and PCI. The local availability of testing and expertise in preforming and interpreting various types of non-invasive imaging need to be considered.

1.4.5 Ethical considerations

Although CCTA and nuclear stress testing are noninvasive tests, they do expose the patient to ionizing radiation, a factor which clinicians need to consider and put in the context of other tests that may be part of the clinical pathway which also may use ionizing radiation. Radiation accountability frameworks have been recommended to promote shared decision making with patients and drive appropriate imaging utilization.[62] There is also lack of consensus regarding how to best handle interpretations and follow-up of non-emergent incidental findings that are frequently seen particularly with CCTA.[24,124,125]

These factors should be considered when weighing the benefits, risks and costs need to be discussed with the patient.

1.5 Outcomes Assessed

The primary clinical outcomes of interest for this report are listed below.

- Myocardial infarction*
- All-cause mortality*
- Cardiac death*
- Safety/adverse events*

The clinical management outcomes of interest for this report include:

- Referral for additional testing (ICA or noninvasive imaging)*
- Referral for treatment (revascularization)*
- Changes in medication therapy
- Hospitalizations or ED visits

Other outcomes reported included, major adverse cardiac events (MACE), other cardiac events as reported (e.g., cardiac arrest, unstable angina, stroke, cerebrovascular accident), the Seattle Angina Questionnaire (SAQ), validated health-related quality of life measures, and length of hospital stay.

Outcomes are detailed in the evidence tables in the appendices and/or the body of the report.

Strength of evidence was assessed only for the outcomes with an asterisk above.

1.6 Washington State Utilization Data

1.6.1 Population

Administrative claims and encounter data for coronary computed tomography angiography (CCTA), stress nuclear imaging, and stress echocardiography from the following Washington State health programs were assessed: the Public Employees Benefit Board Uniform Medical Plan (PEBB/UMP), Medicaid managed care (MC) and fee-for-service (FFS), and the Department of Labor and Industries (L&I) Workers' Compensation Plan.

The assessment includes final paid and adjudicated claims and encounters. Denied claims or rejected encounters are excluded. Individuals that were dually eligible for both Medicare and Medicaid are excluded from the Medicaid program analysis. The PEBB/UMP experience includes claims for non-Medicare services.

1.6.2 Noninvasive cardiac imaging procedures

The assessment includes only procedures and services specific to noninvasive cardiac imaging with a date of service between January 1, 2017, and December 31, 2020. Analysis does not include additional services associated with imaging procedures.

Claims and encounters with qualifying procedures or services according to current procedural terminology (CPT) code or level II healthcare common procedure coding system (HCPCS) during the period were extracted for analysis.

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Table 1. Utilization of noninvasive cardiac imaging, by state health program (2017-2020)

Medicaid	2017	2018	2019	2020	Total (unique)
Fee for service (FFS)					
Individuals with at least one noninvasive cardiac imaging-related procedure	981	940	900	670	**3,248**
Female, count	412	416	394	267	**1,393**
Male, count	569	524	506	404	**1,856**
Amount paid (estimated), noninvasive cardiac imaging	$509,656	$470,920	$455,855	$335,634	**$1,772,065**
Individuals	981	940	900	670	**3,248**
Average payments per individual	$533	$512	$515	$528	**$561**
Managed care (MC)					
Individuals with at least one noninvasive cardiac imaging	10,587	10,440	9,974	8,557	**36,263**
Female, count	5,474	5,365	5,016	4,297	**18,575**
Male, count	5,115	5,076	4,959	4,260	**17,694**
Amount paid (estimated), noninvasive cardiac imaging	$4,979,782	$4,414,031	$4,158,069	$3,627,905	**$17,179,787**
Individuals	10,314	10,211	9,772	8,297	**35,383**
Average payments per individual	$411	$333	$387	$371	**$410**
Public Employees Benefit Board Uniform Medical Plan (PEBB/UMP)					
Individuals with at least one noninvasive cardiac imaging-related procedure/service	6,175	6,227	6,174	5,758	**21,426**
Female, count	2,973	3,029	2,875	2,805	**10,506**
Male, count	3,202	3,198	3,299	2,953	**10,920**
Amount paid, noninvasive cardiac imaging	$3,607,911	$3,638,766	$3,698,590	$3,739,730	**$14,684,997**
Individuals	6,175	6,227	6,174	5,758	**21,426**
Average payments per individual	$598	$596	$613	$669	**$701**

Washington State Department of Labor and Industries (L&I)					
Individuals with at least one noninvasive cardiac imaging-related procedure/service	74	67	60	51	**249**
Female, count	13	NR	11	NR	**41**
Male, count	61	57	49	44	**208**
Amount paid, noninvasive cardiac imaging	$49,611	$43,603	$36,891	$38,631	**$168,735**
Individuals	74	67	60	51	**249**
Average payments per individual	$699	$692	$683	$788	**$718**
Washington State – Combined Medicaid, UMP, L&I					
Individuals with at least one noninvasive cardiac imaging-related procedure/service	17,817	17,674	17,108	15,036	**61,186**
Female, count	8,872	8,820	8,296	7,376	**30,515**
Male, count	8,947	8,855	8,813	7,661	**30,678**
Amount paid, noninvasive cardiac imaging	$9,146,960	$8,567,320	$8,349,405	$7,741,900	**$33,805,584**
Amount paid, by modality and procedure code					
SPECT	$5,500,304	$5,162,988	$4,886,019	$4,606,205	**$20,155,516**
Stress Test	$2,230,498	$2,058,511	$1,965,027	$1,821,426	**$8,075,462**
Stress Echocardiography	$945,737	$900,264	$954,111	$965,075	**$3,765,187**
PET	$180,756	$153,821	$223,613	$70,408	**$628,598**
CCTA	$133,228	$146,242	$188,466	$151,934	**$619,870**
Other Noninvasive Cardiac Imaging	$149,952	$134,222	$117,250	$125,351	**$526,775**
General Nuclear Imaging	$6,485	$11,272	$14,919	$1,500	**$34,176**

Data notes: Annual members for Medicaid excludes members that are dually eligible for Medicaid and Medicare. NR = not reported; small numbers suppressed to protect patient privacy. Managed care amount paid reflects an estimate of the amount paid for the procedure. UMP data does not reflect patient cost share. Individuals who had a procedure in more than one year are only counted once in the "Total" summary. Amounts paid of $0 were excluded from amount paid table value calculations. PET codes revised in 2020 were not included in utilization data; radiopharmaceutical codes for PET scans were not included.

Table 2. Demographics of Medicaid beneficiaries with at least one noninvasive cardiac imaging procedure, SFY 2017-2020

Age	Total (count)
20 years and below	452
21-44 years	10,204
45 years and above	28,865
Total	**39,384**

Table 3. Codes and cost by HCPCS/CPT code (maximum allowable), by state health program and setting

Code	Description	Medicaid FFS		L&I	
		Non-facility	Facility	Non-facility	Facility
75571	Computed tomography, heart, without contrast material, with quantitative evaluation of coronary calcium	$61.60	EAPG pricing	$199.40	$199.40
75572	Computed tomography, heart, with contrast material, for evaluation of cardiac structure and morphology (including 3D image post-processing, assessment of cardiac function, and evaluation of venous structures, if performed)	$146.21	EAPG pricing	$473.25	$473.25
75573	Computed tomography, heart, with contrast material, for evaluation of cardiac structure and morphology in the setting of congenital heart disease (including 3D image post-processing, assessment of LV cardiac function, RV structure, and function and evaluation of venous structures, if performed)	$196.41	EAPG pricing	Not covered	Not covered
75574	Computed tomographic angiography, heart, coronary arteries and bypass grafts (when present), with contrast material, including 3D image post-processing (including evaluation of cardiac structure and morphology, assessment of cardiac function, and evaluation of venous structures, if performed)	$211.41	EAPG pricing	$684.30	$684.30
78451	Myocardial perfusion imaging, tomographic (SPECT) (including attenuation correction, qualitative or quantitative wall motion, ejection fraction by first pass or gated technique, additional quantification, when performed); single study, at rest or stress (exercise or pharmacologic)	$202.01	EAPG pricing	$653.87	$653.87
78452	Myocardial perfusion imaging, tomographic (SPECT) (including attenuation correction, qualitative or quantitative wall motion, ejection fraction by first pass or gated technique, additional quantification, when performed); multiple studies, at rest and/or stress	$282.01	EAPG pricing	$912.83	$912.83

	(exercise or pharmacologic) and/or redistribution and/or rest reinjection				
78453	Myocardial perfusion imaging, planar (including qualitative or quantitative wall motion, ejection fraction by first pass or gated technique, additional quantification, when performed); single study, at rest or stress (exercise or pharmacologic)	$181.81	EAPG pricing	$588.49	$588.49
78454	Myocardial perfusion imaging, planar (including qualitative or quantitative wall motion, ejection fraction by first pass or gated technique, additional quantification, when performed); multiple studies, at rest and/or stress (exercise or pharmacologic) and/or redistribution and/or rest reinjection	$261.01	EAPG pricing	$844.86	$844.86
78459	Myocardial imaging, positron emission tomography (PET), metabolic evaluation	$816.02	EAPG pricing	$2,937.24	$2,937.24
78466	Myocardial imaging, infarct avid, planar	$120.01	EAPG pricing	$388.44	$388.44
78468	Myocardial imaging, infarct avid, planar	$115.41	EAPG pricing	$373.55	$373.55
78469	Myocardial imaging, infarct avid, planar	$134.01	EAPG pricing	$433.76	$433.76
78472	Cardiac blood pool imaging, gated equilibrium; planar, single study at rest or stress (exercise and/or pharmacologic), wall motion study plus ejection fraction, with or without additional quantitative processing	$136.41	EAPG pricing	$89.99	$89.99
78473	Cardiac blood pool imaging, gated equilibrium; multiple studies, wall motion study plus ejection fraction, at rest and stress (exercise and/or pharmacologic), with or without additional quantification	$172.81	EAPG pricing	$559.35	$559.35
78481	Cardiac blood pool imaging (planar), first pass technique; single study, at rest or with stress (exercise and/or pharmacologic), wall motion study plus ejection fraction, with or without quantification (single/multiple)	$105.21	EAPG pricing	$340.53	$340.53
78483	Cardiac blood pool imaging (planar), multiple first pass study at rest and stress, and requires two injections of appropriate radiopharmaceutical agent(s).	$144.01	EAPG pricing	$466.13	$466.13
78491	Myocardial imaging, positron emission tomography (PET), perfusion; single study at rest or stress	$1,502.51	EAPG pricing	$3,066.34	$3,066.34
78492	Myocardial imaging, positron emission tomography (PET), perfusion; multiple studies at rest and/or stress	$1,510.11	EAPG pricing	$3,097.99	$3,097.99
78494	Diagnostic nuclear medicine procedures on the cardiovascular system	$135.21	EAPG pricing	$437.64	$437.64

78496	Diagnostic nuclear medicine procedures on the cardiovascular system	$25.40	EAPG pricing	$82.22	$82.22
78499	Unlisted cardiovascular procedure, diagnostic nuclear medicine	By Report	EAPG pricing	By Report	By Report
93015	Cardiovascular stress test using maximal or submaximal treadmill or bicycle exercise, continuous electrocardiographic monitoring, and/or pharmacological stress; with supervision, interpretation and report	$41.40	Not covered	$134.01	$134.01
93016	Cardiovascular stress test using maximal or submaximal treadmill or bicycle exercise, continuous electrocardiographic monitoring, and/or pharmacological stress; supervision only, without interpretation and report	$12.80	Not covered	$41.43	$41.43
93017	Cardiovascular stress test using maximal or submaximal treadmill or bicycle exercise, continuous electrocardiographic monitoring, and/or pharmacological stress; tracing only, without interpretation and report	$20.00	EAPG pricing	$64.74	$64.74
93018	Cardiovascular stress test using maximal or submaximal treadmill or bicycle exercise, continuous electrocardiographic monitoring, and/or pharmacological stress; interpretation and report only	$8.60	Not covered	$27.84	$27.84
93350	Echocardiography, transthoracic, real-time with image documentation (2D, with or without M-mode recording), during rest and cardiovascular stress test using treadmill, bicycle exercise and/or pharmacologically induced stress, with interpretation and report	$111.61	EAPG pricing	$361.25	$361.25
93351	Echocardiography, transthoracic, real-time with image documentation (2D), includes M-mode recording, when performed	$138.21	EAPG pricing	$447.35	$447.35
93352	Echocardiography procedures	$19.80	Not covered	$64.09	$64.09

Data notes: Medicaid FFS from 10-1-2020 Physician-Related Services Fee Schedule and OPPS Fee Schedule (accessed October 1, 2021; webpage). L&I from 2020 provider fee schedule (accessed October 1, 2021). PEBB/UMP fees are confidential and not publicly available (proprietary).

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2 Background

2.1 Nature and Burden of Disease

Coronary artery disease (CAD), also referred to as coronary heart disease (CHD) or ischemic heart disease (IHD), is a leading cause of death for both men and women in the United States and is the most common form of cardiovascular disease. The public health and economic burdens of CAD are substantial. It is estimated that around 20.1 million individuals in the United States 20 years or older have CAD, with a higher prevalence among males compared with females aged 60 and older.[251] Centers for Disease Control and Prevention (CDC) reported 690,882 deaths related to heart disease alone in the United States in the year 2020.[9] Estimates also suggest that roughly 720,000 individuals will have a new coronary event annually, and 335,000 individuals will have a recurrent event. Recent trends project an estimated incidence of 805,000 myocardial infarction events (605,000 new attacks, 200,000 recurrent attacks); roughly 21% (170,000 MIs) are estimated to be silent events.[251] Accordingly, CAD is associated with significant health system utilization and associated expenses. According to The National Ambulatory Medical Care Survey (NAMCS), around 11.1 million physician office visits occurred for CAD in 2016, and in 2018, 469,000 visits to the emergency department (ED) were identified as having a primary diagnosis of CAD. As of 2016, health care spending related to CAD was over $89 billion (54% public payer, 42% private payer, 4% out of pocket); around half (50%, or 44.5 billion) was attributed to inpatient care services and 24% (or $21.4 billion) was attributed to ambulatory care services. Selecting the appropriate assessment, testing, and treatment approach for an individual with suspected or known CAD has the potential to improve patient outcomes, patient satisfaction and optimal use of health system resources.

CAD is a disease of the blood vessels that supply the heart muscle. Atherosclerosis is the most common underlying cause of CAD and is the result of plaque buildup on artery walls. Plaque is a sticky, fatty deposit comprised of cholesterol and other cellular waste products. The buildup of plaque may partially or completely block blood flow in the coronary arteries via two primary mechanisms: 1) progressive narrowing of the vessel lumen and (2) thrombotic occlusion of the artery wherein the hard surface of the plaque tears away exposing inner fatty prothrombotic and platelet activating components at the site creating enlargement of the obstruction. The resulting decrease in blood flow can be chronic or acute and leads to a deficiency in the amount of oxygen and nutrients getting to the myocardium[50], which subsequently impairs the heart's ability to supply oxygenated blood to the body either at rest or during exertion. Atherosclerosis may lead to disruptions in normal vascular function, i.e., the ability to relax and constrict the artery walls or the microvasculature. Vascular dysfunction resulting from atherosclerosis can occur in instances of significant plaque buildup but may also occur in the absence of significant plaque in individuals with atherosclerotic risk factors or comorbidities such as diabetes, history of smoking, and sedentary lifestyle. Atherosclerotic plaque occurs commonly and is asymptomatic for years; symptoms usually don't occur until the artery is blocked by at least half. Most people with plaque will never develop clinical CAD. Ischemia and impaired function may also be present in the absence of observed obstruction on angiography.[103]

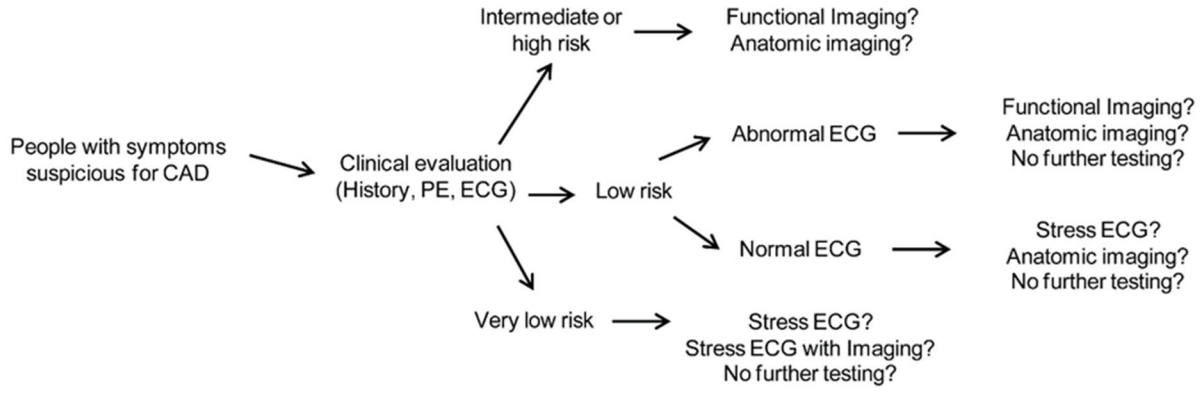
Chest pain (angina) is the most common symptom of obstructive CAD and is the first presenting symptom in most patients. Other symptoms of an acute coronary event related to CAD can include cold sweats, dizziness, light-headedness, nausea or feelings of indigestion, neck pain, shortness of breath, disturbances in sleep, and general weakness; common symptoms of chronic CAD may include shortness of breath with physical exertion, fatigue, and neck pain.[173] Plaque distribution, presence of collateral circulation and degree of vessel narrowing are factors which may influence symptom development and clinical impact of CAD; however, symptoms do not always correlate with lesion severity. For example, patients with obstructive CAD may be asymptomatic for many years (as has been observed in patients with diabetes) or may not present with symptoms until disease has progressed to the stage of heart failure.[118] It is estimated that roughly half of individuals who have a MI and no previous diagnosis of CAD did not report prior symptoms of obstructive CAD.[247] Studies have also shown that common symptoms of obstructive CAD are present in several noncardiac conditions such as gastroesophageal reflux, esophageal spasm, chronic obstructive pulmonary disease, and cervical disc disease, thus they are less reliable predictors of CAD. Non-specific symptoms may promote delayed testing or identification of obstructive CAD. Women and people with diabetes are less likely to experience classic angina, adding to the challenges of early CAD diagnosis in these populations.

2.2 Assessing risk of CAD

When assessing patients presenting with symptoms of CAD, their pretest risk or probability of CAD helps inform the choice and flow of testing. There are many available tools to assess pre-test risk of CAD, but the methods and models used can vary widely. Across included studies for this HTA, a wide variety of methods was used.

The American College of Cardiology (ACC) risk stratification model offers a framework for determining the likelihood that a patient's symptoms are related to obstructive CAD, according to age, sex and presenting symptoms.[71] Other factors, such as comorbid conditions (diabetes, hypertension, dyslipidemia) and the person's health history (smoking, family history of heart disease) may also be considered. A patient's chest pain symptoms are further characterized as typical, atypical, or non-anginal.[230] Risk groups are defined as low (<10%), intermediate (10% to 90%), and high (>90%). Patients assessed to be in the low to intermediate risk group comprises a broad spectrum of patients for whom a noninvasive test is usually recommended. Diagnostic challenges for intermediate risk patients will be discussed more the following section.

Figure 1. Overarching conceptual flow for initiating noninvasive testing based on risk assessment following initial clinical evaluation



Evaluation of patient pre-test probability of CAD has traditionally been assessed according to the Diamond and Forester method[55], a validated risk prediction tool. Recent studies suggest the model may overestimate pre-test risk of CAD among low-risk patients.[38] New prediction tools and methods have since emerged to address concerns of applicability and relevance to certain populations and settings; however, they may not be commonly used in clinical practice and may not prevent unnecessary invasive treatment and testing.[42,150] An assessment of patient history and physical evaluation remains the most routinely used to determine a patient's risk of CAD and is most cost effective. In accordance with the core factors identified in Diamond and Forester and current guidelines, clinicians typically consider patient age, sex, and current symptoms (such as type of chest pain) when assessing pre-test risk of CAD. Recent studies suggest that clinical discretion to defer testing among patients with low pre-test risk of CAD may decrease unnecessary studies and downstream treatments.[221]

In the emergency department setting, the HEART risk score (History, Electrocardiogram, Age, Risk factors, Troponin) is frequently utilized to objectively assess pre-test probability of CAD to support clinical decision making. The AHA recommends this assessment approach in the ED; however there remains uncertainty about the ideal thresholds to define low, moderate, and high pre-test risk to prevent unnecessary testing and invasive procedures.[219] In this setting, clinician assessment of type of chest pain is often a primary factor when determining the course of care, if electrocardiography (ECG) or troponin test results are unclear; however, this subjective assessment may not be accurate in correctly distinguishing patients for next line testing.[12,28,32] Other risk assessment and clinical decision-making tools have been developed for patients presenting with acute coronary syndromes (ACS) (e.g., Global Registry of Acute Coronary Events [GRACE], thrombolysis in myocardial infarction [TIMI] risk scores), but evidence suggests they may not prevent unnecessary care and may increase early invasive testing and treatment.[12,39]

The effectiveness of non-invasive imaging tests is influenced by patient pretest probability/underlying disease prevalence which impacts test performance for measures that are influenced by disease prevalence. The choice of test is influenced by pre-test probability. For example, in patients at high risk of CAD invasive testing is typically the approach taken. In contrast, Anecdotally, in patients with a low

pre-test probability of CAD, CCTA may be more likely to be used, while in patients with intermediate to high pre-test probability, stress echo or SPECT may be more frequently used and be more predictive of CAD presence, based on general precepts from the ACCF/AHA 2012 guideline. For any test, in patients with low pre-test probability of CAD, the number of potential false positive results necessitating further follow-up needs to be weighed against the potential for accurate detection of CAD. In some included RCTs, the frequency of MI and death was low, reflecting the low pre-test probability in these trials. In these instances, the benefit of testing may be unclear as the event rate in a low-risk population would likely be similar whether or not testing was employed.

2.3 Diagnosis of CAD

Accurate and early assessment of patients with symptomatic CAD is important for risk stratification and initiation of appropriate treatments to reduce morbidity and mortality. Noninvasive techniques used to diagnose CAD fall into two general categories, those that evaluate the anatomical aspects of vessel occlusion and those that evaluate the impact of occlusion on cardiac function. Each has strengths and limitations. Noninvasive anatomic tests provide information on location and extent of blockage and include coronary CT angiography (CCTA) and cardiac magnetic resonance imaging (CMRI). Functional tests allow assessment of whether symptoms are correlated with narrowing leading to ischemic areas and include exercise ECG, exercise/pharmacologic stress echocardiography, exercise/pharmacologic cardiac nuclear imaging with single-photon emission computed tomography (SPECT) or positron emission tomography (PET). There has been recent interest in using pharmacologic stress with magnetic resonance imaging (MRI) or computed tomography (CT perfusion imaging) and in determining fractional flow reserve (FFR) with CT. The choice of testing is dependent on a variety of patient and other factors, particularly in patients with stable CAD. The patient's pre-test probability of CAD in addition to accuracy of the test and the likelihood that test results would change management and lead to better outcomes are important considerations, as outlined above. Clinical decision-making regarding choice of test(s) needs to include consideration of the potential for additional/downstream testing, availability of other tests, cumulative radiation exposure and how results will inform appropriate management strategies and lead to improved outcomes while avoiding risks of testing such as additional radiation, false positives and incidental findings. There remains a lack of consensus regarding a single testing strategy or sequence of testing for the diagnosis of CAD, particularly for those at low to intermediate pre-test risk.[19] Low to intermediate pre-test risk as defined in the ACC/AHA guidelines (10% to 90%) may overestimate pre-test risk and observed prevalence has been shown to be much lower in real world clinical setting.[38] It also constitutes a very wide range of CAD risk. There is also recent evidence that suggests guidelines that focus on symptomology at presentation, as opposed to guidelines that take a more formal risk-based assessment, may safely characterize as low risk and prevent unnecessary testing.[5]

Historically, in the outpatient setting, the exercise stress test is used as a gatekeeper to more invasive cardiac testing, though the evidence is unclear on the prognostic benefit for patients with suspected CAD.[206,222] With the advent of low risk, non-invasive cardiac tests, there is a debate about the optimal diagnostic testing strategies for patients with suspicion of CAD[34,201,221] or known CAD. Some experts question the need for testing particularly among low-risk patients. Guidelines and expert opinion are

mixed when it comes to defining the current reference standard among non-invasive cardiac tests.[199,222] ACCF guidelines and ACR AUC recommend that for patients with suspected CAD and stable chest pain who are capable of physical exertion and an interpretable ECG, an exercise stress test with ECG or echocardiogram is the preferred first test among patients with intermediate pre-test probability.[71,222,259] However, NICE updated their guidance in 2016 to remove formal pre-test probability scoring and advised CCTA as the first line diagnostic test for all patients with suspected CAD presenting with chest pain or non-anginal pain with an abnormal electrocardiogram, prior to moving to functional testing as needed.[129] The 2019 ESC guidelines recommend non-invasive functional imaging, or CCTA, as the first line test for suspected CAD; like ACCF guidelines, if the first line CCTA test is equivocal, then functional imaging is recommended.[132] For patients that present to the ED with suspected ACS, CCTA has emerged as the predominant test to differentiate patients at high risk of a serious cardiovascular event.[12,18] High sensitivity troponin assays are increasingly used as a first line noninvasive test to rule out an acute coronary event. The utilization of biomarkers such as troponin may have implications for if and when noninvasive imaging, such as CCTA, is utilized in this setting.[260]

Exercise electrocardiogram treadmill testing (ETT) and the imaging tests CCTA, stress nuclear imaging and stress echocardiography have become established as diagnostic tests for CAD. The focus of this HTA is on the imaging tests and will not include ETT, except as a comparator test. As established testing modalities, the focus will be on evaluating their impact on clinical decision making for directing management that leads to improved patient outcomes. This HTA does not evaluate specific sequences of tests or incremental benefits of adding a specific test to another given the lack of consensus across the cardiology community and vagueness of evidence-based clinical guidelines.

2.4 Technologies and interventions

Given the invasive nature and risks associated with coronary angiography, non-invasive methods of assessing presence of CAD are important. All noninvasive methods have strengths and limitations. There is a continued debate with respect to the roles of various non-invasive tests in both ED and outpatient settings, such as which test should be the first-line test, and which test to use subsequently based on findings of the primary test. In the ED, the goal is to quickly identify patients without CAD who can be discharged, which reduces the need for ICA referral and observation. In an outpatient setting, the focus is on appropriate testing of patients presenting with stable, non-emergent symptoms of suspected CAD. Among patients presenting with stable CAD, there is no definitive algorithm for determining which imaging test to use based on patient outcomes and costs; variations in guidelines present additional complexity for clinical decision making.[250]

2.4.1 Invasive coronary angiography

ICA (also called coronary catheterization) is a 20-to-30-minute procedure where X-rays are taken of the heart's arteries while radiopaque contrast is injected simultaneously via catheter inserted in the wrist or groin artery. ICA provides information about the anatomy of the coronary arteries and size and location of obstructions in the lumen, as well as areas that may be stenotic. This information, taken together, helps to quantify the degree of disease that may be present. When determining a diagnosis of CAD,

thresholds of anywhere from ≥50% to ≥70% occlusion have been used. The rate of nondiagnostic or indeterminate studies from ICA is estimated to be 10%.[27] Potential harms include exposure to radiation, allergic reaction to contrast dye, bruising at site of catheter insertion; major harms are rare but may include arrythmias, blood clots, heart attack or stroke, and very rarely, death.

As stated previously, the advantage of ICA is that it provides accurate information about blockages in the heart's arteries and help identify reasons why the heart may not be functioning correctly. Historically, ICA has been considered the standard reference diagnostic test for anatomic CAD. However, an increasing body of evidence suggests it is an imperfect diagnostic standard. While size and location of plaques are visible, plaques with characteristics that may indicate high risk for future coronary events are not evident when reviewing images obtained from ICA, limiting the prognostic value of the test.[230] Only about 41% of patients undergoing elective procedure of catheter-based coronary angiographies are diagnosed with obstructive CAD.[202] A long-known limitation of the test is in the interpretation of results, due to variation in interobserver and intraobserver findings.[49,214,265] One study however suggests substantial interobserver agreement based on per-segment analysis.[31] There may be issues with accuracy, as evidence has shown that for lesions with less than 60% percent stenosis there may be significant under or over estimation of the severity of lesions.[242,254] Toth et al. similarly found the 50% threshold for the left main region significantly underestimated legion severity when compared to fractional flow reserve.[242] While there have been technological advances for decreasing radiation contrast toxicity and improving effective diagnosis with ICA in the past few decades, potential sources of error due to the equipment operation, technical interpretation, and natural biological fluctuations that may occur in response to the dye or during the procedure, remain. As noted elsewhere, expertise for performance and interpretation is important with all tests for CAD.

2.4.2 Coronary Computed Tomography Angiography

CCTA is a noninvasive, relatively quick anatomic imaging test that obtains x-ray images of the heart. Using contrast dye (iodine-based), images taken by CCTA will visualize the structure of the heart and any obstructive disease present in the heart's anatomy. Many hospitals have access to the machine and complimentary software packages used to process images and state of the art machines have a 64-slice or greater scanner. CCTA is typically used to rule out CAD diagnosis in patients with chest pain and low pretest probability of disease due to its perceived high negative predictive value and high sensitivity. It is also recommended for patients with atypical symptoms, with nondiagnostic results of a stress test or at high risk of catheterization. Abnormal findings on CCTA are defined as any irregularities of the lumen, which will determine next steps in prevention of disease progression and other possible disease sequalae. High risk findings on CCTA are typically defined as ≥50% stenosis in the left main region, proximal LAD stenosis ≥70%, or 3 vessel disease. CCTA is also useful for identifying causes of chest pain unrelated to heart function. The rate of nondiagnostic or indeterminate studies from CCTA imaging is estimated to be 2%.[27]

Key disadvantages to CCTA include exposure to radiation, moderate specificity (60-80%), and issues around diagnostic image quality.[52] There are quantification challenges due to cardiac motion artifact, "bloom artifact" due to calcification, and uncontrolled or irregular heart rate. Optimizing temporal

resolution can be challenging. In addition, distal vessels may be difficult to visualize. Furthermore, CCTA as a standalone test will not confirm ischemia. Regarding harms, aside from exposure to low levels of radiation during the procedure, some patients may experience allergic reaction to the contrast dye, and additional consideration is taken for patients with impaired renal function. Incidental findings on CCTA are not uncommon and can sometimes lead to unnecessary worry for the patient.

2.4.2.1 Fractional flow reserve (FFR) with coronary computed tomography angiography (CTTA)

FFR CT combines the anatomic coronary CT test with a functional test of coronary artery blood flow, providing both a quantification of anatomical obstruction and a calculation of pressure and flow for all coronary artery branches. FFR is defined as the ratio of maximum flow in a stenotic artery to maximum blood flow if the same artery were normal. Thus, the pressure measurements at the distal vessels illustrate the cumulative loss of pressure or blood flow and the effect of any diseased tissue near where the measurement is taken.[178] This relatively new combination approach requires previously acquired CT images of good image quality and there remains uncertainty about the extent to which biological factors affect test accuracy.[67] Currently, the only Food and Drug Administration (FDA) approved device/software for measuring FFR during either ICA or CCTA is Heart Flow. Information on the diagnostic accuracy of FFR CT can be found in the Contextual Question section of this report.

2.4.2.2 CT perfusion imaging

Like FFR CT, stress myocardial computed tomography perfusion (CTP) is a novel examination that provides both anatomic and physiological information (i.e., myocardial perfusion). CTP assesses blood flow distribution to the different regions of the myocardium at rest and after stress by using coronary vasodilator agents (adenosine, dipyridamole, or regadenoson), similarly to other non-invasive imaging techniques such as nuclear imaging myocardial perfusion imaging (MPI).[170] CTP utilizes iodinated contrast which attenuates X-rays proportionally to iodine content in tissue. Thus, myocardial perfusion defects can be directly visualized as hypoattenuating or non-enhancing areas containing reduced amounts of contrast material.[78] Information on the diagnostic accuracy of CTP can be found in the Contextual Question section of this report.

2.4.3 Nuclear stress imaging (myocardial perfusion imaging)

Nuclear stress imaging is a functional, non-invasive imaging test that shows how well blood flows through (perfuses) the heart muscle. It can show areas of the heart muscle that aren't getting enough blood flow by evaluating how well the heart muscle is pumping. It does not directly visualize the coronary arteries. This test is often called a nuclear stress test. There are 2 techniques for MPI: SPECT and PET. Both require injection of radioactive tracers (called radionuclides) which transmit radiation, allowing a specialized camera to take images of the heart that can be converted by a computer program for interpretation.

2.4.3.1 Single Photon Emission Computed Tomography (SPECT)

SPECT is a noninvasive nuclear imaging test. After injection of radionuclides (99mTc- sestamibi or 99mTc- tetrofosmin) into the blood, thin slice images of the heart are taken as a camera detects signals from the tracers and a computer program translates this information into 3-D images. Imaging takes about 20 minutes, with the stress imaging (exercise or pharmacologic) occurring 1 hour after the rest study is complete; overall, the rest-stress protocol is typically completed over 3-4 hours and may be completed in one- or two-day protocols. SPECT can show how well blood is flowing to the heart, how well the heart is working, and whether the patient previously experienced a heart attack. Providers can assess the ventricular size and function, wall motion abnormalities, and overall viability of the heart. SPECT can be used to diagnose CAD. It is a preferred approach for patients with left bundle branch block and is useful for patients with poor echocardiography windows. The rate of indeterminate studies from SPECT imaging is estimated to be 6.9%.[27,220] Compared to other noninvasive methods such as ECG, SPECT provides improved sensitivity and specificity. SPECT can also be used to inform decisions about treatment or therapy, based on findings.

Abnormal findings on SPECT are defined as detection of any perfusion defect and any wall motion abnormalities. High risk findings include a perfusion defect impacting ≥10% of heart tissue, more than one perfusion of moderate concern, a large, fixed defect with transient left ventricular dilation or increase in lung to heart ratio, or a stress induced defect of moderate severity with transient ischemic left ventricular dilation or increase in lung to heart ratio. SPECT results can be limited by soft tissue attenuation and motion artifact. SPECT is also limited in the quantification of blood flow since it measures relative flow, as opposed to absolute flow (and may miss three vessel disease). Harms may include exposure to some radiation from radionucleotides.

2.4.3.2 Positron Emission Tomography (PET)

PET is a noninvasive nuclear imaging test. Radionuclides (15O, 82Rb, 13NH3 or 18F- flurpiridaz) are injected into the blood, and a PET scanner will detect the radiation released by the tracer to produce images of the heart.[54] PET scans can identify diseased or damaged tissue, as well as healthy tissue, and assess whether enough blood is flowing through the heart. Scans take about 30-60 minutes, and the full rest-stress protocol may be completed in either 1 or 2 days. PET scans can be used to diagnose CAD and can identify damage to the heart due to heart attack. PET assesses ventricular size and function, as well as ischemia and viability. PET is also used to determine which patients may benefit from PCI, CABG, or another treatment. PET is the preferred approach for assessment of suspected CAD in women and patients who are obese. Abnormal findings on PET are defined as any perfusion defect. High risk findings are defined as a perfusion defect ≥10% of heart tissue, with particular attention to the anterior myocardium. The rate of indeterminate studies from PET imaging is estimated to be 4%.[220]

PET provides a more accurate assessment of blood flow than SPECT, due to measurement of absolute blood flow with trace kinetic modeling and attenuation correction. PET scans also have high image quality, which support clearer interpretation of findings. Regarding disadvantages, PET scans are expensive, and PET scanners are less available than other noninvasive imaging technologies in clinical

settings due to space and storage requirements. PET scans are limited to pharmacologic stress. Harms may include allergic reaction to the radioactive tracers and minimal exposure to radiation. Patients who are claustrophobic may be uncomfortable during a PET scan.

2.4.4 Stress echocardiography

Echocardiography is a noninvasive test that uses high frequency sound waves (i.e., ultrasound), to produce live images of the heart. Stress echocardiography is an established technique for assessing CAD. It evaluates how the well the heart is functioning under stress and is commonly used to identify areas of the heart affected by ischemia; the coronary vessels are not directly visualized, however. Stress can be induced by either exercise (stationary bicycle or treadmill) or pharmacologic agents (dobutamine typically). The major advantages of stress echocardiography are that the test protocol is simple, inexpensive, takes a relatively short amount of time to complete and it does not expose the patient to radiation, unlike other noninvasive imaging techniques. However, it tends to be less sensitive in detecting single vessel disease or mild stenosis since a significant amount of myocardium needs to be affected by ischemia for the test result to be positive; specificity has been, on average, somewhat higher than nuclear cardiology techniques and exercise ECG. Stress echocardiography also requires a high level of expertise to achieve accurate and reproducible results. Interpretation of findings may be limited by image quality, and it does not allow for quantitative analysis.

Abnormal findings on stress echocardiography are defined as new wall motion abnormalities and abnormal left ventricular ejection function during stress. High risk findings include left ventricular ejection function <35% (rest or exercise), wall motion abnormalities that include a minimum of 2 segments that develops with either exercise or pharmacologic stress, more than two segments displaying wall motion abnormalities at heart rate of <120 bpm, or evidence of severe ischemia during the stress test. The rate of nondiagnostic or indeterminate studies from stress echocardiography imaging is estimated to be 15%.[27,98]

2.4.5 Hybrid tests

Diagnostic tests that combined more than one imaging type also were considered if at least one component focused on myocardial perfusion, including PET/CT, and SPECT/CT. All of these tests are performed in conjunction with exercise- or pharmacologically-induced stress.

2.4.6 Harms

Primary harms identified for noninvasive imaging for suspected CAD include radiation exposure, reactions to stressor or contrasts agents used during the imaging test, possibility of incidental findings unrelated to heart disease, and multifaceted effects of downstream testing.

2.4.6.1 Radiation exposure

Radiation exposure is a measure of the quantity of ionization produced in air by photon irradiation. Radiation dose ("absorbed radiation dose") refers to the amount of radiation energy deposited in the human body as a result of exposure to ionization and is typically calculated from the exposure and from estimates of energy absorption per kilograms of body weight.[167]

Medical imaging is the largest controllable source of radiation exposure in the United States.[79] Cardiovascular-related tests and procedures comprise about 40% of all medical radiation exposure.[107] There is conflicting evidence regarding the risk of developing cancer at the levels and types of radiation associated with medical imaging and with the exception of mammography, there is currently no federal regulation of patient radiation dose.[167] Potential benefits and risks, including any related to not performing the test, should be carefully considered before ordering tests that will expose patients to ionizing radiation. Patient-centered shared decision making can prompt a discussion and improve transparency and education related the justification for the test, expected level of exposure to radiation, and steps the laboratory has taken to optimize the radiation dose used.[62]

As cardiac imaging has increased over time, there are concerns about the effects of increased radiation not only on a test-by-test basis, but also in consideration of the cumulative exposure across other tests that may be utilized as part of a patient's course of care. Excluding radiation therapy, the average per capita radiation exposure from medical sources increased 6 times from the period 19080-1982 to 2006.[61,212] In response, the National Council on Radiation Protection issued a report in 2017 indicating that the steep increase in imaging procedures may have plateaued, and that greater awareness of radiation risk may be a factor. However, large scale registries and international studies have shown wide variation in average radiation dose per procedure, indicating at least one area for improvement in and implementation of best practices (e.g., standard reporting, regional diagnostic reference levels) to minimize or reduce radiation exposure.[106]

A variety of factors can affect the radiation dose administered for a given test, including the model of the machine, the length of the scan, the number of scans, if gating is used, x-ray tube potential, tube current-time product, and patient size.[30] The values in the following table (Table 4) are based on literature estimates and are subject to change dependent on the imaging parameters utilized.

Table 4. Overview of radiation exposure ranges*

Radiation Exposure Type		Total Effective Dose (mSv)
Environmental Exposures	Round-trip flight, New York – Seattle	0.06
	Naturally occurring	3/year
	July 1971 lunar landing	5
	Nuclear worker	20
Diagnostic and Procedural Exposures	Echocardiography	0
	CMRI	0
	ECG	0
	Dental CT	0.2
	Mammogram	0.4

Radiation Exposure Type			Total Effective Dose (mSv)
	ICA	Range reported by Einstein 2014	2–20
		Range reported by ACR	1–10 (with or without ventriculography)
		Carpeggiani, 2017†	Mean (SD): 9.64 (9.7)
	CCTA	Range from studies included in Skelly 2016 (AHRQ report)	3.8–15.1
		Range reported in Einstein 2007 and 2014	<0.5–30
		Range reported by ACR	1–30 (using various contrast and dose techniques)
		Range reported by Cerqueira 2010	5–10
		Hirshfeld, 2018 (consensus document)‡	Helical, no tube current modulation: 8.0 to 30
			Helical, tube current modulation: 6.0 to 20
			Prospectively triggered axial: 0.5 to 7.0
			High-pitch helical: <0.5 to 3.0
		NICE, 2016 (guideline)	2.0 to 5.0
		Carpeggiani, 2017†	Mean (SD): 11.2 (8.1)
		Husmann, 2010	2.1 (0.7)
		Pursnani, 2015	All protocols and scanners: 9.9 (4.9)§
			Prospectively gated CCTA: 6.5 (3.8)
			Retrospectively gated CCTA: 10.4 (4.9)
			128-slice DSCT (n=78): 5.7 (3.7)
			CT scanners, excluding 128-slice DSCT: 10.7 (4.7)
		Mettler 2020 (non-cardiac CCTA)	Based on ICRP Publication 60 tissue weighting factors: 5.4
			Based on ICRP Publication 103 tissue weighting factors: 5.4
		Studies included in this report	Studies reporting mean effective dose: 5.3 to 12.7
			Studies reported median effective dose: 3.5 to 11.8
	Fluoroscopy for PCI	Range reported by Einstein 2014	5–57
	PET	Range from studies included in Skelly 2016 (AHRQ report)	6.0
		Range reported in Einstein	2 (^{13}N ammonia); 4 (^{82}Rb); 7

Radiation Exposure Type			Total Effective Dose (mSv)
		2014	(^{18}F FDG – not currently FDA approved)
		Carpeggiani, 2017†	Mean (SD): 1.4 (0.7)
	SPECT	Range from studies included in Skelly 2016 (AHRQ report)	10.5–14
		Ranges reported in Einstein 2014	2.3–14 (^{99m}Tc Tetrofosmin); 2.7–18 (^{99m}Tc Sestamibi); 15 (^{201}Tl); 22 (^{201}Tl/^{99m}Tc Tetrofosmin dual-isotope); 23 (^{201}Tl/^{99m}Tc Sestamibi dual-isotope)
		Range reported by ACR	10–30
		Reported by Halliburton 2011	11 (^{99m}Tc)
		Carpeggiani, 2017†	Mean (SD): 10.0 (2.7)

CACS=coronary artery calcium scoring, CCTA=coronary computed tomography angiography, CMR=cardiac magnetic resonance imaging, ECG=electrocardiogram, ECHO=echocardiography, ICA=invasive coronary angiography, ICRP = International Commission on Radiological Protection, mSv=milliSeiverts; PCI=percutaneous coronary intervention; PET=positron emission tomography, SPECT=single photon emission tomography

*Adapted using data from[33,35,62,63,79,95,107,110,112,156,157,177,198,230]

† Based on 476 exams with primary aim to detect and characterize ischemic heart disease performed as part of the RADIationdOse subproject of the EVINCI study. Doses varied substantially across 12 study centers)

‡ The data included in this consensus document were reproduced with permission from Einstein, 2014.

Einstein AJ, Berman DS, Min JK, et al. Patient-centered imaging: shared decision making for cardiac imaging procedures with exposure to ionizing radiation. J Am Coll Cardiol. 2014 Apr 22;63(15):1480-9. PMID: 24530677.

2.4.6.2 Contrast materials

Contrast materials are used to better visualize the endocardium and improve interpretability and diagnostic accuracy of noninvasive imaging tests. Contrast materials may lead to decreased renal function or have serious adverse effects in persons with impaired renal function at baseline. Contrast induced nephropathy (CIN) is associated with reduced renal function within 48-72 hours of IV contrast administration. Definitions of CIN have varied over time, and other risk factors for CIA have been proposed in addition to renal insufficiency (e.g., diabetes, dehydration).[255] Patients may experience allergic reactions to iodine-based contrast agents, such as hives, rash, or anaphylaxis. There is evidence that allergic reactions may be infrequent; one study suggested roughly 1.7% of patients experienced an allegoric reaction (mild to severe) during the CCTA test.[23] Similarly, some studies of contrast use in stress echo suggest similar adverse event rates and infrequent allergic reactions when comparing patients who received contrast and those that did not.[4,15] Patient risk for adverse reaction to contrast should be considered when selecting the test technique.

2.4.6.3 Pharmacologic stress agents

Pharmacologic stress agents are used in noninvasive cardiac imaging when a patient does not have the capacity to undergo exercise induced stress, or for MPI tests such as PET (since the radionuclides used

for PET tests have a short half-life, pharmacologic stress is required). Agents include dobutamine (which increases coronary flow reserve in a manner similar to exercise), and coronary vasodilators, such as adenosine, dipyridamole, and regadenoson. Use of pharmacologic stress agents requires patients to limit caffeine intake prior to the test and may necessitate temporary halting of any cardiac medications to minimize risk of interfering with test procedures or results.[183] Side effects of pharmacologic induced stress include dizziness and chest pain; however, the safety profile of specific agents may be lacking in specific subpopulations or patients with certain conditions (e.g., obesity, history of seizures).[65]

2.4.6.4 Incidental findings

Some noninvasive imaging modalities, including CCTA, image other non-cardiac structures, such as the lungs, bones, and upper abdomen. Findings of pathologies unrelated to the heart may be incidentally identified when reviewing the test output. The most common extracardiac findings are pulmonary nodules; other common emphysema, pulmonary infiltration, hiatal hernia, and aortic abnormalities.[125] This can lead to additional specialty referrals and possible invasive procedures. Studies of patients undergoing CCTA suggest that any incidental extracardiac findings are common (range 28-35% of patients); one study suggested that 21% of incidental extracardiac findings led to additional clinical follow up or testing, and that the number of extracardiac findings was associated with increasing patient age and greater experience of the clinician reading the scan.[24,124,200] The potential for identification of other non-cardiac related pathologies is a factor to consider when deciding on a noninvasive diagnostic testing strategy for suspected CAD. The follow-up of incidental findings requires additional resources.

2.4.6.5 Subsequent testing

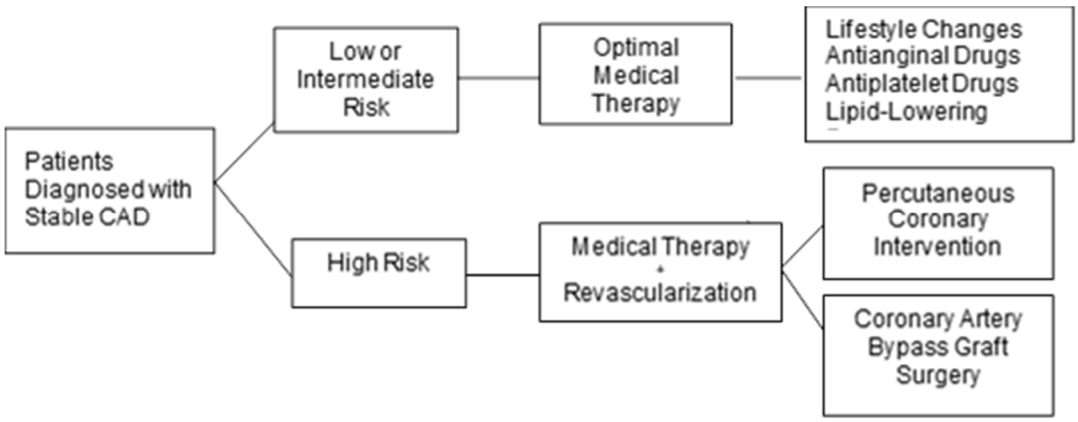
Downstream testing may be ordered if findings are equivocal or indeterminant. Additional testing may increase risk of false positive findings, increase patient anxiety, increase cost of care, and increase potentially avoidable tests.

2.5 Management

This HTA focuses on noninvasive imaging modalities as diagnostic tests for patients with symptomatic CAD. For a diagnostic test to be of value, it must lead to use of effective and appropriate treatments that impact patient outcomes. Where treatment outcomes are comparable, a treatment with higher specificity is a judicious choice to prevent a false positive result. Patients tested for symptomatic CAD have a variety of treatment pathways available and may be referred to different options depending on findings of the diagnostic test. A comparison of referral for treatment by noninvasive imaging modality critical to understanding how utilization of strategies affect the clinical course for the patient.
Once results of the diagnostic test are available, the patient risk of can be calibrated, in combination with pertinent patient history, symptoms and pre-existing comorbidities. Guidelines recommend categorizing patients into three primary risk groups according to their predicted risk of cardiac mortality per year, with low risk defined as <1% , intermediate risk as 1%-3% per year, and high risk defined as >3% rate of cardiac death annually among comparable patients. Patients determined to be at low or

intermediate risk are recommended medical therapy; more intensive revascularization procedures are reserved for patients categorized as high risk, based on their diagnostic test findings. Ultimately, the goal of treatment for stable CAD is to reduce the probability of death or other complications related to CAD, while optimizing the health, well-being, and function of the patient by minimizing symptoms. These considerations are balanced with the preferences and treatment goals of the patient.[71]

Figure 2. Initial treatment pathways for patients diagnosed with CAD



2.5.1 Optimal medical therapy

Optimal (or guideline-directed) medical therapy is optimized on a per-patient basis depending on patient characteristics and guideline recommendations. This may include lifestyle changes to physical activity, smoking cessation, weight management and diet modifications. Therapy will also encompass treatment of comorbidities that can affect (or be affected by) disease progression (e.g., diabetes, hypertension). Evidence suggests that 90% of the risk of having an MI is associated with modifiable risk factors, such as diabetes, smoking, hypertension, obesity; lifestyle modifications are a prudent foundation of any treatment approach for symptomatic CAD.[261] Other risk management strategies may be included, such as antiplatelet drugs and lipid-lowering drugs. Management of comorbidities with appropriate pharmacologic treatment can prevent further plaque buildup, rupture, and thrombosis.[71,232] To support relief of chest pain symptoms, beta-blockers, calcium channel blockers, nitrates, or ranolazine may be prescribed. These drugs reduce oxygen demand by the heart and aim to prevent the occurrence of anginal episodes; there is evidence suggesting up to 50% reduction in anginal episodes for use of beta-blockers and calcium channel blockers, but effect on serious cardiovascular outcomes is uncertain.[253] Medical therapy may be recommended alone, or in addition to revascularization procedures. Evidence suggests that for patients referred for revascularization procedures (along with medical therapy) a reduction in death was not observed, when compared to patients referred to medical therapy alone.[233] The recent ISCHEMIA trial found that patients with moderate to severe ischemia randomized to invasive treatment (revascularization) experienced increased rates of early MI and similar rates of death, when compared to patients randomized to medical therapy only.[152] Most patients with

symptomatic CAD will benefit from comprehensive and personalized guideline directed medical therapy, allowing for the prevention or deferral of unnecessary invasive procedures.

2.5.2 Revascularization

Revascularization methods include coronary artery bypass graft surgery and percutaneous coronary interventions (PCI). The selection of the type of procedure depends on patient presentation and diagnostic findings, as well as patient history. The severity of CAD and related anatomic features, such as the number of vessels involved and the spread and scale of stenosis, is a primary consideration when determining if the patient is a suitable candidate for a particular revascularization approach. The SYNTAX score is recommended as a tool to characterize the complexity, scale, and scope of CAD. In addition to other patient characteristics including age, findings of peripheral vascular disease and whether the patient has a history of smoking are important factors. Revascularization procedures aim to reduce risk of future serious cardiac events and death and have demonstrated success in reducing the risk of death in patients with severe left main artery stenosis, and patients determined to be at highest risk for poor cardiovascular outcomes.

Percutaneous coronary interventions (PCI) are non-surgical, invasive procedures to reduce the narrowing or obstruction of affected coronary arteries to improve blood flow to the heart tissue. PCI involves insertion of a catheter through a main artery to the site of the affected vessel, guided by x-ray images of the heart and the use of contrast dye. There, a device, such as a balloon, is used to open the vessel; a stent may be placed to keep the vessel open. The procedure is performed in a catheterization lab and can take 1-3 hours. A variety of PCI have emerged beyond the standard balloon angioplasty, such as angioplasty with implantation of bare metal stents or drug eluting stents. The introduction of drug eluting stents aims to prevent formation of scar tissue at the site of the stent placement to preserve blood flow and prevent development of further stenosis.

There is mixed evidence on which patient groups may benefit most from PCI, compared to medical therapy alone. There is some evidence suggesting improvement in angina symptoms and events, compared to medical therapy alone.[71] The evidence is less clear for prevention of serious cardiovascular events. One meta-analysis suggested that for patients with symptomatic CAD with ischemia identified by functional diagnostic testing, a significant reduction in death or nonfatal MI was not observed among those treated with PCI (with medical therapy) compared to patients who received medical therapy alone.[236] More recently, a meta-analysis of 10 797 patients with obstructive CAD and ischemia yielded similar results – patients treated with PCI (with medical therapy) did not experience a significant reduction in nonfatal MI, compared to patients who received medical therapy alone at median follow-up of 5 years.[233] This is concordant with earlier trials where the reduction in death and serious nonfatal events from PCI, vs medical therapy lone, yet to be clearly proven.[127,128,244]

Coronary artery bypass graft surgery (CABG) is a surgical procedure to divert blood flow from stenotic or obstructed vessels to improve blood flow to the heart. The procedure involves grafting arteries or veins from another part of the body, such as mammary arteries, radial arteries, or greater saphenous veins, to above and below the ischemic area of the heart. The typical duration of the procedure is 3 to 6

hours. Recent studies in patients with symptomatic CAD suggest that CABG (with medical therapy) appeared to reduce nonfatal MI compared to medical therapy alone; this was not observed when comparing PCI to medical therapy alone.[233] Patients undergoing CABG have a higher rate of complete revascularization, compared with patients undergoing PCI, which has been suggested as an explanation for the observed improved outcomes among patients who undergo CABG vs. PCI long term.[121] CABG may be preferred in patients where the primary goal of treatment is reduction in risk of mortality.

ACC guidelines recommend CABG for patients with significant left main coronary stenosis but suggest PCI as an alternative when patient has low risk of complications with PCI, and clinical factors that would suggest an increased risk of poor surgical outcomes.[71] When comparing PCI to CABG, trials suggest that while survival is similar at 1 and 5 years, relief of chest pain may be more effective with CABG than with PCI at 1 and 5 years, and repeat revascularization was less frequent for patients with CABG than those with PCI.[29]

2.5.3 Management of acute coronary syndromes

The primary goal of treatment for patients presenting with acute coronary syndromes is to relieve pain, improve blood flow and restore heart function as quickly as possible. This typically requires a combination of medical therapy and revascularization, depending on the type of acute coronary syndrome. In patients presenting with STEMI, non-STEMI or unstable angina, revascularization with PCI is considered appropriate if presenting within the first 12 hours of symptom onset.[190] All patients will receive guideline-directed medical therapy as well. Due to the acute presentation of the patient, if PCI is not available or patient is a suitable candidate for PCI then fibrinolytic therapy is recommended (for STEMI only). For non-STEMI patients, pharmacologic therapy, such as antiplatelet therapy and anticoagulants is recommended no matter the initial treatment strategy. Other pharmacologic treatments for either STEMI or non-STEMI may include beta blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers.

2.6 Previous Systematic Reviews of Noninvasive Cardiac Testing for Suspected CAD

Systematic reviews (SRs) were found by searching PubMed, the Cochrane Database of Systematic Reviews, and the ECRI Guideline Trust from database inception to March 23rd, 2021. Reference lists of relevant studies and the bibliographies of SRs were hand searched. See Appendix B for search terms and full search strategy.

Twelve SRs evaluating the effectiveness and/or safety of noninvasive cardiac stress testing in adult patients with suspected coronary artery disease (CAD) (stable or acute) were identified. Of these, eight included high-quality evidence (i.e., RCTs only) of which four were considered to provide the most comprehensive summary of the evidence to date, including trials summarized in the prior HTA and those published subsequently and are summarized below (Table 5).[73,113,227,228] Studies contained in these reviews that met inclusion criteria for this HTA were included. All four SRs provided quantitative syntheses; three did meta-analyses of head-to-head trials[73,113,227] and one conducted a network meta-analysis[228]. All four SRs compared CCTA with functional testing; in addition, the network meta-analysis compared one functional stress test versus another.

Across all three SRs evaluating head-to-head trials, compared with functional stress imaging, CCTA as an initial diagnostic strategy was associated with a reduced incidence of myocardial infarction (MI) but an increased incidence of downstream invasive procedures (i.e., ICA and revascularizations), with no difference in mortality. One SR also reported a reduction in downstream noninvasive testing with CCTA. Similar results were seen across the subgroups of stable chest pain and acute chest pain. One SR[73] evaluated the extent to which stable and unstable patients had different risk estimates by performing a formal test for interaction and found no difference between the two populations. The network meta-analysis found similar results regarding increased ICA and revascularization rates with CCTA versus any functional testing, but no difference in the risk of future MI in either low-risk ACS or stable CAD; however, authors notes that estimates were imprecise, especially for patients with stable CAD, and any differences could not be ruled out. No conclusions could be drawn regarding one functional test versus another, mainly because of the limited number of trials contributing to each comparison.

These SRs differ from our current review in a few important ways. Some include RCTs that were excluded from our review (i.e., did not meet our inclusion criteria) and there were differences in how time periods were considered or evaluated. Regarding statistical methods, we conducted our meta-analyses using profile-likelihood random effects models, which is a more conservative than the Dersimonian and Laird model; this approached is considered standard methodology for meta-analyses.

Table 5. Previous systematic reviews evaluating noninvasive testing for CAD.

Author (year), Search Funding	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions
Siddiqui (2020) **Search:** January 1, 2007 to July 1, 2018 MEDLINE, PubMed, Cochrane Library, Embase **Funding**: None	**Suspected CAD** (N=21,210) • Stable chest pain: 70.5% (n=14,947) • Acute chest pain: 29.5% (n=6,263) **CCTA**: n=10,937 **Functional stress testing**: n=10,273 • With imaging: n=9,758 • Without imaging: n=515 **Pretest risk**: Variable/NR **Setting**: Outpatient (4 RCTs, stable chest pain) and ED (9 RCTs, acute chest pain) **Follow-up**: range, 1 to 25 months • 1 month: 3 RCTs • 2-4 months: 3 RCTs • 6 months: 3 RCTs	**Objective**: To compare CCTA to functional stress testing for suspected underlying CAD in patients who presented with chest pain, with subgroup analyses of stress testing (with and without imaging) and chest pain (acute chest pain or stable chest pain).	**Appraisal:** Cochrane ROB tool for RCTs; overall trial quality not described **Overall Quality** (strength) of evidence: NR **Evidence base:** 16 RCTs (N=21,210) • Stable chest pain: 6 RCTs (n=14,947) • Acute chest pain: 10 RCTs (n=6,263) **Analysis:** Meta-analysis, Head-to-head studies **Publication bias:** Not assessed.	***CCTA vs. any functional test*** No. RCTS (n patients), RR (95% CI): **Clinical outcomes** • New myocardial infarction (during follow-up): ○ Stable: 4 RCTs (n=14,984), **0.66 (0.5-0.88)**, I^2=0% ○ Acute: 8 RCTs (n=5,315), **0.88 (0.54-1.44)**, I^2=0% ○ ST with imaging: 10 RCTs (n=19,249), **0.7 (0.54-0.89)**, I^2=0% ○ ST without imaging: 2 RCTs (n=1,050), **1.14 (0.35-3.75)**, I^2=0% ○ Total: 12 RCTs (n=20,299), **0.71 (0.56-0.91)**, I^2=0% • All-cause mortality: ○ Stable: 4 RCTs (n=14,984), **0.95 (0.71-1.25)**, I^2=0% ○ Acute: 8 RCTs (n=4,715), **0.75 (0.30-1.89)**, I^2=0% ○ ST with imaging: 10 RCTs (n=18,649), **0.92 (0.70-1.21)**, I^2=0% ○ ST without imaging: 2 RCTs (n=1,050), **1.26 (0.21-7.71)**, I^2=0% ○ Total: 12 RCTs (n=19,699), **0.93 (0.71-1.21)**, I^2=0% **Clinical decision making:** • ICA (cumulative): ○ Stable: 5 RCTs (n=11,278), **1.44 (1.30-1.61)**, I^2=0% ○ Acute: 10 RCTs (n=5,775), **1.35 (1.13-1.62)**, I^2=8% ○ ST with imaging: 12 RCTs (n=15,943), **1.37 (1.21-1.55)**, I^2=11% ○ ST without imaging: 3 RCTs (n=1,110), **1.39 (1.04-1.85)**, I^2=0% ○ Total: 15 RCTs (n=17,053), **1.41 (1.28-1.55)**, I^2=1% • Revascularization (cumulative)*: ○ Stable: **1.7 (1.16-2.51)**, I^2=77% ○ Acute: **1.95 (1.42-2.69)**, I^2=17% ○ ST with imaging: **1.77 (1.34-2.33)**, I^2=60% ○ ST without imaging: **2.36 (1.40-3.98)**, I^2=0% ○ Total: **1.84 (1.44-2.35)**, I^2=53% • Follow-up testing (cumulative):

Author (year), Search Funding	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions
	• 12 months: 5 RCTs • 20-25 months: 2 RCTs			○ Stable: 3 RCTs (n=936), **0.17 (0.04-0.77)**, I^2=80% ○ Acute: 4 RCTs (n=1,068), **0.83 (0.44-1.55)**, I^2=70% ○ ST with imaging: 5 RCTs (n=1,456), **0.43 (0.16-1.14)**, I^2=86% ○ ST without imaging: 2 RCTs (n=548), **0.39 (0.28-0.56)**, I^2=0% ○ Total: 7 RCTs, **0.45 (0.22-0.90)**, I^2=86% **Other:** • ER visits or hospitalizations: ○ Stable: 4 RCTs (n=5,153), **0.5 (0.21-1.23)**, I^2=86% ○ Acute: 9 RCTs (n=5,213), **0.86 (0.72-1.04)**, I^2=22% ○ ST with imaging: 11 RCTs (n=9,818), **0.92 (0.83-1.02)**, I^2=0% ○ ST without imaging: 2 RCTs (n=548), **0.27 (0.15-0.48)**, I^2=27% ○ Total: 13 RCTs (n=10,366), **0.75 (0.60-0.94)**, I^2=63% • New unstable anginas*: ○ Stable: **1.21 (0.93-1.58)**, I^2=4% ○ Acute: **1.15 (0.90-1.48)**, I^2=0% ○ ST with imaging: **1.18 (0.98-1.40)**, I^2=0% ○ ST without imaging: **1.09 (0.20-5.92)**, I^2=49% ○ Total: **1.18 (0.99-1.41)**, I^2=0% • True positive ICA: ○ Stable: 4 RCTs (1,210), **2.79 (2.19-3.55)**, I^2=0% ○ Acute: 7 RCTs (n=260), **3.2 (1.83-5.60)**, I^2=0% ○ ST with imaging: 8 RCTs (n=1,310), **2.84 (2.25-3.59)**, I^2=0% ○ ST without imaging: 3 RCTs (n=160), **4.67 (1.15-18.91)**, I^2=48% ○ Total: 11 RCTs (n=1,470), **2.85 (2.28-3.56)**, I^2=0% **Safety/Harms**: • Procedural complications (stroke, bleeding, anaphylaxis, or renal failure)*: ○ Total: **0.98 (0.35-2.74)**, I^2=0% • Cumulative radiation dose* ○ Total: 7.3±6.6 vs. 2.6±6.5, **0.47 (0.08-0.86)**, I^2=97%

Author (year), Search Funding	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions
				Overall Author's Conclusions: Compared with functional stress imaging, CCTA was associated with a significant reduction in downstream MIs, hospital visits, and follow-up testing, but increased ICA and revascularizations; there was no difference in mortality. In the future, more RCTs are needed utilizing scoring methods to identify more robust downstream investigations, cost analysis, and radiation exposure.
Foy (2017) **Search:** January 1, 2000 to July 10, 2016 MEDLINE, PubMed **Funding**: NR	**Suspected CAD** (N=20,092) • Stable chest pain: 73.7% (n=14,817) • Acute chest pain: 26.3% (n=5,275) **CCTA**: n=10,315 **Functional stress testing**: n= 9,777 • Multiple modalities (plus no testing): 31% (4 RCTs) • MPI: 31% (4 RCTs) • Exercise ECG: 23% (3 RCTs) • Stress Echocardiography: 8% (1 RCT) • Modality not specified: 8% (1	**Objective**: To compare the clinical effectiveness of CCTA with that of functional stress testing for patients with suspected CAD. **Key Question**: For patients with suspected coronary artery disease, what is the effect on clinical outcomes of coronary computed tomography angiography	**Appraisal:** Cochrane ROB tool for RCTs; trial quality was variable, overall was considered moderate (45 of 98 domains [46%] judged to be at high or questionable risk for bias). **Overall Quality** (strength) of evidence of high, moderate, low or very low; Authors provide overall rating per outcome but do not provide detail of how this was derived. **Evidence base:** 13 RCTs (N=20,092) • Stable chest pain: 4 RCTs (n=14,817) • Acute chest pain: 9	***CCTA vs. any functional test†*** No. RCTS (n patients), RR (95% CI), quality (strength) of evidence: **Clinical outcomes** • Myocardial infarction: ○ Stable: 4 RCTs, **0.68 (0.49-0.95)**, I^2=0%, Moderate ○ Acute: 9 RCTs, **0.84 (0.44-1.61)**, I^2=0%, Moderate ○ Total: 13 RCTs, **0.71 (0.53-0.96)**, I^2=0%, Moderate • All-cause mortality ○ Stable: 4 RCTS, **0.96 (0.72-1.27)**, I^2=0%, Moderate ○ Acute: 9 RCTs, **0.66 (0.27-1.59)**, I^2=0%, Moderate ○ Total: 13 RCTs, **0.93 (0.71-1.21)**, I^2=0%, Moderate **Clinical decision making:** • ICA referral: ○ Stable: 4 RCTs, **1.27 (0.96-1.70)**, I^2=83%, Moderate ○ Acute: 9 RCTs, **1.39 (1.10-1.76)**, I^2=29%, Moderate ○ Total: 13 RCTs, **1.33 (1.12-1.59)**, I^2=59%, Moderate • Revascularization (any): ○ Stable: 4 RCTs, **1.70 (1.12-2.60)**, I^2=84%, Moderate ○ Acute: 9 RCTs, **1.96 (1.45-2.65)**, I^2=4%, High ○ Total: 13 RCTs, **1.86 (1.43-2.43)**, I^2=60%, High • Therapeutic medication change – aspirin: ○ Stable: 3 RCTs (n=4,814), **3.50 (2.69-4.54)**, I^2=31%, Low

Author (year), Search Funding	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions
	RCT) **Pretest risk**: Variable/NR **Setting**: Outpatient (4 RCTs, stable chest pain) and ED (9 RCTs, acute chest pain) **Mean follow-up**: 18 months • Stable: 23 months • Acute: 5 months	compared with functional stress testing?	RCTs (n=5,275) **Analysis:** Meta-analysis, Head-to-head studies **Assessed publication bias:** Visually using funnel plots; visual asymmetry noted for the following outcomes in favor of CCTA: • All-cause mortality (PROSPECT trial) • ICA (PERFECT trial) • Revascularization (SCOT-HEART, PERFECT trials) • New CAD diagnosis (2 small trials) Removal of trials did not significantly change overall effect estimate	○ Acute: 2 RCTs (n=811), **1.27 (0.99-1.61)**, I^2=16%, Low ○ Total: 5 RCTs (n=5,625), **2.21 (1.20-4.04)**, I^2=93%, Low • Therapeutic medication change – statin: ○ Stable: 3 RCTs (n=4,814), **3.48 (2.63-4.61)**, I^2=34%, Low ○ Acute: 2 RCTs (n=811), **1.21 (0.93-1.58)**, I^2=0%, Low ○ Total: 5 RCTs (n=5,625), **2.03 (1.09-3.76)**, I^2=92%, Low **Other:** • Cardiac hospitalization: ○ Stable: 4 RCTs (n=14,817), **1.21 (0.96-1.53)**, I^2=0%, Moderate ○ Acute: 8 RCTs (n=4,584), **0.83 (0.66-1.04)**, I^2=0%, Moderate ○ Total: 12 RCTs (n=19,401), **0.98 (0.79-1.21)**, I^2=23%, Moderate • New CAD diagnosis: ○ Stable: 3 RCTs (n=4,814), **2.35 (1.51-3.66)**, I^2=69%, High ○ Acute: 6 RCTs (n=3,979), **3.37 (1.92-5.89)**, I^2=75%, High ○ Total: 9 RCTs (n=8,793), **2.80 (2.03-3.87)**, I^2=71%, High **Safety/Harms**: • NR **Economic**: NR **Overall Author's Conclusions**: Compared with functional stress testing, CCTA is associated with a reduced incidence of myocardial infarction but an increased incidence of invasive coronary angiography, revascularization, CAD diagnoses, and new prescriptions for aspirin and statins. Despite these differences, CCTA is not associated with a reduction in mortality or cardiac hospitalizations. Tradeoffs involve an increase in downstream invasive procedures, many of which may be unnecessary.
Hwang (2017) **Search:**	**Suspected CAD** (N=20,014) • Stable chest pain:	**Objective:** To investigate the mid- to long-term	**Appraisal:** Cochrane ROB tool for RCTs. Overall trial quality was not reported	***CCTA vs. any functional test*** No. RCTS (n patients), RR (95% CI) **Clinical outcomes**

Author (year), Search Funding	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions
January 1, 2000 to July 10, 2016 MEDLINE, Embase, Cochrane **Funding**: Grant from the National Evidence-based Healthcare Collaborating Agency, Republic of Korea	76.5% (n=15,302) • Acute chest pain: 23.5% (n=4,712) **CCTA**: n=10,268 **Functional stress testing**: n= 9,627 **Pretest risk**: Variable/NR **Setting**: Outpatient (5 RCTs, stable chest pain) and ED (7 RCTs, acute chest pain) **Follow-up**: Mean 20.5 months (range, 6 to 42 months)	clinical outcomes following the initial strategies of noninvasive testing in patients with suspected CAD by comparing anatomical testing using CCTA with usual care with functional testing.	but all were considered Low ROB for detection bias, reporting bias and other bias; Low or Unclear ROB for selection bias and attrition bias; and High RoB (all but the CATCH trial) for performance bias. **Overall Quality** (strength) of evidence not assessed. **Evidence base:** 12 RCTs (N=20,014) • Stable chest pain: 5 RCTs • Acute chest pain: 7 RCTs **Analysis:** Meta-analysis, Head-to-head studies **Assessed publication bias:** Funnel plots suggested the presence of publication bias for ICA, however the influence was not significant (trim-and-fill analysis)	• Myocardial infarction: ○ Stable: 4 RCTs (n=14,984), **0.68 (0.48-0.97)**, I^2=0% ○ Acute: 5 RCTs (n=3,328), **0.74 (0.42-1.29)**, I^2=15% ○ Total: 9 RCTs (n=18,312), **0.70 (0.52-0.94)**, I^2=0% • All-cause mortality ○ Stable: 5 RCTS (n=15,281), **0.96 (0.72-1.26)**, I^2=0% ○ Acute: 5 RCTs (n=3,604), **0.50 (0.19-1.30)**, I^2=10% ○ Total: 10 RCTs (n=18,885), **0.91 (0.69-1.18)**, I^2=0% • MACE ○ Stable: 4 RCTS (n=14,793), **0.68 (0.39-1.20)**, I^2=71% ○ Acute: 7 RCTs (n=4,472), **0.82 (0.64-1.06)**, I^2=0% ○ Total: 11 RCTs (n=19,265), **0.82 (0.64-1.04)**, I^2=38% **Clinical decision making:** • ICA ○ Stable: 5 RCTS (n=15,279), **1.98 (1.10-3.55)**, I^2=88% ○ Acute: 6 RCTs (n=3,844), **1.32 (0.86-2.02)**, I^2=59% ○ Total: 11 RCTs (n=19,123), **1.61 (1.14-2.27)**, I^2=80% • Revascularization (any) ○ Stable: 5 RCTS (n=15,237), **1.52 (1.05-2.20)**, I^2=77% ○ Acute: 7 RCTs (n=3,881), **1.97 (1.15-3.35)**, I^2=29% ○ Total: 12 RCTs (n=19,118), **1.65 (1.23-2.21)**, I^2=60% Similar results were observed in subgroup analyses of the RCTs with long-term follow-up durations. **Safety/Harms**: • NR **Economic**: NR **Overall Author's Conclusions**: Anatomical testing with CCTA as an

Author (year), Search Funding	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions
				initial diagnostic strategy reduced the risk of nonfatal MI in patients with suspected CAD, compared with the usual care, during mid- to long-term follow-up. The reduction in the risk of nonfatal MI was at the expense of increased use of ICA and coronary revascularization. Future trials of advanced CT technology may further demonstrate the clinical benefits of the anatomical testing strategy over usual care.
Siontis 2018 **Search:** 2005 to November 2015 Medline, Medline in process, Embase, Cochrane Library for clinical trials, PubMed, Web of Science, SCOPUS, WHO International Clinical Trials Registry Platform, and Clinicaltrials.gov. **Funding**: None	**Suspected CAD** (N=33,391) • Stable CAD: 66.1% (n=22,062) • Low-risk ACS: 33.9% (n=11,329) **Pretest risk**: Variable/NR **CCTA vs. various functional testing** **Functional testing vs. functional testing** **Setting**: Outpatient and ED **Follow-up**: Variable	**Objective:** To evaluate differences in downstream testing, coronary revascularization, and clinical outcomes following non-invasive diagnostic modalities used to detect coronary artery disease.	**Appraisal:** Cochrane ROB tool for RCTs. Overall, ROB ratings were: Low, 43% (13 RCTs); Moderate, 43% (13 RCTs); and High, 14% (4 RCTs) **Overall Quality** (strength) of evidence not assessed. **Evidence base:** 30 RCTs (N=33,391) • **Stable CAD: 12 RCTs (N=22,062)** ○ CCTA vs. any functional (2 RCTs) ○ CCTA vs. SPECT (2 RCTs) ○ CCTA vs. stress ECG (1 RCT) ○ CCTA vs. standard care (1 RCT) ○ SPECT vs. stress ECG	***CCTA vs. <u>individual</u> diagnostic strategies*** OR (95% CI) **Clinical outcomes** • Myocardial infarction: ○ Stable CAD ▪ Stress echo: **2.14 (0.03-162.0)** ▪ CMR: **2.62 (0.67-10.30)** ▪ Stress ECG: **2.11 (0.34-13.0)** ▪ SPECT: **1.31 (0.84-2.06)** ▪ RTMCE: **3.26 (0.04-286.0)** ▪ Standard care: **1.66 (0.99-2.79)** τ^2<0.001 ○ Low-risk ACS ▪ Stress echo: **0.78 (0.10-6.30)** ▪ CMR: **2.46 (0.29-20.7)** ▪ Stress ECG: **0.54 (0.08-3.60)** ▪ SPECT: **2.38 (0.77-7.34)** ▪ Standard care: **1.36 (0.80-2.31)** τ^2<0.001 • Death: ○ Stable CAD ▪ Stress echo: **3.90 (0.12-123)** ▪ CMR: **1.05 (0.28-3.93)**

Author (year), Search Funding	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions
			(2 RCTs) ○ Stress echo vs. exercise ECG (1 RCT) ○ RTMCE vs. Stress echo: (2 RCTs) ○ CMR vs. SPECT vs. standard care (1 RCT) • **Low-risk ACS: 18 RCTs (N=11,329)** ○ CCTA vs. standard care (7 RCTs) ○ CCTA vs. SPECT (2 RCTs) ○ CCTA vs. stress ECG (1 RCT) ○ SPECT vs. standard care (2 RCTs) ○ Stress echo vs. stress ECG (3 RCTs) ○ Stress echo vs. stress ECG vs. standard care (1 RCT) ○ CMR vs. standard care (2 RCTs) **Analysis:** Meta-analysis, Network	▪ Stress ECG: **1.27 (0.35-4.60)** ▪ SPECT: **0.98 (0.72-1.35)** ▪ RTMCE: **3.70 (0.11 to 121.0)** ▪ Standard care: **1.27 (0.69-2.32)** τ^2<0.001 ○ Low-risk ACS: NR **Clinical decision making:** • ICA: ○ Stable CAD ▪ Stress echo: **0.57 (0.12-2.79)** ▪ CMR: **0.50 (0.15-1.65)** ▪ Stress ECG: **0.90 (0.45-1.80)** ▪ SPECT: **0.54 (0.30-0.98)** ▪ RTMCE: **1.10 (0.15 to 7.95)** ▪ Standard care: **1.44 (0.60-3.45)** τ^2=0.336 ○ Low-risk ACS ▪ Stress echo: **0.28 (0.14-0.57)** ▪ CMR: **0.32 (0.15-0.71)** ▪ Stress ECG: **0.53 (0.28-1.00)** ▪ SPECT: **0.78 (0.58-1.03)** ▪ Standard care: **0.85 (0.69-1.05)** τ^2=0.023 • Revascularization (any): ○ Stable CAD ▪ Stress echo: **0.64 (0.19-2.14)** ▪ CMR: **0.84 (0.40-1.74)** ▪ Stress ECG: **0.63 (0.38-1.04)** ▪ SPECT: **0.57 (0.37-0.87)** ▪ RTMCE: **1.36 (0.36 to 5.10)**

Author (year), Search Funding	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions
				▪ Standard care: **0.75 (0.45-1.24)** τ^2=0.084 ○ Low-risk ACS ▪ Stress echo**: 0.44 (0.16-1.24)** ▪ CMR: **0.17 (0.04-0.65)** ▪ Stress ECG: **0.56 (0.21-1.49)** ▪ SPECT: **0.57 (0.41-0.79)** ▪ Standard care: **0.68 (0.53-0.88)** τ^2<0.001 • Downstream testing ○ Stable CAD ▪ Stress echo: **0.24 (0.08-0.74)** ▪ CMR: **0.95 (0.41-2.22)** ▪ Stress ECG: **3.87 (2.33-6.41)** ▪ SPECT: **0.57 (0.37-0.87)** ▪ Standard care: **1.11 (0.61-2.01)** τ^2=0.137 ○ Low-risk ACS ▪ Stress echo: **0.27 (0.04-1.67)** ▪ CMR: **2.87 (0.32-25.9)** ▪ Stress ECG: **0.69 (0.14-3.44)** ▪ SPECT: **0.60 (0.12-2.98)** ▪ Standard care: **4.11 (1.74-9.74)** τ^2=1.21 ***CCTA vs. grouped diagnostic strategies*** OR (95% CI) **Clinical outcomes** • Myocardial infarction: ○ Stable CAD

Author (year), Search Funding	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions
				▪ Functional testing: **1.35 (0.87-2.09)** ▪ CMR: **2.66 (0.68-10.41)** ▪ Standard care: **1.66 (0.99-2.79)** τ^2<0.001 ○ Low-risk ACS ▪ Functional testing: **1.59 (0.60-4.23)** ▪ CMR: **2.52 (0.30-21.28)** ▪ Standard care: **1.40 (0.82-2.37)** τ^2<0.001 • Death: ○ Stable CAD ▪ Functional testing: **0.99 (0.73-1.36)** ▪ CMR: **1.06 (0.28-3.95)** ▪ Standard care: **1.27 (0.69-2.32)** τ^2<0.001 ○ Low-risk ACS: NR **Clinical decision making:** • ICA: ○ Stable CAD ▪ Functional testing: **0.63 (0.44-0.90)** ▪ CMR: **0.56 (0.27-1.13)** ▪ Standard care: **1.51 (0.90-2.53)** τ^2=0.102 ○ Low-risk ACS ▪ Functional testing: **0.71 (0.53-0.96)** ▪ CMR: **0.32 (0.15-0.72)** ▪ Standard care: 0.85 **(0.68-1.07)** τ^2=0.032 • Revascularization (any): ○ Stable CAD

Author (year), Search Funding	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions
				▪ Functional testing: **0.57 (0.41-0.78)** ▪ CMR: **0.84 (0.48-1.44)** ▪ Standard care: **0.77 (0.54-1.10)** τ^2=0.029 ○ Low-risk ACS ▪ Functional testing: **0.57 (0.42-0.78)** ▪ CMR: **0.17 (0.04-0.65)** ▪ Standard care: **0.68 (0.53-0.88)** τ^2<0.001 • Downstream testing ○ Stable CAD ▪ Functional testing: **1.18 (0.61-2.29)** ▪ CMR: **1.63 (0.35-7.48)** ▪ Standard care: **1.56 (0.51-4.81)** τ^2=0.578 ○ Low-risk ACS ▪ Functional testing: **0.58 (0.17-1.92)** ▪ CMR: **2.99 (0.33-27.50)** ▪ Standard care: **4.28 (1.79-10.23)** τ^2=1.23 ***Functional vs. Functional*** • Limited evidence for the various comparisons **Overall Author's Conclusions**: **Among patients with low-risk ACS**, initial functional testing in terms of stress echocardiography or CMR was most strongly associated with a reduction of referrals for downstream ICA and revascularization procedures, compared with anatomical testing using CCTA. No diagnostic strategy had an apparent effect on the

Author (year), Search Funding	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions
				subsequent risk of MI, although estimates were imprecise. **Among patients with suspected stable CAD**, no clear discrimination was seen across *individual diagnostic strategies* for ICA referrals, mainly because of the limited number of trials contributing to each comparison. Stress echocardiography and SPECT resulted in less overall downstream testing than CCTA, whereas exercise ECGs required the most downstream testing. *After grouping of widely available functional tests*, a functional testing approach yielded fewer referrals for ICA and subsequent revascularizations than CCTA. Again, estimates were imprecise for the outcome of MI, and any differences could not be ruled out.

ACS = acute coronary syndrome; CAD = coronary artery disease; CCTA = coronary computed tomographic angiography; CI = confidence interval; CMR = cardiovascular magnetic resonance; ECG = electrocardiography; echo=echocardiography; ED = emergency department; ICA = invasive coronary angiography; MI = myocardial infarction; NR= not reported; RCT = randomized controlled trial; ROB = risk of bias; RR = risk ratio; RTMCE = real time myocardial contrast echocardiography; SPECT = single photon emission computed tomography; ST = stress testing; WHO = World Health Organization.

* No plot provided in article, number of RCTs (n patients) contributing to estimate not reported.

†Authors evaluated the extent to which stable and unstable patients had different risk estimates, and did a formal test for interaction – there was no modification of the treatment effect by the different populations.

2.7 Prior Government Report and Rapid Reviews

Two prior reports, one comparative effectiveness review published in 2016 by the Agency for Healthcare Research and Quality (AHRQ)[230] and one rapid review from 2019 prepared by the Veterans Affairs (VA) Evidence Synthesis Program[100], were identified searching PubMed, the Cochrane Database of and the ECRI Guideline Trust from database inception to March 23rd, 2021, and our summarized in Table 6 below. See Appendix B for search terms and full search strategy.

The most recent report was a VA Evidence Synthesis rapid review that evaluated evidence related to the capabilities, benefits and harms, and impact on resource use within the VA health system of CCTA with fractional flow reserve (FFRCT) technology (i.e., HeartFlow) for the diagnosis of CAD.[100] Since it is a rapid review, however, it does not provide a formal, systematic review of the available evidence. Evidence related to diagnostic accuracy from this review can be found in the Contextual Questions section. Regarding clinical and management outcomes (Table 6 below), the authors concluded that regular use of HeartFlow FFRCT in place of other noninvasive tests does not appear warranted, as HeartFlow FFRCT led to a higher rate of use of ICA when used as a substitute for planned noninvasive cardiovascular testing. They also found no evidence to support wider use of CCTA in place of other noninvasive tests in the VA healthcare system.

The AHRQ comparative effectiveness review evaluated noninvasive testing strategies for the diagnosis of CAD in symptomatic patients with suspected CAD, who had no known history of CAD, and whose condition was stable.[230] Results were stratified first based on pretest risk and then by anatomic versus functional tests and functional versus functional tests. Given the heterogeneity in how pretest risk was measured and defined across the studies, the results were organized by pretest risk as defined by the study authors (rather than by distinct pretest risk groups as originally intended), which included low-risk, intermediate-risk, low-to-intermediate-risk, intermediate-to-high-risk, high-risk, and mixed-risk populations (or pretest risk not reported). This review found no clear differences between testing strategies across settings with regard to clinical or management outcomes to recommend one strategy over another for any given pretest risk group that included intermediate pretest risk patients. Limited evidence from RCTs suggest anatomic testing may result in a higher frequency of referral for ICA and revascularization. The frequency of all-cause mortality and MI was low across studies in all settings. Assessment of harms was limited and there was inadequate comparative evidence to make judgments regarding radiation exposure for initial test or downstream testing. (See Table 6 below for details.) In contrast to the AHRQ report, this current report included symptomatic patients both with and without a history of CAD, as well as those who presented with acute coronary syndrome (ACS). We did not stratify results by pretest risk but did indicate pretest risk as defined by the authors. Since the AHRQ report, several new trials evaluating noninvasive treatment for CAD have been published and are included in this re-review.

A third review was identified by the Health Evidence Review Commission (HERC) which provided evidence on nuclear cardiac imaging for screening, diagnosis or risk stratification of CAD[99]; however, this report essentially relied on the evidence from the prior WA State HTA on nuclear cardiac imaging, so it is not summarized below.

Table 6. Prior government reports and rapid reviews evaluating noninvasive testing for CAD

Author (year), Search Funding AMSTAR-2	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions
Helfand (2019) Search: 2017 to August 2019 MEDLINE, Cochrane Database of Systematic reviews, Cochrane Central Register of Controlled trials. Funding: Department of Veteran Affairs, Veterans Health Administration (VHA), Health Services Research and Development. AMSTAR-2: NA	Symptomatic patients with Suspected CAD Pretest risk: Intermediate (primarily) Outpatient and ED settings Test comparisons: • CCTA-FFR vs. any functional test* • CCTA-FFR vs. ICA • CCTA-FFR vs. CCTA alone	Objective\Key Question: This is a rapid review intended to provide a conceptual overview of the capabilities, benefits and harms, and anticipated impact on resource use within the Veterans Health Administration of CCTA with FFR technologies for the diagnosis of CAD.	Appraisal: Cochrane ROBIS tool for SR's, QUADAS-2 for Diagnostic accuracy or therapeutic impact, and Cochrane ROBINS-I tool for cohort studies. Overall Quality: used Agency for *Healthcare Research and Quality Methods Guide for Comparative Effectiveness Reviews*; Ratings ranged from high to insufficient. Evidence received a rating of low to moderate strength if it was comprised of several studies with low to moderate risk of bias and had consistent findings. Evidence base: N=6 studies (in 9 publications), 90-days (primarily) to 1 year CCTA-FFR vs. any functional test*: 2 studies (total N=3,727) (1 prospective [PLATFORM trial], 1 retrospective	*CCTA-FFR vs. Any functional testing** MACE • 1 prospective cohort (vs. any functional testing): 0% vs. 1% Downstream ICA utilization • 1 prospective cohort (vs. any functional testing): 21% vs. 16%, p=NS • 1 retrospective cohort (vs. MPI): RD –4.2% (95% CI –6.9% to –1.6%)† Planned ICA with no obstructive disease • 1 prospective cohort (vs. any functional testing): 13% vs. 6%, p=NS • 1 retrospective cohort (vs. MPI): RD –12.8% (95% CI –22.2% to –3.4%)† Downstream noninvasive testing • 1 retrospective cohort (vs. MPI): 23% vs. 20%‡ Revascularization • 1 prospective cohort (vs. any functional testing): 10% vs. 7%, p=NS • 1 retrospective cohort (vs. MPI): RD 14.1% (95% CI 3.3 to 24.9%)† Safety/Harms: Cumulative radiation exposure: • 1 prospective cohort (vs. any functional testing): 9.6 vs. 6.4 mSv through 12 months; MD 3.1 (95% CI 0.6 to 5.7) Economic • 1 prospective cohort (vs. any functional testing): Mean 1 year of patient cost did not differ when using

Author (year), Search Funding AMSTAR-2	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions

			comparative cohort)
			
			CCTA-FFR vs. ICA:
			1 prospective observational study (N=380)
			
			CCTA-FFR vs. CCTA alone:
			4 studies (total N=7,180) (3 retrospective comparative cohorts, 1 comparative registry study)
			
			Analysis: Qualitative analysis
			
			Publication bias:
			Assessed using Quadas-2 section bias was mostly Low with 2 studies being unclear.
				an CCTA-FFR cost weight of zero, but were higher when using an CCTA-FFR cost weight equal to CCTA.
				
				CCTA-FFR vs. ICA
				MACE: 1% vs. 1%, p=NS
				Planned ICA with no obstructive disease: 12% vs. 73%, RD –61% (95% CI –68.7% to –53.0%)
				Revascularization: 34% vs. 36%, p=NS
				Safety/Harms:
				• Cumulative radiation exposure: 10.7 vs. 10.4 mSv through 12 months, p=NS
				Economic
				• Mean 1 year patients' cost was 33% lower in CCTA-FFR vs. ICA group.
				
				CCTA-FFR vs. CCTA alone
				MACE
				• 1 registry:
				  ○ CCTA-FFR >0.80 = no death/MI within 90 days
				  ○ CCTA-FFR ≤0.80 = MACE, 0.6%; death/MI, 0.3%
				• 2 retrospective cohorts:
				  ○ No significant difference in 1-year cardiovascular events between patients with changed vs. unchanged management after CCTA-FFR
				  ○ 4 serious clinical events occurred, but not in any patients with cancelled ICA by CCTA-FFR
				Change in management plans (1 registry, 1 retrospective cohort)
				• 55% to 67% of patients
				Impact on subsequent ICA (2 retrospective cohorts)
				• Potentially reduced in the need for ICA in 48%

Author (year), Search Funding AMSTAR-2	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions
				• In high-risk CCTA-FFR patients, ICA was cancelled in 75% Economic • According to the authors, key factors that could influence the impact and cost-effectiveness of HeartFlow FFRCT in VA include: reasons for direct referral to ICA with no noninvasive testing, frequency of CCTA use, probability of ICA referral after positive CCTA, and prevalence of intermediate stenosis identified by CCTA and functionally significant CAD in the population. The authors did not find data on these factors. Author's Conclusions: Regular use of HeartFlow FFRCT in place of other noninvasive tests does not appear warranted, as HeartFlow FFRCT led to a higher rate of use of ICA when used as a substitute for planned noninvasive cardiovascular testing. We found no evidence to support wider use of CCTA in place of other noninvasive tests in VA. The effect of FFRCT on MACE outcomes is uncertain. Future research should evaluate MACE outcomes on a longer-term basis. The effect of FFRCT on MACE outcomes is uncertain. Future research should evaluate MACE outcomes on a longer-term basis.
AHRQ (2016) *Noninvasive Testing for Coronary Artery Disease* Search: through July 2015	Stable, symptomatic patients with suspected CAD (no known history of CAD) Pretest risk: Variable	Objective: To assess the effectiveness of noninvasive technologies for the diagnosis of CAD or dysfunction that results in symptoms attributable to myocardial ischemia in	Low pretest risk (2 RCTs) • CCTA vs. UC (N=99, low risk subgroup) • SPECT vs. Exercise ECG (N=71, low risk subgroup) Intermediate pretest risk (7 comparative studies)	Low pretest risk (2 RCTs) • Insufficient evidence for all outcomes for both comparisons; evidence based on subgroup analyses from RCTs. Intermediate pretest risk • CCTA vs. UC: ○ No differences between groups for all-cause mortality (28-30 days in 2 trials), MI (index visit in 1

Author (year), Search Funding AMSTAR-2	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions

MEDLINE, Cochrane Database of Systematic reviews, Cochrane Central Register of Controlled trials, Evidence-Based Medicine Reviews–Health Technology Assessment	Outpatient and ED settings	patients who present with signs or symptoms suggestive of CAD, whose condition is stable, and who have no known history of CAD.
		
		Key Questions:
		1. For patients considered to be at *very low or low risk* for CAD, what is the comparative effectiveness of anatomic tests (compared with each other, usual care, or no testing)?
		2. For patients considered to be at *very low or low risk* for CAD, what is the comparative effectiveness of functional tests (compared with each other, usual care, or no testing)?
		3. For patients considered to be at *intermediate to high*
			• CCTA vs. UC: 2 RCTs (N=1,111), 1 prospective cohort (N=200)
			• CCTA vs. various functional testing: 1 RCT (N=10,003)
			• CCTA vs. SPECT: 1 RCT (N=400)
			• SPECT vs. exercise ECG: 2 RCTs (N=1,104)
			
			Low-to-Intermediate pretest risk
			(8 comparative studies)
			• CCTA vs. UC: 2 RCTs (N=1,430), 1 retrospective cohort (N=1,788)
			• CCTA vs. SPECT: 2 RCTs (N=952), 1 retrospective cohort (N=252)
			• CCTA vs. exercise ECG: 1 RCT (N=562), 1 retrospective cohort (N=498)
			
			Intermediate-to-High pretest risk
			(2 comparative studies)
			• CCTA vs. SPECT: 1 RCT
				trial, 28-30 days in 2 trials and 3 months in 1 observational), ICA referral (index visit in 1 trial and 28-30 days in 2 trials), any revascularization (index visit in 2 trials), PCI (index visit and 28 days in 1 trial, and 3 months in 1 observational), CABG (28 days in 1 trial and 3 months in 1 observational), additional noninvasive testing (index visit and 28 days in 1 RCT), and cardiac hospitalizations (ED index visit in 2 trials, 3 months in 1 observational). (Low SOE)
				• CCTA vs. functional testing:
				  ○ No differences between groups for all-cause mortality (12 months and 25 months), nonfatal MI (12 months and 25 months), cardiac hospitalization (25 months), and major procedural complications (stroke, major bleeding). (Moderate SOE).
				  ○ CCTA was associated with a significantly higher referral rate through 3 months for ICA (12.19% vs. 8.11%, RD 4.08, 95% CI 2.90 to 5.26 per 100), any revascularization (6.22% vs. 3.16%, RD 3.07, 95% CI 2.24 to 3.90 per 100), PCI (4.8% vs. 2.4%, RD 2.4, 95% CI 1.7 to 3.1 per 100), and CABG (1.44% vs. 0.76%, RD 0.68, 95% CI 0.27 to 1.09 per 100) (High SOE).
				  ○ CCTA was associated with a significantly increased risk of hospitalization for unstable angina (1.22% vs. 0.82%, RD 0.40, 95% CI 0.01 to 0.80 per 100) and minor side effects from testing (e.g., stress-induced symptoms, mild contrast reactions) (0.74% vs. 0.42%, RR 1.77, 95% CI 1.05 to 3.01) although it is unclear if the differences are clinically meaningful.
				• CCTA vs. SPECT:

Author (year), Search Funding AMSTAR-2	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions
		risk for CAD, what is the comparative effectiveness of anatomic tests (compared with each other, usual care, or no testing)? 4. For patients considered to be at *intermediate to high risk* for CAD, what is the comparative effectiveness of functional tests (compared with each other, usual care, or no testing)? 5. What is the comparative effectiveness of anatomic tests versus functional tests in those who are at *very low or low risk* for CAD? 6. What is the comparative effectiveness of anatomic tests versus functional tests in those who are at	(N=180) • PET vs. SPECT: 1 registry study (N=1,113) High pretest risk (2 comparative studies) • CCTA vs. UC: 1 RCT (N=56, high-risk subgroup) • SPECT vs. exercise ECG: 1 RCT (N=106, high-risk subgroup) Mixed pretest risk (9 comparative studies) • CCTA vs. UC: 1 RCT (N=266) • CCTA vs. exercise ECG: 1 RCT (N=500), 1 administrative database (N=69,883) • CCTA vs. SPECT: 1 prospective registry (N=2,442), 1 administrative database (N=9,690) • CCTA vs. nuclear MPI: 1 prospective registry (N=1,856), 1 administrative database	○ No differences between tests for all-cause mortality (median 24.5 months), cardiac hospitalization (median 40.4 months), for ICA referral, any revascularization, PCI, and additional noninvasive testing, including myocardial perfusion imaging, stress echocardiography, and CCTA (through 12 months); and for minor adverse reactions (including headache, nausea, dizziness, or feeling of warmth), rash or pruritus, and posttest renal dysfunction. (Low SOE). ○ CCTA was associated with a higher risk of CABG procedures through 12 months (3.5% vs. 0.5%, RD 3.0, 95% CI 0.3 events to 5.7 per 100 persons) and a significantly lower incidence of the composite of periprocedural chest pain, shortness of breath, or palpitations (0.5% vs. 15.9%, RD -15.4, 95% CI -20.8 to -10.1 per 100) (Low SOE). • SPECT vs. exercise ECG: ○ No difference between groups in mortality, revascularization and hospitalization for chest pain (Low SOE) through 24 months in one trial in woman only. ○ No difference between groups in ICA through 24 months in 1 trial (woman only), but SPECT was associated with fewer ICAs through 22 months in the second trial (Low SOE) ○ Across both trials, SPECT was associated with less additional noninvasive testing (Low SOE in 1 trial, Moderate SOE in 1 trial). Low-to-Intermediate pretest risk

Author (year), Search Funding AMSTAR-2	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions
		intermediate to high risk for CAD?	(N=141,163) • CCTA vs. stress echocardiography: 1 administrative database (N=89,424) • SPECT vs. exercise ECG: 1 RCT (N=457) • Stress echocardiography vs. exercise ECG: 1 RCT (N=158), 1 prospective cohort (N=5,894), 1 administrative database (N=144,667) • Stress echocardiography vs. SPECT: 1 administrative database (N=212,947) • Exercise ECG vs. Nuclear MPI: 1 administrative database (N=193,406)	• CCTA vs. UC: ○ No differences between tests for all-cause mortality (at 1 month in 1 trial and in the observational study), MI (at index visit and 1 month in 1 trial, and up to 1 month in the observational study), ICA referral (at index visit in 1 trial and at 1-3 months in two trials), any revascularization (at 1-3 months in 2 trials and through 1 month in the observational study), PCI and CABG (both at 3 months in 1 trial), bradyarrhythmia (1 trial) (Low SOE), and cardiac hospitalization (after index visit through 1 month in 1 trial) (Moderate SOE). ○ CCTA was associated with a decreased risk of additional noninvasive testing at the index visit (13.7% vs. 57.8%, RD -44.1, 95% CI -49.2 to -39.1 per 100) as well as through 1 month (23.1% vs. 66.4%, RD -43.3, 95% CI -48.4 to -38.1 per 100) in 1 trial and in one observational study (4% vs. 21%, p<0.001) and of cardiac hospitalization at the ED index visit in 1 trial (50% vs. 77%, RD -26.8, 95% CI -31.9 to -21.8 per 100) (Moderate SOE). • CCTA vs. SPECT ○ No differences between groups in all-cause mortality at 6 months (2 trials) and at 30 months (1 observational study), MI and ICA referral at index visit and through 6 months (2 trials) (Low SOE), any revascularization through 6 months (2 trials), and cardiac hospitalization through 6 months (1 trial) and 30 months (1 observational) (Moderate SOE). ○ CCTA was associated with higher rates of additional noninvasive testing at the index visit: 10.2% vs. 0.9%

Author (year), Search Funding AMSTAR-2	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions

				in the larger trial (RD 9.4, 95% CI 6.1 to 12.7 per 100 patients) and 24% vs. 0% in the smaller trial (RD 24 per 100 people, p<0.001) (SOE High).
				• CCTA vs. Exercise ECG
				  ○ No difference between groups in all-cause mortality (at 30 days in 1 trial and at 12 months in both studies) and MI (at index visit and 30 days in 1 trial, and at 12 months in the observational study). (Low SOE).
				  ○ CCTA was associated with higher referral rate for ICA (9.0% vs. 2.3%, RD 4.8, 95% CI 0.8 to 8.9 per 100 patients) and revascularizations (4.3% vs. 1.3%, RD 3.1, 95% CI 0.5 to 5.7 per 100 patients) through 12 months in 1 trial (Low SOE).
				
				Intermediate-to-High pretest risk
				• CCTA vs. SPECT:
				  ○ Insufficient evidence for death and MI (no incidences through a mean 1.8 months).
				  ○ No differences between tests through a mean 1.8 months for ICA referral, additional noninvasive testing, and CAD-related hospitalization (Low SOE).
				  ○ CCTA was associated with more revascularizations through a mean of 1.8 months (8% vs. 1%, RD 6.6, 95% CI 0.7 to 12.5) (Low SOE).
				• PET vs. SPECT:
				  ○ Insufficient evidence for all outcomes from one large, fair-quality, registry study.
				
				High pretest risk
				• Insufficient evidence for all outcomes for both

Author (year), Search Funding AMSTAR-2	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions

				comparisons; evidence based on subgroup analyses from RCTs.
				
				Mixed pretest risk
				• CCTA vs. UC:
				  ○ No differences between tests through 30 days for MI and contrast-inducted nephropathy in 1 RCT (Low SOE).
				• CCTA vs. Exercise ECG:
				  ○ No differences between tests for all-cause mortality, MI, referral for ICA, and CABG through 12 months in 1 RCT.
				  ○ CCTA was associated with a significantly decreased risk of additional noninvasive testing (2.4% vs. 31.3%, RD -29, 95% CI -37 to -23 per 100) and cardiac rehospitalizations (0.8% vs. 6.9%, RD -6.1, 95% CI -9.5 to -2.7 per 100) (Moderate SOE), but an increased risk of any revascularization (15.2% vs. 7.7%, RD 7.5, 95% CI 1.9 to 13.0 per 100) and PCI (11.9% vs. 4.9%, RD 7, 95% CI 2 to 12 per 100) through 12 months in 1 RCT (Low SOE).
				• CCTA vs. Nuclear MPI
				  ○ No differences between tests for all-cause mortality at 6 months in 1 observational study (Medicare population) (Low SOE).
				  ○ CCTA was associated with significantly higher referral rates for ICA (22.94% vs. 12.13%, adjusted OR 2.19, 95% CI 2.08 to 2.32), PCI (7.85% vs. 3.37%, adjusted OR 2.49, 95% CI 2.28 to 2.72), CABG (3.71% vs. 1.29%, adjusted OR 3.00, 95% CI 2.63 to 3.42), and additional testing (4.98% vs. 3.22%, adjusted OR

Author (year), Search Funding AMSTAR-2	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions

				1.52, 95% CI 1.37 to 1.69) through 6 months in the observational cohort of Medicare patients; and for any revascularization through 6 months in the Medicare population (11.41% vs. 4.59%, adjusted OR 2.76, 95% CI 2.56 to 2.98) and a median 1.42 years in the second observational study in the general population (% NR, adjusted OR 1.62, 95% CI 1.20 to 2.18) (Low SOE).
				• SPECT vs. Exercise ECG:
				  ○ No differences between tests for all-cause mortality and MI but SPECT was associated with significantly fewer revascularizations (10.8% vs. 17.9%, RD -7.1, 95% CI -13.6 to -0.6 per 100) in 1 RCT with 22 months of follow-up (SOE Low).
				• Exercise ECG vs. Nuclear MPI:
				  ○ No differences between tests for all-cause mortality at 6 months in 1 observational study (Low SOE).
				  ○ ECG was associated with significantly fewer referrals for ICA (9.04% vs. 12.13%, adjusted OR 0.72, 95% CI 0.70 to 0.75), any revascularization (4.31% vs. 4.59%, adjusted OR 0.90, 95% CI 0.85 to 0.94), and PCI (2.57% vs. 3.37%, adjusted OR 0.72, 95% CI 0.68 to 0.77), and significantly higher rates of CABG (1.82% vs. 1.29%, adjusted OR 1.37, 95% CI 1.26 to 1.49) and additional noninvasive testing (19.34% vs. 3.22%, adjusted OR 7.46, 95% CI 7.16 to 7.77) through 6 months in 1 observational study, although it is unclear if the differences for any revascularization, PCI and CABG are clinically meaningful (Low SOE).
				• Stress echocardiography vs. Nuclear MPI:

Author (year), Search Funding AMSTAR-2	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions
				○ No between tests for all-cause mortality at 6 months in 1 observational cohort (Low SOE). ○ Stress echocardiography was associated with significantly fewer referrals for ICA (9.50% vs. 12.13%; adjusted OR 0.78, 95% CI 0.76 to 0.81), any revascularization (4.22% vs. 4.59%, adjusted OR 0.93, 95% CI 0.88 to 0.98), and PCI (2.61% vs. 3.37%, adjusted OR 0.76, 95% CI 0.72 to 0.81), and significantly higher rates of CABG (1.69% vs. 1.29%, adjusted OR 1.40, 95% CI 1.29 to 1.52) and additional noninvasive testing (5.57% vs. 3.22%; adjusted OR 1.92, 95% CI 1.83 to 2.0) through 6 months in 1 observational cohort, although it is unclear if the differences for any revascularization, PCI and CABG are clinically meaningful (Low SOE). • Stress echocardiography vs. Exercise ECG: ○ Insufficient evidence from 2 observational studies. Author's Conclusions: A review of current studies found no clear differences between testing strategies across settings regarding clinical or management outcomes to recommend one strategy over another for any given pretest risk group that included intermediate pretest risk patients. No conclusions regarding low-risk patients or those without ACS at high risk are possible. Limited evidence from RCTs trials found no clear differences between CCTA versus other strategies in clinical outcomes across risk groups, although anatomic testing may result in a higher frequency of referral for ICA and revascularization. The frequency of all-cause mortality and MI was low across studies in all settings. The absence of

Author (year), Search Funding AMSTAR-2	Patient Population Setting	Objective, Key Questions	Critical Appraisal of Studies Evidence Base Analysis	Outcomes/Conclusions
				information on posttest risk stratification and subsequent decision-making precluded evaluation of the impact of testing on patient management or outcomes of management. Testing strategies vary in radiation exposure; there is inadequate comparative evidence to make judgments regarding exposure for initial test or downstream testing. Assessment of harms was limited. Future research using more refined, evidence-based definitions of pretest risk coupled with information on posttest risk stratification, its impact on clinical management (treatment and referral for additional testing), and longer term follow up to assess clinical outcomes is needed to determine optimal testing strategies and roles of tests in different pretest risk groups.

ACS = acute coronary syndrome; CABG = coronary artery bypass graft; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CCTA FFR = coronary computed tomography angiography with fractional flow reserve; CI = confidence interval; ECG = electrocardiography; ED=emergency department; CABG = coronary artery bypass graft; ICA= invasive coronary angiography; MACE = major adverse cardiovascular events; MD = mean difference; MI = myocardial infarction; MPI = myocardial perfusion imaging; NR= not reported; OR = odds ratio; PCI = percutaneous coronary intervention; PET = positron emission tomography; RCT = randomized controlled trial; RD = risk difference; ROB= risk of bias; RR = risk ratio; SOE = strength of evidence; SPECT = single positron emission computed tomography; UC = usual care; VA = Veterans Affairs.
*Includes: CCTA, Stress Echo, Nuclear MPI, Ex ECG, CMR, other.
†Propensity score-matched analysis; however, sufficient information about the propensity scoring to assess its validity was not provided.
‡Unadjusted scores.

2.8 Clinical Guidelines

Table 7. Summary of Clinical Practice Guidelines for the Diagnosis of CAD in patients with chest pain

	Imaging Modality or Diagnostic Consideration	Evidence Base	Recommendation	Strength of Recommendation
American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons[71] 2012* *Guideline for the Diagnosis and Management of Patients with Stable Ischemic Heart Disease*	CCTA in patients able **or** unable to exercise	5 meta-analyses, 3 controlled clinical trials	Because the presence of significant calcification often can preclude the accurate assessment of lesion severity or cause a false positive study, CCTA should not be performed in patients who have known extensive calcification or a high risk of CAD. CCTA is reasonable for patients with a low to intermediate pretest probability of IHD who are incapable of at least moderate physical functioning or have disabling comorbidity. CCTA might be reasonable for patients with an intermediate pretest probability of IHD who have at least moderate physical functioning or no disabling comorbidity.	• Class of recommendation: IIa • Level of evidence: B (Recommendation in favor of treatment or procedure being useful. Some conflicting evidence from single randomized trial or nonrandomized studies)
	CCTA in patients with inconclusive functional tests	1 prognostic study	CCTA is reasonable for patients with an intermediate probability of CAD who has any of the following: a) Continued symptoms with prior normal test, or b) Inconclusive exercise or pharmacological stress, or	• Class of recommendation: IIa • Level of evidence: C (Recommendation in favor of treatment or procedure being useful.

	Imaging Modality or Diagnostic Consideration	Evidence Base	Recommendation	Strength of Recommendation
			c) Unable to undergo stress with MPI or Echo	Only divergent expert opinion, case studies, or standard of care available).
	Exercise with nuclear MPI or Echo in patients able to exercise	5 meta-analyses, 2 cost effectiveness studies, and 2 additional publications of unknown study design	Exercise stress with nuclear MPI or echocardiography is recommended for patients with an intermediate to high pretest probability of IHD who have an uninterpretable ECG and at least moderate physical functioning or no disabling comorbidity.	• Class of recommendation: I • Level of evidence: B
			Exercise stress with nuclear MPI or echocardiography is reasonable for patients with an intermediate to high pretest probability of obstructive IHD who have an interpretable ECG and at least moderate physical functioning or no disabling comorbidity.	• Class of recommendation: IIa • Level of evidence: B (Recommendation in favor of treatment or procedure being useful. Some conflicting evidence from single randomized trial or nonrandomized studies)
			Exercise stress with nuclear MPI is not recommended as an initial test in low-risk patients who have an interpretable ECG and at least moderate physical functioning or no disabling comorbidity.	• Class of recommendation: III (no benefit) • Level of evidence: C
	Pharmacological stress with nuclear MPI, Echo, or CMR in	1 observational study, 2 economic evaluations	Pharmacological stress with nuclear MPI, echocardiography, or CMR is not recommended for patients who have	• Class of recommendation: III (no benefit)

	Imaging Modality or Diagnostic Consideration	Evidence Base	Recommendation	Strength of Recommendation
	patients able to exercise		an interpretable ECG and at least moderate physical functioning or no disabling comorbidity.	• Level of evidence: C
	Pharmacological stress with nuclear MPI or Echo in patients unable to exercise	5 meta-analyses, 1 observational study, 1 position statement, 1 economic evaluation	Pharmacological stress with nuclear MPI or echocardiography is recommended for patients with an intermediate to high pretest probability of IHD who are incapable of at least moderate physical.	• Class of recommendation: I • Level of evidence: B
	Pharmacological stress CMR in patients able to exercise	3 meta-analyses	Pharmacological stress with CMR can be useful for patients with an intermediate to high pretest probability of obstructive IHD who have an *un*interpretable ECG and at least moderate physical functioning or no disabling comorbidity.	• Class of recommendation: I • Level of evidence: B
	Pharmacological stress CMR in patients unable to exercise	3 meta-analyses, 1 RCT	Pharmacological stress CMR is reasonable for patients with an intermediate to high pretest probability of IHD who are incapable of at least moderate physical functioning or have disabling comorbidity.	• Class of recommendation: IIa • Level of evidence: B (Recommendation in favor of treatment or procedure being useful. Some conflicting evidence from single randomized trial or nonrandomized studies)

	Imaging Modality or Diagnostic Consideration	Evidence Base	Recommendation	Strength of Recommendation
	Hybrid Imaging	N/A	This diagnostic imagining modality is discussed, but no specific recommendations for the use of hybrid imaging are included in this guideline.	N/A
The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC)[133] 2019 *2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes*	Stress echocardiography, stress CMR, SPECT, PET, or CCTA	5 RCTs, 1 meta-analysis, and 1 recommendation document	Stress echocardiography, stress CMR, SPECT, PET, or CCTA is recommended as the initial test to diagnose CAD in symptomatic patients in whom obstructive CAD cannot be excluded by clinical assessment alone.	• Class of recommendation: I • Level of evidence: B
	Selection of initial non-invasive diagnostic test.	None cited.	It is recommended that selection of the initial non-invasive diagnostic test is done based on the clinical likelihood of CAD and other patient characteristics that influence test performance (e.g. characteristics determining ability to exercise, likelihood of good image quality, expected radiation exposure, and risks or contraindications), local expertise, and the availability of tests	• Class of recommendation: I • Level of evidence: C
	CCTA	None cited.	CCTA should be considered as an alternative to invasive angiography if another non-invasive test is equivocal or non-diagnostic.	• Class of recommendation: IIa • Level of evidence: C
			CCTA is not recommended when extensive coronary calcification, irregular heart rate, significant obesity, inability to cooperate with breath-hold commands, or any other conditions make obtaining good image quality unlikely.	• Class of recommendation: III • Level of evidence: C

	Imaging Modality or Diagnostic Consideration	Evidence Base	Recommendation	Strength of Recommendation
National Institute for Health and Care Excellence (NICE)[2] 2016 *Recent-onset chest pain of suspected cardiac origin: assessment and diagnosis*	CCTA	Specific references used to make this recommendation were not explicitly stated.	Offer 64-slice (or above) CCTA if: • clinical assessment indicates typical or atypical angina†, or • clinical assessment indicates non-anginal chest pain but 12-lead resting ECG has been done and indicates ST-T changes or Q waves. The committee's view is that CCTA should be considered the first choice diagnostic test for all people assessed as having typical or atypical angina. However individual circumstances, including potential contraindications, should be considered when deciding the most appropriate strategy for diagnostic investigation.	NR
American College of Cardiology (ACC) and the American Heart Association (AHA)[14] 2014 *Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes*	ECG	1 position statement	In patients with chest pain or other symptoms suggestive of ACS, a 12-lead ECG should be performed and evaluated for ischemic changes within 10 minutes of the patient's arrival at an emergency facility.	• Level of evidence: C • Class of recommendation: I
	ECG	None cited.	If the initial ECG is not diagnostic but the patient remains symptomatic and there is a high clinical suspicion for ACS, serial ECGs (eg, 15- to 30-minute intervals during the first hour) should be performed to detect ischemic changes.	• Level of evidence: C • Class of recommendation: I
	Treadmill ECG, Stress MPI, Stress Echo	Treadmill ECG: 3 RCTs	It is reasonable for patients with possible ACS who have normal serial	• Treadmill ECG - Level of evidence: A

	Imaging Modality or Diagnostic Consideration	Evidence Base	Recommendation	Strength of Recommendation
		Stress MPI/Stress Echo: 1 comparative cohort, 1 prognostic study	ECGs and cardiac troponins to have a treadmill ECG, stress myocardial perfusion imaging, or stress echocardiography before discharge or within 72 hours after discharge.	- Class of recommendation: IIa • Stress MPI, stress echo - Level of evidence: B - Class of recommendation: IIa
	CCTA	3 RCTs	In patients with possible ACS and a normal ECG, normal cardiac troponins, and no history of CAD, it is reasonable to initially perform (without serial ECGs and troponins) coronary CT angiography to assess coronary artery anatomy	• Level of evidence: A • Class of recommendation: IIa
	MPI	1 RCT, 1 case series	In patients with possible ACS and a normal ECG, normal cardiac troponins, and no history of CAD, it is reasonable to initially perform (without serial ECGs and troponins) rest myocardial perfusion imaging with a technetium-99m radiopharmaceutical to exclude myocardial ischemia	• Level of evidence: B • Class of recommendation: IIa
	Stress testing	4 observational studies	Noninvasive stress testing is recommended in low and intermediate-risk patients who have been free of ischemia at rest or with low-level activity for a minimum of 12 to 24 hours	• Level of evidence: B • Class of recommendation: I
	Exercise stress test	3 observational studies	Stress testing with an imaging modality should be used in patients who are	• Level of evidence: B

	Imaging Modality or Diagnostic Consideration	Evidence Base	Recommendation	Strength of Recommendation
			able to exercise but have ST changes on resting ECG that may interfere with interpretation. In patients undergoing a low-level exercise test, an imaging modality can add prognostic information.	• Class of recommendation: I
	Pharmacological stress test	None cited.	Pharmacological stress testing with imaging is recommended when physical limitations preclude adequate exercise stress.	• Level of evidence: C • Class of recommendation: I

CCTA = coronary computed tomography, CMR = cardiac magnetic resonance, ECG = electrocardiogram, ECHO = echocardiography, IHD = ischemic heart disease, MPI = myocardial perfusion imaging, N/A = not applicable, NR = not reported, PET = positron emission tomography, RCT = randomized control trial, SPECT = single photon emission computed tomography.

* In 2014, an update to this guideline was published. However, none of the updates involved imagining modalities of interest to this review.

† According to NICE Guideline recommendation 1.3.3.1, assessing the typicality of chest pain should be done as follows:

· Presence of three of the features below is defined as typical angina.

· Presence of two of the three features below is defined as atypical angina.

· Presence of one or none of the features below is defined as non-anginal chest pain.

Anginal pain is:

· constricting discomfort in the front of the chest, or in the neck, shoulders, jaw, or arms

· precipitated by physical exertion

· relieved by rest or GTN within about 5 minutes.

2.9 Appropriate Use Criteria

Table 8. Summary of Appropriate Use Criteria for the Diagnosis of CAD in patients with chest pain

AUC Developing Organization(s) Year Title	Imaging Modality	Recommendation	AUC score
American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and the Society of Thoracic Surgeons[56]* 2019 *2019 Appropriate Use Criteria for Multimodality Imaging in the Assessment of Cardiac Structure and Function in Nonvalvular Heart Disease*	F-18 FDG PET	Use of F-18 FDG PET for the initial evaluation when symptoms or signs suggest heart disease is rarely appropriate (test is not generally acceptable and is not a reasonable approach for the indication).	Median Appropriate Use Score: 2
		Use of F-18 FDG PET for the Initial evaluation of known or suspected HF (systolic or diastolic) based on symptoms, signs, or abnormal test results to assess systolic or diastolic function and to assess for possible etiology (CAD, valvular disease) is rarely appropriate (test is not generally acceptable and is not a reasonable approach for the indication).	Median Appropriate Use Score: 3
	MPI (SPECT/PET)	Use of MPI (SPECT/PET) for the initial evaluation when symptoms or signs suggest heart disease is rarely appropriate (test is not generally acceptable and is not a reasonable approach for the indication).	Median Appropriate Use Score: 2
		Use of MPI (SPECT/PET) for the Initial evaluation of known or suspected HF (systolic or diastolic) based on symptoms, signs, or abnormal test results to assess systolic or diastolic function and to assess for possible etiology (CAD, valvular disease) is appropriate (test is generally acceptable and is a reasonable approach for the indication).	Median Appropriate Use Score: 7
	CT (including CCTA)	Use of CT (including CCTA) for the initial evaluation when symptoms or signs suggest	Median Appropriate

AUC Developing Organization(s) Year Title	Imaging Modality	Recommendation	AUC score
		heart disease may be appropriate (test may be generally acceptable and may be a reasonable approach for the indication). This also implies that more research and/or patient information is needed to classify the indication definitively.	Use Score: 4
		Use of CT (including CCTA) for the Initial evaluation of known or suspected HF (systolic or diastolic) based on symptoms, signs, or abnormal test results to assess systolic or diastolic function and to assess for possible etiology (CAD, valvular disease) may be appropriate (test may be generally acceptable and may be a reasonable approach for the indication). This also implies that more research and/or patient information is needed to classify the indication definitively.	Median Appropriate Use Score: 6
American College of Cardiology Foundation Appropriate Use Criteria Task Force, the American Society of Nuclear Cardiology, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the Society of Cardiovascular Computed Tomography, the Society for Cardiovascular Magnetic Resonance, and the Society of Nuclear Medicine[101]† 2009 *2009 Appropriate Use Criteria for Cardiac Radionuclide Imaging*	Radionuclide Imaging	Use of Radionuclide Imaging for evaluation of ischemic equivalent (non-acute) in patients with: ● Low pretest probability of CAD ● ECG interpretable AND able to exercise is considered inappropriate.	Median Appropriate Use Score: 3
		Use of Radionuclide Imaging for evaluation of ischemic equivalent (non-acute) in patients with: ● Low pretest probability of CAD ● ECG uninterpretable OR unable to exercise is considered appropriate.	Median Appropriate Use Score: 7
		Use of Radionuclide Imaging for evaluation of ischemic equivalent (non-acute) in patients with: ● Intermediate pretest probability of CAD	Median Appropriate Use Score: 7

AUC Developing Organization(s) Year Title	Imaging Modality	Recommendation	AUC score
		● ECG interpretable AND able to exercise is considered appropriate.	
		Use of Radionuclide Imaging for evaluation of ischemic equivalent (non-acute) in patients with: ● Intermediate pretest probability of CAD ● ECG uninterpretable OR unable to exercise is considered appropriate.	Median Appropriate Use Score: 9
		Use of Radionuclide Imaging for evaluation of ischemic equivalent (non-acute) in patients with: ● High pretest probability of CAD ● Regardless of ECG interpretability and ability to exercise is considered appropriate.	Median Appropriate Use Score: 9
		Use of Radionuclide Imaging in patients with chest pain and: ● Possible ACS ● ECG—no ischemic changes or with LBBB or electronically ventricular paced rhythm ● Low-risk TIMI score ● Peak troponin: borderline, equivocal, minimally elevated is considered appropriate.	Median Appropriate Use Score: 8
		Use of Radionuclide Imaging in patients with chest pain and: ● Possible ACS ● ECG—no ischemic changes or with LBBB or electronically ventricular paced rhythm ● High-risk TIMI score ● Peak troponin: borderline, equivocal, minimally elevated is considered appropriate.	Median Appropriate Use Score: 7

AUC Developing Organization(s) Year Title	Imaging Modality	Recommendation	AUC score
		Use of Radionuclide Imaging in patients with chest pain and: ● Possible ACS ● ECG—no ischemic changes or with LBBB or electronically ventricular paced rhythm ● Low-risk TIMI score ● Negative peak troponin levels is considered appropriate.	Median Appropriate Use Score: 8
		Use of Radionuclide Imaging in patients with chest pain and: ● Possible ACS ● ECG—no ischemic changes or with LBBB or electronically ventricular paced rhythm ● High-risk TIMI score ● Negative peak troponin levels is considered appropriate.	Median Appropriate Use Score: 8
		Use of Radionuclide Imaging in patients with chest pain and definite ACS is considered inappropriate.	Median Appropriate Use Score: 1
		Use of Radionuclide Imaging in patients with chest pain (rest imaging only) and: ● Possible ACS ● ECG—no ischemic changes or with LBBB or electronically ventricular paced rhythm ● Initial troponin negative ● Recent or ongoing chest pain is considered appropriate.	Median Appropriate Use Score: 7
American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular	CCTA	Use of CCTA for the detection of CAD in symptomatic patients with the following conditions: ● ECG interpretable AND ● Able to exercise	Median Appropriate Use Score: 5

AUC Developing Organization(s) Year Title	Imaging Modality	Recommendation	AUC score
Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance[240] 2010 *Appropriate Use Criteria for Cardiac Computed Tomography*		● Low pretest probability of CAD Is considered uncertain.	
		Use of CCTA for the detection of CAD in symptomatic patients with the following conditions: ● ECG interpretable AND ● Able to exercise ● Intermediate pretest probability of CAD Is considered appropriate.	Median Appropriate Use Score: 7
		Use of CCTA for the detection of CAD in symptomatic patients with the following conditions: ● ECG interpretable AND ● Able to exercise ● High pretest probability of CAD Is considered inappropriate.	Median Appropriate Use Score: 3
		Use of CCTA for the detection of CAD in symptomatic patients with the following conditions: ● ECG interpretable AND ● Able to exercise ● Low pretest probability of CAD Is considered appropriate.	Median Appropriate Use Score: 7
		Use of CCTA for the detection of CAD in symptomatic patients with the following conditions: ● ECG interpretable AND ● Able to exercise ● Intermediate pretest probability of CAD Is considered appropriate.	Median Appropriate Use Score: 8

AUC Developing Organization(s) Year Title	Imaging Modality	Recommendation	AUC score
		Use of CCTA for the detection of CAD in symptomatic patients with the following conditions: ● ECG interpretable AND ● Able to exercise ● High pretest probability of CAD Is considered uncertain.	Median Appropriate Use Score: 4
		Use of CCTA for the detection of CAD in patients with acute symptoms with suspicion of ACS (urgent presentation) and definite MI is considered inappropriate.	Median Appropriate Use Score: 1
		Use of CCTA for the detection of CAD in patients with acute symptoms with suspicion of ACS (urgent presentation) and persistent ECG ST-segment elevation following exclusion of MI is considered uncertain.	Median Appropriate Use Score: 6
		Use of CCTA for the detection of CAD in patients with acute symptoms with suspicion of ACS (urgent presentation) and acute chest pain of uncertain cause (differential diagnosis includes pulmonary embolism, aortic dissection, and ACS [“triple rule out”]) is considered uncertain.	Median Appropriate Use Score: 6
		Use of CCTA for the detection of CAD in symptomatic patients with low pretest probability of CAD and normal ECG and cardiac biomarkers is considered appropriate.	Median Appropriate Use Score: 7
		Use of CCTA for the detection of CAD in symptomatic patients with intermediate pretest probability of CAD and normal ECG and cardiac biomarkers is considered uncertain.	Median Appropriate Use Score: 7
		Use of CCTA for the detection of CAD in symptomatic patients with high pretest	Median Appropriate

AUC Developing Organization(s) Year Title	Imaging Modality	Recommendation	AUC score
		probability of CAD and normal ECG and cardiac biomarkers is considered uncertain.	Use Score: 4
		Use of CCTA for the detection of CAD in symptomatic patients with low pretest probability of CAD and an uninterpretable ECG is considered appropriate.	Median Appropriate Use Score: 7
		Use of CCTA for the detection of CAD in symptomatic patients with intermediate pretest probability of CAD and an uninterpretable ECG is considered uncertain.	Median Appropriate Use Score: 7
		Use of CCTA for the detection of CAD in symptomatic patients with high pretest probability of CAD and an uninterpretable ECG is considered uncertain.	Median Appropriate Use Score: 4
		Use of CCTA for the detection of CAD in symptomatic patients with low pretest probability of CAD and a nondiagnostic ECG or equivocal biomarkers is considered appropriate.	Median Appropriate Use Score: 7
		Use of CCTA for the detection of CAD in symptomatic patients with intermediate pretest probability of CAD and a nondiagnostic ECG or equivocal biomarkers is considered uncertain.	Median Appropriate Use Score: 7
		Use of CCTA for the detection of CAD in symptomatic patients with high pretest probability of CAD and a nondiagnostic ECG or equivocal biomarkers is considered uncertain.	Median Appropriate Use Score: 4
		Use of CCTA in patients with a prior normal ECG exercise test but continued symptoms is considered appropriate regardless of pretest probability of CAD.	Median Appropriate Use Score: 7
		Use of CCTA in patients with prior ECG exercise	Median

AUC Developing Organization(s) Year Title	Imaging Modality	Recommendation	AUC score
		testing and a Duke Treadmill Score pointing to low risk findings is considered inappropriate.	Appropriate Use Score: 2
		Use of CCTA in patients with prior ECG exercise testing and a Duke Treadmill Score pointing to intermediate risk findings is considered appropriate.	Median Appropriate Use Score: 7
		Use of CCTA in patients with prior ECG exercise testing and a Duke Treadmill Score pointing to high risk findings is considered inappropriate.	Median Appropriate Use Score: 3
		Use of CCTA for sequential testing after stress imaging procedures resulting in discordant ECG exercise and imaging results is considered appropriate.	Median Appropriate Use Score: 8
		Use of CCTA on patients with prior stress imagining procedures and equivocal ischemia is considered appropriate.	Median Appropriate Use Score: 8
		Use of CCTA on patients with prior stress imagining procedures and mild ischemia is considered uncertain.	Median Appropriate Use Score: 6
		Use of CCTA on patients with prior stress imagining procedures and moderate or severe ischemia is considered inappropriate.	Median Appropriate Use Score: 2
		Use of CCTA on patients with a prior CAC score of zero >5 years ago is considered uncertain.	Median Appropriate Use Score: 2
		Use of CCTA on patients with a positive CAC score >2 years ago is considered inappropriate.	Median Appropriate Use Score: 2
		Use of CCTA on patients with a CAC score of <100 is considered appropriate.	Median Appropriate Use Score: 8

AUC Developing Organization(s) Year Title	Imaging Modality	Recommendation	AUC score
		Use of CCTA on patients with a CAC score of 100 to 400 is considered appropriate.	Median Appropriate Use Score: 8
		Use of CCTA on patients with a CAC score of 401 to 1000 is considered uncertain.	Median Appropriate Use Score: 6
		Use of CCTA on patients with a CAC score of >1000 is considered uncertain.	Median Appropriate Use Score: 4
ACR/ACC/AHA/AATS/ACEP/ASNC/NASCI/ SAEM/SCCT/SCMR/SCPC/SNMMI/STR/STS[208] 2015 *Appropriate Utilization of Cardiovascular Imaging in Emergency Department Patients with Chest Pain*	CCTA	Use of CCTA in patients presenting to the ED with chest pain and who have had serial ECG and Troponin Negative for NSTEMI or ACS is considered appropriate.	NR
		Use of CCTA in patients presenting to the ED with chest pain and who have had serial ECG and Troponin borderline for NSTEMI or ACS is considered appropriate.	NR
	SPECT/PET Rest	Use of SPECT/PET Rest in patients presenting to the ED with chest pain and who have had serial ECG and Troponin Negative for NSTEMI or ACS is considered to be rarely appropriate.	NR
		Use of SPECT/PET in patients presenting to the ED with chest pain and who have had serial ECG and Troponin borderline for NSTEMI or ACS is considered to be rarely appropriate.	NR
	SPECT/PET Stress/Rest	Use of SPECT/PET Stress/Rest in patients presenting to the ED with chest pain and who have had serial ECG and Troponin Negative for NSTEMI or ACS is considered to be appropriate.	NR
		Use of SPECT/PET Stress/Rest in patients presenting to the ED with chest pain and who	NR

AUC Developing Organization(s) Year Title	Imaging Modality	Recommendation	AUC score
		have had serial ECG and Troponin borderline for NSTEMI or ACS is considered to be appropriate.	
American College of Radiology[11] 2016 *Appropriateness Criteria®* *Chronic Chest Pain—High Probability of Coronary Artery Disease*	Tc-99m SPECT MPI rest and stress	Use of Tc-99m SPECT MPI rest and stress in patients with chronic chest pain and a high probability of CAD is considered to be usually appropriate.	Appropriate use rating: 9
	Arteriography coronary	Use of Arteriography coronary in patients with chronic chest pain and a high probability of CAD is considered to be usually appropriate.	Appropriate use rating: 9
	Rb-82 PET heart stress	Use of Rb-82 PET heart stress in patients with chronic chest pain and a high probability of CAD is considered to be usually appropriate.	Appropriate use rating: 8
	CTA coronary arteries with IV contrast	Use of CTA coronary arteries with IV contrast in patients with chronic chest pain and a high probability of CAD is considered to be usually appropriate.	Appropriate use rating: 8
	CT	Use of CT chest without and with IV contrast without and with IV contrast in patients with a high probability of CAD is considered to maybe be appropriate.	Appropriate use rating: 4
American College of Radiology[21] 2020 *Acute Nonspecific Chest Pain-Low Probability of Coronary Artery Disease*	CCTA	Use of CCTA coronary arteries with IV contrast in patients with acute nonspecific chest pain and low probability of CAD is considered to be usually appropriate.	NR
		Use of CCTA chest with IV contrast in patients with acute nonspecific chest pain and low probability of CAD is considered to be maybe appropriate.	NR
	CT	Use of CT chest without and with IV contrast in patients with acute nonspecific chest pain and low probability of CAD is considered to be	NR

AUC Developing Organization(s) Year Title	Imaging Modality	Recommendation	AUC score
		maybe appropriate.	
		Use of CT heart function and morphology with IV contrast coronary in patients with acute nonspecific chest pain and low probability of CAD is considered to be usually not appropriate.	NR
	Arteriography coronary	Use of Arteriography coronary in patients with acute nonspecific chest pain and low probability of CAD is considered to be usually not appropriate.	NR
	SPECT or SPECT/CT MPI rest and stress	Use of SPECT or SPECT/CT MPI rest and stress in patients with acute nonspecific chest pain and low probability of CAD is considered to be usually not appropriate.	NR
American College of Radiology[216] 2018 *Chronic Chest Pain-Noncardiac Etiology Unlikely: Low to Intermediate Probability of Coronary Artery Disease*	CCTA	Use of CCTA coronary arteries with IV contrast in patients with chronic chest pain, noncardiac etiology unlikely, and low to intermediate probability of coronary artery disease is considered to be usually appropriate.	NR
	Rb-82 PET/CT heart	Rb-82 PET/CT heart in patients with chronic chest pain, noncardiac etiology unlikely, and low to intermediate probability of coronary artery disease is considered to be usually appropriate.	NR
	SPECT or SPECT/CT MPI	SPECT or SPECT/CT MPI rest and stress in patients with chronic chest pain, noncardiac etiology unlikely, and low to intermediate probability of coronary artery disease is considered to be usually appropriate.	NR
		SPECT or SPECT/CT MPI stress only in patients with chronic chest pain, noncardiac etiology unlikely, and low to intermediate probability of coronary artery disease is considered to be	NR

AUC Developing Organization(s) Year Title	Imaging Modality	Recommendation	AUC score
		usually appropriate.	
		SPECT or SPECT/CT MPI rest only in patients with chronic chest pain, noncardiac etiology unlikely, and low to intermediate probability of coronary artery disease is considered to be usually not appropriate.	NR
	Arteriography coronary	Use of Arteriography coronary arteries without and with IV contrast in patients with chronic chest pain, noncardiac etiology unlikely, and low to intermediate probability of coronary artery disease is considered to be usually not appropriate.	NR
AIM Specialty Health[10] 2021 *Appropriate Use Criteria: Imaging of the Heart*	Nuclear Cardiology Myocardial Perfusion Imaging	**Among symptomatic patients with suspected CAD who have not had evaluation of CAD (MPI, stress echo, cardiac PET, coronary CTA or cardiac catheterization) within the preceding sixty (60) days, MPI is considered medically necessary in any of the following scenarios:** • Chest pain - With intermediate or high pretest probability of CAD **OR** - With low or very low pretest probability of CAD and high risk of CAD (using ASCVD Pooled Cohort Equations) • Atypical symptoms: shortness of breath (dyspnea), neck, jaw, arm, epigastric or back pain, sweating (diaphoresis), or exercise-induced syncope - With intermediate or high risk of CAD (using ASCVD Pooled Cohort Equations) • Other symptoms: palpitation, nausea, vomiting, anxiety, weakness, fatigue, or	NR

AUC Developing Organization(s) Year Title	Imaging Modality	Recommendation	AUC score
		exercise-induced dizziness, lightheadedness, or near syncope, etc. - With high risk of CAD (using ASCVD Pooled Cohort Equations) • Patients with any cardiac symptom who have diseases/conditions with which coronary artery disease commonly coexists such as: - Abdominal aortic aneurysm; **OR** - Established and symptomatic peripheral vascular disease; **OR** - Prior history of cerebrovascular accident (CVA), transient ischemic attack (TIA) or carotid endarterectomy (CEA) or high grade carotid stenosis (>70%); **OR** - Chronic renal insufficiency or renal failure; **OR** • Patients who have undergone cardiac transplantation; **OR** • Patients in whom a decision has been made to treat with Interleukin 2; **OR** Patients awaiting solid organ transplantation **MPI is considered medically necessary for patients with established flow-limiting CAD (diagnosed by MPI, cardiac PET, stress echo, or coronary angiography (CCTA or invasive) demonstrating coronary stenosis greater than 70% or FFR less than or equal to 0.8) in patients who:** • Have new or worsening symptoms. • Have not undergone revascularization and have no symptoms or stable symptoms and	

AUC Developing Organization(s) Year Title	Imaging Modality	Recommendation	AUC score
		either of the following scenarios applies: - No evaluation of coronary artery disease (MPI, stress echo, cardiac PET, coronary CTA, or cardiac catheterization) within the preceding 3 years - No evaluation of coronary artery disease (MPI, cardiac PET, stress echo, coronary CTA, or cardiac catheterization) within the preceding one (1) year in a patient who has undergone cardiac transplantation and has been found to have coronary artery disease since transplantation **MPI is considered medically necessary for patients who have established CAD and have had MI or unstable angina within the previous 90 days when BOTH the following criteria are met:** • Patient did not undergo coronary angiography at time of acute event • Patient is currently clinically stable **MPI is considered medically necessary for patients who have new onset arrhythmias (patient can be symptomatic or asymptomatic) in any of the following scenarios:** • Patients with sustained (lasting more than 30 seconds) or non-sustained (more than 3 beats but terminating within 30 seconds) ventricular tachycardia; OR • Patients with atrial fibrillation or flutter and high or intermediate risk of CAD (using ASCVD	

AUC Developing Organization(s) Year Title	Imaging Modality	Recommendation	AUC score
		Pooled Cohort Equations); OR • Patients with atrial fibrillation or flutter and established CAD; OR • Patients who have frequent premature ventricular contractions (PVC) defined as more than thirty (30) PVCs per hour on ambulatory EKG (Holter) monitoring - It is not clinically indicated to perform MPI for evaluation of infrequent premature atrial or ventricular depolarizations **MPI is considered medically necessary for patients with abnormal exercise treadmill test (performed without imaging). This guideline applies to patients with suspected or established CAD.** • Abnormal findings on an exercise treadmill test include (chest pain, ST segment change, abnormal BP response or complex ventricular arrhythmias) **MPI is considered medically necessary for patients with abnormal findings on cardiac CT or CCTA** • Symptomatic patients with EITHER of the following: - Coronary artery calcium score > 400 Agatston units - Intermediate severity coronary stenosis on coronary CTA	
	CCTA and CT	**Indications where FFR-CT may be appropriate**	NR

AUC Developing Organization(s) Year Title	Imaging Modality	Recommendation	AUC score

	Derived Fractional Flow Reserve (FFR-CT)	**but is not a required capability of the performing imaging facility**
		• Suspected CAD in patients who have had abnormal exercise EKG test (performed without imaging) within the past 60 days.
		  ○ When both the following apply:
		  - Patient is symptomatic
		  - During testing the patient had exercise-induced chest pain, ST segment change, abnormal blood pressure response, or complex ventricular arrhythmias.
		• Suspected CAD in patients who have had equivocal MPI or stress echocardiography within the past 60 days.
		  ○ When both the following apply:
		  - Patient is symptomatic
		  - The imaging portion of the study is neither clearly normal nor clearly abnormal
		• Suspected CAD in patients who have had abnormal MPI or stress echocardiography within the past 60 days.
		  ○ When both the following apply:
		  - Patient is symptomatic
		  - The imaging portion of the study is abnormal
		
		Indications where FFR-CT may be appropriate and is a required capability of the imaging facility
		• In symptomatic patients with suspected coronary artery disease who have abnormal	

AUC Developing Organization(s) Year Title	Imaging Modality	Recommendation	AUC score
		resting EKG • In symptomatic patients with suspected coronary artery disease who have not had recent CAD evaluation - When no CAD imaging evaluation (MPI, cardiac PET, stress echo, CCTA or coronary angiography) has been performed within the preceding sixty (60) days.	
	PET Myocardial Imaging	Clinical Indications for PET Perfusion Imaging include: **Suspected coronary artery disease in symptomatic patients who have not had evaluation of coronary artery disease (MPI, stress echo, cardiac PET, coronary CTA or cardiac catheterization) within the preceding sixty (60) days** • Chest pain - With intermediate or high pretest probability of CAD (Table 1); **OR** - With low or very low pretest probability of CAD (Table 1) and high risk of CAD (SCORE) • Atypical symptoms: shortness of breath (dyspnea), neck, jaw, arm, epigastric or back pain, sweating (diaphoresis), or exercise-induced syncope - With intermediate or high risk of coronary artery disease (using ASCVD Pooled Cohort Equations) • Other symptoms: palpitation, nausea, vomiting, anxiety, weakness, fatigue, or exercise-induced dizziness, lightheadedness,	NR

AUC Developing Organization(s) Year Title	Imaging Modality	Recommendation	AUC score
		or near syncope, etc. - With high risk of coronary artery disease (using ASCVD Pooled Cohort Equations) • Patients with any cardiac symptom who have diseases/conditions with which coronary artery disease commonly coexists such as: - Abdominal aortic aneurysm; **OR** - Established and symptomatic peripheral vascular disease; **OR** - Prior history of cerebrovascular accident (CVA), transient ischemic attack (TIA) or carotid endarterectomy (CEA) or high grade carotid stenosis (>70%); **OR** - Chronic renal insufficiency or renal failure; **OR** • Patients who have undergone cardiac transplantation; **OR** • Patients in whom a decision has been made to treat with Interleukin 2; **OR** • Patients awaiting solid organ transplantation **Patients with new onset arrhythmias (patient can be symptomatic or asymptomatic). (This guideline applies to patients with suspected or established CAD).** **Patients with new onset congestive heart failure or recently recognized left ventricular systolic dysfunction (patient can be symptomatic or asymptomatic). (This guideline applies to patients with suspected or established CAD).**	

AUC Developing Organization(s) Year Title	Imaging Modality	Recommendation	AUC score
		Patients with abnormal exercise treadmill test (performed without imaging). (This guideline applies to patients with suspected or established CAD). **Patients with abnormal findings on cardiac CT or CCTA** • PET perfusion imaging is considered medically necessary in the following scenarios: • Symptomatic patients with EITHER of the following: - Coronary artery calcium score > 400 Agatston units - Intermediate severity coronary stenosis on coronary CTA	

ACS = acute coronary syndrome, ASCVD = AHA/ACC risk calculator, AUC = appropriate use criteria, CAC = coronary artery calcium, CAD = coronary artery disease, CCTA = coronary computed tomography, CT = computed tomography, ECG = electrocardiogram, ED = emergency department, FDG = Fludeoxyglucose, FFR = fractional flow reserve, IV = intravenous, MI = myocardial infarction, MPI = myocardial perfusion imaging, NR = not reported, NSTEMI = Non-ST-Segment Elevation Myocardial Infarction, PET = positron emission tomography, SPECT = single photon emission computed tomography, TIMI = Thrombolysis in Myocardial Infarction

* Imaging for each indication was then rated and classified as Appropriate (A), May Be Appropriate (M), or Rarely Appropriate (R) on the basis of these multiple rounds of review and revision.

Median Score 7 to 9: Appropriate test for specific indication (test is generally acceptable and is a reasonable approach for the indication).

Median Score 4 to 6: May Be Appropriate test for specific indication (test may be generally acceptable and may be a reasonable approach for the indication). May Be Appropriate also implies that more research and/or patient information is needed to classify the indication definitively.

Median Score 1 to 3: Rarely Appropriate test for specific indication (test is not generally acceptable and is not a reasonable approach for the indication).

† Score 7–9: Appropriate test for specific indication (test **is** generally acceptable and **is** a reasonable approach for the indication).

Score 4–6: Uncertain for specific indication (test **may** be generally acceptable and **may** be a reasonable approach for the indication). (Uncertainty also implies that more research and/or patient information is needed to classify the indication definitively.)

Score 1–3: Inappropriate test for that indication (test **is not** generally acceptable and **is not** a reasonable approach for the indication).

2.10 Expert Consensus Statements

Table 9. Summary Table of Expert Consensus Statements

Contributing Organization **Year** ***Document Title***	**Consensus**
CCTA	
Society of Cardiovascular Computed Tomography[172] 2021 ***Expert consensus document on coronary computed tomographic angiography: A report of the society of Cardiovascular Computed Tomography***	**Evaluation of Stable Coronary Artery Disease: Coronary CTA in Native Vessels** • It is appropriate to perform CTA as the first line test for evaluating patients with no known CAD who present with stable typical or atypical chest pain, or other symptoms which are thought to represent a possible anginal equivalent (e.g. dyspnea on exertion, jaw pain). • It is appropriate to perform CTA as a first line test for evaluating patients with known CAD who present with stable typical or atypical chest pain, or other symptoms which are thought to represent a possible anginal equivalent (e.g. dyspnea on exertion, jaw pain • It is appropriate to perform coronary CTA following a non-conclusive functional test, in order to obtain more precision regarding diagnosis and prognosis, if such information will influence subsequent patient management. • It is recommended to perform CTA as the first line test when considering evaluation for revascularization strategies using the ISCHEMIA Trial. • It may be appropriate to perform CTA in selected asymptomatic high risk individuals, especially in those who have a higher likelihood of having a large amount of noncalcified plaque • It is rarely appropriate to perform coronary CTA in very low risk symptomatic patients, e.g., <40 years of age with non-cardiac symptoms (chest wall pain, pleuritic chest pain). • It is rarely appropriate to perform CTA in low- and intermediate risk asymptomatic patients **Evaluation of Stable Coronary Artery Disease: Coronary CTA Post Revascularization** • It is appropriate to perform coronary CTA in symptomatic patients with intracoronary stent diameter 3.0 mm. Measures to improve accuracy of stent imaging should be utilized, to include strict heart rate control (goal <60 bpm), iterative reconstruction,

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	sharp kernel reconstruction, and mono-energetic reconstructions (when available). Protocols to optimize stent imaging should be developed and followed. • It may be appropriate to perform coronary CTA in symptomatic patients with stents <3.0 mm, especially those known to have thin stent struts (<100 mm) in proximal, non-bifurcation locations. • It is appropriate to perform CTA for evaluation of patients with prior CABG, particularly if graft patency is the primary objective. • It is appropriate to perform CTA to visualize grafts and other structures prior to re-do cardiac surgery. **Evaluation of Stable Coronary Artery Disease: Coronary CTA with FFR or CTP** • It may be appropriate to perform CT derived FFR and CT myocardial perfusion Imaging to evaluate the functional significance of intermediate stenoses on CTA (30-90% diameter stenosis) particularly in the setting of multivessel disease to help guide ICA referral and revascularization treatment planning. LM stenosis ≥50% and severe triple vessel disease should undergo invasive coronary angiography. • Adding FFRCT and stress-CTP to CTA increases specificity, positive predictive value, and diagnostic accuracy over regular CTA. • FFRCT and stress-CTP may be largely comparable in diagnostic utility. CTP is a potentially valuable alternative particularly when CT-FFR is technically difficult (e.g., suboptimal CTA quality, prior revascularization). **Evaluation of Stable Coronary Artery Disease: Coronary CTA in Other Conditions** • It is appropriate to perform CTA for coronary artery evaluation prior to noncoronary cardiac surgery as an equivalent alternative to invasive angiography in selected patients, e.g., low-intermediate probability of CAD, younger patients with primarily non-degenerative valvular conditions. • CTA may be considered an appropriate alternative to other noninvasive tests for evaluation of selected patients prior to noncardiac surgery. • It is appropriate to perform CTA to exclude coronary artery disease in patients with suspected non-ischemic cardiomyopathy.

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	• It may be appropriate to perform late enhancement CT imaging to detect infiltrative heart disease or scar in selected patients who have non-ischemic or ischemic cardiomyopathy and who cannot undergo cardiac MRI. Such imaging may be performed if it has the potential to impact the diagnosis and/or treatment (e.g. planning for ablation therapy) • It may be appropriate to perform CTA as an alternative to invasive coronary angiography for the screening of patients for coronary allograft vasculopathy in selected clinical practice settings. • It is appropriate to perform CTA for the evaluation of coronary anomalies. • It is appropriate to EKG gate aortic dissection and aneurysm CTA, as well as pulmonary embolus studies in men >45 years and women >55 years, and analyze and report the coronary arteries. • CTA with a limited delayed image (60e90 sec) is an appropriate alternative to TEE when the primary aim is to exclude LA/LAA thrombus and in patients where the risks associated with TEE outweigh the benefits. In all situations CTA and TEE should be discussed with the patient in the setting of shared decision making. • It may be appropriate to perform late enhancement CT imaging for the evaluation of myocardial viability in selected patients who cannot undergo cardiac MRI. Such imaging may be performed if it has the potential to impact the diagnosis and/or treatment (e.g. planning for revascularization). **Reporting on CTA: Coronary and Non Coronary Information** • The CAD-RADs reporting is recommended. • It is appropriate to report prior myocardial infarction when its features are evident on CTA. • It is appropriate to report remote myocardial infarction when fatty metaplasia or calcification within an area of infarction are present.
Cardiovascular Medicine and Society[195] 2020	**To move forward toward a coronary CTA–first paradigm, this ACC Summit Team recommends the following:** 1. Use coronary CTA as the default test for evaluating patients with stable chest pain and low-

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Current Evidence and Recommendations for Coronary CTA First in Evaluation of Stable Coronary Artery Disease	to-intermediate pre-test probability of obstructive CAD and for those with high pre-test probability of significant obstructive CAD, to rule out the presence of left main CAD, particularly when a conservative treatment strategy is selected. 2. Increase payment for coronary CTA. Specifically, cardiac CT services should be moved to an Ambulatory Payment Classification group with tests that are more similar with respect to clinical scope and resource use. Importantly, increased advocacy, support, and collaboration with ACC will be needed to work with CMS and congress to implement such changes effectively. 3. Explore options for "bundled payments" for cardiac testing. Value-based models would increase incentives to use coronary CTA to avoid other, more costly noninvasive or invasive diagnostic procedures. To start, shared savings models that reduce current average cost from first chest pain onset to 90 days post-evaluation or postintervention could be developed. 4. Identify expert and financial support to increase the number of capable coronary CTA providers. 5. Develop strategies to improve provider and delivery team competency in performing coronary CTA: update training guidelines for cardiovascular fellows, CT technologists, and other ancillary staff, including continuing education and periodic quality assessment. Grandfather training rules to allow more practicing cardiologists to obtain credentials with the support of ACC and industry sponsors. Use remote technologies such as telemedicine to expand the reach of training and delivery. 6. Establish an ACC coronary CTA registry for evaluating chest pain. This registry should include medical and economic variables to evaluate "total cost of care" associated with coronary CTA. Ideally, commercial payers will collaborate with the ACC on this registry to validate costs. 7. Improve advocacy for coronary CTA by direct engagement with public and private payers. Work with CMS and Congress to establish more equitable payment for coronary CTA procedures. 8. Engage commercial payers in discussions on eliminating pre-approvals for coronary CTA and FFR CT for providers participating in the coronary CTA registry. 9. Improve education of cardiologists and primary care physicians on when to consider coronary CTA testing (vs. other techniques) and how to use the

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	results in patient management.
Canadian Cardiovascular Society, Canadian Association of Radiologists Canadian Association of Nuclear Medicine, Canadian Nuclear Cardiology Society, Canadian Society of Cardiac Magnetic Resonance[22] 2007 ***Joint Position Statement on Advanced Non-invasive Cardiac Imaging using Positron Emission Tomography, Magnetic Resonance Imaging and Multi-Detector Computed Tomographic Angiography in the Diagnosis and Evaluation of Ischemic Heart Disease***	**CAD Detection with CT Angiography** *Class I Indication* 1. Assessment of anomalous coronary arteries (Level C evidence). *Class IIa Indications* 1. 16- or 64-slice MDCT for patient diagnosis of significant coronary artery disease (≥ 50% diameter stenosis)(Level B evidence); 2. 16- or 64-slice MDCT for identification of coronary artery segments with significant stenosis (≥ 50% diameter stenosis) in coronary segments ≥ 1.5 mm in diameter (Level B evidence); 3. 16- and 64-slice MDCT for the assessment of graft patency (Level B evidence). *Class IIb Indication* 1. 64-slice MDCT for the assessment of all coronary segments including those with vessel diameters < 1.5 mm (Level B evidence). *Class III (no benefit or harmful)* 1. Diagnosis of CAD in patients with a. irregular dysrhythmias (atrial fibrillation, frequent extrasystoles); b. severe coronary calcification; c. inability to perform sufficient breath-holds; d. renal failure or other contraindications to intravenous contrast agents; e. contraindications to radiation exposure.
Quantitative Cardiac Imaging Study Group[53] 2020 ***Clinical quantitative cardiac imaging for the assessment of myocardial ischemia***	**Cardiac CT** • CT perfusion imaging is not frequently used, whereas CT angiography offers highly accurate coronary angiography. • Challenges of cardiac CT include limited temporal resolution, beam and scatter artefacts, radiation dose and low contrast-to-noise ratios. • CT systems with increased rotation speed, photon counting energy-selective X-ray detectors and advanced machine learning technology, as well as two-compartment analysis could overcome the technological challenges. • The combined assessment of stenosis and characterization of atherosclerosis in

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	relation to myocardial ischemia promises the greatest clinical value but requires testing in trials. • Evaluation of patients with insufficient angiographic image quality or borderline stenosis on coronary CT angiography might be improved with the use of CT for myocardial ischemia.
Nuclear Imaging (SPECT/PET)	
Canadian Cardiovascular Society, Canadian Association of Radiologists Canadian Association of Nuclear Medicine, Canadian Nuclear Cardiology Society, Canadian Society of Cardiac Magnetic Resonance[22] 2007 ***Joint Position Statement on Advanced Non-invasive Cardiac Imaging using Positron Emission Tomography, Magnetic Resonance Imaging and Multi-Detector Computed Tomographic Angiography in the Diagnosis and Evaluation of Ischemic Heart Disease***	**Myocardial Perfusion Imaging (MPI) using PET for Diagnosis and/or Risk Stratification of CAD** *Class I Indications* 1. Pharmacological MPI using PET for the diagnosis of CAD* and/or risk stratification of patients who a. have non-diagnostic non-invasive imaging tests or where such a test does not agree with clinical diagnosis (Level B evidence). b. may be prone to artifact that could lead to an equivocal other test, such as obese patients (Level B evidence); c. are unable to exercise or have left bundle branch block (LBBB) or ventricular pacing (Level B evidence). *Class IIa Indications* 1. Pharmacological MPI using PET for the diagnosis of CAD for patients with intermediate pretest likelihood of disease and/or risk stratification of patients who are able to exercise (Level B evidence); 2. For diagnosis and risk stratification of patients being considered for high-risk non-cardiac surgery who have intermediate clinical risk predictors; or have mild clinical risk predictors with poor functional capacity (<4 METS) (Level B/C evidence). *Class IIb Indications* 1. Exercise PET using MPI for the diagnosis of CAD and/or risk stratification (Level B evidence); 2. Quantification of myocardial flow to determine the hemodynamic significance of a given coronary stenosis or to diagnose balanced multivessel disease (Level B/C evidence); 3. Quantification of myocardial flow to define impaired microvascular function (e.g. Syndrome

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	X) (Level B/C evidence). *Class III (no benefit or harmful)* 1. Contraindications to all pharmacological agents (dipyridamole, adenosine, dobutamine); 2. Unstable pattern of ischemic chest pain; 3. Contraindications to radiation exposure.
Quantitative Cardiac Imaging Study Group[53] 2020 ***Clinical quantitative cardiac imaging for the assessment of myocardial ischemia***	**SPECT** • SPECT is most commonly used in the clinic for myocardial perfusion imaging. • Challenges of SPECT include radiation dose and limited quantification of myocardial perfusion. • Dedicated cardiac SPECT cameras have emerged, with improved sensitivity and resolution at lower radiation doses and in patients with challenging features (including those with a high BMI). • Quantitative measures of the perfusion defect size have become more widely available as diagnostic and prognostic markers with the introduction of solid- state detector CZT technology. • Dynamic imaging enables compartmental modelling and provides absolute measures of myocardial ischemia, thereby bringing SPECT closer to PET as the reference standard. **PET** • PET is the clinical reference standard for the quantification • of myocardial perfusion. • Challenges of PET use include limited visual assessment of quantitative 15O- water PET and the lower spatial resolution of PET compared with CT or MRI perfusion imaging. • Small or 13N- ammonia cyclotrons, as well as the availability of 18F- labelled tracers, could improve the cost- effectiveness of cardiac PET imaging, as well as logistics and dissemination. • Quantitative measures of myocardial ischemia are provided with the addition of the measurement of viability and functional parameters during a single scan.

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	• Hybrid imaging combining PET perfusion imaging with coronary CT angiography data might provide comprehensive assessment, especially in patients with multivessel disease.
Society of Nuclear Medicine and Molecular Imaging & ASNC[169] 2018 ***Clinical Quantification of Myocardial Blood Flow Using PET: Joint Position Paper of the SNMMI Cardiovascular Council and the ASNC***	**Assessment of Myocardial Blood Flow (MBF) and Myocardial Flow Reserve (MFR) using PET** • A relationship between the severity of epicardial coronary artery stenoses and PET measures of both peak hyperemic stress MBF and MFR has been established for more than 2 decades. • Though initially established using 15O-water, this finding was quickly replicated using 13N-ammonia and more recently using 82Rb. • The application of stress MBF and MFR for improving the diagnostic accuracy of PET MPI with clinical protocols has been investigated by many groups with both 13N-ammonia and 82Rb. • Although these studies have consistently demonstrated improved diagnostic sensitivity, at least 2 large studies have raised concerns about potential for decreased specificity, possibly due to the contributions of diffuse atherosclerosis and microvascular disease to stress MBF and MFR measurements. • Consequently, the positive predictive value of even severely depressed (<1.5) MFR is only modest. • Conversely, preserved MFR (>2.0) has an excellent negative predictive value for high-risk CAD (i.e., left main and 3-vessel disease), and high-risk disease is extremely uncommon with an MFR of more than 2.5.
Myocardial CT Perfusion	
Society of Cardiovascular Computed Tomography[188] 2020 ***Society of cardiovascular computed tomography expert consensus document on myocardial computed tomography perfusion imaging***	**Absolute contraindications to pharmacologic stress myocardial CT perfusion** • High-risk unstable angina • Decompensated or inadequately controlled CHF • Uncontrolled hypertension (BP > 200/110) • Hypotension (SBP<90 mm Hg) • Known contrast allergy, unless pre-treated • Allergy to stress agent • Uncontrolled cardiac arrhythmias

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	• Severe symptomatic aortic stenosis. • Bronchospastic Lung Disease (avoid adenosine and dipyridamole; regadenoson may be considered unless active wheezing) • Acute pulmonary embolism. • Active CVA • Acute myocarditis or pericarditis. • Acute aortic dissection. • Severe pulmonary hypertension. • Acute myocardial infarction. • Acutely ill for any reason. • Severe renal Insufficiency (GFR<30mi/min/BSA) • High-degree (AV) block. • Unable to cooperate with breath hold instructions. • Any caffeine, theophylline, or chocolate consumption in the last 12 hours **Relative contraindications to pharmacologic stress myocardial CT perfusion** • Known left main coronary stenosis >50% • Hypertrophic obstructive cardiomyopathy or other forms of outflow tract obstruction • Electrolyte abnormalities • Significant tachyarrhythmias or bradyarrhythmia • Recent stroke • Recent seizure • Heart rate >100, and cannot be treated with beta blockers • Moderate renal insufficiency (GFR 30-60mi/min/BSA) • Morbid Obesity (BMI>40) **Key Consensus Statements for Myocardial CT Perfusion** 1. We recommend that myocardial CTP may be added to coronary CTA when there is a high likelihood of ischemic heart disease, known CAD, prior coronary intervention, or significant calcifications, Additionally, CTP may be added when there is a known stenosis of indeterminate functional significance. In such cases, myocardial CTP is

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	recommended if knowledge regarding the presence and severity of ischemia would impact patient management and CTP is feasible. 2. Myocardial CTP imaging with pharmacologic stress testing requires supervision by a trained medical provider who is experienced in the administration of pharmacologic stress agents and stress testing. 3. Continuous 12-lead ECG monitoring may be performed using radiolucent electrodes and leads. Alternatively, 12-lead ECG monitoring can be interrupted during scan acquisition while continuous rhythm is still being recorded and monitored by the scanner console. Upon the completion of imaging, a 12 lead ECG should be performed to ensure there are no significant changes from baseline suggestive of post-stress myocardial ischemia or injury. 4. If an automated bolus-tracking algorithm is utilized, a region of interest should be defined in either the proximal-ascending or mid-descending thoracic aorta. The automated trigger should be set to a Hounsfield Unit (HU) threshold that is ~80-100HU above the baseline HU of the selected reference area immediately prior to the contrast injection. After the scanner is triggered, a short pause (~5 seconds) is required to allow for breath-hold instructions to be given. Contrast dose and flow rate is typically ~60–70ml injected at 5–6ml/sec. 5. The optimal sequence of scans (rest first versus stress first) has not been determined and either sequence has advantages and disadvantages. Our committee suggests assessment of factors that could impair exclusion of obstructive CAD on coronary CTA (e.g. significant coronary calcium, prior coronary event or coronary revascularization, high pre-test probability of obstructive CAD) prior to decision to perform CTP. Those patients with a high likelihood or known significant coronary disease or severe amount of CAC may undergo stress myocardial perfusion imaging first; whereas, patients who lack the above features may undergo coronary CTA first. 6. A delay of 10–20 minutes between the rest and stress CT acquisitions is recommended to minimize myocardial contrast agent contamination and to eliminate the potential adverse interaction of pharmacologic stress agents and nitroglycerin administration. 7. There is no consensus about whether imaging should be performed at end-systole or during diastasis although most larger trials to date have selected diastole. A

Contributing Organization **Year** ***Document Title***	**Consensus**
	multiphase acquisition which includes phases from both systole and diastole can be considered so that the phase with the least amount of artifact can be selected for analysis retrospectively. 8. For optimal image interpretation, images may be reconstructed from multiple phases of the cardiac cycle, typically at 5–10% intervals of the R-R image acquisition window and raw CTA and CTP data files should be retained until image interpretation is complete. 9. In static visual CTP interpretation, myocardial images are typically arranged using three standard orthogonal views - the short axis, vertical long axis, and horizontal long axis. CTP images usually use a narrow window width of ~200–300 and level setting of ~100–150 with an average slice thickness of 5–8 mm. Images may be viewed in minimal intensity projection (MinIP) or average intensity projections 10. Perfusion defects should be described in terms of size, transmurally, and reversibility in the context of the degree of stenosis in the supplying coronary artery.
Echocardiography	
Quantitative Cardiac Imaging Study Group[53] 2020 ***Clinical quantitative cardiac imaging for the assessment of myocardial ischemia***	**Echocardiography** • Echocardiography is most commonly applied for cardiac function imaging but is increasingly also being used for the assessment of myocardial perfusion and can be performed at the bedside. • The challenges of echocardiography include the common presence of noise and artefacts, lack of reproducibility, variable image quality and time- consuming manual analysis. • High frame rate echocardiography allows the estimation of myocardial blood velocity as a semiquantitative measure of myocardial ischemia with improved image quality. • Artificial intelligence solutions using machine learning for automated myocardial segmentation promise automated and fast segmentation and perfusion quantification. • Evaluation of patients with suspected acute coronary syndrome at the bedside is the primary strength of echocardiography when performed by experienced operators.

BMI = body mass index, CABG = coronary artery bypass graft, CAC = coronary artery calcium, CAD = coronary artery disease, CHF = congestive heart failure, CT = computed tomography, CTA = computed tomography angiogram, CTP = computed tomography perfusion, ECG = electrocardiogram, FFR = fractional flow reserve, MDCT = multi-detector

computed tomography, mm = millimeter, MPI = myocardial perfusion imaging, MRI = magnetic resonance imaging, PET = positron emission tomography, TEE = transesophageal echocardiogram.

2.11 Medicare and Representative Private Insurer Coverage Policies

Table 10. Summary table of payer policies for CCTA (including FFR)

Payer (year)	Evidence Base	Covered	Not Covered
CMS (2021) National Coverage Determination (NCD) for Noninvasive Fractional Flow CT *No other NCD was determined to be appropriate at this time*	2 SRs of diagnostic accuracy 5 diagnostic accuracy studies 1 prospective observational cohort 3 retrospective observational studies 1 registry study	FDA-approved FFRct technology may be considered reasonable and necessary in the management of patients with symptomatic, stable ischemic heart disease (SIHD) when the CCTA analysis is completed and demonstrates one of the following criteria: 1. Left main disease with intermediate coronary stenosis (lumen diameter reduction of 30-50%); **OR** 2. Proximal and mid-left anterior descending (LAD) coronary artery disease with intermediate stenosis (lumen reduction 40-70%); OR Proximal and mid-left circumflex disease with intermediate coronary stenosis (lumen reduction 40-70%; (considered equivalent to two-vessel disease); OR 3. Proximal two- or three-vessel disease with intermediate coronary stenosis in at least two vessels; OR 4. Right coronary disease with intermediate (lumen reduction 40-70%) coronary stenosis This service should be performed in patients with stable coronary symptoms. It should not be performed until after the base study (CCTA) has been completed and interpreted. If higher grade stenoses (i.e., >70%) are present, this study is not medically necessary, as the patient should proceed to catheterization. Similarly, low-grade stenoses (< 30%) do not require additional confirmatory data. If more than two intermediate risk coronary lesions are identified, the clinical situation is considered high risk, and the patient should proceed directly to catheterization.	FFRct is not considered reasonable in the following clinical circumstance: 1. Severe obesity (BMI > 39 kg/m2) 2. Prior placement of prosthetic valves 3. Known severe aortic stenosis 4. Prior placement of grafts in coronary bypass surgery 5. Suspicion of acute coronary syndrome (where MI or unstable angina have not been ruled out) 6. Intracoronary metallic stent 7. Status post-heart transplantation 8. Recent MI (30 days or less) 9. Prior pacemaker or defibrillator lead placement 10. Newly diagnosed systolic heart failure, with no prior left heart catheterization 11. Left main coronary artery disease with Intermediated Coronary Stenosis (lumen reduction less than or equal to 30%) 12. Non-obstructing stenosis (<50% of all major epicardial vessels) on CTA or catherization in the past twelve months, in the absence of a new symptom complex

Payer (year)	Evidence Base	Covered	Not Covered
Aetna (2019)	See Appendix N for references	Using 64-slice or greater, medically necessary for the following indications: A. Rule out obstructive coronary stenosis in persons with a low or intermediate pre-test probability of coronary artery disease or atherosclerotic cardiovascular disease by Framingham risk scoring, Pooled Cohort Equations, or by American College of Cardiology (ACC) criteria (see Appendix) who: i. Are symptomatic ii. Have a positive (i.e., greater than or equal to 1 mm ST segment depression) stress test C. Evaluation of asymptomatic persons at an intermediate pre-test probability of coronary heart disease or atherosclerotic cardiovascular disease by Framingham risk scoring or Pooled Cohort Equations who have an equivocal or uninterpretable exercise or pharmacological stress test or have resting electrocardiogram (ECG) changes (such as left bundle branch block (LBBB), pathologic q-waves, or right bundle branch block (RBBB) with left anterior fascicular block (LAFB) in which coronary artery disease (CAD) is a possible etiology. Note: Current guidelines from the American Heart Association recommend against routine stress testing for screening asymptomatic adults. D. Pre-operative assessment of/for: i. Persons scheduled to undergo 'high-risk" non-cardiac surgery, where an imaging stress test or invasive coronary angiography is being deferred unless absolutely necessary. The ACC defines high-risk surgery as emergent operations, especially in the elderly, aortic and other major vascular surgeries, peripheral vascular surgeries, and anticipated prolonged surgical procedures with large fluid shifts and/or blood loss involving the abdomen and thorax. ii. Planned non-coronary cardiac surgeries including valvular heart disease, congenital heart disease, and pericardial disease, in lieu of cardiac catheterization as the initial imaging study, in persons with low or intermediate pretest	Experimental and investigational for persons with any of the following contraindications to the procedure because its effectiveness above has not been established: • Body mass index (BMI) greater than 40 (except when 3rd generation Dual-Source CT (DSCT) 120-kv tube voltage is utilized). • Inability to image at desired heart rate (under 80 beats/min), despite beta blocker administration. • Person with allergy or intolerance to iodinated contrast material • Persons in atrial fibrillation (except when rate-controlled and 3rd generation Dual-Source CT (DSCT) 120-kv tube voltage is utilized) or with other significant arrhythmia. • Persons with extensive coronary calcification by plain film or with prior Agatston score greater than 1000. • for screening of asymptomatic persons, evaluation of atherosclerotic burden, evaluation of persons at high pre-test probability of coronary artery disease, evaluation of stent occlusion or in-stent restenosis, evaluation of persons with an equivocal PET rubidium study, identification of vulnerable plaques, monitoring of atheroma burden,

Payer (year)	Evidence Base	Covered	Not Covered
		risk of obstructive CAD. F. Detection and delineation of suspected coronary anomalies in young persons (less than 30 years of age) with suggestive symptoms (e.g., angina, syncope, arrhythmia, and exertional dyspnea without other known etiology of these symptoms in children and adults; dyspnea, tachypnea, wheezing, periods of pallor, irritability (episodic crying), diaphoresis, poor feeding and failure to thrive in infants). G. Calculation of fractional flow reserve (HeartFlow FFR) for persons who have a coronary CTA that has shown coronary artery disease of uncertain functional significance, or is non-diagnostic.	and for all other indications (e.g., atrial angiosarcoma). Note: The selection of CT angiography should be made within the context of other testing modalities such as stress myocardial perfusion images or cardiac ultrasound results so that the resulting information facilitates the management decision and does not merely add a new layer of testing. • Aetna considers coronary CT angiography experimental and investigational for assessment of coronary atherosclerosis in asymptomatic diabetics who do not otherwise meet the above criteria for CT coronary angiography because of insufficient evidence.
BCBS of NC Corporate Medical Policy (2018)	See Appendix N for references	The use of CT Coronary Angiography (CCTA), with or without Fractional Flow Reserve assessed by CT (FFR-CT) may be covered when accompanied by pre-test considerations as well as supporting clinical data and prerequisite information based on the following diagnostic indications: A. Indications where FFR-CT will not be required in conjunction with CCTA: i. Congenital coronary artery anomalies • For evaluation of suspected congenital anomalies of the coronary arteries. B. Indications where FFR-CT may be appropriate but is not a required capability of the performing imaging facility: i. Congestive heart failure/cardiomyopathy/LV dysfunction • For exclusion of coronary artery disease in patients with	The use of CT Coronary Angiography (CCTA), with or without Fractional Flow Reserve assessed by CT (FFR-CT) is considered investigational for all other indications.

Payer (year)	Evidence Base	Covered	Not Covered
		left ventricular ejection fraction <55% and low to moderate coronary heart disease risk (using standard methods of risk assessment, such as SCORE risk calculation) in whom CAD had not been excluded as the etiology of the cardiomyopathy. • Patients with high coronary heart disease risk should undergo cardiac catheterization. ii. Pre-operative evaluation for patients undergoing non-coronary cardiac surgery • Evaluation of symptomatic* or asymptomatic patients at moderate coronary heart disease risk (using standard methods of risk assessment, such as the SCORE risk calculation) to avoid an invasive angiogram, where all the necessary pre-operative information can be obtained using cardiac CT. • Procedures include open and percutaneous valvular procedures or ascending aortic surgery iii. Suspected coronary artery disease in symptomatic* patients who: • Have *not had evaluation* of coronary artery disease (MPI, cardiac PET, stress echo, CCTA or cardiac catheterization) within the preceding 60 days a. When both of the following apply: 1. Patient has low or moderate coronary heart disease risk (using standard methods of risk assessment such as the SCORE risk calculation) AND 2. During testing the patient had exercise-induced chest pain, ST segment change, abnormal BP response or complex ventricular arrhythmias • Have *had equivocal MPI or SE* within the past 60 days a. When both of the following apply: 1. Patient has low or moderate coronary heart disease risk (using standard methods of risk	

Payer (year)	Evidence Base	Covered	Not Covered
		assessment such as the SCORE risk calculation)AND 2. The imaging portion of the study is neither clearly normal nor clearly abnormal • Have had *abnormal MPI or stress echo* within the past 60 days a. When both of the following apply: 1. Abnormal MPI or stress echo is suspected to be false positive on the basis of low coronary heart disease risk (using standard methods of risk assessment such as the SCORE risk calculation) AND 2. The imaging portion of the study is abnormal • Have abnormal resting EKG • Have not had a recent CAD evaluation (MPI, cardiac PET, stress echo, CCTA or coronary angiography) within the preceding 60 days C. Indications where FFR-CT may be appropriate and is a required capability of the imaging facility i. Suspected CAD in symptomatic* patients who have abnormal resting EKG • When resting EKG abnormalities (left bundle branch block, electronically paced ventricular rhythm, left ventricular hypertrophy with repolarization abnormalities, resting ST segment depression 1 mm or more, digoxin effect or pre-excitation syndrome) would render an exercise treadmill test (without imaging) uninterpretable ii. Suspected CAD in symptomatic* patients who have not had recent CAD evaluation • When no CAD imaging evaluation (MPI, cardiac PET, stress echo, CCTA or coronary angiography) has been performed within the preceding sixty (60) days	

Payer (year)	Evidence Base	Covered	Not Covered
Cigna 2020	See Appendix N for references	A. Symptomatic individuals who have a 'low' or 'intermediate' pretest probability of CAD* B. 'Low' or 'intermediate' pre-test probability of coronary disease with persistent symptoms after a stress test. C. Replace performance of invasive coronary angiogram in individuals with low risk of CAD (i.e. Pre-op non-coronary surgery). D. For symptomatic individuals, evaluate post-CABG graft patency when only graft patency is a concern and imaging of the native coronary artery anatomy is not needed, such as in early graft failure. Additional Indications: E. Re-do CABG F. Evaluate coronary artery anomalies and other complex congenital heart disease of cardiac chambers or great vessels. G. Anomalous coronary artery(ies) suspected for diagnosis or to plan treatment and less than age 40 with a history that includes one or more of the following : i. Persistent exertional chest pain and normal stress test, ii. Full sibling(s) with history of sudden death syndrome before age 30 or with documented anomalous coronary artery, iii. Resuscitated sudden death and contraindications for conventional coronary angiography. iv. Prior nondiagnostic coronary angiography in determining the course of the anomalous coronary artery in relation to the great vessels, origin of a coronary artery or bypass graft location. H. Unexplained new onset of heart failure. I. Evaluation of newly diagnosed congestive heart failure or cardiomyopathy. i. No prior history of coronary artery disease, the ejection fraction is less than 50 ii. percent, and low or intermediate risk on the pre-test probability assessment, and iii. No exclusions to cardiac CT angiography.	NR

Payer (year)	Evidence Base	Covered	Not Covered
		iv. No cardiac catheterization, SPECT, cardiac PET, or stress echocardiogram has been performed since the diagnosis of congestive heart failure or cardiomyopathy. J. Ventricular tachycardia (6 beat runs or greater) if CCTA will replace conventional invasive coronary angiography. K. Equivocal coronary artery anatomy on conventional cardiac catheterization. L. Newly diagnosed dilated cardiomyopathy. M. Preoperative assessment of the coronary arteries in individuals who are going to undergo surgery for aortic dissection, aortic aneurysm, or valvular surgery if CCTA will replace conventional invasive coronary angiography. N. Vasculitis/Takayasu's/Kawasaki's disease O. Cardiac Trauma Indications for FFR-CT A. To further assess CAD seen on a recent CCTA that is of uncertain physiologic significance	
Wisconsin Physicians Service Insurance Corporation (2017) Local Coverage Determination States covered: Iowa, Kansas, Missouri, Nebraska, Indiana, Michigan.	None cited.	A. Alternative to invasive angiography and stress testing. For patients with anginal symptoms, patients with unclear stress tests results, patients in whom the stress test result contradicts the clinical assessment, to determine the patency of coronary artery bypass grafts, as an alternative when cardiac catheterization is impossible or carries a high risk, to rule out stenosis before non-coronary cardiac surgery such as valve replacement or resection of tumors, and clarifying unclear finding after invasive angiography. B. Assess patients suspected of having a congenital coronary anomaly of great vessels, cardiac chambers and valves. It is often used after an anomaly has been identified following a different test such as prior invasive coronary angiogram. CCTA is used to decide if surgery is indicated and for surgical planning. C. Evaluate acute chest pain in the emergency department (ED). The rationale is to quickly triage patients in order to rule out coronary artery disease as a possible cause of symptoms. Many will present	A. The test is never covered for screening, i.e., in the absence of signs, symptoms or disease. B. The test will be considered not medically necessary if the anticipated results are not expected to provide new, additional information to that already previously obtained from other tests (such as stress myocardial perfusion images or cardiac ultrasound). New or additional information should facilitate the management decision, not merely add a new layer of testing. C. The test will be considered not

Payer (year)	Evidence Base	Covered	Not Covered
		with a normal electrocardiogram and myocardial enzymes. D. Assess coronary or pulmonary venous anatomy. Coronary mapping is primarily for pre-surgical planning such as pacemaker lead placement in the lateral coronary vein to resynchronize cardiac contraction in patients with heart failure, or guiding biventricular pacemaker placement. Pulmonary vein anatomy can vary from patient to patient. Pulmonary vein mapping is primarily for catheter ablation which can isolate electrical activity from the pulmonary veins and allow for the elimination of recurrent atrial fibrillation, or help eliminate procedural complications. E. Assess etiology with new onset heart failure for evaluation of coronary arteries.	medically necessary if pretest evaluation indicates that the patient would require invasive cardiac angiography for further diagnosis or for therapeutic intervention. D. The test may be denied, on post-pay review, as not medically necessary when used for cardiac evaluation if there were pre-test knowledge of sufficiently extensive calcification of the suspect coronary segment that would diminish the interpretive value. (e.g., angina decubitus, unstable angina, Prinzmetal angina, etc.) E. Coverage is limited to devices that process thin, high resolution slices (1mm or less). The multi-detector scanners must have at least 64 slices per rotation capability. F. The administration of beta blockers and the monitoring of the patient during MDCT/CCTA by a physician experienced in the use of cardiovascular drugs is included as part of the test and is not a separately payable service. G. All studies must be ordered by the physician/qualified non-physician practitioner treating the H. patient and who will use the results of the test in the management of the patient. I. The test must be performed under

Payer (year)	Evidence Base	Covered	Not Covered
			the direct supervision of a physician, similar to the stress myocardial perfusion imaging. J. This LCD does not address electron beam tomography (EBT) technology or Ultrafast CT for coronary artery examination. There is no extension of coverage of EBT based on this policy. K. Quantitative calcium scoring is not a covered service and will be denied as not medically necessary. Calcium scoring reported in isolation is considered a screening service. When performed in association with CT angiography, there is neither separate nor additional included reimbursement for the calcium scoring. L. Atrial fibrillation or atrial flutter alone is not an indication; atrial fibrillation or atrial flutter with planned ablation therapy is allowed.
National Government Services, Inc. (2016) Local Coverage Determination Covered States: Connecticut, Illinois, Maine, Massachusetts, Minnesota, New Hampshire, New York	See Appendix N for references	A. **Patient presenting with chest pain syndrome.** These tests may be used in lieu of an imaging stress test. The clinician must have a high degree of suspicion that CAD is high on the differential diagnosis of the symptoms. B. **To facilitate the management decision of a patient with an equivocal stress test.** These tests might be chosen in select patients who have an equivocal stress (or stress imaging) test. The rationale is that a noninvasive coronary anatomic test (CCTA) allows an alternate method of assessing the coronary arteries, which would limit the number of negative invasive coronary angiograms.	A. These tests are never covered for screening, i.e., in the absence of signs, symptoms or disease. B. These tests will be considered not medically necessary if the anticipated results are not expected to provide new, additional information to that already previously obtained from other tests (such as stress myocardial perfusion images or cardiac ultrasound). New or additional

Payer (year)	Evidence Base	Covered	Not Covered
(Entire state, Downstate, Upstate, Queens), Rhode Island, Vermont, Wisconsin		C. **When the recurrence of symptoms in patients with known coronary artery disease may be related to progression/exacerbation of underlying disease.** The use of these tests in this setting would be to evaluate the extent of previously diagnosed coronary artery disease. Patients with known disease may have had remote invasive angiography and/or stress testing to evaluate prior events or symptoms. New or recurrent symptoms may relate to a change in the coronary anatomy that can be assessed with these tests. D. **When patients with prior bypass surgery or intracoronary artery stent placement present with chest pain or dyspnea.** Coronary bypass grafts are relatively well seen with these tests. The rationale for the tests would be to determine the patency and severity of possible graft stenoses that may be the source of chest pain. Patients with prior intracoronary stents often present with recurrent chest pain. The rationale for these tests as an alternative to invasive angiography is to rule out in-stent restenosis as the cause of symptoms. (Accurate assessment of in-stent restenosis may be limited by the artifact caused by the stent material itself and the quality of the scan and scanner). E. **Suspected congenital anomalies of the coronary circulation.** These tests are used to assess patients suspected of having a congenital coronary anomaly. The cross-sectional nature of this technique allows one to determine accurately both the presence and possible future harm that could result from the anomaly. It is often used after an anomaly has been identified following a different test such as prior invasive coronary angiogram. These tests are used to decide if surgery is indicated and for surgical planning. F. **The assessment of coronary or pulmonary venous anatomy.** This application of the tests for the coronary and pulmonary veins is primarily for pre-surgical planning. Coronary venous anatomy can be useful for the cardiologist who needs to place a pacemaker lead in the lateral coronary vein in order to resynchronize cardiac	information should facilitate the management decision, not merely add a new layer of testing. C. These tests will be considered not medically necessary if it is anticipated that the patient would require invasive cardiac angiography for further diagnosis or for therapeutic intervention. (e.g., angina decubitus, unstable angina, Prinzmetal angina, etc.) D. These tests may be denied, on post-pay review, as not medically necessary when used for cardiac evaluation if there were pre-test knowledge of sufficiently extensive calcification of the suspect coronary segment that would diminish the interpretive value. E. The administration of beta blockers and the monitoring of the patient during MDCT/CCTA by a physician experienced in the use of cardiovascular drugs is included as part of the test and is not a separately payable service. F. All studies must be ordered by the physician/qualified non-physician practitioner treating the patient and who will use the results of the test in the management of the patient. G. CCTA must be performed under the direct supervision of a physician. H. This LCD does not address electron

Payer (year)	Evidence Base	Covered	Not Covered
		contraction in patients with heart failure. This may be helpful to guide biventricular pacemaker placement. Pulmonary vein anatomy can vary from patient to patient. Pulmonary vein catheter ablation can isolate electrical activity from the pulmonary veins and allow for the elimination of recurrent atrial fibrillation. The presence of a pulmonary venous anatomic map may help eliminate procedural complications and allow for the successful completion of the procedure. G. **The patient undergoing non-coronary artery cardiac surgery.** - Certain patients who have non-coronary artery cardiac surgery (valve or ascending aortic surgery) may need a pre-operative invasive coronary angiogram. The surgical planning may also depend upon the exact location of the coronary arteries. The rationale for the use of CCTA in these patient subsets is to avoid potentially unnecessary invasive testing and still provide appropriate pre-surgical information. - The test may be medically necessary in patients presenting to the emergency room with complaints consistent with cardiac ischemia, but without diagnostic electrocardiography (ECG) or enzymes. - The test may be considered medically necessary in patients status post revascularization procedures who present with recurrent symptoms not clearly identifiable as ischemic. H. **FFRCT -** this test may be considered medically necessary when CCTA shows CAD of uncertain functional significance, or is non-diagnostic and where the addition of functional information provided by FFRCT can help the physician determine which patient may require invasive evaluation and / or treatment.	beam tomography (EBT) technology or Ultrafast CT for coronary artery examination. There is no extension of coverage of EBT based on this policy. I. Quantitative calcium scoring (CPT 75571) is not a covered service and will be denied as not medically necessary. Calcium scoring reported in isolation is considered a screening service. When performed in association with CT angiography, there is neither separate nor additional included reimbursement for the calcium scoring.
Noridian Healthcare Solutions, LLC (2020) Local Coverage	See Appendix N for references	FDA-approved FFRct technology may be considered reasonable and necessary in the management of patients with symptomatic, stable ischemic heart disease (SIHD), when the CCTA analysis is completed and demonstrates one of the following criteria:	FFRct is not considered reasonable in the following clinical circumstances: 1. Prior placement of prosthetic valves 2. Extensive coronary calcification

Payer (year)	Evidence Base	Covered	Not Covered
Determination Covered States: Alaska, Idaho, Oregon, Washington, Arizona, Montana, North Dakota, South Dakota, Utah, Wyoming		1. Left main disease with intermediate coronary stenosis (lumen diameter reduction of 30-50%); OR 2. Proximal left anterior descending (LAD) coronary artery disease with intermediate coronary stenosis (lumen reduction 50-70%); OR 3. Proximal left dominant circumflex disease with intermediate (lumen reduction 50-70%) coronary stenosis (considered equivalent to two-vessel disease); OR 4. Proximal two- or three vessel disease with intermediate coronary stenosis in at least 2 vessels.	3. Known severe aortic stenosis 4. Known severe 3-vessel disease 5. Prior placement of venous grafts in coronary bypass surgery 6. Suspicion of acute coronary syndrome 7. Severe obesity (BMI > 35 kg/m2)

CABG = coronary artery bypass graft, CAD = coronary artery disease, CCTA = coronary computed tomography, CT = computed tomography, ECHO = echocardiography, EKG = electrocardiogram, FFR = fractional flow reserve, MDCT = multi-detector computed tomography, MPI = myocardial perfusion imaging, PET = positron emission tomography, SPECT = single photon emission computed tomography.

* For the purposes of this guideline, a patient is considered to be "symptomatic" when one of the following (A-D) applies:

A. Chest pain

- With intermediate or high pretest probability of CAD; OR
- With low or very low pretest probability of CAD and high risk of CAD (SCORE)

B. Atypical symptoms: syncope, shortness of breath (dyspnea), neck, jaw, arm, epigastric or back pain, or sweating (diaphoresis)

- With moderate or high risk of CAD (SCORE)

C. Other symptoms; palpitation, dizziness, lightheadedness, near syncope, nausea, vomiting, anxiety, weakness, fatigue etc.

- With high risk of CAD (SCORE)

D. Patients with any cardiac symptom who have diseases/conditions with which coronary artery disease commonly coexists such as:

- Diabetes mellitus; OR
- Abdominal aortic aneurysm; OR
- Established and symptomatic peripheral vascular disease; OR
- Prior history of cerebrovascular accident (CVA), transient ischemic attack (TIA) or carotid endarterectomy (CEA) or high grade carotid stenosis (>70%); OR
- Chronic renal insufficiency or renal failure

Table 11. Summary table of payer policies for PET

Payer (year)	Evidence Base	Covered	Not Covered
CMS (2002)	• **Positron Emission Tomography (Australia , 2000):** This review of PET literature focused on the added value of PET in patients who have already had SPECT. The review found that PET seems more sensitive and specific than SPECT but that the two tests disagree on a relatively small number of patients. Only one study was correctly designed to determine the incremental value of PET over SPECT. Of the patients with discordant results, PET was overall the better predictor of myocardial recovery, with almost all PET results correct and SPECT results incorrect predictors. • **Functional Diagnostic Imaging in the Assessment of Myocardial Viability (Alberta, Canada, 1999):** This is a comprehensive review of many different functional diagnostic imaging tests including PET, SPECT anLLd dobutamine echo. This report found that there are few good data on the influence of any of the tests on patient management. Overall, the sensitivity of PET, SPECT and dobutamine echo was similar. The specificity of PET and dobutamine echo was similar, and both were better than SPECT. • **INAHTA summary (1999):** This summary of 11 different technology assessments found a general agreement on the "comparable or superior performance of PET to other myocardial perfusion imaging alternatives, particularly thallium-201 SPECT" but with no clear conclusions about the extent of the improvement due to PET. The summary notes that PET is more costly than other alternatives and that consideration should be given to the most overall cost-effective approach	On December 15, 2000, CMS published a Decision Memorandum on a request for broad coverage of PET for all oncological indications, heart disease, and neurological disorders. The December 15th decision memorandum stated that CMS had insufficient evidence to support coverage for the indication of myocardial viability except for the decision to cover the service following an inconclusive SPECT. CMS intends to revise the NCD at CIM 50-36 to state that: 1. Both SPECT or FDG PET are reasonable and necessary as a primary or initial diagnostic study for determining myocardial viability prior to revascularization 2. PET continues to be reasonable and necessary following an inconclusive SPECT 3. The greater specificity of PET makes using SPECT following an inconclusive PET of no added value and	NR

Payer (year)	Evidence Base	Covered	Not Covered
		thus not reasonable and necessary.	
Aetna (2020)	Not specified.	A. Evaluation of Coronary Artery Disease PET scans using rubidium-82 (Rb-82) or N-13 ammonia done at rest or with pharmacological stress are considered medically necessary for non-invasive imaging of the perfusion of the heart for the diagnosis and management of members with known or suspected coronary artery disease, provided such scans meet either one of the two following criteria: i. The PET scan is used in place of, but not in addition to, a single photon emission computed tomography (SPECT), in persons with conditions that may cause attenuation problems with SPECT (obesity (BMI	NR

Payer (year)	Evidence Base	Covered	Not Covered
		greater than 40), large breasts, breast implants, mastectomy, chest wall deformity, pleural or pericardial effusion); or ii. The PET scan is used following an inconclusive SPECT scan (i.e., the results of the SPECT are equivocal, technically uninterpretable, or discordant with a member's other clinical data). • In these cases, the PET scan must have been considered necessary in order to determine what medical or surgical intervention is required to treat the member.	
Cigna (2020)	1. Einstein AJ, Moser KW, Thompson RC, et al. Radiation Dose to Patients From Cardiac Diagnostic Imaging. Circulation. 2007;116(11):1290-1305.	PET – Perfusion B. Meets all of the criteria	PET – Absolute quantitation or

Payer (year)	Evidence Base	Covered	Not Covered
	doi:10.1161/circulationaha.107.688101. 2. Okumura W, Iwasaki T, Toyama T, et al. Usefulness of Fasting 18F-FDG PET in Identification of Cardiac Sarcoidosis. Journal of Nuclear Medicine. http://jnm.snmjournals.org/content/45/12/1989.full. Published December 1, 2004. 3. Sharkey RM, Goldenberg DM. Perspectives on Cancer Therapy with Radiolabeled Monoclonal Antibodies. Journal of Nuclear Medicine. http://jnm.snmjournals.org/content/46/1_suppl/115S.full. Published January 1, 2005. 4. Yoshinaga K, Chow BJ, Williams K, et al. What is the Prognostic Value of Myocardial Perfusion Imaging Using Rubidium-82 Positron Emission Tomography? Journal of the American College of Cardiology. 2006;48(5):1029-1039. doi:10.1016/j.jacc.2006.06.025. http://www.sciencedirect.com/science/article/pii/S073510970601641X?via%3Dihub. 5. Youssef G, Mylonas I, Leung E, et al. The Use of 18F-FDG PET in the Diagnosis of Cardiac Sarcoidosis: A Systematic Review and Metaanalysis Including the Ontario Experience. Journal of Nuclear Medicine. http://jnm.snmjournals.org/content/53/2/241.long. Published February 1, 2012. 6. Blankstein R, Osborne M, Naya M, et al. Cardiac Positron Emission Tomography Enhances Prognostic Assessments of Patients With Suspected Cardiac Sarcoidosis. Journal of the American College of Cardiology. 2014;63(4):329-336. doi:10.1016/j.jacc.2013.09.022.	for an imaging stress test and additionally any one of the following: i. Individual is obese (for example BMI >40 kg/m2) or ii. Individual has large breasts or implants C. Equivocal nuclear perfusion (MPI) stress test D. Routine use in post heart transplant assessment of transplant CAD PET – Metabolic A. Cardiac PET Metabolic (CPT® 78459 or CPT® 78429): To determine myocardial viability when a previous study has shown significant left ventricular dysfunction when under consideration for revascularization B. Cardiac PET Metabolic and Perfusion (MPI SPECT CPT® 78451 and CPT® 78459, or CPT® 78432, or CPT® 78433): to identify and monitor response to	myocardial blood flow • Performance of quantitation of myocardial blood flow by Cardiac PET is currently non-standardized between different vendor products. • Absolute quantitation of myocardial blood flow is considered experimental, investigational and/or unproven.

Payer (year)	Evidence Base	Covered	Not Covered
		therapy for established or strongly suspected cardiac sarcoid.	

BMI = body mass index, CMS = Centers for Medicare and Medicaid, FDG = Fludeoxyglucose, MPI = myocardial perfusion imaging, NR = not reported, PET = positron emission tomography, SPECT = single photon emission computed tomography.

Table 12. Summary table of payer policies for SPECT

Payer (year)	Evidence Base	Covered	Not Covered
CMS (2002)	• **Positron Emission Tomography (Australia , 2000):** This review of PET literature focused on the added value of PET in patients who have already had SPECT. The review found that PET seems more sensitive and specific than SPECT but that the two tests disagree on a relatively small number of patients. Only one study was correctly designed to determine the incremental value of PET over SPECT. Of the patients with discordant results, PET was overall the better predictor of myocardial recovery, with almost all PET results correct and SPECT results incorrect predictors. • **Functional Diagnostic Imaging in the Assessment of Myocardial Viability (Alberta, Canada, 1999):** This is a comprehensive review of many different functional diagnostic imaging tests including PET, SPECT and dobutamine echo. This report found that there are few good data on the influence of any of the tests on patient management. Overall, the sensitivity of PET, SPECT and dobutamine echo was similar. The specificity of PET and dobutamine echo was similar, and both were better than SPECT. • **INAHTA summary (1999):** This summary of 11 different technology assessments found a general agreement on the "comparable or superior performance of PET to other myocardial perfusion imaging alternatives, particularly thallium-201 SPECT" but with no	The single photon emission computed tomography (SPECT) acquires information on the concentration of radionuclides introduced into the patient's body. It is useful in the diagnosis of several clinical conditions including: • stress fracture. • spondylosis. • infection (e.g., discitis). • tumor (e.g., osteoid osteoma). • analyze blood flow to an organ, as in the case of myocardial viability. • differentiate ischemic heart disease from dilated cardiomyopathy.	• Frequency limitations: Medicare Administrative Contractor discretion. • In the case of myocardial viability, FDG positron emission tomography (PET) may be used following a SPECT that was found to be inconclusive. However, SPECT may not be used following an inconclusive FDG PET performed to evaluate myocardial viability.

Payer (year)	Evidence Base	Covered	Not Covered
	clear conclusions about the extent of the improvement due to PET. The summary notes that PET is more costly than other alternatives and that consideration should be given to the most overall cost effective approach		
Aetna (2019)	Not specified.	Aetna considers SPECT medically necessary for the diagnosis of coronary artery disease and for the assessment of prognosis in persons with coronary artery disease except as outlined in "exclusion criteria" below."	Aetna considers SPECT experimental and investigational for all other cardiac indications because its effectiveness for indications other than the ones listed above has not been established. Exclusion criteria: Aetna considers SPECT myocardial perfusion imaging experimental and investigational for the following indications for which the study is considered “inappropriate” according to appropriateness criteria from the American College of Cardiology (ACC): A. As a routine screening evaluation after a percutaneous transluminal coronary angioplasty (PTCA) with or without stenting or coronary artery bypass surgery (CABG) prior to discharge from the acute care setting; *or* B. As a routine screening evaluation after a re-vascularization procedure (PTCA with stenting or CABG) at an interval of less than 2 years from the procedure if there is no worsening in the members symptomatology and if the member had symptoms prior to the intervention, and there is no history of congestive heart failure. **Note**: If there is a history of congestive heart failure and the member is status post re-vascularization,

Payer (year)	Evidence Base	Covered	Not Covered
			repeat nuclear imaging as frequently as annually may be medically necessary; *or* C. Assessment of vulnerable plaque; *or* D. Evaluation of a member with an acute coronary event and hemodynamic instability, shock, or mechanical complications of the event; *or* E. In the setting of acute chest pain or equivalent symptoms with a high likelihood of being acute coronary syndrome, when there has been a diagnosis of acute myocardial infarction, in the immediate post-thrombolytic period, or when there is a high pre-test likelihood of significant coronary disease as demonstrated by marked ST segment elevation on the ECG; *or* F. Prior to high-risk surgery when the member is asymptomatic and there was a normal cardiac catheterization, coronary intervention (PTCA, stenting, CABG), or normal nuclear stress test less than 1 year before the surgical date; *or* G. Prior to intermediate-risk non-cardiac surgery if the member is capable of, and has no contraindication to standard stress testing**; *or* H. Prior to low-risk non-cardiac surgery for risk assessment; *or* I. Re-evaluation of members without chest pain or equivalent symptoms, without known coronary disease, at high-risk for coronary disease (based upon the Framingham score greater than 10)*, who have an initial negative radionuclear imaging study, when it has been less than 2 years since the last radionuclear

Payer (year)	Evidence Base	Covered	Not Covered
			study; *or* J. Re-evaluation of members without chest pain or equivalent symptoms or with stable symptoms, with known coronary disease as determined by prior abnormal catheterization or SPECT cardiac study (but without prior infarction), when it has been less than 1 year since the last radionuclear study. Note: if the member has worsening symptoms or if the member had silent ischemia, more frequent imaging or other diagnostic testing or interventions may be medically necessary; *or* K. Screening of members with chest pain or chest pain equivalent symptoms when there is a low probability of coronary disease (Framingham score less than 10)*, no history of diabetes, and there are no impediments or contraindications to non-nuclear stress testing; *or* L. Screening of members without chest pain or equivalent symptoms when there is a low probability of coronary disease (Framingham score less than 10)* and no history of diabetes

CABG = coronary artery bypass graft, FDG = Fludeoxyglucose, PET = positron emission tomography, PTCA = percutaneous transluminal coronary angioplasty, SPECT = single photon emission computed tomography.

3 The Evidence

3.1 Methods of the Systematic Literature Review

3.1.1 Objectives

The aim of this report is to evaluate the clinical impact, safety and cost-effectiveness of the three primary noninvasive imaging methods of diagnosing CAD, namely CCTA (including use of FFR), CT perfusion imaging, stress nuclear imaging and stress echocardiography. This review updates the 2008 CCTA HTA and 2013 nuclear imaging HTA and adds evaluation of stress echocardiography.

3.1.2 Contextual Questions

Prior to addressing research questions related to the impact of cardiac imaging on clinical outcomes ***the diagnostic accuracy (validity)*** of these modalities compared with invasive coronary angiography (the usual reference standard) will be briefly summarized for context, given the clinical maturity of these imaging modalities.

In patients with known or suspected CAD who are *symptomatic:*

1. What is the diagnostic accuracy of *CCTA* for anatomical confirmation of obstructive CAD? Is there evidence of differential test accuracy for specific subpopulations (e.g., women, patients with comorbidities, the elderly)?

2. What is the diagnostic accuracy of *CCTA with determination of fractional flow reserve (FFR)* for the diagnosis of CAD? Is there evidence of differential test accuracy for specific subpopulations (e.g., women, patients with comorbidities, the elderly)?

3. What is the diagnostic accuracy of *stress CCTA* for the diagnosis of CAD? Is there evidence of differential test accuracy for specific subpopulations (e.g., women, patients with comorbidities, the elderly)?

4. What is the diagnostic accuracy of *stress nuclear imaging*? Is there evidence of differential test accuracy for specific subpopulations (e.g., women, patients with comorbidities, the elderly)?

5. What is the diagnostic accuracy of *stress echocardiography*? Is there evidence of differential test accuracy for specific subpopulations (e.g., women, patients with comorbidities, the elderly)?

3.1.3 Research Key Questions

The scope of this report and final key questions were refined based on input from clinical experts. Clinical expert input was sought to confirm critical outcomes on which to focus. Draft Key Questions and PICOTS scope were published on the HCA website for public comment. None were received. Public comments as well as those from clinical experts and peer-reviewers were considered for finalization of this report.

The following Key Questions focus on ***the impact on clinical outcomes*** for the use of CCTA, stress nuclear imaging, and stress echocardiography to diagnose CAD **in patients with known or suspected CAD who are *symptomatic.***

1. What is the comparative effectiveness of noninvasive cardiac anatomic or functional imaging modalities (CCTA, stress nuclear imaging, stress echocardiography) in leading to improved *clinical outcomes* (e.g., MI, mortality)?

2. What is the comparative effectiveness of noninvasive cardiac anatomic or functional imaging modalities (CCTA, stress nuclear imaging, stress echocardiography) with respect to *clinical decision-making* including additional testing and treatments?

3. What is the comparative effectiveness of noninvasive cardiac anatomic or functional imaging modalities (CCTA, stress nuclear imaging, stress echocardiography) with regard to *harms or adverse events* which may result directly from testing or additional, downstream testing?

4. Does effectiveness (in terms of clinical outcomes) or safety of noninvasive cardiac anatomic or functional imaging (CCTA, stress nuclear imaging, stress echocardiography) differ in *special populations* (e.g., women, those with comorbidities, the elderly)?

5. What is the *cost-effectiveness* of noninvasive cardiac anatomic or functional imaging modalities (CCTA, stress nuclear imaging, stress echocardiography) for clinical outcomes?

3.1.4 Inclusion/Exclusion Criteria

Table 13 below provides a summary of the inclusion and exclusion criteria. Briefly, included studies met the following requirements with respect to participants, intervention, comparators, outcomes, and study design:

- **Population**: Adults with (1) symptoms of suspected (previously undiagnosed) CAD who present with stable (nonemergent) typical or atypical symptoms suspicious for CAD or suspected acute coronary syndrome (ACS) in emergency departments, or (2) known/established CAD.

- **Intervention:** CCTA (including use of FFR and pharmacologic stress with 64 slice or higher CT), stress nuclear imaging and stress echocardiography.

- **Comparators:** No testing, usual care, comparison of the above interventions with each other, and invasive coronary angiography.

- **Outcomes:** Primary clinical outcomes are 1) myocardial infarction (MI), 2) cardiac death, and 3) all-cause mortality. Clinical Decision-Making outcomes are 1) referral for treatment and 2) referral for additional testing. Safety outcomes include harms of testing (e.g., adverse events related to contrast agents, medication for pharmacologic stress testing), vascular complications (e.g., stroke) and risks and consequences of testing (radiation exposure, psychological

consequences of diagnosis, ramifications of additional testing, other). [redacted]

- **Studies:** The focus was on high quality (low risk of bias) comparative studies (e.g., randomized controlled trials, comparative cohort studies with concurrent controls) for Key Questions 1-3. Comparative cohort studies that were designed specifically to evaluate safety or comprehensive systematic reviews specifically on safety were considered for inclusion. For Key Question 4, RCTs that stratified on baseline patient characteristics and evaluated effect modification were included. Full, comparative, formal economic studies (i.e., cost-effectiveness, cost-utility, cost-minimization, and cost-benefit studies) were sought for Key Question 5; studies using modeling may be used to determine cost-effectiveness.

Table 13. Summary of inclusion and exclusion criteria

Study Component	Inclusion	Exclusion
Patients	Adult patients (≥18 years of age) with symptoms of suspected (previously undiagnosed) CAD who present with • Stable (nonemergent) typical or atypical symptoms suspicious for CAD (e.g., chest pain, chest tightness, chest burning, shoulder pain, palpitations, jaw pain, or non-chest pain symptoms, such as dyspnea or worsening effort tolerance) • Suspected acute coronary syndrome (ACS) in emergency departments. Symptomatic adults with known/established CAD including those who have had prior MI and/or revascularization. For all questions, data on special populations and circumstances including the following will be evaluated: • Women • Patients with atypical symptoms • Elderly patients • Patients with comorbidities (including renal insufficiency, DM), LBBB)	• Asymptomatic patients • Patients presenting for evaluation of cardiac pathologies other than CAD (e.g., congenital abnormalities, valvular disease, evaluation of cardiomyopathy etiology, CHF) • Patients with STEMI
Intervention	• Coronary CT Angiography (including use of FFR) and CT perfusion imaging (pharmacologic stress) with 64 slice or higher CT • Stress nuclear imaging (including PET, SPECT) • Stress echocardiography	• CACS • Screening • Novel uses of any of these tests • MRI/MRA • Comparisons of technical

Study Component	Inclusion	Exclusion
		performance parameters or variations of a testing modality (e.g., comparison different CT techniques) • Outdated equipment or methods
Comparator(s)	• No testing • Usual care* • Comparison of the above interventions with each other • Invasive coronary angiography	
Outcomes	Clinical health outcomes (PRIMARY) • MI, cardiac death, all-cause mortality Clinical decision making • Referral for treatment • Referral for additional testing Harms, risks and consequences of testing (initial testing and subsequent testing) • Harms of testing (e.g., adverse events related to contrast agents, medication for pharmacologic stress testing), vascular complications (e.g., stroke) • Risks and consequences of testing (radiation exposure, psychological consequences of diagnosis, ramifications of additional testing, other†) Economic: Incremental cost-effectiveness or similar outcome	• Intermediate outcomes
Timing	• Emergent or non-emergent • Any point in the diagnostic workup	• none
Setting(s)	• Emergency department • Non-emergent settings	• none
Studies	• Focus will be on studies with the least potential for bias. Focus will start with RCT evidence; in the absence of RCTs, high quality comparative observational studies that control for potential confounding will be considered. Observational studies will primarily be considered for test-related harms. • Studies published in English in peer-reviewed journals, technology assessments or publicly available FDA reports. • Full (comparative) economic studies • Studies published after 2000 (except for stress	• Non-comparative studies • Modeling studies for prediction • Prognostic studies • Costing studies • Studies evaluating the incremental benefit of adding a test to another. • Studies published prior to 2000 (except for stress echocardiography)

Study Component	Inclusion	Exclusion
	echocardiography)	

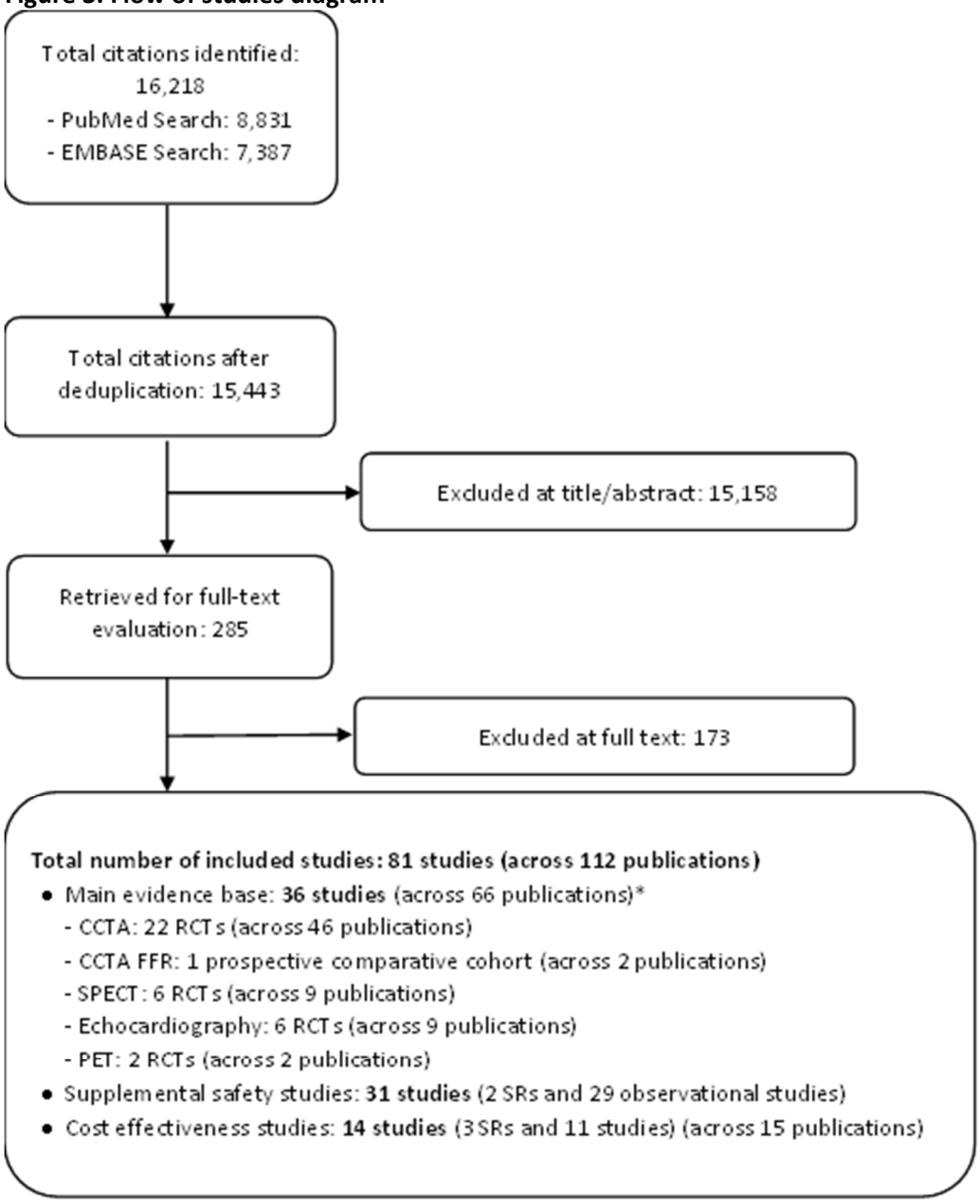
CACS = coronary artery calcium scoring; CAD = coronary artery disease; CHF = congestive heart failure; CT = computed tomography; DM = diabetes mellitus; FFR = fractional flow reserve; LBBB = left bundle branch block; RCT = randomized controlled trials; MI = myocardial infarction; PET = positron emission tomography; SPECT = single photon emission computed tomography; STEMI = ST-segment elevation myocardial infarction.
*Usual care typically includes no treatment/nothing if low pretest probability, "watchful waiting", or medical treatment if high pretest probability.
†Other may include impact on patients such as days lost from work, procedures cancelled (waiting for tests), vacations cancelled, etc.

3.1.5 Data Sources and Search Strategy

We searched electronic databases from January 1, 2000 to March 23, 2021 (for PubMed) and from database inception to March 23, 2021 (for all other databases) to identify publications assessing the capabilities of CCTA, stress nuclear imaging and stress echocardiography as diagnostic tests for CAD to direct patient management and improve patient outcomes that had been published since the prior reports. A formal, structured systematic search of the peer-reviewed literature was performed across a number of databases including PubMed, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews (see Appendix B for full search strategy) to identify relevant peer reviewed literature as well as other sources (ClinicalTrials.gov, ECRI Guidelines Trust, Center for Reviews and Dissemination Database) to identify pertinent clinical guidelines and previously performed assessments. We also hand searched the reference lists of relevant studies and the bibliographies of systematic reviews.

The clinical studies included in this report were identified using the algorithm shown in Appendix A. The process involves four stages. The first stage of the study selection process consisted of the comprehensive electronic search and bibliography review. We then screened all possible relevant articles using titles and abstracts in stage two. This was done by two individuals independently. Those articles that met a set of *a priori* retrieval criteria were included for full-text review. We excluded conference abstracts, non-English-language articles, duplicate publications that did not report different data or follow-up times, white papers, narrative reviews, preliminary reports, and incomplete economic evaluations. Any disagreement between screeners that were unresolved resulted in the article being included for the next stage. Stage three involved retrieval of the full text articles remaining. The final stage of the study selection algorithm consisted of the review and selection of those studies using a set of *a priori* inclusion criteria, again, by two independent investigators. Discrepancies were resolved through discussion and if necessary, adjudicated by a third investigator. A list of excluded articles along with the reason for exclusion is available in Appendix C. The remaining articles form the evidence base for this report.

Figure 3. Flow of studies diagram



CCTA = coronary computed tomography angiography; FFR = fractional flow reserve; PET = positron emission tomography; RCT = randomized control trial; SPECT = single photon emission tomography; SR = systematic review
* One trial (CECaT trial) provided data for both SPECT and Stress Echocardiogram.

3.1.6 Data Extraction

Reviewers extracted the following data from the clinical studies: study design, setting, country, source of funding, sample size, inclusion and exclusion criteria, study population characteristics, follow-up time, noninvasive testing protocol, definition of a positive test, study outcomes and adverse events. For economic studies, data related to sources used, economic parameters and perspectives, results, and sensitivity analyses were abstracted. An attempt was made to reconcile conflicting information among multiple reports presenting data from the same study. Detailed study and patient characteristics and results are available in Appendices F–L.

3.1.7 Quality Assessment: RoB, QHES Evaluation, and Overall SOE

The method used by Aggregate Analytics, Inc. (AAI) for assessing the quality of evidence of individual studies as well as the overall strength of evidence (SOE) are based on established methods for systematic reviews. Included studies reporting on primary outcomes of interest were critically appraised independently by two reviewers evaluating the methodological quality, study limitations and potential for bias based on study design as well as factors which may bias studies using defined templates and pre-specified criteria. Assessment of RCTs followed appropriate criteria based on methods described in *the Cochrane Handbook for Systematic Reviews of Interventions*[40,104] and guidance from the Agency for Healthcare Research and Quality (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews.*[1] In keeping with the AHRQ methods and the 2016 report on non-invasive imaging for CAD[230], each study was given a final rating of “good”, “fair”, or “poor” quality as described below. Discrepancies in ratings between reviewers were resolved through discussion and consensus. Criteria are detailed in Appendix D.

Table 14. Criteria for grading the quality of individual studies

Rating	Description and Criteria
Good	• Low risk of bias; study results generally considered valid • Employed valid methods for selection, inclusion, and allocation of patients to treatment; report similar baseline characteristics/key risk factors for testing groups being compared; clearly describe attrition and have low attrition; use appropriate means for preventing bias (e.g., blinded outcomes assessment); and use appropriate analytic methods (e.g., intention-to-test analysis); full reporting on pre-specified outcomes. • For studies of testing, pre-specification of thresholds for a positive test,
Fair	• Study is susceptible to some bias but not enough to necessarily invalidate results • May not meet all criteria for good quality, but no flaw is likely to cause major bias; the study may be missing information making it difficult to assess limitations and potential problems • This category is broad; studies with this rating will vary in strengths and weaknesses; some fair-quality studies are likely to be valid, while others may be only possibly valid
Poor	• Significant flaws that imply biases of various kinds that may invalidate results; the study contains "fatal flaws" in design, analysis or reporting; large amounts of missing information; discrepancies in reporting or serious problems with intervention or test delivery • Study results are at least as likely to reflect flaws in the study design or execution as the true difference between the compared interventions • Considered to be less reliable than higher quality studies when synthesizing the evidence, particularly if discrepancies between studies are present

Risk of bias was not assessed for case series (single arm studies); all case series were considered to be at high risk of bias. Economic studies were evaluated according to The Quality of Health Economic Studies (QHES) instrument developed by Ofman et al. in conjunction with consideration of epidemiologic principles that may impact findings.[182] Systematic reviews included as primary evidence were assessed using the AMSTAR-2tool.[224,225] Based on these quality criteria, each comparative study chosen for inclusion for a Key Question was given a risk of bias (RoB) (or QHES) rating; details of each rating are available in Appendix E. For contextual questions, general risk of bias was assessed for systematic reviews of diagnostic accuracy and reliability based on AMSTAR-2.[224,225] Individual reliability studies were assessed as described in Appendix D. Individual studies for diagnostic accuracy were not assessed.

SOE was assessed by two researchers following the principles for adapting GRADE (Grades of Recommendation Assessment, Development and Evaluation)[89,92,93] as outlined by the Agency for Healthcare Research and Quality (AHRQ).[7] The strength of evidence was based on the highest quality evidence available for the primary outcomes.

In determining the strength of body of evidence regarding a given outcome, the following domains were considered:

- **Risk of bias**: the extent to which the included studies have protection against bias
- **Consistency:** the degree to which the included studies report results that are similar in terms of effect sizes, range and variability.
- **Directness**: describes whether the evidence is directly related to patient health outcomes or comparisons of interventions are direct (head to head).

- **Precision:** describes the level of certainty surrounding the effect estimates.
- **Publication or reporting bias:** is considered when there is concern of selective publishing or selective reporting. This is difficult to assess particularly for nonrandomized studies.

Bodies of evidence consisting of RCTs are initially considered as High SOE. In general, the GRADE and AHRQ methodologies initially consider nonrandomized studies as Low SOE as such studies typically are at higher risk of bias due to lack of randomization and inability of investigators to control for critical confounding factors. The SOE could be downgraded based on the limitations described above. There are also situations where studies (particularly observational studies) could be upgraded if the study had large magnitude of effect (strength of association) or if a dose-response relationship is identified and there are no downgrades for the primary domains listed above and confounding is not a concern. Publication and reporting bias are difficult to assess, particularly with fewer than 10 RCTs and for observational studies.[25,213] Publication bias was unknown in all studies and thus this domain was eliminated from the strength of evidence tables. The final SOE was assigned an overall grade of high, moderate, low, or insufficient, which are defined as follows:

- High - Very confident that effect size estimates lie close to the true effect for this outcome; there are few or no deficiencies in the body of evidence; we believe the findings are stable.
- Moderate – Moderately confident that effect size estimates lie close to the true effect for this outcome; some deficiencies in the body of evidence; we believe the findings are likely to be stable but some doubt remains.
- Low – Limited confidence that effect size estimates lie close to the true effect for this outcome; major or numerous deficiencies in the body of evidence; we believe that additional evidence is needed before concluding that findings are stable or that the estimate is close to the true effect.
- Insufficient – We have no evidence, are unable to estimate an effect or have no confidence in the effect estimate for this outcome; OR no available evidence or the body of evidence has unacceptable efficiencies precluding judgment.

Assessing the SOE for studies performing subgroup analysis for evaluation of differential effectiveness or safety requires additional considerations discussed below. Methods for determining the overall quality (strength) of evidence related to economic studies have not been reported, thus the overall strength of evidence for outcomes reported in Key Question 5 was not assessed.

3.1.8 Analysis

Evidence was summarized qualitatively and quantitatively. Risk ratio (RR) and 95% confidence intervals were used for dichotomous outcomes to evaluate the presence of an association between testing and the outcome. Risk differences (RD) and 95% CIs were calculated if an association was seen for “hard” outcomes that might be reliably measured (e.g., death). Risk differences were not calculated for observational studies as causality cannot be inferred. In the absence of adjusted effect size estimates, for dichotomous outcomes, crude risk ratios (RR) and 95% confidence intervals (CI) were calculated using either STATA 14.0[235] or Rothman Episheet.[3] For instances with fewer than five observations per cell, exact methods were employed. Where effect estimates that were adjusted for confounding were

reported by study authors, they were preferred and reported. For continuous variables, mean differences (MD) and associated 95% CIs were calculated if the outcomes were reported using the same scale, and standardized mean difference (SMD) and 95% CI were used when the outcomes were reported in different scale

Meta-analyses were conducted as appropriate in order to summarize primary outcome data from multiple studies and to obtain more precise and accurate estimates using STATA 14.0. [235]To determine the appropriateness of meta-analysis, we considered clinical and methodological diversity and assessed statistical heterogeneity. To determine the appropriateness of meta-analysis, we considered clinical and methodological diversity and assessed statistical heterogeneity. Statistical heterogeneity among the studies was assessed using Cochran's χ^2 test and the I^2 statistic.[105] To combine trials, we used a random effects model based on the profile likelihood method which provides a more conservative effect estimate. In the case of non-convergence with profile likelihood, the Der Simonian and Laird estimates were reported.[97] For continuous variables, differences in mean follow-up scores between treatments were analyzed to determine mean differences as an effect size. Methods for calculating the standard deviations and for imputing missing standard deviations followed the recommendations given in The Cochrane Handbook 7.7. Where no events occurred in one arm of a study, a value of 0.50 was used for that arm in accordance with Cochrane methods. Studies in which no events occurred in either study arm did not contribute to effect estimates (0% weight) but were retained in some plots for visual effect and completeness. Sensitivity analyses were conducted excluding poor-quality studies, outlying data and clinically heterogeneous trials where there were sufficient data. Given the limitations of ETT as a functional test, sensitivity analyses comparing CCTA with functional imaging tests only were also conducted. Tests for interaction related to study populations were done. Given that patients with acute symptoms presenting to the ED may have different need for and timing of hospitalization, we did not pool data for this outcome. Outcomes are detailed in the evidence tables in the appendices and/or the body of the report. Where results were reported at different time frames, we stratified by timing to evaluate results at the time of index test (primarily in studies in an ED setting) and then along common follow-up times as reported in included studies.

We did not conduct analyses to evaluate potential markers for publication bias given the substantial heterogeneity in study designs, programs, length of follow-up and patient populations and small number of trials available for some analyses in specific populations.[174,226]

To evaluate differential efficacy and safety (heterogeneity of effect, interaction), we focused on RCTs as they have the least potential for bias and confounding thus allowing for causal inference. Further, only RCTs that formally tested for interaction between subgroups were reported for Key Question 4. SOE for these studies is based on consideration of the overall study risk of bias (study quality) as well as whether subgroup variables and analyses were specified a priori, the hypothesized impact of a subgroup on the outcome/effect and sample size as evaluation of interaction requires greater sample size. Such analyses should be interpreted cautiously and consider the biologic plausibility of differential efficacy or safety. Such analyses are generally considered hypothesis generating, and additional confirmatory evidence should be sought.[185,239,252]

4 Contextual Questions

Diagnostic tests are recommended when evaluating the severity of a condition or predicting therapeutic response. However, for testing to be of value, results must lead to meaningful action that improve an individual's wellbeing. They must be accurate and reliable while minimizing harms, including those related to downstream testing. They must also impact the process of care and impact key patient outcomes. For years CCTA, stress nuclear imaging, and stress echocardiography as diagnostic tests for coronary artery disease (CAD) have been investigated for their abilities to direct patient management and improve patient outcomes, as well as for their cost-effectiveness. These tests are the most common modalities for CAD diagnosis in symptomatic patients other than ECG and ECG treadmill testing.

In the past decade, a growing number of randomized control trials have provided additional evidence to describe the impact of noninvasive imaging on clinical outcomes. Two prior reports published over a decade ago focused mostly on diagnostic accuracy. With more published data comes increased clinical evidence available for most modalities. In the last decade in particular, there is much more clinical evidence related to CCTA. However, it is still critical to consider the reliability and accuracy of available tests.

In recent years, the technologies and their application have evolved, and due to clinical maturity, we are now focusing on clinical characteristics of the tests, while simultaneously providing important context for accuracy, particularly compared with the historical referent of invasive angiography. Diagnostic accuracy and validity are addressed via the contextual questions below. Contextual questions represent issues in a review for which a valid, but not necessarily systematic, summary of current research is needed to provide important context. The contextual questions will provide important background information on diagnostic validity and reliability for the included tests.

In patients with known or suspected CAD who are *symptomatic:*

1. What is the diagnostic accuracy of CCTA for anatomical confirmation of obstructive CAD? Is there evidence of differential test accuracy for specific subpopulations (e.g., women, patients with comorbidities, the elderly)?
2. What is the diagnostic accuracy of CCTA with determination of fractional flow reserve (FFR) for the diagnosis of CAD? Is there evidence of differential test accuracy for specific subpopulations (e.g., women, patients with comorbidities, the elderly)?
3. What is the diagnostic accuracy of stress CCTA for the diagnosis of CAD? Is there evidence of differential test accuracy for specific subpopulations (e.g., women, patients with comorbidities, the elderly)?
4. What is the diagnostic accuracy of stress nuclear medicine imaging? Is there evidence of differential test accuracy for specific subpopulations (e.g., women, patients with comorbidities, the elderly)?
5. What is the diagnostic accuracy of stress echocardiography? Is there evidence of differential test accuracy for specific subpopulations (e.g., women, patients with comorbidities, the elderly)?

4.1 Terms and definitions

Diagnostic test performance measures were used in this report. Briefly for the contextual questions:

- **True positive (TP):** patients who test positive and who have the disease
- **False positive (FP):** patients who test positive but do not have the disease
- **False negative (FN):** patients who test negative but do have the disease
- **True negative (TN):** patients who test negative and do not have the disease
- **Sensitivity** (true positive rate) measures the ability of a diagnostic test to correctly identify patients with the disease, and can be calculated as follows: TP/(TP + FN) usually expressed as % of patients with the disease who test positive
- **Specificity** (true negative rate) measures the ability of a diagnostic test to minimize false positives, and can be calculated as follows: TN/ (FP + TN) usually expressed as % of patients who do not have disease who test negative
- Note that sensitivity and specificity are negatively correlated with one another: if the threshold of a positive test is set higher to maximize sensitivity, specificity will be lower, and vice versa.
- **Negative Predictive Value (NPV):** % of patients with negative test who do not have the disease; depends on prevalence can be calculated one of two ways: TN/(TN+FN) or

$$\text{NPV} = \frac{\text{specificity x (1-prevalence)}}{\text{(1-sensitivity) x prevalence + sp1ecificity x (1-prevalence)}}$$

- **Positive Predictive Value (PPV):** % of patients with positive test who have the disease; depends on prevalence; can be calculated one of two ways: TP/(TP+FP) or

$$\text{PPV} = \frac{\text{sensitivity x prevalence}}{\text{sensitivity x prevalence + (1-specificity) x (1-prevalence)}}$$

- **1 – negative predictive value (NPV).** The negative predictive value is the % of patients with a negative test who do not have the disease so 1- NPV is the percent of patients with a negative test who *do* have the disease.
- **Positive Likelihood Ratio (LR+):** how much odds of disease increase with a positive test; depends on sensitivity and specificity; can be calculated as follows: sensitivity/(1-specificity)
- **Negative Likelihood Ratio (LR-):** how much odds of disease decrease with a negative test; depends on sensitivity and specificity; can be calculated as follows: (1-sensitivity)/specificity)
- **Kappa statistic:** represents the extent to which the agreement observed exceeds that which would be expected by chance alone, and can be calculated as follows:

$$\text{Kappa} = \frac{\text{(\% agreement observed) – (\% agreement expected by chance alone)}}{\text{100\% – (\% agreement expected by chance alone)}}$$

4.2 Results for Diagnostic Accuracy

To provide a general overview of the diagnostic accuracy of the included noninvasive tests in the target population of symptomatic patients with suspected or known CAD in emergent or non-emergent settings, a targeted search of the literature was done to identify moderate- to high-quality systematic reviews (based on a modified AMSTAR-2 checklist[51,225]) that compared noninvasive tests included in this report with the historic gold standard of ICA in terms of traditional diagnostic test performance measures (i.e., sensitivity, specificity, positive/negative predictive value, positive/negative likelihood ratio). Where relevant, we included data on noninvasive tests compared with fractional flow reserve. Noninvasive tests included CT angiography, stress nuclear imaging, and stress echocardiography. Most studies reported 50% or greater stenosis in ICA, however some reported diagnostic accuracy of the test relative to a higher threshold or stenosis of 70%, see tables for details. ICA is an anatomic test, so accuracy for anatomic tests such as CCTA may differ from functional tests such as stress nuclear imaging or stress echocardiography when compared with ICA; a strict correspondence between ICA and functional tests is not expected.

The diagnostic test characteristics of all the included tests compared with the test results from ICA are summarized below in Table 15 through Table 25, with more specific details available in Appendix L**.** The values of the various diagnostic test characteristics in these tables were taken from or calculated from the values reported in the included systematic reviews. Generally, authors did not describe the disposition or proportion of uninterpretable tests or account for them in the calculation of diagnostic accuracy parameters. [redacted].[184] This method assumes that clinicians refer non-diagnostic and indeterminate tests to ICA for further non-invasive testing, and conservatively estimates such cases to ultimately be false positive. This approach therefore may underestimate specificity and PPV because measures take into account false positives in their calculations.

Overall, evidence on diagnostic accuracy was available from five government-related reports[2,100,183,184,230] and nine systematic reviews[6,86,94,132,194,234,264] published in the peer review literature. The overall quality of systematic reviews published in the peer reviewed literature was moderate based on modified AMSTAR-2 ratings. Unfortunately, many studies were graded lower due to methodological issues, particularly a lack of rationale or listing of excluded studies and issues related to publication bias. The summary below provides information for each modality compared with the usual referent of ICA. Additional information for other comparators is found in Appendix L. Summary bullets are across the two ICA threshold of 50% or 70% stenosis, see tables for details. No studies focusing on specific subpopulations were identified. Additionally, key questions included considering differential accuracy based on specific populations, however included studies did not provide this.

<u>For the diagnostic accuracy in patients with stable symptoms in outpatient settings</u>:

- The diagnostic accuracy of **CCTA for anatomic imaging compared with ICA** across sources had the following ranges. Among these, Haase[94] investigated diagnostic accuracy using individual patient data.

  - Sensitivity (93.4% to 98%), specificity (72% to 84.4%)
  - PPV (58% to 93%), NPV (89% to 99%)
  - LR+ (3.43 to 5.98), LR- (0.02 to 2.64)
  - Prevalence of CAD (24.2% to 75.5%)
- The diagnostic accuracy of **CT myocardial perfusion compared with ICA** across sources had the following ranges
  - Sensitivity (54% to 66%), specificity (98% to 100%)
  - PPV (96% to 100%), NPV (66% to 100%)
  - LR+ (33.00 to 54.00), LR- (0.45 to 0.47)
  - Prevalence of CAD (NR)
- The diagnostic accuracy of **stress SPECT compared with ICA** across sources had the following ranges
  - Sensitivity (76% to 87%), specificity (70% to 78%)
  - PPV (32% to 95%), NPV (47% to 97%)
  - LR+ (2.88 to 3.68), LR- (0.24 to 2.33)
  - Prevalence of CAD (14.1% to 86%)
- The diagnostic accuracy of **stress PET compared with ICA** across sources had the following ranges
  - Sensitivity (90% to 91%), specificity (85% to 86%)
  - PPV (78% to 91%), NPV (84% to 94%)
  - LR+ (5.87 to 6.50), LR- (0.10 to 0.12)
  - Prevalence of CAD (36.5 to 62.5%)
- The diagnostic accuracy of **stress echocardiography compared with ICA** across sources had the following ranges
  - Sensitivity (64% to 90%), specificity (73% to 90%)
  - PPV (72% to 98%), NPV (36% to 97%)
  - LR+ (3.21 to 6.40), LR- (0.14 to 2.95)
  - Prevalence of CAD (35.1% to 90.8%)

For the diagnostic accuracy in patients with suspected or known CAD in outpatient settings:

- The diagnostic accuracy of **CCTA for anatomic imaging compared with ICA** across sources had the following ranges
  - Sensitivity (98.2% to 100%), specificity (81.6% to 89%)
  - PPV (90.5% to 93%), NPV (99%)
  - LR+ (9.20), LR- (0.00)
  - Prevalence of CAD (58% to 59.9%)
- The diagnostic accuracy of **stress SPECT compared with ICA** across sources had the following ranges
  - Sensitivity (83% to 85%), specificity (77% to 85%)
  - PPV (72% to 85%), NPV (79% to 85%)
  - LR+ (3.56 to 5.13), LR- (0.18 to 0.22)
  - Prevalence of CAD (41% to 50%)
- The diagnostic accuracy of **stress PET compared with ICA** across sources had the following ranges
  - Sensitivity (82% to 91%), specificity (82% to 91%)

    - PPV (93% to 96%), NPV (53% to 84%)
    - LR+ (4.97 to 8.89), LR- (0.11 to 0.21)
    - Prevalence of CAD (63% to 80%)
- The diagnostic accuracy of **stress echocardiography compared with ICA** across sources had the following ranges
    - Sensitivity (84% to 88%), specificity (72% to 89%)
    - PPV (85% to 93%), NPV (69% to 80%)
    - LR+ (3.08 to 8.35), LR- (0.13 to 0.21)
    - Prevalence of CAD (64% to 68%)

In addition to CCTA for anatomic imaging in particular, two systematic reviews[6,86] and one government report[100] describe diagnostic accuracy for the inclusion of FFRct to evaluate function. It is important to note that the government report was not a full systematic review, but a rapid response review that included two systematic reviews and one primary study.

For the diagnostic accuracy of FFRct in patients with suspected or known CAD in outpatient settings:

- The diagnostic accuracy of **FFRct compared with FFR via ICA** across sources had the following ranges
    - Sensitivity (84% to 91%), specificity (55% to 84%)
    - PPV (58% to 100%), NPV (0% to 90%)
    - LR+ (2.02 to 3.70), LR- (0.16 to 0.23)
    - Prevalence of CAD (32% to 100%)

Only one systematic review[114] reported on diagnostic accuracy across patients in an emergent setting. The patient population included those with suspected or known CAD, and the authors only reported sensitivity, specificity, positive and negative likelihood ratios. However, this study was done in patients with non-ST segment elevation myocardial infarction and without troponin, therefore the population is of lower risk of CAD. The prior ICER[184] study also included studies in emergency department settings but pooled all data across emergent and non-emergent settings. 3 prospective cohort studies[108,120,207] were identified from that report and data was abstracted.

For the diagnostic accuracy in patients with suspected or known CAD, presenting with or without ACS, or with possible ischemic chest pain in emergency departments:

- The diagnostic accuracy of **CCTA for anatomic imaging compared with ICA** across one systematic review and across three primary studies[108,120,207] from the prior ICER report had the following ranges
    - Sensitivity (93% to 100%), specificity (77% to 92%)
    - PPV (47% to 87%), NPV (91% to 100%)
    - LR+ (4.08 to 12.50), LR- (0.00 to 0.08)
    - Prevalence of CAD (NR)
    - The percentage of patients with a negative test that do have the disease (0% to 9%)
- The diagnostic accuracy of **stress SPECT compared with ICA** across sources had the following estimates

  - Sensitivity (85%), specificity (92%)
  - PPV (NR), NPV (NR)
  - LR+ (10.48), LR- (0.19)
  - Prevalence of CAD (NR)
- The diagnostic accuracy of **stress echocardiography compared with ICA** across sources had the following estimates
  - Sensitivity (75%), specificity (96%)
  - PPV (NR), NPV (NR)
  - LR+ (18.67), LR- (0.25)
  - Prevalence of CAD (NR)

In general, compared with FFR via ICA in the stress tests, sensitivity was similar or somewhat less while specificity was usually less than tests compared to the gold standard of ICA. Details are found in Tables 22-25.

Table 15. Summary of systematic review findings on diagnostic accuracy of coronary computed tomography angiography compared with invasive coronary angiography

Author, year AMSTAR-2	Population	Sensitivity	Specificity	PPV	NPV	LR +	LR -	CAD prevalence
Coronary Computed Tomography Angiography (Radiation dose not specified)								
2016 AHRQ REPORT	Suspected CAD	98.2%	81.6%	90.5%	99.0%	NR	NR	59.9%
Coronary Computed Tomography Angiography (Low radiation dose)*								
2016 AHRQ REPORT	Suspected CAD	100%	89%	93%	99%	9.2	0.00	58%
Coronary Computed Tomography Angiography (≥50% stenosis)								
NICE 2016	Stable chest pain	96%	79%	84%†	97%†	4.57†	0.05†	NR
ICER 2008	Stable chest pain	98%	82%	89%†	97%†	5.44†	0.02†	59%
Haase 2019 Low‡	Stable chest pain	93.4%	84.4%	83.6%	93.7%	5.98	0.08	46.1%
Knuuti 2018 Low	Stable CAD (not acute coronary syndromes)	97%	78%	58% to 93%†	89% to 99%†	4.44	2.64	24.2% to 75.5
Coronary Computed Tomography Angiography (70% stenosis)								
NICE 2016	Stable chest pain	96%	72%	67%†	99%†	3.43†	0.06†	NR

AHRQ = Agency for Healthcare Research and Quality; CAD = coronary artery disease; [redacted] Review; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; NICE = National Institute for Health and Care Excellence; NPV = negative predictive value; NR = not reported; PPV = positive predictive value.

* All included studies used prospective electrocardiography gating for CT; uses much lower radiation doses than other techniques.

† Calculated from other values the authors provide.

‡ Reports on individual patient data.

Table 16. Summary of systematic review findings on diagnostic accuracy of coronary computed tomography angiography compared with computed tomography derived fractional flow reserve

Author, year AMSTAR-2	Population	Sensitivity	Specificity	PPV	NPV	LR +	LR -	CAD prevalence
Coronary Computed Tomography Angiography (radiation dose NR)								
Pontone 2019 Low	Suspected or known CAD	93%	42%	62%	93%	1.72	0.17	NR
Coronary Computed Tomography Angiography (50% stenosis)								
Zhuang 2020 Low	Suspected or known CAD	88%	32%	55%	73%	1.37	0.23	NR
Coronary Computed Tomography Angiography (>50% stenosis)								
Gonzalez 2015 Low	Suspected or known CAD	92%	43%	57%	87%	1.64	0.19	45%

CAD = coronary artery disease; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; NPV = negative predictive value; NR = not reported; PPV = positive predictive value.

Table 17. Summary of systematic review findings on diagnostic accuracy of computed tomography (CCTA, FFRct) compared with fractional flow reserve via invasive coronary angiography

Author, year AMSTAR-2	Population	Sensitivity	Specificity	PPV	NPV	LR +	LR -	CAD prevalence
Coronary Computed Tomography Angiography (≥50% Stenosis)								
Knuuti 2018 Low	Stable CAD (not acute coronary syndromes)	93%	53%	60% to 88%*	68% to 91%*	1.97	0.13	43.6% to 78.3%
Computed Tomography derived Fractional Flow Reserve (0.75 to 0.80)								
Gonzales 2015 Low†	Suspected or known CAD	90%	72%	70%	90%	3.70	0.16	42%
Computed Tomography derived Fractional Flow Reserve (<0.80)								
Agasthi 2018 Low	Suspected CAD	83%	72%	58% to 100%*	0% to 90%*	3.00	0.23	32% to 100%
Helfand 2019 High‡	Stable chest pain with suspected CAD§	84% to 85%	73% to 84%	NR	NR	NR	NR	NR
	Stable chest pain with suspected or known CAD**	84% to 86%	75% to 80%	NR	NR	NR	NR	NR

Author, year AMSTAR-2	Population	Sensitivity	Specificity	PPV	NPV	LR +	LR -	CAD prevalence
	Suspected CAD with at least 1 coronary stenosis of 40% to 90% on CCTA undergoing clinically indicated ICA with FFR††	91%	55%	58%*	89%*	2.02*	0.16*	41%

CAD = coronary artery disease; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; NPV = negative predictive value; NR = not reported; PPV = positive predictive value.
* Calculated from other values the authors provide.
† Focused on HeartFlow technology.
‡ Study is not a full SR. Instead, it is a rapid response review.
§ SRs, focused on HeartFlow technology.
** SRs, focused on non-HeartFlow technology.
†† Single primary study, focused on HeartFlow technology.

Table 18. Summary of systematic review findings on diagnostic accuracy of CT myocardial perfusion imaging compared with invasive coronary angiography

Author, year AMSTAR-2	Population	Sensitivity	Specificity	PPV	NPV	LR +	LR -	CAD prevalence
CT myocardial perfusion (stenosis ≥50%)								
Sogaard 2016* Low	Suspected CAD	91%	77%	87%	83%	3.96†	0.12†	63%
NICE 2016	Stable chest pain	54%	100%	100%†	66%†	54.00†	0.47†	NR
CT myocardial perfusion (stenosis ≥70%)								
NICE 2016	Stable chest pain	66%	98%	96%†	80%†	33.00†	0.45†	NR

CAD = coronary artery disease; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; NICE = National Institute for Health and Care Excellence; NPV = negative predictive value; NR = not reported; PPV = positive predictive value.
* CT perfusion test is combined with CCTA (≥50% stenosis).
† Calculated from other values the authors provide.

Table 19. Summary of systematic review findings on diagnostic accuracy of CT myocardial perfusion imaging compared with computed tomography derived fractional flow reserve

Author, year AMSTAR-2	Population	Sensitivity	Specificity	PPV	NPV	LR +	LR -	CAD prevalence
CT myocardial perfusion (stenosis NR)								

Author, year AMSTAR-2	Population	Sensitivity	Specificity	PPV	NPV	LR +	LR -	CAD prevalence
Pontone 2019 Low	Suspected or known CAD	79%	88%	84%	81%	5.15	0.26	63%
CT myocardial perfusion (stenosis >50%)								
Gonzalez 2015 Low	Suspected or known CAD	94%	77%	83%	92%	3.85	0.09	54%

CAD = coronary artery disease; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; NPV = negative predictive value; NR = not reported; PPV = positive predictive value.

Table 20. Summary of systematic review findings on diagnostic accuracy of stress nuclear testing (SPECT, PET) compared with invasive coronary angiography

Author, year AMSTAR-2	Population	Sensitivity	Specificity	PPV	NPV	LR +	LR -	CAD prevalence
Single Photon Emission Computed Tomography (Radiation dose not specified)								
2016 AHRQ REPORT	Overall	83% to 85%	77% to 85%	79% to 85%	79% to 85%	3.56 to 5.13	0.18 to 0.22	50%
	Suspected CAD	83% to 84%	79% to 85%	72% to 85%	84%	3.88 to 5.01	0.19 to 0.21	41%
Single Photon Emission Computed Tomography (50% stenosis)								
NICE 2016	Stable chest pain	81%	78%	88%	65%	3.68	0.24	NR
Single Photon Emission Computed Tomography (>50% stenosis)								
Knuuti 2018 Low	Stable CAD (not acute coronary syndromes)	87%	70%	32% to 95%*	47% to 97%*	2.88	2.33	14.1% to 86%
Single Photon Emission Computed Tomography (70% stenosis)								
NICE 2016	Stable chest pain	76%	76%	86%*	56%*	3.17*	0.32*	NR
Positron Emission Tomography (Radiation dose not specified)								
2016 AHRQ REPORT	Overall	82% to 90%	86% to 88%	93% to 96%	53% to 84%	5.57 to 5.88	0.11 to 0.21	63% to 80%
	Suspected CAD	90% to 91%	82% to 91%	94%	75% to 84%	4.97 to 8.89	0.11	75%
Positron Emission Tomography (>50% stenosis)								

Author, year AMSTAR-2	Population	Sensitivity	Specificity	PPV	NPV	LR +	LR -	CAD prevalence
Knuuti 2018 Low	Stable CAD (not acute coronary syndromes)	90%	85%	78% to 91%*	84% to 94%*	5.87	0.12	36.5% to 62.5%
Positron Emission Tomography (70% stenosis)								
NICE 2016	Stable chest pain	91%	86%	87%*	90%*	6.50*	0.10*	NR

AHRQ = Agency for Healthcare Research and Quality; CAD = coronary artery disease; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; NICE = National Institute for Health and Care Excellence; NPV = negative predictive value; NR = not reported; PPV = positive predictive value.
* Calculated from other values the authors provide.

Table 21. Summary of systematic review findings on diagnostic accuracy of nuclear stress testing (SPECT, PET) compared with computed tomography derived fractional flow reserve

Author, year AMSTAR-2	Population	Sensitivity	Specificity	PPV	NPV	LR +	LR -	CAD prevalence
Single Photon Emission Computed Tomography (radiation dose NR)								
Pontone 2019 Low	Suspected or known CAD	71%	79%	75%	70%	2.94	0.42	NR
Positron Emission Tomography (radiation dose NR)								
Pontone 2019 Low	Suspected or known CAD	88%	86%	85%	88%	6.35	0.13	NR

CAD = coronary artery disease; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; NPV = negative predictive value; NR = not reported; PPV = positive predictive value.

Table 22. Summary of systematic review findings on diagnostic accuracy of nuclear stress testing (SPECT, PET) compared with fractional flow reserve via invasive coronary angiography

Author, year AMSTAR-2	Population	Sensitivity	Specificity	PPV	NPV	LR +	LR -	CAD prevalence
Single Photon Emission Computed Tomography (>50% stenosis)								
Knuuti 2018 Low	Stable CAD (not acute coronary syndromes)	73%	83%	52% to 81%*	76% to 92%*	4.21	0.33	20% to 49.6%
ICER 2013	Suspected or known CAD	66% to 90%	50% to 100%	73% to 81%	58% to 91%	1.32 to 9.00*	0.10 to 0.68*	NR
Positron Emission Tomography (>50% stenosis)								

Author, year AMSTAR-2	Population	Sensitivity	Specificity	PPV	NPV	LR +	LR -	CAD prevalence
Knuuti 2018 Low	Stable CAD (not acute coronary syndromes)	89%	85%	80% to 82%	91% to 92%	6.04	0.13	39.9% to 44.1%
[redacted] 2013	Suspected or known CAD	76% to 95%	83% to 91%	76% to 86%	83% to 97%	4.47 to 10.56*	0.05 to 0.29*	NR

CAD = coronary artery disease; [redacted] LR+ = positive likelihood ratio; LR- = negative likelihood ratio; NPV = negative predictive value; NR = not reported; PPV = positive predictive value.
* Calculated from other values the authors provide.

Table 23. Summary of systematic review findings on diagnostic accuracy of stress echocardiography compared with invasive coronary angiography

Author, year AMSTAR-2		Population	Sensitivity	Specificity	PPV	NPV	LR +	LR -	CAD prevalence
Stress echocardiography (Stenosis NR)									
De Jong 2012 Low	Compared to ICA stenosis ≥50% to 75%	Suspected or known CAD	87%	72%	85%	73%	3.08	0.18	66%
	Compared to ICA Stenosis ≥50 stenosis	Suspected CAD	88%	89%	93%	80%	8.35	0.13	64%
2016 AHRQ REPORT		Overall	84% to 87%	72% to 77%	85% to 89%	69% to 73%	3.08 to 3.65	0.18 to 0.21	66% to 68%
		Suspected CAD	88%	89%	93%	80%	8.35	0.13	64%
Lapado 2013 Critically low		Suspected or known CAD	84%	77%	89%	69%	3.65	0.21	68%
Stress Echocardiography (50% stenosis)									
NICE 2016	Perfusion	Stable chest pain	84%	79%	88%*	71%*	4.00*	0.21*	NR
	Wall motion, vasodilators	Stable chest pain	77%	76%	93%*	97%*	3.21*	0.30*	NR
	Wall motion, heart rate modifiers	Stable chest pain	76%	80%	88%	62%	3.80	0.30	NR

Author, year AMSTAR-2		Population	Sensitivity	Specificity	PPV	NPV	LR +	LR -	CAD prevalence
Stress Echocardiography (>50% stenosis)									
Knuuti 2018 Low		Stable CAD (not coronary syndromes)	85%	82%	72% to 98%*	36% to 91%*	4.67	2.95	35.1% to 90.8%
Stress Echocardiography, perfusion (70% stenosis)									
NICE 2016	Perfusion	Stable chest pain	90%	73%	74%*	55%*	3.33*	0.14*	NR
	Wall motion, vasodilators	Stable chest pain	64%	90%	91%*	66%*	6.40*	0.40*	NR
	Wall motion, heart rate modifier	Stable chest pain	75%	88%	90%*	84%*	6.25*	0.28*	NR

AHRQ = Agency for Healthcare Research and Quality; CAD = coronary artery disease; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; NICE = National Institute for Health and Care Excellence; NPV = negative predictive value; NR = not reported; PPV = positive predictive value.
* Calculated from other values the authors provide.

Table 24. Summary of systematic review findings on diagnostic accuracy of stress echocardiography compared with computed tomography derived fractional flow reserve

Author, year AMSTAR-2	Population	Sensitivity	Specificity	PPV	NPV	LR +	LR -	CAD prevalence
Stress Echocardiography (Stenosis NR)								
Pontone 2019 Low	Suspected or known CAD	64%	84%	81%	70%	3.51	0.45	NR

CAD = coronary artery disease; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; NPV = negative predictive value; NR = not reported; PPV = positive predictive value.

Table 25. Summary of systematic review findings on diagnostic accuracy of non-invasive diagnostic tests (CCTA, SNI, stress echo) compared with invasive coronary angiography in Emergency Departments

Author, year AMSTAR-2	Population	Sensitivity	Specificity	PPV	NPV	LR +	LR -	CAD prevalence
Coronary computed tomography angiography (Stenosis NR)								
Iannaconne 2019* Low	Suspected or known CAD	93%	90%	NR	NR	9.40	0.10	NR

Author, year AMSTAR-2	Population	Sensitivity	Specificity	PPV	NPV	LR +	LR -	CAD prevalence
ICER 2008†	Patients presenting to the ED with and without ACS, or with possible ischemic chest pain	94% to 100%	77% to 92%	47% to 87%	91% to 100%	4.08 to 12.5‡	0.0 to 0.08‡	NR
Single Photon Emission Computed Tomography (Stenosis NR)								
Iannaconne 2019* Low	Suspected or known CAD	85%	92%	NR	NR	10.48	0.19	NR
Stress echocardiography (Stenosis NR)								
Iannaconne 2019* Low	Suspected or known CAD	75%	96%	NR	NR	18.67	0.25	NR

CAD = coronary artery disease; [redacted] LR+ = positive likelihood ratio; LR- = negative likelihood ratio; NPV = negative predictive value; NR = not reported; PPV = positive predictive value.
* Patient population were patients with non-ST segment elevation myocardial infarction (NSTEMI) and without troponin. Authors do not report prevalence of CAD, pretest likelihood, or true and false positives or negative.
† Abstracted from 3 primary studies included in this report.
‡ Calculated from values given by authors.

4.3 Results for Reliability

To provide a general overview of reliability of the included non-invasive tests, we performed a search of the literature to identify studies that included assessments of intra- and interobserver agreement using Cohen's Kappa. Cohen suggests that Kappa results be interpreted as follows: values ≤0 as indicating no agreement, 0.01 to 0.20 as none to slight agreement, 0.21 to 0.40 as fair, 0.41 to 0.60 as moderate, 0.61 to 0.80 as substantial, and 0.81 to 1.00 as almost perfect agreement.

Intraobserver reliability in CCTA ranged from substantial agreement to almost perfect agreement (k=0.72 to 0.96) in 3 studies.[137,205,258] Between observer reliability was investigated in six studies[31,90,109,137,205,258] and ranged from moderate agreement to almost perfect agreement (k=0.58 to 0.94). Intraobserver reliability was investigated in two studies[41,80] for FFRct and found fair to almost perfect agreement (k=0.40 to 0.97), but no studies were found on interobserver agreement. CT perfusion was only investigated in one study[43] and found interobserver reliability ranging from substantial to almost perfect agreement (k=0.72 to 0.86).

SPECT studies found almost perfect agreement across one intraobserver[70] and two interobserver studies[43,70] (k=0.96 and k=0.91 to 0.95 respectively). Similarly, one study[258] investigating PET found almost perfect agreement for both intra- and interobserver reliability (k=0.94 and k=0.82 respectively).

Reliability studies on stress echocardiography included both exercise and dobutamine for inducing stress. In general, three intraobserver studies[70,75,102] all found almost perfect agreement for stress echocardiography (k=0.81 to 0.90). Meanwhile, between observer reliability ranged from moderate to almost perfect agreement across 5 studies[70,74,75,102,130] (k=0.56 to 0.87).

Although ICA is commonly considered the gold standard for identifying CAD, there are well known limitations regarding variability, reliability, and image distortion in its use. Nevertheless, one study that we identified for CCTA also investigated the interobserver reliability of ICA and found substantial agreement between observers (k=0.79).[31]

Risk of bias was assessed using the following criteria: 1) Broad spectrum of persons with expected conditions, 2) Adequate methods description for replication, and 3) Blinded performance of tests/interpretations. A good-quality study includes all three criteria and drops one level for each violation. Our assessment found that study quality ranged from poor to good, with the majority of studies rated as good quality (Appendix E).

Table 26. Summary of intraobserver reliability studies for each test modality

Study, year Risk of Bias*	Test modality and criteria	Intraobserver Cohen's Kappa interpretation (k, 95% CI)
Computed Tomography (CCTA, FFRct)		
Lehman 2009 Good quality	CCTA (Stenosis NR)	Almost perfect agreement (k=0.95, 95% CI: NR)
Rinehart 2010 Good quality	CCTA (Stenosis NR)	Degree of stenosis: Almost perfect agreement (k=0.96, 95% CI: NR) Plaque classification: Almost perfect agreement (k=0.96, 95% CI: NR)
Williams 2017 Good quality	CCTA (>50% stenosis)	Substantial agreement (k=0.72, 95% CI: NR)
Ghaemian 2020 Moderate quality	FFRct (<0.80)	Whole population: Fair agreement (k=0.40, 95% CI: NR) True SPECT: Almost perfect agreement (k=0.97, 95% CI: NR)†
Collet 2018 Good quality	FFRct (<0.80)	Almost perfect agreement (k=0.82, 95% CI: 0.73 to 0.90) ‡
Stress Nuclear Imaging (SPECT, PET)		
Ferro 2007 Good quality	SPECT (Stenosis NR)	Almost perfect agreement (k=0.96, 95% CI: NR)
Williams 2017 Good quality	PET (Stenosis NR)	Almost perfect agreement (k=0.94, 95% CI: NR)
Stress Echocardiography		
Ferro 2007 Good quality	Dobutamine stress echo (Stenosis NR)	Almost perfect agreement (k=0.81, 95% CI: NR)
Hernandez-Gonzalez 2015 Moderate quality	Dobutamine stress echo (≥70% stenosis)	Almost perfect agreement (k=0.81, 95% CI: NR)
Gaibazzi 2010 Good quality	Wall motion stress echo (>70% stenosis)	Almost perfect agreement (k=0.90, 95% CI: NR)

CCTA = computed coronary tomography angiography; CI = confidence interval; DSE = dobutamine stress echocardiography; FFR = fractional flow reserve; FFRct = computed tomography derived fractional flow reserve; ICA = invasive coronary angiography; NR = not reported; PET = positron emission tomography; SPECT = single-photon emission computed tomography; WM = wall motion; WMS = wall motion scoring.

* Based on Risk of Bias for Diagnostic Reliability Studies (Appendix D). The three criteria include 1) Broad spectrum of persons with expected conditions, 2) Adequate methods description for replication, and 3) Blinded performance of tests/interpretations. A good-quality study includes all three criteria, and drops one level for each violation.

† Whole population = concordance between FFR and SPECT in patient population as a whole; True SPECT = concordance between FFR and SPECT in patients in whom SPECT was truly positive and truly negative.

‡ Compares agreement concerning recommendation of revascularization strategy between FFRct and ICA

Table 27. Summary of Interobserver reliability studies for each test modality

Study (Year) Risk of Bias*	Test modality and criteria	Interobserver Cohen's Kappa interpretation (95% CI)
Computed Tomography (CCTA, CT perfusion)		
Hoffman 2012 Poor quality	CCTA (Stenosis NR)	Almost perfect agreement (k=0.94, 95% CI: NR)
Lehman 2009 Good quality	CCTA (Stenosis NR)	Almost perfect agreement (k=0.93, 95% CI: NR)
Rinehart 2010 Good quality	CCTA (Stenosis NR)	Degree of Stenosis: Almost perfect agreement (k=0.90, 95% CI: NR) Plaque classification: Almost perfect agreement (k=0.88, 95% CI: NR)
Williams 2017 Good quality	CCTA (>50% stenosis)	Substantial agreement (k=0.77, 95% CI: NR)
Butler 2007 Good quality	CCTA (>50% stenosis)	Substantial agreement (k=0.77, 95% CI: NR)
Gueret 2013 Good quality	CCTA (≥50% stenosis)	Moderate agreement (k=0.58, 95% CI: 0.29 to 0.88)
Cury 2015 Good quality	CT Perfusion (<50% or ≥50% and 70% or ≥70%)	Reversible perfusion defects† Agreement between observers 1 and 2: Substantial agreement (k=0.77, 95% CI: 0.69 to 0.85) Agreement between observers 1 and 3: Almost perfect agreement (k=0.84, 95% CI: 0.77 to 0.91) Agreement between observers 2 and 3: Substantial agreement (k=0.80, 95% CI: 0.72 to 0.88) Fixed perfusion defects‡ Agreement between observers 1 and 2: Substantial agreement (k=0.72, 95% CI: 0.63 to 0.81) Agreement between observers 1 and 3: Almost perfect agreement (k=0.86, 95% CI: 0.79 to 0.92) Agreement between observers 2 and 3: Substantial agreement (k=0.74, 95% CI: 0.66 to 0.83)
Stress Nuclear Imaging (SPECT, PET)		
Ferro 2007 Good quality	SPECT (Stenosis NR)	Almost perfect agreement (k=0.92, 95% CI: NR)
Cury 2015 Good quality	SPECT (<50% or ≥50% and 70% or ≥70%)	Agreement between observers 1 and 2: Almost perfect agreement (k=0.92, 95% CI: 0.86 to 0.97) Agreement between observers 1 and 3: Almost perfect agreement (k=0.91, 95% CI: 0.85 to 0.96) Agreement between observers 2 and 3: Almost perfect agreement (k=0.95, 95% CI: 0.93 to 1.00)
Williams 2017 Good quality	PET (Stenosis NR)	Almost perfect agreement (k=0.82, 95% CI: NR)
Stress Echocardiography		
Khan 2017 Poor quality	Stress echo (Stenosis NR)	Rest: Almost perfect agreement (k=0.87, 95% CI: 0.75 to 0.96) Stress: Substantial agreement (k=0.70, 95% CI: 0.60 to 0.79)
Ferro 2007	Dobutamine stress echo	Moderate agreement (k=0.56, 95% CI: NR)

Study (Year) Risk of Bias*	Test modality and criteria	Interobserver Cohen's Kappa interpretation (95% CI)
Good quality	(Stenosis NR)	
Hernandez-Gonzalez 2015 Moderate quality	Dobutamine stress echo (≥70% stenosis)	Almost perfect agreement (k=0.81, 95% CI: NR)
Gaibazzi 2013 Good quality	Wall motion stress echo (Stenosis NR)	Almost perfect agreement (k=0.86, 95% CI: NR)
Gaibazzi 2010 Good quality	Wall motion stress echo (>70% stenosis)	Substantial agreement (k=0.80, 95% CI: NR)
Invasive Coronary Angiography		
Butler 2007 Good quality	ICA (>50% stenosis)	Substantial agreement (k=0.79, 95% CI: NR)

CCTA = computed coronary tomography angiography; CI = confidence interval; DSE = dobutamine stress echocardiography; FDG = F-18-fluoro-2-deoxyglucose; FFR = fractional flow reserve; FFRct = computed tomography derived fractional flow reserve; ICA = invasive coronary angiography; IHP = International Harmonization Project; NR = not reported; PET = positron emission tomography; PET-CT = positron emission tomography-computed tomography; SPECT = single-photon emission computed tomography; WM = wall motion; WMS = wall motion scoring.

* Based on Risk of Bias for Diagnostic Reliability Studies (Appendix D). The three criteria include 1) Broad spectrum of persons with expected conditions, 2) Adequate methods description for replication, and 3) Blinded performance of tests/interpretations. A good-quality study includes all three criteria, and drops one level for each violation.

† The number of reversible defects was calculated as the number of segments with positive differences (stress score rest score) for segments with a stress score >1. A subject was determined to be ischemic if ≥2 segments had reversible defects according to the median count across the 3 readers.

‡ The segment was considered fixed if the segment was scored >1 and was equal at both rest and stress. A subject was determined to have the presence of fixed defects if ≥1 segment had a fixed defect according to the median count across the 3 readers.

5 Key Questions Results Overview

5.1 Number of studies retained

From 15,443 unique citations identified via systematic data base searching, 81 studies across 112 publications were retained (Figure 3). A total of 36 studies (in 66 publications) (35 RCTs and 1 prospective comparative cohort)[5,17,36,37,47,48,52,57-60,83-85,88,91,96,109,111,117,126,135,138-146,148,149,151,153,159-161,163,168,171,175,176,180,186,187,189,192,204,209-211,215,217,218,220,223,237,238,241,245,246,248,256,257,262] comprised the primary evidence base for Key Questions 1–4 and an additional 31 studies (2 SRs and 29 nonrandomized observational studies)[4,13,15,20,23,24,33,45,64,66,69,72,76,77,81,87,119,122,124,125,134,155,158,164-166,181,191,193,200,229] provided supplemental data on safety (Key Question 3; see Appendix Tables O23-O25 for details). For cost-effectiveness (Key Question 5), 14 studies across 15 publications (3 systematic reviews and 11 formal economic analyses) were included.[8,26,27,82,91,116,123,136,147,162,196,197,243,249,263]

5.1.1 Primary evidence base for Key Questions 1–4

A total of 35 trials (in 64 publications) [5,17,36,37,47,48,52,58,59,83-85,88,91,96,109,111,117,126,135,138-146,148,149,151,153,159-161,163,168,171,175,176,180,186,187,189,192,204,209-211,215,217,218,220,223,237,238,241,245,246,248,256,257,262] and one prospective comparative cohort study (in 2 publications)[57,60] that met inclusion criteria were identified and comprise the primary the evidence base for evaluation of efficacy and safety in this report. The bulk of the new trials evaluated CCTA. Most trials were considered fair (17 RCTs) with 11 considered good and seven considered poor quality (see Appendix E for details).

Although we sought studies in the three symptomatic populations of interest (i.e., patients with unknown but suspected CAD, those with known/established CAD and those with suspected ACS), only 1 trial (which evaluated PET) was specifically in patients with known CAD.[189] Populations in 13 trials[36,52,59,88,126,153,163,209,211,215,223,238,262] and one prospective comparative cohort[60] were predominately (≥80%) those with unknown/suspected CAD presenting to in an outpatient setting and are described as stable outpatients in the results. Five trials enrolled a mixed population of known and suspected CAD.[48,117,168,210,220] Sixteen trials were in patients presenting acutely to the ED or similar setting with suspected ACS (unstable angina or NSTEMI).[37,47,84,85,96,109,138,140,142,144,145,161,171,180,192,248] Studies in patients with STEMI were excluded. There was heterogeneity across trials regarding how pre-test risk was determined and reported. Given this heterogeneity it was not possible to stratify results by this variable. Appendix M provides information as reported by trial authors, and patient and study characteristics can be found in Appendix Q.

Table 28 below provides an overview of the included studies by test and comparator as well as population.

Table 28. Overview of included studies comprising the primary evidence base for Key Questions 1–4 arranged by test and comparator as well as population of interest.

Test	Comparator	Population					Total
		Stable, OP			Acute, ED/similar setting		
		Suspected CAD only	Mixed suspected or known CAD	Known CAD	Suspected ACS only	Mixed suspected or known CAD	
CCTA	**Any functional testing**	*Low to intermediate pre-test risk:* 1. Douglas 2015 (PROMISE)[59]			*Low pre-test risk:* 1. Dedic 2016 (BEACON)[47] *Low to intermediate pretest risk:* 2. Litt 2012 (ACRIN-PA)[145] 3. Linde 2013 (CATCH)[144] 4. Miller 2011[161] *Intermediate pre-test risk:* 5. Hoffman 2012 (ROMICAT-II)[109] *Mixed* pretest risk:* 6. Chang 2008[37]		**7 RCTs**
	SPECT	*Intermediate pre-test risk:* 1. Karthikeyan 2017 (IAEA-SPECT/CTA)[126] *Intermediate to high pre-test risk:* *2.* Min *2012*[163] *Pre-test risk NR:* 3. Stillman 2020 (RESCUE)[238]			*Low pre-test risk:* 1. Goldstein 2011 (CT-STAT)[84] 2. Goldstein 2007[85] *Low to intermediate pre-test risk* 3. Nabi 2016[171] *Intermediate pre-test risk:* 4. Levsky 2015 (PROSPECT)[140]		**7 RCTs**
	Stress Echo				*Low to intermediate pre-test risk* 1. Levsky 2018[138] 2. Pineiro-Portela 2021[192] *Pre-test risk NR* 3. Uretsky 2017 (PERFECT)[248]		**3 RCTs**
	ETT ECG	*Mixed* pre-test risk* 1. McKavanagh 2015 (CAPP)[153] *Pretest risk NR:* 2. SCOT-HEART Investigators 2015 (SCOT-HEART)[215]†			*Low to intermediate pre-test risk:* 1. Hamilton-Craig 2014 (CT-COMPARE)[96]		**3 RCTs**
	ICA	*Intermediate pre-test risk:* 1. Dewey 2016 (CAD-Man)[52] 2. Chang 2019 (CONSERVE)[36]					**2 RCTs**
	Any comparator	**8 RCTs**	**-----**	**-----**	**14 RCTs**	**-----**	**22 RCTs**

CCTA FFR	**Any functional testing**	*Intermediate pre-test risk* 1. Douglas 2015 (PLATFORM)[60] [Pro observational]					**1 pro CC**
	ICA						**1 pro CC**
	Any comparator	**1 prospective CC**	-----	-----	-----	-----	**1 pro CC**
SPECT	**Stress Echo**		1. Sharples 2007 (CeCaT)[220]			1. Salame 2018[210]	**2 RCTs**
	ETT ECG	*Intermediate pre-test risk* 1. Shaw 2011 (WOMEN)[223] *Mixed* pretest risk:* 2. Sabharwal 2007 [209]					**2 RCTs**
	NICE guidelines-directed care‡	*Intermediate pre-test risk* 1. Greenwood 2016 (CE-MARC 2)[88]					**1 RCT**
	Clinical assessment only§				*Mixed* pre-test risk* 1. Lim 2013[142]		**1 RCT**
	ICA		1. Sharples 2007 (CeCaT)[220]				**1 RCT**
	Any comparator	**3 RCTs**	**1 RCT**	-----	**1 RCT**	**1 RCT**	**6 RCTs**
STRESS ECHO	**ETT ECG**	*Mixed* pre-test risk* 1. Zacharias 2017[262] *Pretest risk NR* 2. Sanfilippo 2005[211]			*Low pre-test risk* 1. Nucifora 2009 (ASSENCE)[180]	1. Jeetley 2006[117] 2. Desideri 2005 (COSTAMI-II)[48]	**5 RCTs**
	"Standard care"**				*Low pre-test risk* 1. Nucifora 2009 (ASSENCE)[180]		**1 RCT**
	ICA		1. Sharples 2007 (CECaT)[220]				**1 RCT**
	Any comparator	**2 RCTs**	**1 RCT**	-----	**1 RCT**	**2 RCTs**	**6 RCTs**
PET	**SPECT**		1. Mullani 2000[168]	1. Patel 2019[189]			**2 RCTs**
TOTAL		**13 RCTs** **1 prospective CC**	**2 RCTs**	**1 RCT**	**16 RCTs**	**3 RCTs**	**35 RCTs** **1 pro CC**

CCTA = coronary computed tomography angiography; ETT ECG = exercise treadmill test with electrocardiography; FFR = fractional flow reserve; ICA = invasive coronary angiography; PET = positron emission tomography; Pro CC = prospective comparative cohort; RCT = randomized controlled trial; SPECT = single photon emission computed tomography; Stress Echo = stress echocardigraphy

* **McKavanagh 2015 (CAPP)**: Low risk: 43%; Intermediate risk: 24%; High risk: 34%.
Sabharwal 2007: Low risk: 16%; Intermediate risk: 61%; High risk: 23%.

Chang 2008: Low risk: 37%; Intermediate risk: 42%; High risk: 21%.
Lim 2013: unclear distribution
Zacharias 2017: Low risk: 41%; Intermediate risk: 34%; High risk: 25%.

† 85% of patients in the CCTA arm also received ETT ECG so this is not a true CCTA vs. ETT ECG comparison.

‡ From Supplemental material, CE-MARC 2 trial: "In essence, the guidelines recommend invasive angiography as the most cost-effective first test if the likelihood of CHD is 61-90%, non-invasive functional testing (SPECT, stress echocardiography or stress CMR) if the likelihood of CHD is 30-60%, CT scanning (with 64 slices or above) if the likelihood of CHD is 10-29% or no further testing if the likelihood of CHD is low (<10%)."

§ 6-hour observation period followed by hospital admission if deemed (by ED physician) high to intermediate risk for ACS (by the ED physician) or discharge (discharged patients followed-up at the cardiology clinic within 2 weeks). Further investigations (i.e., ICA or non-invasive cardiac function testing—including stress echocardiography, SMPI, or exercise ECG testing) performed at discretion of the attending cardiologist either during index hospitalization or on an outpatient basis (32% had MPI or stress echo; 24% had stress ECG only; 11% had ICA).

****** Hospitalized until a positive or negative diagnosis was reached according to local protocols without imposing any time constraints on investigators. The final diagnosis was achieved using clinical judgment only without performing additional diagnostic examinations in 39 cases (71%), using stress echo in 6 (11%), using EET in 7 (13%), and using coronary angiography in 3 (5%).

A total of 22 trials across 46 publications evaluated CCTA (see Appendix Table O34 for a list of the index trial and its affiliated publications). Twenty trials compared CCTA with functional testing.[59,126,153,163,215,238] Of these, six trials evaluated stable patients with suspected CAD[59,126,153,163,215,238] and 14 trials evaluated patients with suspected ACS.[37,47,84,85,96,109,138,140,144,145,161,171,192,248] Two RCTs compared CCTA versus direct referral to ICA in patients with suspected CAD (known CAD was an exclusion criteria)[36,52] One prospective nonrandomized comparative cohort compared CCTA plus Fractional Flow Reserve (FFR) versus any non-invasive testing and versus ICA in patients with suspected CAD treated on an outpatient basis.[57,60] Of the 22 RCTs, seven were considered good quality[47,52,59,84,126,215,238], 12 fair quality[36,37,96,109,138,140,144,145,153,171,192,248] and three poor quality[85,161,163]; the prospective comparative cohort was considered good quality[57,60] (see Appendix E for details).

A total of six trials evaluated SPECT. Two trials compared SPECT imaging with stress echocardiography in mixed populations of patients with suspected or known CAD, one in stable and one in acute patients.[210,220,241] Two trials compared SPECT with exercise ECG in stable outpatients with suspected CAD (known CAD was an exclusion criteria).[209,223] One trial compared SPECT imaging versus clinical assessment only in acute patients with suspected ACS presenting to the ED.[142]

One trial compared SPECT with NICE guideline-directed care in stable outpatients with suspected CAD.[88] Lately, one trial compared SPECT with ICA in stable patients with suspected or known CAD.[220,241] This latter trial also compared SPECT with exercise ECG. Of the six RCTs, two were considered good quality[88,220,241] and four fair quality[142,209,210,223] (see Appendix E for details).

A total of six, primarily older trials (2009 or earlier) evaluated stress echocardiography. Five trials compared stress echocardiography with exercise ECG, two in stable outpatients with suspected CAD (known CAD was an exclusion criteria)[91,211,262] and three in patients with acute symptoms presenting to the ED or hospital[48,117,180]. One trial compared stress echocardiography with "standard care" in low-risk patients with suspected ACS presenting to the ED.[180] One trial compared stress echocardiography with direct referral to ICA in stable patients with suspected or known CAD.[220,241] One of these trials included both an exercise ECG and a standard care comparison arm.[180] Of the six RCTs, two were considered good quality[91,220,241,262], one fair quality[48] and three poor quality[117,180,211] (see Appendix E for details).

A total of two trials evaluated PET and both compared PET with SPECT in outpatient settings. One poor-quality trial included stable patients with a mixed of suspected or known CAD[168] and the second good-quality trial included stable patients with known CAD presenting with new or worsening symptoms.[189]

See Appendix E for study quality details.

5.1.2 Evidence base for Key Question 5

In addition to the trials evaluating efficacy and safety, a total of three systematic reviews[243,249,263] and 11 primary studies were included that formally evaluated cost-effectiveness. Eight of the studies (in nine publications) were in stable outpatients with suspected CAD,[8,26,27,91,116,123,136,147,162] and three were in patients with suspected ACS.[82,196,197] Formal economic studies identified for inclusion primarily

compared combinations of testing strategies involving CCTA, stress nuclear imaging (primarily SPECT), stress echocardiography, exercise ECG treadmill testing and invasive coronary angiography, with only few directly comparing one specific test to another. Given the complexity of interpreting these studies, all cost-effectiveness data is summarized under section 6.1.5 under the CCTA heading. Across the studies, scores on the Quality of Health Economic Studies (QHES), the instrument used to systematically assess the quality of each study, ranged from 50 to 94 out of 100 (See Appendix E for details).

5.2 Comparison with the 2008 and 2013 reports

CCTA

The 2008 review of CCTA primarily focused on diagnostic accuracy (34 for the 41 included studies) for 64 slice or higher resolution equipment and most included patient already scheduled for ICA. A variety of scenarios were modeled for clinical impact and cost-effectiveness of CCTA related to CAD prevalence. Only one RCT[85] measured the impact of CCTA on patient outcomes was identified. The report included patients with acute chest pain presenting in an ED setting (7 studies, total N=496) and patients with stable chest pain at low to intermediate CAD risk presenting to outpatient settings (34 studies, total N 3349, CAD prevalence range 2–40%); most reported on diagnostic accuracy. Approximately two-thirds of studies excluded patients with known CAD or revascularization.

Primary findings from the 2008 report include:

- Based on ICER's modeling, Integrated Evidence Rating method and assuming a CCTA reimbursed price of $466:
    - For the triage of patients with acute chest pain at low to intermediate risk of ACS in an ED setting, CCTA was considered to be of comparative clinical effectiveness versus usually care/other diagnostic strategies and of high value based on their economic modeling.
    - In outpatients with or without signs and symptoms of unstable chest pain and at low to intermediate risk of significant CAD, the comparative clinical effectiveness of CCTA was rated as "unproven but with evidence of potential net benefit" (limited confidence of small or moderate-large net health benefit) and reasonable or comparable value.
- CCTA was considered highly sensitive with moderately high specificity (See Executive Summary and other tables in this report).
- Data on clinical outcomes and decision making not synthesized across studies; all but one study was observational.
- For triage of ED patients, their models suggested that ICA may be reduced if CCTA were to be employed compared with usual care.
- Regarding safety, CCTA was considered safe with risks similar to other tests employing contrast media. A range of CCTA-related radiation exposure values was reported (2 mSv to 14 mSv). As noted, small but definite risks may exist related to radiation exposure. Incidental/extra cardiac findings requiring further evaluation was reported to range from 5 to 20% of patients. Authors note the need to consider incidental findings in economic analyses.

Comparison with this update:

Since 2008, 19 additional RCTs (43 publications, total N >20,000 patients) comparing CCTA with functional testing have been published and are included in this re-review and constitute the primary evidence base for CCTA effectiveness and safety. This update reports on an expanded evidence base of higher quality studies. Thus, this update focused on the impact of CCTA on clinical outcomes and decision making with information regarding diagnostic accuracy summarized for contes making direct comparison to the 2008 report challenging

- In general, for CCTA compared with functional imaging in particular, there were no clear differences in clinical outcomes (MI, all-cause mortality), use of additional testing or hospitalization for patients presenting to the ED or for stable outpatients. (See Executive Summary and full report for details).
- In contrast to modeling done in the 2008 report, data synthesized across more recent RCTs suggests that ICA is more common (as is PCI) with CCTA versus functional imaging
- Safety findings in this update are overall consistent with the 2008 report. Continued improvement in methods for reducing test-related radiation exposure are noted.
- Definitive conclusions for cost-effectiveness of CCTA specifically from published included studies were not possible.

Cardiac nuclear imaging

The key questions for 2013 review of cardiac nuclear imaging differed from this review evaluation and the prior review included screening of asymptomatic patients. The review included 34 studies, 26 of which evaluated clinical outcomes. Nine studies were comparative cohort studies comparing different protocols and 12 were case series. The 2013 report included patients with known CAD, including asymptomatic patients, who receive nuclear imaging test for prognostic purposes such as risk stratification, treatment selection or follow-up monitoring. Most studies were in "mixed" populations which included symptomatic and asymptomatic patients, those with suspected and known CAD. Most studies of symptomatic patients were in higher risk patients.

Primary findings of the 2013 report relevant to this update:

- For diagnostic accuracy, the report compared PET and SPECT with ICA-derived fractional flow reserve and summarized accuracy data from systematic reviews for the comparison with ICA. (See report and Executive Summary Tables).
- Overall, based on ICER's modeling, Integrated Evidence Rating method for symptomatic patients at low to intermediate CAD risk,
    - Clinical effectiveness of SPECT was considered to be comparable or better versus ETT and based on HCA payment schedules, was more costly as an initial test, but that a 2-stage strategy of ETT followed by SPECT may provide cost savings but the comparative value was considered to be low.
    - SPECT and stress echo were considered to provide similar diagnostic and prognostic performance and SPECT was rated as "reasonable/comparable" for both clinical effectiveness and value.
    - In symptomatic patients with known CAD, SPECT and stress echo were considered comparable in clinical effectiveness and they expected it to be of "reasonable/comparable" value based on one RCT. Evidence comparing SPECT with ETT was considered to be insufficient as no studies were identified.

  - SPECT and PET were considered to be safe, but lack of comparative effectiveness evidence was noted. AEs were generally considered to be insignificant and due to exercise or pharmacologic stressors. Effective radiation does for SPECT (7–30 mSv) and PET (2–14 mSV) were reported.
- Evidence for PET was considered to be insufficient for all populations

- Evidence related to differential effectiveness or safety for key subgroups was considered insufficient.

Comparison with this update:

Our update focuses on the clinical impact of stress nuclear imaging (SPECT and PET).

- This update does not include asymptomatic patients based on clinical input at the time of topic development, nor does it include patients at high CAD risk or studies of prognosis.
- A total of six RCTs (including three from the prior report) for SPECT and two RCTs for PET (including one from the previous report. RCTs comparing SPECT with NICE guideline directed care and clinical assessment where part of this update as was one RCT comparing it with ICA which were not part of the 2013 report. (Please see full report and executive summary)
- For SPECT compared with other functional test (ETT, stress echo), there were no differences in all-cause mortality, ICA referral, hospitalization, subsequent ED visits (SOE low for all) or revascularization (SOE Moderate). Findings and conclusions regarding safety are similar to the prior report.
- For PET, was insufficient for all clinical outcomes. There was no difference in ICA or revascularization between PET and SPECT based on the newly identified RCT in patients with known CAD with new or worsening symptoms (SOE Low).
- Definitive conclusions for cost-effectiveness of CCTA specifically from published included studies were not possible.

Given that stress echocardiography is an established modality for evaluating cardiac function, based on clinical input it is included in this HTA.

6 Coronary Computed Tomography Angiography (CCTA) Results

6.1 CCTA versus Any Functional Testing

A total of 20 trials comparing CCTA with functional testing that met inclusion criteria were identified.[59,126,153,163,215,238] Six trials evaluated stable patients with suspected CAD[59,126,153,163,215,238] and 14 trials evaluated patients with suspected ACS.[37,47,84,85,96,109,138,140,144,145,161,171,192,248]

Since studies of patient with STEMI were excluded, ACS for included studies pertains to patients with unstable angina or NSTEMI as described in the studies. Some studies focused on patients with normal ECG and negative troponins. No studies specifically in patients with known CAD were identified.

CCTA vs. functional testing in stable patients with suspected CAD

Six randomized control trials (across 23 publications)[5,58,59,115,126,135,146,148,149,151,153,163,175,176,186,187,215,217,218,237,238,256,257] compared CCTA with functional testing in patients with suspected CAD in the outpatient setting. (See Appendix Q for details). All trials used a 64-slice (or higher) CT scanner for CCTA imaging and four[153,163,215,238] reported the use of iodinated contrast agents. Two trials[153,215] included CACS imaging as part of their CCTA protocol and three trials[59,163,238] did not. In one trial,[126] 3% of patients randomized to the CCTA arm received CACS. Specific functional tests included SPECT in three trials [126,163,238](across 4 publications, N=1,533), exercise ECG in two trials[153,215] (across 7 publications, N=4,646), and any functional testing in one trial[59] (across 12 publications, N=10,003). In the latter trial, most patients (63%) underwent nuclear stress testing as their index test, though patients could have received CACS, stress echocardiography, exercise ECG, ICA, or no testing at index visit. In one trial, the SCOT-HEART trial,[215] 85% of *all* patients in the CCTA arm had exercise treadmill tests (ETT) (as standard care) and the function testing arm was predominately ETT making this trial more of an adjunctive comparison.

Across all six trials, sample sizes ranged from 180 to 10,003 (total N=16,182). Mean patient age ranged from 57 to 61 years and the proportion of females ranged from 44% to 53%. Less than a third of participants were non-white (range, 22% to 29%) across the three trials reporting race.[59,126,238] Five trials specifically excluded patients with known CAD[59,126,153,163,238] and four trials excluded patients with prior revascularizations.[59,126,163,238] Patients' pre-test risk for CAD was low to intermediate one trial,[59] intermediate in one trial,[126] intermediate to high in one trial,[163] mixed in two trials,[153,215] and not reported in one trial.[238] Across all six trials, the proportion of patients reporting chest pain ranged from 73% to 100% (four trials reported on the specific sub-type of chest pain: typical [range, 12% to 35%] atypical [7% to 78%] and non-anginal [11% to 40%][59,153,163,215]); hypertension, from 31% to 65%; diabetes, from 11% to 28%; and smoking (past or current), from 15% to 53%. None of the trials reported on the proportion of patients with unstable angina. The proportion of patients presenting with dyspnea was reported by two trials (range, 10% to 15%)[59,126] and hyperlipidemia by three trials (range, 57% to 68%).[59,126,163] Duration of follow-up ranged from 2 months to 5 years. See Appendix Q for details.

Three trials were conducted in the United States,[59,163,238] two trials in the United Kingdom,[153,215] and one trial in multiple countries (Brazil, Czech Republic, India, Mexico, Slovenia, and Turkey).[126] Investigators

received funding from the government in four trials,[153,215,238] industry in one trial,[238] and an international organization in one trial.[126]

Four trials were rated good quality,[59,126,215,238] one fair quality,[153] and one poor quality.[163] The major methodological limitations in the fair-quality trial were unclear allocation concealment methods and unclear blinding of outcome assessors. In the poor-quality trial, limitations included unclear randomization and allocation concealment methods, failure to blind outcomes assessors, differences in key CAD risk factors at baseline between groups, it was unclear if follow-up times were comparable between groups.

CCTA vs. functional testing among patients with suspected ACS

Fourteen randomized control trials[37,47,84,85,96,109,138,140,144,145,161,171,192,248] (across 21 publications) compared CCTA with functional testing in patients with suspected ACS. (See Appendix Q for details). Ten trials took place in the Emergency Department,[37,47,84,85,96,109,138,145,161,248] three trials in the inpatient setting,[140,171,192] and one trial in the outpatient setting.[144] All trials used a 64-slice (or higher) CT scanner for CCTA imaging and nine reported the use of iodinated contrast agents.[37,84,85,96,109,140,171,192,248] Seven trials[84,85,109,140,145,161,171] included CACS imaging as part of their CCTA protocol and six trials[37,47,96,138,144,192] did not. In one trial,[248] 1% of patients randomized to the CCTA arm received CACS. Specific functional tests included SPECT in four trials[84,85,140,171] (across 5 publications, N=1,944), stress echocardiography in three trials[138,192,248] (across 4 publications, N=1,014), exercise ECG in one trial (across 1 publication, N=562),[96] and any functional testing in six trials[37,47,109,144,145,161] (across 11 publications, N=3,818).

Across all 14 trials, sample sizes ranged from 60 to 1,392 (total N=7,338). Mean patient age ranged from 49 to 64 years and the proportion of females ranged from 39% to 63%. A large majority of the patients identified as non-white (range, 33% to 95%) across the 7 trials reporting race.[109,138,140,145,161,171,248] Eight trials specifically excluded patients with known CAD,[85,96,109,138,140,161,171,248] and in two trials, 14% and 15% of patients had known CAD.[37,144] The remaining four trials did not report on patient's CAD status.[47,84,145,192] Two trials reported excluding patients with prior revascularizations[109,161] and one trial reported excluding patients with prior MI.[109] In two trials, 1% of patients had a prior MI.[84,145] The remaining trials did not report on patients' history of MI or revascularizations. Patients' pre-test risk for CAD was very low to low in one trial,[85] low in one trial,[47] low to intermediate in eight trials,[84,96,138,144,145,161,171,192] intermediate in two trials,[109,140] mixed in one trial,[37] and not reported in one trial.[248] In the trial including patients with varied risk statuses, 37% were low risk, 42% were intermediate risk, and 21% high risk.[37] All patients in all trials reported having chest pain (four trials reported on the specific sub-type of chest pain; typical [range, 12% to 90%] atypical [10% to 39%] and non-anginal [2% to 49%][109,140,144,192]). One trial reported that 1% of patients had unstable angina.[84] Two trials reported the proportion of patients with dyspnea (range, 2% to 49%),[109,248] 13 trials reported the proportion of patients with hypertension (range, 17% to 72%),[37,47,84,85,96,109,138,140,144,145,171,192,248] 12 trials reported the proportion of patients with diabetes (range, 6% to 32%),[37,84,85,96,109,138,140,144,145,171,192,248] 11 trials reported the proportion of patients with hyperlipidemia (range, 25% to 52%),[37,84,85,96,109,138,140,144,145,171,248] and 13 trials reported the proportion of smokers (past or current) (range, 14% to 49%).[37,47,84,85,96,109,138,140,144,145,171,192,248] Duration of follow-up ranged from 1 month to 4.7 years.

Nine trials were conducted in the United States,[84,85,109,138,140,145,161,171,248] one trial in Australia,[96] one trial in Denmark,[144] one trial in the Netherlands,[47] one trial in South Korea,[37] and one trial in Spain.[192] Investigators received funding from the government in four trials,[47,109,145,161] industry in two trials,[84,85] and non-profit foundations in four trials.[96,138,140,144] One trial reported receiving no funding[248] and three trials provided no information on funding.[37,171,192]

Two trials were rated good quality,[47,84] 10 trials were rated fair quality,[37,109,138,140,144,145,171,192,248] and two were rated poor quality.[85,161] The major methodological limitations in the fair-quality trials were unclear randomization and allocation concealment methods and failure to blind outcomes assessors. Other methodological shortcomings in the poor-quality trials included difference in key CAD risk factors between groups at baseline which were not controlled for and no prespecified definition for a positive test in one trial.

6.1.1 Key Question 1: Primary Outcomes (MI, all-cause mortality, cardiac death)

6.1.1.1 <u>Summary of results for primary outcomes</u>

There were 17 RCTs comparing CCTA with functional testing, six RCTs[59,126,153,163,215,238] in stable patients with suspected CAD and 11 RCTs (12 publications)[37,47,84,85,96,109,111,138,143,145,192,248] in patients with suspected ACS that reported primary clinical outcomes. Functional testing included imaging tests (stress nuclear, stress echocardiography and ETT. Given the limitations of ETT as a functional test, sensitivity analyses comparing CCTA with functional imaging tests only were conducted. There was no statistical interaction between the patient populations for any outcome.

Across studies that include stable patients with suspected CAD and patients with suspected ACS presenting to an emergency department or similar setting:

- There is no clear difference in the frequency of MI between CCTA and functional imaging tests (SOE Moderate).
    - Three smaller RCTs, one in stable patients and two in those with suspected ACS, reported no MI in either testing arm.
    - CCTA was associated with lower MI risk compared with functional testing based on pooled estimates across the 14 remaining RCTs (14 RCTs, pooled RR 0.70, 95% CI 0.56 to 0.89, I^2=0%), however, the RD (0.4, 95% CI 0.1 to 0.8 per 100 patients) was small. The association was no longer clearly significant following exclusion of one RCT in stable patients with suspected CAD in which 85% of all patients had ETT in addition to CCTA (13 RCTs, pooled RR 0.75, 95% CI 0.57 to 0.99, I^2=0). This pattern was seen across RCTs of stable patients when the one trial was excluded. Across 10 RCTs in patients with suspected ACS, there was no difference in the frequency of MI between CCTA and functional testing at any time.
- There was no association between CCTA and reduction in all-cause mortality compared with functional testing (SOE Moderate).
    - Six RCTs reported no mortality in either testing arm (1 RCT in stable patients, 5 RCTs in suspected ACS patients).

  - There was no difference in all-cause mortality between CCTA and functional testing across the remaining 11 RCTs (pooled RR 0.99 95% CI 0.40 to 2.68, I^2=0%). There was also no difference in all-cause mortality when the populations were considered separately.
- Cardiac death was rare in both patient populations, with six total cardiac deaths reported in patients receiving CCTA and 13 reported in patients receiving functional testing (SOE Insufficient).
- It is possible that smaller trials in particular may have been underpowered to detect differences in MI, all-cause mortality, and cardiac death between CCTA and functional testing given that many trials enrolled patients with low or low to intermediate pre-test risk.

Detailed results

6.1.1.2 Myocardial infarction

Across populations, 17 RCTs (N=22,238) reported on myocardial infarction; six RCTs[59,126,153,163,215,238] were in stable patients with suspected CAD and 11 RCTs (12 publications)[37,47,84,85,96,109,111,138,143,145,192,248] were in patients with suspected ACS presenting to an emergency department or similar setting. Across trials, the cumulative incidence of MI was 1.5 per 100 patients, with 3 smaller trials (N=667), two in the stable, suspected CAD population[126,163] and one in the suspected ACS population[85], reporting no MI in either testing arm. CCTA was associated with CCTA was associated with lower MI risk compared with functional testing based on pooled estimates across the 14 remaining RCTs (14 RCTs, pooled RR 0.70, 95% CI 0.56 to 0.89, I^2=0%)[37,47,59,84,96,109,111,143,145,153,192,215,238,248] however the RD (0.4, 95% CI 0.1 to 0.8 per 100 patients, I^2=19%) was small. Only one RCT (SCOT-HEART)[215] in a population of stable patients with suspected CAD at intermediate pre-test risk reported a statistically significant decrease in MI favoring CCTA over ETT. However, 85% of *all* patients had ETT (as standard care) and the function testing arm was predominately ETT in this trial, raising concern regarding substantial clinical heterogeneity compared with other RCTs where stress echocardiography and SPECT were more common in the functional testing arm. Exclusion of this trial did not impact statistical heterogeneity, (no change in I^2) however, the confidence interval for the pooled estimate across the remaining RCTs the null value of 1.0 suggesting no clear association between CCTA and reduced MI (13 RCTs RR 0.75, 95% CI 0.57 to 0.99). Exclusion of two poor-quality studies[85,163] did not affect pooled estimates as both had reported that no MI occurred (Figure 4, Table 29). There was no statistical interaction between the stable and suspected ACS populations (p = 0.23).

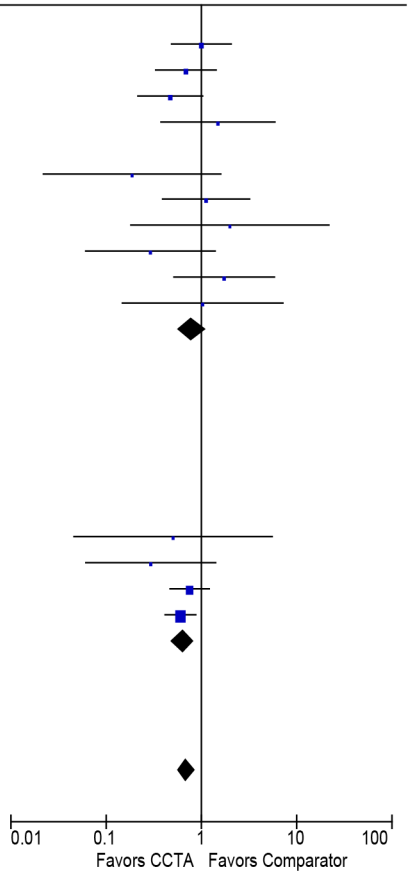
In stable outpatients with suspected CAD, MI was evaluated in six RCTs (N= 16,154)[59,126,153,163,215,238] comparing CCTA with functional testing in stable outpatients. Two smaller RCTs, one poor-quality (N= 173) with 55 days follow-up[163] in intermediate to high-risk patients and one good-quality RCT (N = 297)[126] in intermediate risk patients reported no MI in either testing arm. Four RCTs reported occurrence of MI. CCTA was associated with lower risk of MI compared with functional testing across six RCTs reporting various lengths of follow-up (4 RCTs, pooled RR 0.64, 95% CI 0.44 to 0.87, I^2=0%)[59,153,215,238] after testing in stable outpatients

suspected of CAD across time frames ranging from 12 to 58 months. The risk difference was small however across trials (pooled RD 1, 95% CI –1 to 0 per 100 people I^2=42%). Only one RCT (SCOT-HEART)[215] in a population that appears to have enrolled patients at intermediate pre-test risk of CAD reported a statistically significant decrease in MI favoring CCTA over ETT, however 85% of *all* patients had ETT and the function testing arm was predominately ETT (as standard care) in this trial, raising concern regarding substantial clinical heterogeneity compared with other RCTs where stress echocardiography and SPECT were more common in the functional testing arms. Exclusion of this trial did not impact statistical heterogeneity, (no change in I^2) however. The impact of the longer follow-up time (58 months) than reported for other trials is unknown. Results were no longer statistically significant based on sensitivity analysis excluding the SCOT-HEART trial (3 RCTs, pooled RR 0.69, 95% CI 0.27 to 1.14 I^2=0%).[59,153,238]

In patients with suspected ACS *presenting to an emergency room or similar acute care setting*, seven trials evaluated MI at or shortly after index visits (N=4584).[37,47,85,96,109,145] There was no difference in MI frequency between CCTA and functional testing at time of index testing (6 trials, pooled RR 0.8, 95% CI 0.53 to 1.19, I^2=21.6%). One smaller (N= 197) poor-quality trial in very low risk patients reported no MI occurred in either testing arm.[85] At 1 to 6.5 months, there were also seven trials that reported on MI.[37,84,85,96,109,144,145] No MI was reported for any testing arm when CCTA was compared with either SPECT (two RCTs)[84,85] or ETT (one RCT)[96]. Across the four other trials of CCTA versus any type of functional test the difference between tests on the occurrence of MI failed to reach statistical significance (4 trials, pooled 0.28, 95% CI 0.07 to 1.09 I^2= 0%). Similarly at time frames ≥12 months, there was no difference in MI between CCTA and functional testing (5 trials, pooled RR 1.22 (95% CI 0.51 to 2.74 I^2=0%)[111,138,143,192,248] There was little or no statistical heterogeneity in the analyses. In some trials, patients were only randomized to index testing after normal ECG and normal serum biomarkers were obtained and/or the tests were performed after the time of the index visits.

Figure 4. Comparison of CCTA and functional testing: Myocardial infarction

Study or Subgroup	Comparator	Follow-up	CCTA Events	CCTA Total	Comparator Events	Comparator Total	Weight	Risk Ratio [95% CI]
ACS ED								
Dedic 2016	ANY	Index	14	245	14	245	9.2%	1.00 [0.49, 2.05]
Chang 2008	ANY	1 month	11	133	16	133	8.9%	0.69 [0.33, 1.43]
Hoffmann 2012	ANY	1 month	9	501	19	499	7.7%	0.47 [0.22, 1.03]
Hamilton-Craig 2014	ANY	1 month	6	322	3	240	2.5%	1.49 [0.38, 5.90]
Goldstein 2007	SPECT	6 months	0	99	0	98		Not estimable
Goldstein 2011	SPECT	6 months	1	361	5	338	1.0%	0.19 [0.02, 1.59]
ACRIN-PA 2012	ANY	12 months	11	908	5	462	4.3%	1.12 [0.39, 3.20]
Uretsky 2017	ECHO	12 months	2	206	1	205	0.8%	1.99 [0.18, 21.78]
Linde 2015	ANY	12 months	2	285	7	291	1.9%	0.29 [0.06, 1.39]
Levksy 2018	ECHO	24 months	7	201	4	199	3.2%	1.73 [0.52, 5.83]
Pineiro-Portela 2021	ECHO	56 months	2	100	2	103	1.3%	1.03 [0.15, 7.17]
Subtotal (95% CI)				3361		2813	41.0%	0.80 [0.56, 1.16]
Total events			65		76			
Heterogeneity: Tau² = 0.00; Chi² = 9.03, df = 9 (P = 0.43); I² = 0%								
Test for overall effect: Z = 1.32 (P = 0.19)								
Stable Outpatient								
Min 2012	SPECT	55 days	0	86	0	87		Not estimable
Karthikeyan 2017	SPECT	12 months	0	148	0	149		Not estimable
McKavanagh 2014	ETT	12 months	1	243	2	245	0.8%	0.50 [0.05, 5.52]
Stillman 2020	SPECT	16 months	2	516	7	531	1.9%	0.29 [0.06, 1.41]
Douglas 2015	ANY	25 months	30	4996	40	5007	21.4%	0.75 [0.47, 1.20]
SCOT-HEART 2015	ETT	58 months	44	2073	73	2073	34.9%	0.60 [0.42, 0.87]
Subtotal (95% CI)				8062		8092	59.0%	0.64 [0.44, 0.88]
Total events			77		122			
Heterogeneity: Tau² = 0.00; Chi² = 1.53, df = 3 (P = 0.67); I² = 0%								
Test for overall effect: Z = 3.12 (P = 0.002)								
Total (95% CI)				11423		10905	100.0%	0.70 [0.56, 0.89]
Total events			142		198			
Heterogeneity: Tau² = 0.00; Chi² = 11.52, df = 13 (P = 0.57); I² = 0%								
Test for overall effect: Z = 3.25 (P = 0.001)								
Test for subgroup differences: Chi² = 0.97, df = 1 (P = 0.33), I² = 0%								



ACS = acute coronary syndrome; CCTA = coronary computed tomography angiography; CI = confidence interval; ECHO = stress echocardiography; ED = emergency department; ETT = exercise treadmill test; SPECT = single photon emission computed tomography.

Table 29. Summary of effect estimates including sensitivity analyses for CCTA versus functional testing across studies in patients with suspected CAD who are stable and patients with suspected ACS

Outcome Analysis # RCTs (N=) reporting	Risk CCTA vs. Functional (per 100 persons)*	Pooled estimates Number RCTs (N) for pooled RR RR, 95% CI, I^2 RD, 95% CI, per 100†, I^2	Interaction: Suspected ACS, Stable suspected CAD p-value
MI‡			
Primary analysis 17 RCTs (N=22,328)	1.2 vs. 1.8	14 RCTs (N=21,661) RR 0.70, 95% CI 0.56 to 0.89, I^2=0% RD 0.4, 95% CI 0.1 to 0.8 per 100, I^2=19%*	0.23
Exclude SCOT-HEART	1.0 vs. 1.4	13 RCTs (N =17,515)	0.623

Outcome Analysis # RCTs (N=) reporting	Risk CCTA vs. Functional (per 100 persons)*	Pooled estimates Number RCTs (N) for pooled RR RR, 95% CI, I^2 RD, 95% CI, per 100†, I^2	Interaction: Suspected ACS, Stable suspected CAD p-value
16 RCTs (N=18,182)		RR 0.75, 95% CI 0.57 to 0.99, I^2=0% RD 0.3, 95% CI 0 to 0.5 per 100, I^2=0%	
Exclude ETT as comparator 14 RCTs (N=17,132)	1.0 vs. 1.4	11 RCTs (N=16,465) RR 0.74, 95% CI 0.55 to 0.98, I^2=0%	0.660
Exclude poor RCTs 15 RCTs (N=21,958)	1.3 vs. 1.8	14 RCTs (N=21,661) RR 0.70, 95% CI 0.56 to 0.89, I^2=0% RD 0.5, 95% CI 0.1 to 0.9 per 100, I^2=28%	0.345
All-cause mortality§			
Primary analysis 17 RCTs (N=21,680)	1.2 vs. 1.3	11 RCTs (N=18,935) RR 0.99, 95% CI 0.40 to 2.68, I^2=0% NS, no RD	0.985
Exclude SCOT-HEART 16 RCTs (N=18,902)	1.0 vs. 1.1	Pooled 10 RCTs (N=17,534) RR 1.00, 95% CI 0.69 to 1.00, I^2=0% NS, no RD	0.985
Exclude poor RCTs 15 RCTs (N= 21,680)	1.2 vs. 1.3	Pooled 11 RCTs (N=21,310) RR 1.00, 95% CI 0.77 to 1.30, I^2=0% NS, no RD	0.984
ICA			
Primary analysis 19 RCTS (N=22,335)	14.4 vs. 12.0	RR 1.25, 95% CI 1.09 to 1.47, I^2=67% RD 2.7, 95% CI 1 to 4 per 100, I^2=59%	0.922
Exclude SCOT-HEART 18 RCTs (N=18,1888)	12.3 vs. 9.1	RR 1.31, 95% CI 1.12 to 1.51, I^2=45% RD 3, 95% CI 1.3 to 4.7 per 100, I^2=55%	0.578
Exclude poor RCTs 16 RCTs (N=21,904)	14.2 vs. 12.0	RR 1.25, 95% CI 1.07 to 1.45, I^2= 72% RD 2.6, 95% CI 0.9 to 4.4 per 100, I^2= 65%	0.887
Exclude outlier** 18 RCTs (N=21,923)	14.5 vs. 12.1	RR 1.23, 95% CI 1.07 to 1.41, I^2=64.6% RD 2.3, 95% CI 0.08 to 4.3 per 100, I^2= 51%	0.885
Exclude ETT as comparator RCTs (N=17,138)	12.0 vs. 8.8	RR 1.28, 95% CI 1.07 to 1.51, I^2= 49% NS, no RD	0.120
Any additional NIT			
Primary analysis 17 RCTs (N=11,595)	7.2 vs. 7.6	RR 0.82, 95% CI 0.53 to 1.28, I^2=83% NS, no RD	0.37
Exclude SCOT-HEART 16 RCTs (N=7,449)	10.9 vs. 12.0	RR 0.82, 95% CI 0.52 to 1.32, I^2= 83% NS, no RD	0.333
Exclude poor RCTs 14 RCTs (N=11,165)	7.3 vs. 7.4	RR 0.92, 95% CI 0.56 to 1.54 I^2=85% NS, no RD	0.491

Outcome Analysis # RCTs (N=) reporting	Risk CCTA vs. Functional (per 100 persons)*	Pooled estimates Number RCTs (N) for pooled RR RR, 95% CI, I^2 RD, 95% CI, per 100†, I^2	Interaction: Suspected ACS, Stable suspected CAD p-value
Exclude outliers†† 15 RCTs (N=10,841)	7.4 vs. 6.7	RR 0.94, 95% CI 0.68 to 1.25, I^2=69% NS, no RD	0.449
Any revascularization			
Primary analysis 19 RCTs (N=23,124)	9.5 vs. 7.1	RR 1.52, 95% CI 1.26 to 1.90 I^2=66% RD 2.4, 95% CI 1.4 to 3.3 per 100, I^2=46%	0.779
Exclude SCOT-HEART 18 RCTs (N=18,978)	6.2 vs. 3.6	RR 1.63, 95% CI 1.33 to 1.98, I^2=31% RD 2.4, 95% CI 1.4 to 3.5 per 100, I^2=51%	0.391
Exclude poor RCTs 16 RCTs (N=22,694)	9.5 vs. 7.2	RR 1.48, 95% CI 1.22 to 1.83, I^2=68% RD 2.2, 95% CI 1.2 to 3.2 per 100, I^2=51%	0.839
Exclude ETT as comparator 16 RCTs (N=17,280)	6.0 vs. 3.6	RR 1.53, 95% CI 1.20 to 1.94, I^2=23%	0.583
PCI			
Primary analysis 12 RCTs (N=18,960)	8.2 vs. 6.0	RR 1.63, 95% CI 1.22 to 2.35, I^2=74% RD 2.4, 95% CI 1.3 to 3.6 per 100, I^2=51%	0.946
Exclude SCOT-HEART 11 RCTs (N=14,814)	5.1 vs. 2.6	RR 1.89, 95% CI 1.38 to 2.43, I^2=36% RD 2.6 95% CI 1.3 to 4.0 per 100, I^2=55%	0.431
Exclude poor RCTs 10 RCTs (N=18,703)	8.3 vs. 6.1	RR 1.60, 95% CI 1.18 to 2.30, I^2=78% RD 2.4, 95% CI 1.1 to 3.7 per 100, I^2=60%	0.961
Exclude outlier** 11 RCTs (N=18,549)	8.3 vs. 6.1	RR 1.58, 95% CI 1.18 to 2.22, I^2=73% RD 2.1, 95% CI 1.0 to 3.2 per 100, I^2=60%	0.906
Exclude ETT as comparator 9 RCTs (N=13,854)	4.9 vs. 2.5	RR 1.68, 95% CI 1.09 to 2.45, I^2=28%	0.46

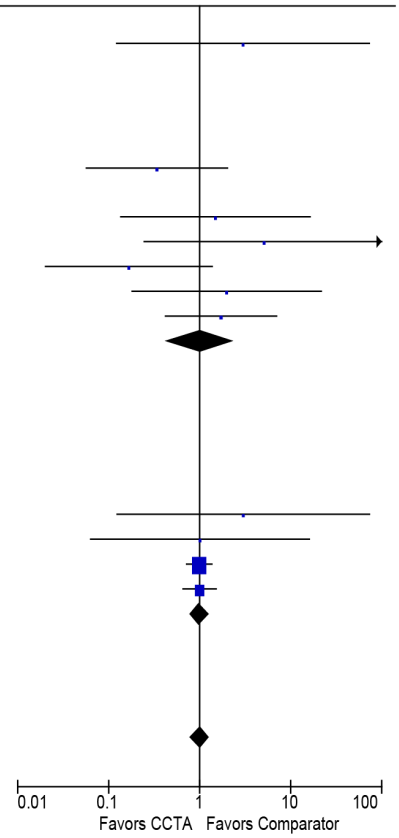
ACS = acute coronary syndrome; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CI = confidence interval; ETT = exercise treadmill test; ICA = invasive coronary angiography; MI = myocardial infarction; NA = not applicable; NIT = noninvasive testing; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; RD = risk difference; RR = risk ratio.
*Absolute risk estimates and risk differences (RD) include RCTs reporting no events in either arm for MI and no events for all-cause mortality in the denominator.
†Reported only if association observed (i.e., RR is statistically significant).
‡Pooled estimates for RR do not include 3 RCTs (N=667) in which no MI occurred in either arm as RR is not estimable.
§Pooled estimates for RR do not include 6 RCTs (N=2746) in which no deaths occurred in either arm as RR is not estimable; 11 RCTS reported one or more deaths and were pooled.
**Uretsky 2017
††McKavanagh 2015, Chang 2008

6.1.1.3 All-cause mortality and cardiac mortality

Across populations, seventeen RCTs (N= 21,680) reported on all-cause mortality; five RCTs[59,126,153,163,215] were in stable patients with suspected CAD and 12 were in patients with suspected ACS.[37,47,84,85,96,109,111,138,140,143,145,192,248] Across trials, the cumulative incidence of all-cause mortality was 1.3 per 100 patients. There was no difference in all-cause mortality between CCTA and functional testing (1.2 versus 1.3 per 100 patients). No mortality was observed in six trials (n=2746) including one RCT in stable patients[163] and five RCTs in patients with suspected ACS.[84,85] Across the remaining 11 RCTs reporting events (N=18,935), there was no association between CCTA and mortality compared with functional testing (11 RCTs, pooled RR 0.99 95% CI 0.40 to 2.68, I^2=0%). Figure 5. Exclusion of SCOT-HEART or poor-quality RCTS did not impact effect size estimates, heterogeneity or conclusions (Table 29). There was no statistical interaction between the stable and suspected ACS populations (p=0.985).

Figure 5. Comparison of CCTA and functional testing: All-cause mortality

Study or Subgroup	Comparator	Follow-up	CCTA Events	CCTA Total	Comparator Events	Comparator Total	Weight	Risk Ratio [95% CI]
ACS ED								
Dedic 2016	ANY	1 month	1	245	0	245	0.6%	3.00 [0.12, 73.28]
Chang 2008	ANY	1 month	0	133	0	133		Not estimable
Hoffmann 2012	ANY	1 month	0	501	0	499		Not estimable
Goldstein 2007	SPECT	6 months	0	99	0	98		Not estimable
Goldstein 2011	SPECT	6 months	0	361	0	337		Not estimable
ACRIN-PA 2012	ANY	12 months	2	908	3	462	1.8%	0.34 [0.06, 2.02]
Uretsky 2017	ECHO	12 months	0	206	0	205		Not estimable
Hamilton-Craig 2014	ETT	12 months	2	322	1	240	1.0%	1.49 [0.14, 16.34]
Linde 2015	ANY	19 months	2	285	0	291	0.6%	5.10 [0.25, 105.87]
Levksy 2015	SPECT	24 months	1	200	6	200	1.3%	0.17 [0.02, 1.37]
Levksy 2018	ECHO	24 months	2	201	1	199	1.0%	1.98 [0.18, 21.66]
Pineiro-Portela 2021	ECHO	56 months	5	100	3	103	2.9%	1.72 [0.42, 6.99]
Subtotal (95% CI)				3561		3012	9.2%	0.99 [0.40, 2.68]
Total events			15		14			
Heterogeneity: Tau² = 0.15; Chi² = 6.76, df = 6 (P = 0.34); I² = 11%								
Test for overall effect: Z = 0.01 (P = 0.99)								
Stable Outpatient								
Min 2012	SPECT	55 days	0	86	0	87		Not estimable
Karthikeyan 2017	SPECT	12 months	1	148	0	149	0.6%	3.02 [0.12, 73.54]
McKavanagh 2014	ETT	12 months	1	243	1	245	0.8%	1.01 [0.06, 16.03]
Douglas 2015	ANY	25 months	74	4996	75	5007	56.6%	0.99 [0.72, 1.36]
SCOT-HEART 2015	ETT	58 months	43	2073	43	2073	32.9%	1.00 [0.66, 1.52]
Subtotal (95% CI)				7546		7561	90.8%	1.00 [0.76, 1.35]
Total events			119		119			
Heterogeneity: Tau² = 0.00; Chi² = 0.47, df = 3 (P = 0.93); I² = 0%								
Test for overall effect: Z = 0.00 (P = 1.00)								
Total (95% CI)				11107		10573	100.0%	1.00 [0.77, 1.30]
Total events			134		133			
Heterogeneity: Tau² = 0.00; Chi² = 7.20, df = 10 (P = 0.71); I² = 0%								
Test for overall effect: Z = 0.00 (P = 1.00)								
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.99), I² = 0%								



ACS = acute coronary syndrome; CCTA = coronary computed tomography angiography; CI = confidence interval; ECHO = stress echocardiography; ED = emergency department; ETT = exercise treadmill test; SPECT = single photon emission computed tomography.

Evidence was insufficient to draw conclusions regarding the impact of CCTA versus functional testing on cardiac mortality. The pre-test CAD probability across most studies was low to intermediate and cardiac

death was rare; studies may not have been adequately powered to detect cardiac death. Cardiac mortality was evaluated in 13 RCTs, four RCTs in stable patients[153,163,238] (N=5854) and nine RCTs in patients with suspected ACS (N= 5793).[84,85,96,109,111,138,143,145,171,248] Ten RCTs reported no cardiac deaths in either testing arm. Individual study sample sizes ranged from N=173 to N=4146.

Across populations, six cardiac deaths in those receiving CCTA and 13 in those receiving functional testing were observed in three RCTs.[111,143,215] In stable patients, cardiac death occurred in 0.24% (5/2073) CCTA patients and 0.28% (12/2073) of ETT patients RR 0.42, 95% CI 0.15 to 1.18) in one RCT.[215] In patients with suspected ACS, across two RCTs (N= 1942), only two cardiac deaths were reported, one in each study arm (RR 0.72, 95% CI 0.04 to 13.3) in each trial.[111,143]

***In stable outpatients with suspected CAD*,** there were no differences between CCTA and functional testing in in all-cause mortality across five individual trials (N= 15,107)[59,126,153,163,215] from 55 days up to 58 months after testing. No mortality was seen in either testing arm in one smaller (N= 173) poor-quality trial.[163] Across trials in which death occurred, there was no difference between CCTA and functional testing (4 trials, pooled RR 1.0, 95% CI 0.76 to 1.3, I^2=0%)[59,126,153,215]. Exclusion of the SCOT-HEART comparing CCTA with ETT did not change the effect estimate, statistical heterogeneity or conclusions. (3 trials, RR 1.0, 95% CI 0.61 to 1.89, I^2=0%).[59,126,153,163] One trial also comparing CCTA with ETT in a mixed risk population (N= 488) (McKavanagh) in which 38% of patients were at higher risk reported only one death in each arm.

Four RCTs (N= 5854)[153,163,215,238] reported on cardiac death. Three reported that no cardiac deaths occurred in either testing arm; there was no difference between CCTA (0.2%, 5/2073) and ETT (0.58% 12/2073), in the one RCT in which cardiac death occurred RR 0.42, 95% CI 0.15 to 1.18). To the extent that cardiac death is rare in these populations, individual studies may have been underpowered to detect cardiac death or differences in cardiac death.

In patients with suspected ACS *presenting to an emergency room or similar acute care setting,* there was no difference in all-cause mortality across 13 RCTs (N= 7941)[37,47,84,85,96,109,111,138,140,143,145,192,248] comparing CCTA to functional tests and time frames ranging from one-month post ED/observational unit discharge to 56 months. No deaths were observed in six[37,84,85,109,145,248] of the 13 trials (N= XXX) . Across the seven trials reporting one or more deaths, there was no different between testing arms (pooled RR 1.0, 95% CI 0.40 to 2.69, I^2= 11%).[47,96,111,138,140,143,192]

There was no difference in cardiac mortality across 10 RCTs (N=7163)[84,85,96,109,111,138,140,143,145,248] comparing CCTA to functional tests and time frames ranging from one-month post ED/observational unit discharge to 56 months. Eight of the trials found no cardiac mortality. Across the two other trials, no difference was seen between testing arms, RR 0.72, 95CI 0.4 to 13.3 I^2= 0%. Pre-test risk in patient populations across studies were most generally low[47,84] or low to intermediate[96,138,144,145,161,171,192], with one reporting very low pre-test probability.[85] Two trials focused on patient with intermediate risk.[109,140] To the extent that cardiac death is rare in these populations, individual studies may have been underpowered to detect cardiac death or differences in cardiac death.

6.1.1.4 Other clinical outcomes

See Appendix O for summary tables.

Acute coronary syndrome, unstable angina (Appendix O, Tables O29 and O30)

No trials in stable outpatients reported on the frequency of ACS. Across five trials in *patients with suspected ACS*[37,47,96,109,111,143-145], there was no difference between CCTA and functional testing in the cumulative frequency ACS (as defined by the authors). There was no difference between testing arms in the cumulative frequency of unstable angina (UA) across nine RCTs, one in stable outpatients[153] and eight in patients with suspected ACS[37,47,84,85,96,109,143,144,248]. One RCT, in stable outpatients, reported that at 12 months there was no difference in UA between testing arms at 12 months, but more CCTA patients had UA at a median of 25 months compared with functional testing (1.2% vs. 0.8%, p=0.045).

Nonfatal stroke, cardiac arrest, continued chest pain, recurrent ischemia

Across populations, stroke and cardiac arrest were rare, occurring in ≤ 1% of any testing arm. No differences in cumulative frequency of these was see between testing arms were reported at any time frame. Five RCTs reported on nonfatal stroke,[59,138-140,175,215,238] one RCT reported on cardiac arrest[138,139], Many trials may have been underpowered to detect these events or evaluate differences between arms.

The cumulative frequency of continued chest pain varied substantially across trials (0.8% to 28%).

> ***In stable outpatients***, CCTA was associated with lower frequency of revisit to the ED with chest pain compared with ETT in one RCT (0.8 vs 6.9%) within 12 months[153], but a second larger RCT[175] reported no difference (3.7% vs. 3.3%) at a median of 1.7 years.
>
> ***In patients with suspected ACS***, across four RCTs[85,143,144,171,192] there were no difference between testing arms in the cumulative frequency of continued or recurrent chest pain at any time frame, however one RCT reported that CCTA was associated with a higher frequency compared with stress echocardiography (28% vs. 19%) at one month.[138] There was no difference between CCTA and SPECT in the cumulative frequency of recurrent ischemia in one trial of stable outpatients.[126] One RCT in patients with suspected ACS reported that recurrent ischemia occurred in 10% of those who had functional testing but no data for the CCTA arm were provided.[143,144]

Composite outcomes (MACE)

Across populations composite outcomes (MACE) were the primary endpoint(s) in many trials. Components of the composites varied across trials and within trials, different combinations of components were used. The PROMISE trial[59] reported on four different composite outcomes in stable outpatients. Appendix O, Table O31 summarizes the findings for the composites. In general, across trials, there were no statistically significant differences between CCTA and functional testing for various composite outcomes in stable outpatients or in patients with suspected ACS. There were two exceptions. The PROMISE trial[59] reported a marginally insignificant association between CCTA and

slightly lower occurrence of their primary MACE (which included all-cause mortality, nonfatal MI, hospitalization for UA, or major procedural complication) plus catheterization showing no obstructive CAD at 12 months, based on adjusted hazard ratios, but the risk differences were small (RD –0.4 per 100 patients). Their composite of mortality or nonfatal MI was similarly marginally insignificant with a small RD. The SCOT-HEART trial[175,215] compared CCTA with ETT (although 85% of CCTA patients also receive ETT). CCTA was associated with reduction of both composite outcomes evaluated.

Health status (Seattle Angina Questionnaire)

Four RCTs[59,153,163,256], ***all in stable outpatients*** administered the Seattle Angina Questionnaire (SAQ). The SAQ scores range from 0 to 100 and assess the following domains: Physical Limitation (9 items), Angina Stability (1 item), Angina Frequency (2 items), Treatment Satisfaction (4 items), and Quality of Life(QOL) (3 items). For the QOL domain (scale 0–100) higher scores indicate increased QOL, fewer symptoms and better health status. None of the RCTs in patients with suspected ACS reported on this outcome. There were no differences between CCTA and functional tests for the physical limitation or treatment satisfaction domains in any RCT. Results across trials for the other domains were inconsistent with only one or two of the four RCTs finding an association with the testing strategy. Results for the remaining domains are summarized as follows:

- Anginal stability: In three RCTs, there was no difference between testing groups on this domain at any time frame[59,163,215]; one RCT reported that CCTA was associated with less angina at 3 and 12 months.[153]
- Anginal frequency: Three trials reported no difference between testing groups for this domain at any time frame.[59,163,215] One RCT reported that CCTA was associated with less frequent angina at 6 months, but there was no difference at six weeks from index testing compared with ETT.[256]
- QOL: Two RCTs, including the largest (PROMISE) reported no difference in the QOL domain at any time frame.[59,163] One RCT reported that CCTA was associated with improved QOL at 6 months but not at 6 weeks[256]; another reported an association between CCTA and improved QOL at both 3 and 12 months.[153]

6.1.2 Key Question 2: Clinical decision making

6.1.2.1 Summary of results

The majority of RCTs comparing CCTA with functional testing which reported one or more of the following outcomes in either stable patients with suspected CAD or patients presenting emergently with suspected ACS: Referral for ICA (19 RCTs, N=22,335), any additional noninvasive testing (17 RCTs, N=11,595), referral for any revascularization (19 RCTs, N=23,124) and referral for PCI specifically (12 RCTs, N=18,960). There was no statistical interaction between the patient populations for any outcome.

Summary of results across populations

Across studies that include stable patients with suspected CAD and patients with suspected ACS presenting to an emergency department or similar setting:

- **ICA referral:** CCTA was associated with more frequent ICA referral compared with functional testing (19 RCTs, 14.4 vs. 12 per 100 patients, pooled RR 1.25, 95% CI 1.09 to 1.47, I^2=67%, RD 2.7, 95% CI 1 to 4 per 100, I^2=59%) (SOE Moderate).
    - **In stable outpatients**, ICA referral was more frequent following CCTA), but the association bordered the null and there was substantial heterogeneity. However, exclusion of SCOT-HEART increased the effect size and strengthen the association between CCTA and ICA referral compared with functional testing and substantially reduced the heterogeneity (4 RCTS pooled RR 1.57, 95% CI 1.21 to 1.65, I^2=0%, RD 4.1, 95% CI 3.0 to 5.2 per 100 patients).
    - **In patients with suspected ACS**, ICA referral (cumulative) was also more frequent following CCTA compared with functional testing but was less than the frequency seen in stable outpatients. Referral for ICA was highest at the index evaluation.
- **Referral for any additional noninvasive testing** was not different between CCTA and functional testing groups across populations (17 RCTs, 7.2 versus 7.6 per 100, pooled RR 0.82, 95% CI 0.53 to 1.28, I^2=83%) (SOE Low) or when populations were considered individually. Type of additional testing was inconsistently reported but appears to be primarily stress imaging.
- **Revascularization:** CCTA was associated with more frequent revascularization (9.5 per 100 patients) compared with functional testing (7.1 per 100 patients), 19 RCTs, pooled RR 1.52, 95% CI 1.26 to 1.90 I^2=66%, RD 2.4, 95% CI 1.4 to 3.3 per 100) (SOE Moderate). Again, this was also true when the populations were considered individually.
- **PCI for revascularization:** CCTA was associate with higher frequency of PCI as a revascularization procedure compared with functional testing (12 RCTs, 8.2 vs. 6.0 per 100 patients, pooled RR 1.63, 95% CI 1.22 to 2.35, I^2=74%, RD 2.4, 95% CI 1.3 to 3.6 per 100 patients) across populations (SOE Moderate).
    - In stable outpatients with suspected CAD, PCI was more common with CCTA, but the association failed to reach statistical significance (pooler RR 1.16, 95% CI 0.96 to 2.99).
    - In patients with suspected ACS the association between CCTA and PCI was seen at index testing but there was no difference between CCTA and functional testing at 1 to 6.5 months or ≥ 12 months.
- **Hospitalization**:
    - **In stable outpatients t**here was no difference in hospitalization between CCTA and functional testing across 4 RCTs (SOE Moderate).
    - **In patients with suspected ACS**,
        - At index testing, across comparators with CCTA there is substantial heterogeneity and results are mixed. While 4 RCTs comparing CCTA with any functional test suggest that hospitalization is less common with CCTA, large studies of CCTA vs echo and SPECT suggest that hospitalization may be more with CCTA (SOE Insufficient).
        - There was no difference in hospitalization between CCTA and functional testing across studies, regardless of comparator, at 1 to 6.5 months after index testing (9 RCTs, 3.0 vs. 3.9 per 100 patients, pooled RR 0.76, 95% CI 0.49 to 1.1, I^2=18%) (SOE High). Similarly, there was no difference between testing arms at ≥12

months (6 RCTs 14.9 vs. 17.4 per 100 patients, pooled RR 0.90, 95% CI 0.77 to 1.03, I^2=0%) (SOE High).

- **Subsequent ED visits:** In patients with suspected ACS there was no difference in emergency department visits after index testing between CCTA and functional testing across studies, regardless of comparator, at 1 to 6.5 months (7 RCTs, pooled RR 0.84, 95% CI 0.66 to 1.06, I^2=0%) or at ≥12 months (5 RCTs, pooled RR 1.06, 95% CI 0.93 to 1.56, I^2=16%) (SOE High for both time frames).

Medication: CCTA was not consistently associated with initiation of, discontinuation of or changes in medications and results for many mediations were mixed. Evidence is insufficient to draw firm conclusions about the impact of testing on medication use (SOE insufficient).

Detailed results

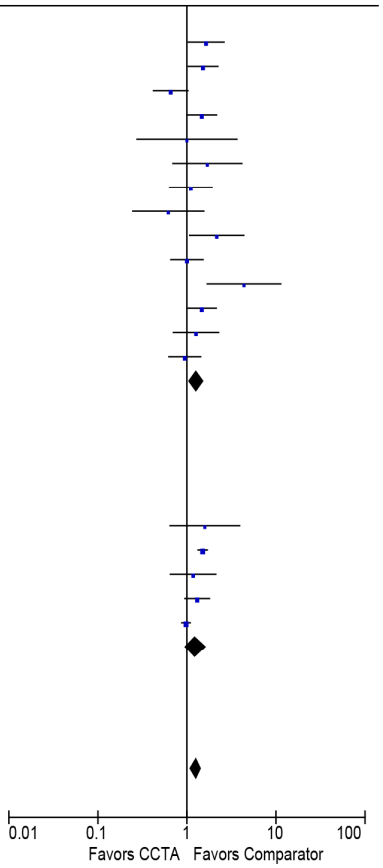
6.1.2.2 Additional testing (ICA, other noninvasive testing)

Referral for ICA was reported in 19 RCTs, of which 14 were in patients with suspected ACS [37,47,84,85,96,111,138,140,143,145,161,171,192,248] and five were in stable patients with suspected CAD.[59,126,153,163,215] Five RCTs were considered good quality,[47,59,84,126,215] three were considered poor [85,161,163] and the remaining 10 were considered fair.[37,96,109,111,138,140,143,145,153,171,192,248]

Across populations, CCTA was associated with higher frequency of ICA referral (14.4 per 100 patients) compared with functional testing (12 per 100 patients) across 19 RCTs (pooled RR 1.25, 95% CI 1.09 to 1.47, I^2=67%, RD 2.7, 95% CI 1 to 4 per 100, I^2=59%). (Figure 6) There was no statistical interaction between the stable and suspected ACS populations (p= 922). Exclusion of the SCOT-HEART trial[215] had no substantial impact on effect size or conclusions but did decrease heterogeneity from I^2 of 67% to 45%. Effect sizes and heterogeneity were similar following exclusion of three poor-quality trials[85,161,163] and exclusion of one outlier trial.[248] (Table 29)

Figure 6. Comparison of CCTA and functional testing: ICA referral

Study or Subgroup	Comparator	Follow-up	CCTA Events	CCTA Total	Comparator Events	Comparator Total	Weight	Risk Ratio [95% CI]
ACS ED								
Dedic 2016	ANY	Index	41	250	25	250	5.6%	1.64 [1.03, 2.61]
Chang 2008	ANY	Index	47	133	31	133	6.6%	1.52 [1.03, 2.23]
Pineiro-Portela 2021	ECHO	Index	23	100	36	103	5.9%	0.66 [0.42, 1.03]
Hoffmann 2012	ANY	1 month	59	501	40	499	6.7%	1.47 [1.00, 2.15]
Miller 2011	ANY	3 months	4	30	4	30	1.3%	1.00 [0.28, 3.63]
Goldstein 2007	SPECT	6 months	12	99	7	98	2.4%	1.70 [0.70, 4.13]
Goldstein 2011	SPECT	6 months	26	361	22	338	4.7%	1.11 [0.64, 1.91]
Nabi 2016	SPECT	6 months	7	283	12	300	2.3%	0.62 [0.25, 1.55]
Hamilton-Craig 2014	ETT	12 months	29	322	10	240	3.5%	2.16 [1.07, 4.35]
ACRIN-PA 2012	ANY	12 months	61	908	31	462	6.2%	1.00 [0.66, 1.52]
Uretsky 2017	ECHO	12 months	22	206	5	205	2.2%	4.38 [1.69, 11.34]
Linde 2013	ANY	19 months	56	285	39	291	6.8%	1.47 [1.01, 2.13]
Levksy 2018	ECHO	24 months	23	201	18	199	4.4%	1.27 [0.70, 2.27]
Levksy 2015	SPECT	24 months	36	200	38	200	6.3%	0.95 [0.63, 1.43]
Subtotal (95% CI)				3879		3348	64.8%	1.27 [1.04, 1.58]
Total events			446		318			
Heterogeneity: Tau² = 0.07; Chi² = 26.61, df = 13 (P = 0.01); I² = 51%								
Test for overall effect: Z = 2.30 (P = 0.02)								
Stable Outpatient								
Min 2012	SPECT	55 days	11	86	7	87	2.4%	1.59 [0.65, 3.91]
Douglas 2015	ANY	3 months	609	4996	406	5007	10.4%	1.50 [1.33, 1.69]
Karthikeyan 2017	SPECT	6 months	21	148	18	149	4.3%	1.17 [0.65, 2.11]
McKavanagh 2014	ETT	12 months	66	243	51	245	7.6%	1.30 [0.95, 1.80]
SCOT-HEART 2015	ETT	58 months	491	2073	502	2073	10.5%	0.98 [0.88, 1.09]
Subtotal (95% CI)				7546		7561	35.2%	1.24 [0.98, 1.61]
Total events			1198		984			
Heterogeneity: Tau² = 0.07; Chi² = 28.22, df = 4 (P < 0.0001); I² = 86%								
Test for overall effect: Z = 1.58 (P = 0.11)								
Total (95% CI)				11425		10909	100.0%	1.26 [1.09, 1.47]
Total events			1644		1302			
Heterogeneity: Tau² = 0.06; Chi² = 55.20, df = 18 (P < 0.0001); I² = 67%								
Test for overall effect: Z = 2.91 (P = 0.004)								
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.92), I² = 0%								



ACS = acute coronary syndrome; CCTA = coronary computed tomography angiography; CI = confidence interval; ECHO = stress echocardiography; ED = emergency department; ETT = exercise treadmill test; ICA = invasive coronary angiography; SPECT = single photon emission computed tomography.

In stable outpatients with suspected CAD, ICA referral was more frequent following CCTA, compared with functional testing (15.9 vs. 13.0 per 100), but the association bordered the null and there was substantial heterogeneity (5 RCTs, pooled RR 1.24, 95% CI 1.00 to 1.61, I^2=86, RD 2.0, 95% CI –0.3 to 5.8 per 100 patients).[59,126,153,163,215] Exclusion of one poor-quality trial[163] had no impact on effect size, the association or heterogeneity (4 RCTs, 1.23, 95% CI 0.94 to 1.6, I^2=89%). However, exclusion of SCOT-HEART[215] increased the effect size and strengthen the association between CCTA and ICA referral and substantially reduced the heterogeneity (4 RCTS pooled RR 1.57, 95% CI 1.21 to 1.65, I^2=0%, RD 4.1, 95% CI 3.0 to 5.2 per 100 patients).

In patients with suspected ACS *presenting to an emergency room or similar setting,* ICA referral (cumulative) was also more frequent following CCTA compared with functional testing, (11.5 vs. 9.5 per 100 patients, 14 RCTS pooled RR 1.27, 95% CI 1.04 to 1.58, I^2= 51%, RD 2.8, 95%VI 0.6 to 5.0 per 100 patients),[37,47,84,85,96,109,111,138,140,143,145,161,171,192,248] but was less than the frequency seen in stable outpatients. Exclusion of two poor-quality trials[85,161] did not impact effect estimates

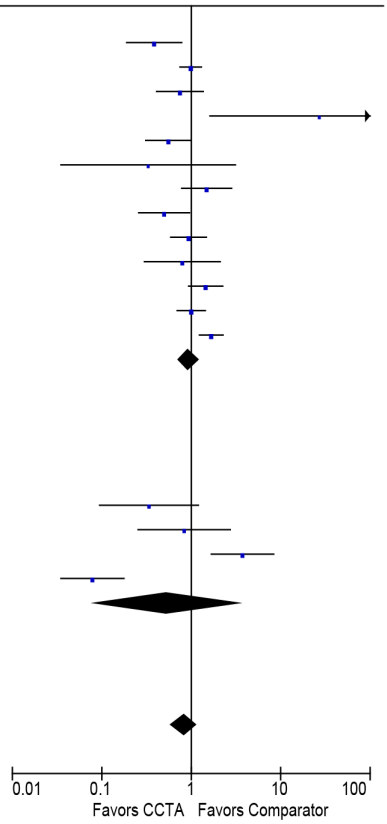
and slightly increased heterogeneity (12 RCTs, pooled RR 1.26, 95% CI 1.01 to 1.60, I^2= 58%). Referral for ICA was highest at the index evaluation (10.6 and 10.7 per 100 patients) and ≥12 months (6.5 vs. 5.5 per 100 patients) for CCTA and functional testing respectively with only 1.4 vs. 1.6 per 100 patients receiving ICA between 1 and 6.5 months. Pooled estimates at individual time frames however were not statistically significant; Index evaluation (8 RCTs, pooled RR 1.11, 95% CI 0.87 to 1.48),[37,47,84,85,109,144,145,192] 1 to 6.5 months (7 RCTs pooled RR 0.96, 95% CI 0.57 to 1.67),[47,84,85,109,145,161,171] ≥12 months (6 RCTS, pooled RR 1.45, 95% CI 0.87 to 2.69).[96,111,138,140,143,248] Exclusion of one outlying trial[248] for the ≥12-month time frame, slightly decreased effect size (3 RCTs, pooled RR 1.34, 95% CI 0.76 to 2.54) but did not change conclusions.

Referral for any additional noninvasive testing was reported in 17 RCTs (N=11,595), of which four were in stable patients[126,153,163,215] and 13 were in patients with suspected ACS.[37,47,84,85,96,109,111,138,140,143,145,161,192,248]

Across populations referral for additional noninvasive testing was not different between CCTA and functional testing groups (7.2 versus 7.6 per 100, pooled RR 0.82, 95% CI 0.53 to 1.28, I^2=83%), however substantial heterogeneity was noted. (Figure 7) Exclusion of two outlier RCTS resulted in a slight increase in the pooled RR (15 RCTS RR 0.94, 95% CI 0.68 to 1.25, I^2=69.3%) and reduced heterogeneity, but conclusions of no association did not change. Exclusion of three poor-quality trials[85,161,163] also resulted in the same slight increase in effect size but heterogeneity was similar. Exclusion of SCOT-HEART, in which 85% of patients received ETT, did not impact effect size, heterogeneity, or conclusions across the populations. Exclusion of two outliers[37,153] resulted in a larger effect size and reduced heterogeneity (15 RCTS, pooled RR 0.94, 95% CI 0.68 to 1.25 I^2=69%) but no difference in conclusions. (Table 29)

Figure 7. Comparison of CCTA and functional testing: Referral for any additional noninvasive testing

Study or Subgroup	Comparator	Follow-up	CCTA Events	CCTA Total	Comparator Events	Comparator Total	Weight	Risk Ratio [95% CI]
ACS ED								
Dedic 2016	ANY	1 month	10	245	26	245	6.3%	0.38 [0.19, 0.78]
ACRIN-PA 2012	ANY	1 month	130	905	66	454	8.1%	0.99 [0.75, 1.30]
Hoffmann 2012	ANY	1 month	18	501	24	499	6.8%	0.75 [0.41, 1.36]
Chang 2008	ANY	1 month	13	133	0	133	1.3%	27.0 [1.6, 449.6]
Miller 2011	ANY	3 months	10	30	18	30	6.9%	0.56 [0.31, 1.00]
Goldstein 2007	SPECT	6 months	1	99	3	98	1.9%	0.33 [0.03, 3.12]
Nabi 2016	SPECT	6 months	21	283	15	300	6.6%	1.48 [0.78, 2.82]
Hamilton-Craig 2014	ETT	12 months	14	322	21	240	6.5%	0.50 [0.26, 0.96]
Uretsky 2017	ECHO	12 months	30	198	32	197	7.4%	0.93 [0.59, 1.47]
Linde 2015	ANY	19 months	7	285	9	291	5.1%	0.79 [0.30, 2.10]
Levksy 2018	ECHO	24 months	41	201	28	199	7.5%	1.45 [0.93, 2.25]
Levksy 2015	SPECT	24 months	45	200	45	200	7.8%	1.00 [0.70, 1.44]
Pineiro-Portela 2021	ECHO	56 months	60	100	37	103	8.0%	1.67 [1.23, 2.26]
Subtotal (95% CI)				3502		2989	80.1%	0.94 [0.70, 1.23]
Total events			400		324			
Heterogeneity: Tau² = 0.14; Chi² = 37.67, df = 12 (P = 0.0002); I² = 68%								
Test for overall effect: Z = 0.52 (P = 0.61)								
Stable Outpatient								
Min 2012	SPECT	55 days	3	86	9	87	4.0%	0.34 [0.09, 1.20]
SCOT-HEART 2015	ETT	6 weeks	5	2073	6	2073	4.3%	0.83 [0.25, 2.73]
Karthikeyan 2017	SPECT	6 months	26	148	7	149	5.9%	3.74 [1.68, 8.35]
McKavanagh 2014	ETT	12 months	6	243	77	245	5.8%	0.08 [0.03, 0.18]
Subtotal (95% CI)				2550		2554	19.9%	0.54 [0.09, 3.38]
Total events			40		99			
Heterogeneity: Tau² = 3.63; Chi² = 46.58, df = 3 (P < 0.00001); I² = 94%								
Test for overall effect: Z = 0.63 (P = 0.53)								
Total (95% CI)				6052		5543	100.0%	0.82 [0.53, 1.28]
Total events			440		423			
Heterogeneity: Tau² = 0.37; Chi² = 91.48, df = 16 (P < 0.00001); I² = 83%								
Test for overall effect: Z = 1.06 (P = 0.29)								
Test for subgroup differences: Chi² = 0.30, df = 1 (P = 0.58), I² = 0%								



ACS = acute coronary syndrome; CCTA = coronary computed tomography angiography; CI = confidence interval; ECHO = stress echocardiography; ED = emergency department; ETT = exercise treadmill test; SPECT = single photon emission computed tomography.

In stable outpatients with suspected CAD, there was no association between CCTA and referral for any additional noninvasive testing (4 RCTs, pooled RR 0.54, 95% CI 0.09 to 3.38, I^2=94%), but heterogeneity was substantial. Exclusion of one poor-quality RCT[163] slightly increased the effect size and exclusion SCOT-HEART decreased the effect size estimate, but neither of these exclusions impacted heterogeneity or conclusions. Exclusion of an outlier trial[153] resulted in a higher effect estimate and decreased heterogeneity, however the conclusion of no association remained.

Referral for additional stress imaging specifically in general and stress imaging that involved additional radiation was rarely described across trials. The evidence is sparse and conflicting and may be related to the comparator for CCTA. CTTA was associated with referral for additional stress imaging within 6 months of initial evaluation in one small good-quality RCT (RR 3.60, 95% CI 1.6 to 8.1)[126] compared with SPECT (16.9 vs. 4.7 per 100 patients, RD 11, 95% CI 4 to 18 per 100). Stress imaging involving radiation was done 23 of the 25 patients in the CCTA group (15.5 per 100 patients in the group) and in all seven patients in the SPECT group. At ≥12 months one

trial reported that CCTA was associated with less frequent referral for stress imaging compared with ETT (RR 0.08, 95% CI 0.03 to 0.18, RD –29, 95% CI –35 to –22).[153] All six patients in the CCTA group received additional stress imaging involving radiation as did 76 of the 77 patients in the ETT group (31 per 100 patients in the ETT group). Another larger trial which compared CCTA to ETT reported no association between CCTA and use of additional noninvasive testing (RR, 0.83, 95% CI 0.25 to 2.73).[215] This may in part be due to use of ETT across 85% of the enrolled patients in this trial. Authors do not report whether additional stress imaging involved radiation. (APPENDIX P)

In patients with suspected ACS *presenting to an emergent setting,* again, no association between CCTA and additional noninvasive testing was observed (13 RCTS, pooled RR 0.94, 95% CI 0.69 to 1.23, I^2=68%). Exclusion of an outlier trial[37] or two poor-quality trials[85,161] did not change effect size, heterogeneity, or conclusions. Similarly, no differences in referral for any additional noninvasive testing between testing groups was seen at < 6 months after index testing (7 RCTs, pooled RR 0.82, 95% CI 0.51 to 1.41)[37,47,85,109,145,161,171] or ≥12 months (7 RCTs, pooled RR 1.05, 95% CI 0.74 to 1.39.[96,111,138,140,143,192,248] Removal of one outlying trial[37] at the < 6 month time frame slightly increased effect size, but did not change conclusions.

Referral for additional stress imaging specifically in general and stress imaging that involved additional radiation was inconsistently described across trials. Across time frames after index testing (< 6 months and ≥ 12 months after index test), there was no difference between CTTA and functional tests in referral for stress imaging (11 RCTs, pooled RR 0.97, 95% CI 0.73 to 1.19, I^2=38%). Similarly, there was no difference between CCTA and functional tests regarding referral for additional noninvasive stress testing involving radiation (10 RCTs, pooled RR 0.68, 95% CI 0.37 to 1.04, I^2=54%), however, these findings should be interpreted cautiously as authors were vague about which specific tests were performed. (APPENDIX P)

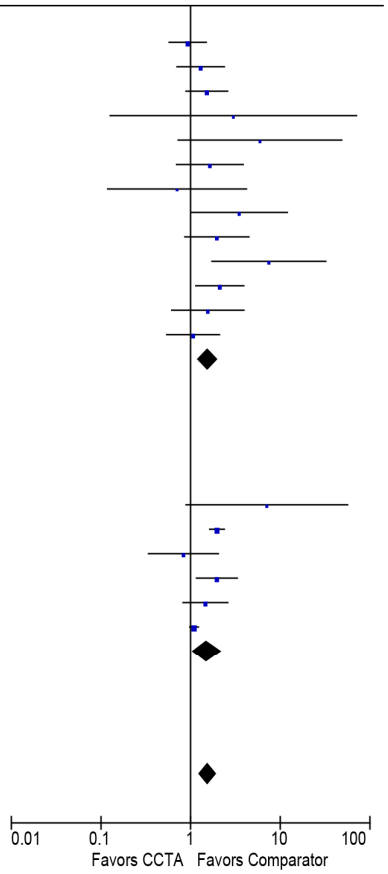
6.1.2.3 Treatment

Referral for any revascularization was reported in 19 RCTS (N= 23,124), six were in stable outpatients with suspected CAD[59,126,153,163,215,238] and 13 were in patients with suspected ACS.[37,47,84,85,96,109,111,138,140,143,145,161,192,248] There was no statistical interaction between the patient populations for any outcome.

Across patient populations, CCTA was associated with more frequent revascularization (9.5 per 100) compared with functional testing (7.1 per 100), pooled RR 1.52, 95% CI 1.26 to 1.90 I^2=66%, RD 2.4, 95% CI 1.4 to 3.3 per 100). (Figure 8) Exclusion of the SCOT-HEART resulted in a slight increase the effect estimate but heterogeneity decreased substantially (1.63, 95% CI 1.33 to 1.98, I^2=31%) and exclusion of three poor-quality RCTs[85,161,163] resulted in a slight diminution of the effect size but did not impact heterogeneity (RR 1.48, 95% CI 1.22 to 1.83, I^2=68%). (Table 29)

Figure 8. Comparison of CCTA and functional testing: Referral for any revascularization

Study or Subgroup	Comparator	Follow-up	CCTA Events	CCTA Total	Comparator Events	Comparator Total	Weight	Risk Ratio [95% CI]
ACS ED								
Chang 2008	ANY	Index	26	133	28	133	8.2%	0.93 [0.58, 1.50]
Dedic 2016	ANY	1 month	22	245	17	245	6.7%	1.29 [0.70, 2.38]
Hoffmann 2012	ANY	1 month	32	501	21	499	7.5%	1.52 [0.89, 2.59]
Miller 2011	ANY	3 months	1	30	0	30	0.5%	3.00 [0.13, 70.83]
Goldstein 2007	SPECT	6 months	6	99	1	98	1.1%	5.94 [0.73, 48.43]
Goldstein 2011	SPECT	6 months	14	361	8	338	4.5%	1.64 [0.70, 3.86]
Nabi 2016	SPECT	6 months	2	283	3	300	1.4%	0.71 [0.12, 4.20]
Hamilton-Craig 2014	ETT	12 months	14	322	3	240	2.7%	3.48 [1.01, 11.97]
ACRIN-PA 2012	ANY	12 months	27	908	7	462	4.8%	1.96 [0.86, 4.47]
Uretsky 2017	ECHO	12 months	15	206	2	205	2.0%	7.46 [1.73, 32.22]
Linde 2013	ANY	19 months	29	285	14	291	6.6%	2.12 [1.14, 3.92]
Levksy 2018	ECHO	24 months	11	201	7	199	4.1%	1.56 [0.62, 3.93]
Levksy 2015	SPECT	24 months	16	200	15	200	6.0%	1.07 [0.54, 2.10]
Subtotal (95% CI)				3774		3240	55.9%	1.52 [1.19, 2.10]
Total events			215		126			
Heterogeneity: Tau² = 0.06; Chi² = 16.01, df = 12 (P = 0.19); I² = 25%								
Test for overall effect: Z = 3.21 (P = 0.001)								
Stable Outpatient								
Min 2012	SPECT	55 days	7	86	1	87	1.1%	7.08 [0.89, 56.34]
Douglas 2015	ANY	3 months	311	4996	158	5007	11.7%	1.97 [1.64, 2.38]
Karthikeyan 2017	SPECT	12 months	8	124	10	129	4.3%	0.83 [0.34, 2.04]
McKavanagh 2014	ETT	12 months	37	243	19	245	7.6%	1.96 [1.16, 3.32]
Stillman 2020	SPECT	16 months	27	516	19	531	7.0%	1.46 [0.82, 2.60]
SCOT-HEART 2015	ETT	58 months	512	2073	468	2073	12.4%	1.09 [0.98, 1.22]
Subtotal (95% CI)				8038		8072	44.1%	1.50 [1.08, 2.16]
Total events			902		675			
Heterogeneity: Tau² = 0.14; Chi² = 35.19, df = 5 (P < 0.00001); I² = 86%								
Test for overall effect: Z = 2.14 (P = 0.03)								
Total (95% CI)				11812		11312	100.0%	1.52 [1.26, 1.90]
Total events			1117		801			
Heterogeneity: Tau² = 0.11; Chi² = 52.58, df = 18 (P < 0.0001); I² = 66%								
Test for overall effect: Z = 3.83 (P = 0.0001)								
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.92), I² = 0%								



ACS = acute coronary syndrome; CCTA = coronary computed tomography angiography; CI = confidence interval; ECHO = stress echocardiography; ED = emergency department; ETT = exercise treadmill test; SPECT = single photon emission computed tomography.

In stable outpatients with suspected CAD the association between CCTA and more frequent revascularization versus functional testing (11.2 vs. 8.4 per 100) was seen across RCTs (6 RCTs, N=16,115, pooled RR 1.5, 95% CI 1.08 to 2.16, I^2=86%, RD 2.8, 95% CI 1.4 to 4.2) but there was substantial heterogeneity. Exclusion of one poor-quality trial,[163] which also an outlier, had little impact on the effect size or heterogeneity (5 RCTs, pooled RR 1.46, 95% CI 1.02 to 2.04, I^2=88%). Exclusion on of the SCOT-HEART[215] resulted in a larger effect size and substantially reduced heterogeneity but did not alter overall conclusions (5 RCTs, pooled RR 1.8, 95 %CI 1.37 to 2.24, I^2=31%, RD 2.2, 95% CI 0.9 to 3.4 per 100 patients).

Similarly, *in* ***patients with suspected ACS***, CCTA was associated with more frequent revascularization compared with functional testing (13 RCTS, 5.7 vs 3.9 per 100, pooled RR 1.52, 95% CI 1.19 to 2.10, I^2=25%, RD 2.4, 95% CI 0.7 to 4.2 per 100 patients). Exclusion of two poor-quality trials[85,161] slightly decrease effect size (11 RCTs, pooled RR 1.48, 95% CI 1.16 to 2.02, I^2=29%).

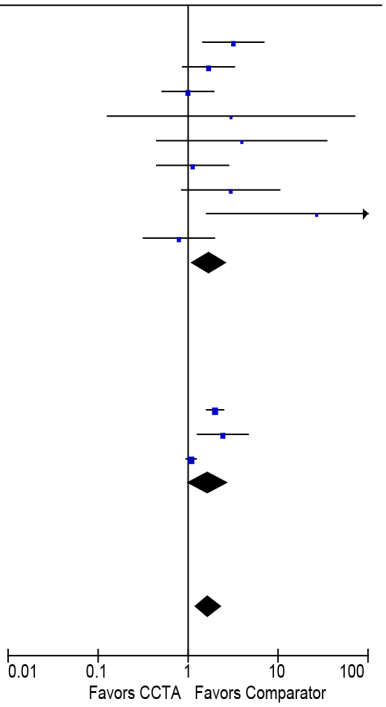
Type of revascularization

PCI was more commonly performed (8 per 100 patients) than CABG as a revascularization procedure in both stable outpatients with suspected CAD and in those with suspected ACS presenting to an emergent setting. Surprisingly it was more common in stable outpatients versus those presenting with suspected ACS (8.0 vs 4.0 per 100 patients)

Across patient populations, CCTA was associated with higher frequency **of PCI** as a revascularization procedure compared with functional testing across (12 RCTs, 8.2 vs. 6.0 per 100, pooled RR 1.63, 95% CI 1.22 to 2.35, I^2=74%, RD 2.4, 95% CI 1.3 to 3.6 per 100),[47,59,84,85,96,109,138,143,153,161,215,248] (Figure 9). Exclusion of two poor-quality RCTs[85,161] or exclusion of one outlier trial,[248] had little impact on effect estimates or heterogeneity. Exclusion of SCOT-HEART,[215] however, increased effect size and reduced heterogeneity by 49% (11 RCTs, pooled RR 1.89, 95% CI 1.3 to 4.0, I^2=36%). The impact of CCTA combined with ETT in this trial on the need for revascularization is unclear (Table 29).

Figure 9. Comparison of CCTA and functional testing: Referral for PCI

Study or Subgroup	Comparator	Follow-up	CCTA Events	CCTA Total	Comparator Events	Comparator Total	Weight	Risk Ratio [95% CI]
ACS ED								
Linde 2013	ANY	Index	25	285	8	291	9.1%	3.19 [1.46, 6.96]
Dedic 2016	ANY	1 month	22	245	13	245	10.5%	1.69 [0.87, 3.28]
Hoffmann 2012	ANY	1 month	17	501	17	499	10.6%	1.00 [0.51, 1.93]
Miller 2011	ANY	3 months	1	30	0	30	1.1%	3.00 [0.13, 70.83]
Goldstein 2007	SPECT	6 months	4	99	1	98	2.1%	3.96 [0.45, 34.80]
Goldstein 2011	SPECT	6 months	10	330	8	297	7.7%	1.13 [0.45, 2.81]
Hamilton-Craig 2014	ETT	12 months	12	322	3	240	5.1%	2.98 [0.85, 10.45]
Uretsky 2017	ECHO	12 months	13	206	0	205	1.3%	26.9 [1.61, 449.0]
Levksy 2018	ECHO	24 months	8	201	10	199	7.7%	0.79 [0.32, 1.97]
Subtotal (95% CI)				2219		2104	55.1%	1.65 [1.08, 2.93]
Total events			112		60			
Heterogeneity: Tau² = 0.20; Chi² = 14.06, df = 8 (P = 0.08); I² = 43%								
Test for overall effect: Z = 2.23 (P = 0.03)								
Stable Outpatient								
Douglas 2015	ANY	3 months	239	4996	120	5007	16.7%	2.00 [1.61, 2.48]
McKavanagh 2014	ETT	12 months	29	243	12	245	10.7%	2.44 [1.27, 4.66]
SCOT-HEART 2015	ETT	58 months	403	2073	372	2073	17.5%	1.08 [0.95, 1.23]
Subtotal (95% CI)				7312		7325	44.9%	1.61 [0.96, 3.00]
Total events			671		504			
Heterogeneity: Tau² = 0.18; Chi² = 26.99, df = 2 (P < 0.00001); I² = 93%								
Test for overall effect: Z = 1.88 (P = 0.06)								
Total (95% CI)				9531		9429	100.0%	1.63 [1.22, 2.35]
Total events			783		564			
Heterogeneity: Tau² = 0.16; Chi² = 42.42, df = 11 (P < 0.0001); I² = 74%								
Test for overall effect: Z = 3.02 (P = 0.003)								
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.93), I² = 0%								



ACS = acute coronary syndrome; CCTA = coronary computed tomography angiography; CI = confidence interval; ECHO = stress echocardiography; ED = emergency department; ETT = exercise treadmill test; PCI = percutaneous coronary intervention; SPECT = single photon emission computed tomography.

In stable outpatients with suspected CAD, the overall frequency of **PCI** was 8 per 100 patients. PCI was more commonly performed following CCTA (8.4 per 100 patients) compared with functional testing (6.9 per 100 patients) and the association approached statistical significance, but substantial heterogeneity was noted (3 RCTS, pooled RR 1.61, 95% CI 0.96 to 3.00, I^2=93%; Figure 9).[59,153,215] Exclusion of the SCOT-HEART[215] substantially increased the effect size and reduced heterogeneity to 0% and resulted in a stronger association between CCTA and PCI, (2 RCTS, pooled RR 2.04, 95% CI 1.57 to 2.87, I^2=0%). The impact of CCTA combined with ETT in this trial on the need for revascularization is unclear.

In contrast, **CABG** was performed in 1.7 per 100 patients across testing arms and was more common following CCTA versus functional testing (2.0 vs. 1.5 per 100) but there was no association with CCTA compared with functional testing based on the pooled estimate (3 RCTs, pooled RR 1.39, 95% CI 0.85 to 2.23, I^2=53%). The largest trial[59] did however show an association (RR 1.90, 95% CI 1.28 to 2.81) comparing CCTA with any functional testing but the other two trials comparing CCTA with ETT did not[153,215]; in the largest of these trials,[215] however 85% of patients in the CCTA arm received ETT. The pretest risk across these trials appears to primarily be low to intermediate, which may partially explain less frequent use of CABG. See Appendix P for figure.

In patients with suspected ACS presenting to an emergency setting, **PCI** frequency overall was 4 per 100 patients, with greater cumulative frequency following CCTA compared with functional testing (9 RCTs, 5.0 vs. 2.8 per 100, pooled RR 1.65, 95% CI 1.08 to 2.93, I^2=43%; Figure 9).[47,84,85,96,109,138,144,161,248] With regard to timing, at index testing, CCTA was associated with more frequent PCI use compared with functional testing (4 RCTs, 5.0 vs. 2.6 per 100 patients, pooled RR 1.89, 95% CI 1.02 to 3.48, I^2= 19%).[84,85,109,144] There was, however, no differences between testing arms at 1 to 6.5 months (5 RCTs, pooled RR 1.65, 95% CI 0.83 to 3.31, I^2= 0%)[47,84,85,109,161] or ≥12 months after index testing (4 RCTs, pooled RR, 1.43, 95% CI 0.54 to 7.83, I^2= 71%).[96,138,140,248] Exclusion of one outlying trial[248] for this later time frame reduced the effect estimate and heterogeneity but did not impact conclusions (3 RCTS, pooled RR 1.04, 95% CI 0.45 to 3.12, I^2=51%).[96,138,140]

CABG was less commonly performed than PCI in patients with suspected ACS. There was no association between CCTA and CABG related to timing of the index test (4 RCTs, pooled RR I^2=). At >1 month following index testing, four of the nine RCTs reported that no patients received CABG and pooled estimates across the remaining trials, showed no difference between testing arms (5 RCTs, pooled RR 1.27, 95% CI 0.26 to 6.20, I^2=51%).[47,96,138,140,248] Less frequent use of CABG may in part be due to the low to intermediate pre-test risk of CAD in patients across these trials. See Appendix P for figure.

6.1.2.4 Hospitalization

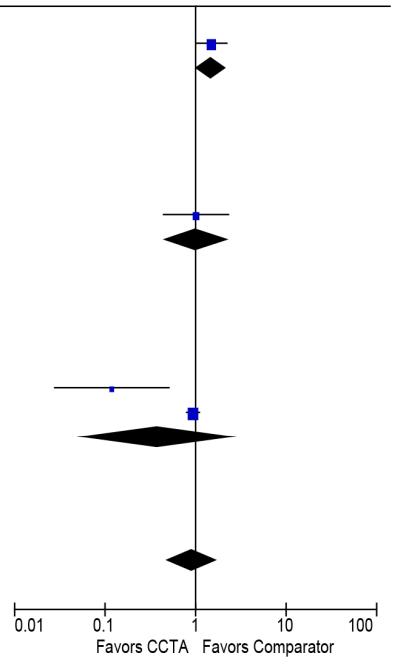
Four RCTs in stable outpatients with suspected CAD[59,153,163,215] and 14 RCTs in patients with suspected ACS[37,47,84,85,96,109,111,138,140,143,145,161,171,192,248] reported on hospitalization. In theory the need for and timing of hospitalization may be different in these populations, thus, we did not pool data for this outcome across them.

Across populations, in general across time frames, there were no differences in hospitalization between CCTA and functional testing. However, there was heterogeneity within populations, so each will be addressed separately.

In stable outpatients with suspected CAD, across four RCTs, there was no difference in hospitalization between CCTA and functional testing (4.3 vs. 4.5 per 100 patients, pooled RR 1.00, 95% CI 0.29 to 1.75, I^2=77%). Heterogeneity is likely related to one RCT[153] which reported that CCTA was associated with lower risk of hospitalization compared with ETT (RR 0.12, 95% CI 0.03 to 0.51) (Figure 10).

Figure 10. Comparison of CCTA and functional testing: Hospitalization in stable outpatients with suspected CAD

Study or Subgroup	Follow-up	CCTA Events	CCTA Total	Comparator Events	Comparator Total	Weight	Risk Ratio [95% CI]
CCTA vs. Any Functional							
Douglas 2015	25 months	61	4996	41	5007	32.3%	1.49 [1.01, 2.21]
Subtotal (95% CI)			4996		5007	32.3%	1.49 [1.01, 2.21]
Total events		61		41			
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.99 (P = 0.05)							
CCTA vs SPECT							
Min 2012	55 days	10	86	10	87	19.9%	1.01 [0.44, 2.31]
Subtotal (95% CI)			86		87	19.9%	1.01 [0.44, 2.31]
Total events		10		10			
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.03 (P = 0.98)							
CCTA vs ETT							
McKavanagh 2014	12 months	2	243	17	245	9.7%	0.12 [0.03, 0.51]
SCOT-HEART 2015	58 months	247	2073	264	2073	38.1%	0.94 [0.80, 1.10]
Subtotal (95% CI)			2316		2318	47.8%	0.38 [0.05, 2.87]
Total events		249		281			
Heterogeneity: Tau² = 1.89; Chi² = 7.77, df = 1 (P = 0.005); I² = 87%							
Test for overall effect: Z = 0.94 (P = 0.35)							
Total (95% CI)			7398		7412	100.0%	1.00 [0.30, 1.75]
Total events		320		332			
Heterogeneity: Tau² = 0.18; Chi² = 12.82, df = 3 (P = 0.005); I² = 77%							
Test for overall effect: Z = 0.38 (P = 0.70)							
Test for subgroup differences: Chi² = 2.22, df = 2 (P = 0.33), I² = 10.0%							

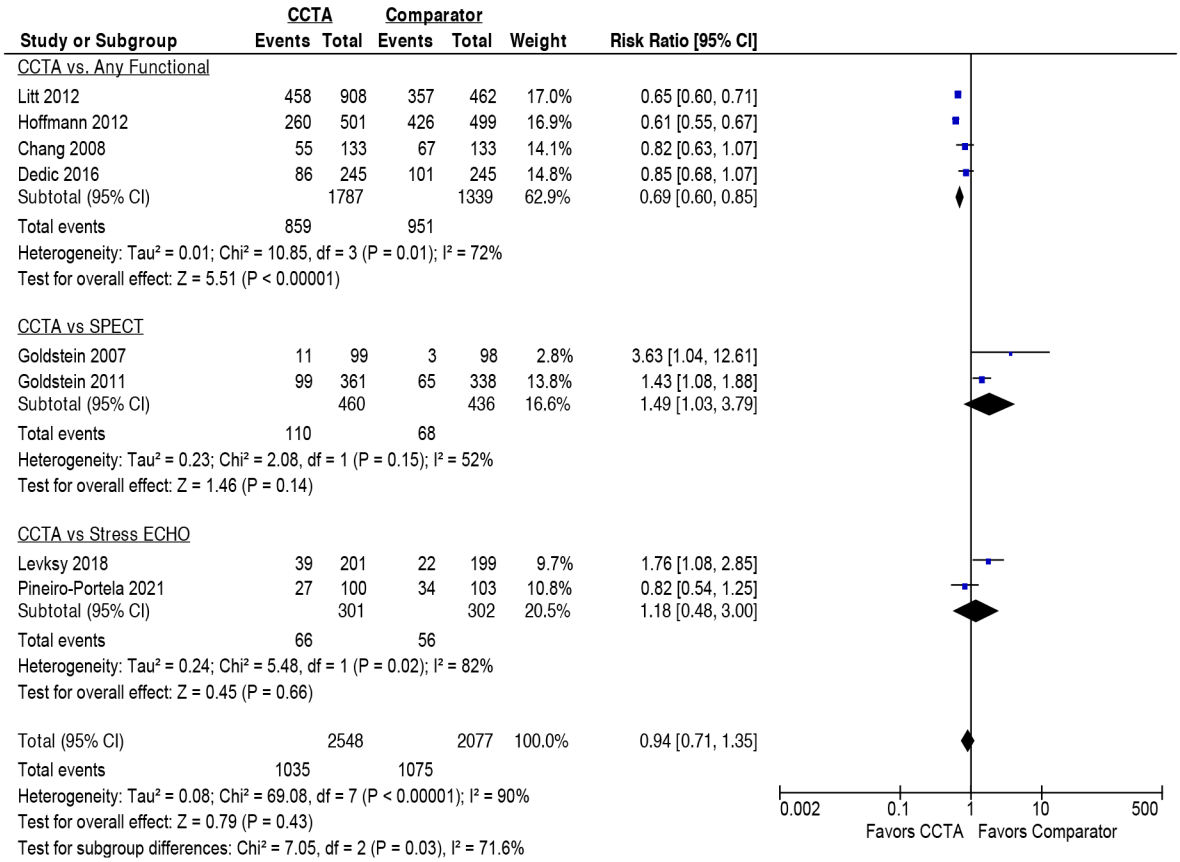


CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CI = confidence interval; ETT = exercise treadmill test; SPECT = single photon emission computed tomography.

In patients with suspected ACS *presenting to an emergency setting*, at the time of index testing, CCTA was not associated with hospitalization across all functional testing comparators, but substantial heterogeneity was noted (8 RCTs, pooled RR 0.94, 95% CI 0.70 to 1.35, I^2=90%) and the test for interaction suggests that there may be differences based on comparators. (Figure 11) Across four fair-quality RCTs comparing CCTA with any (unspecified) functional testing, CCTA was associated with lower risk of hospitalization (4 RCTS 48 vs. 71 per 100 patients, pooled RR 0.69, 95% CI 0.60 to 0.85, I^2= 93.2, RD –19.6 per 100, 95% CI –31.7 to –7.5 per 100) with the two largest RCTs reaching statistical significance.

In contrast, two RCTs[84,85] individually found an association between CCTA and increased risk of hospitalization compared with use of SPECT, although the pooled estimate was not statistically significant (pooled RR 1.49, 95% CI 1.03 to 3.79). In the larger good-quality RCT (N= 699) in low pre-test risk patients,[84] 27 per 100 patients in the CCTA group were hospitalized versus 19 per 100 patients who received SPECT (RR 1.43, 95% CI 1.08 to 1.88). Across two fair-quality RCTs comparing CCTA with stress echo, hospitalization was overall more common in patients who received CCTA (21.9 vs. 18.5 per 100 persons).[138,192] However, again the pooled estimate showed no association (pooled RR 1.18, 95% CI 0.48 to 3.00). The largest RCT (N=400) found an association between increased in hospitalization and CCTA (RR 1.76, 95% CI 1.08 to 2.85) compared with stress echo.[138] In some trials, patients were only randomized to index testing after ruling out ACS, after normal ECG and normal serum biomarkers, were obtained and/or the tests were performed after the time of the index visits. In addition, not all patients received functional testing.

Figure 11. Comparison of CCTA and functional testing: Hospitalization in patients with suspected ACS at time of index ED visit

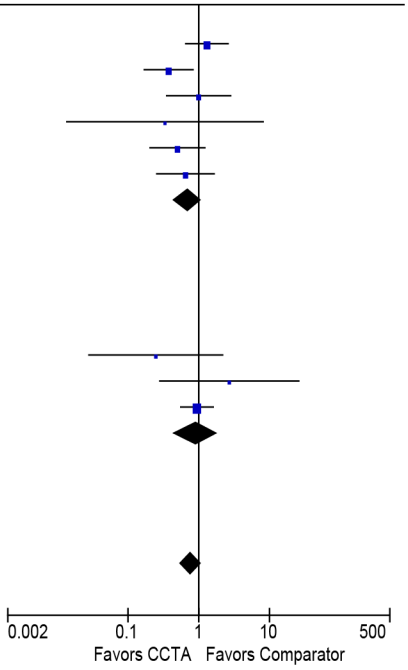


ACS = acute coronary syndrome; CCTA = coronary computed tomography angiography; CI = confidence interval; ECHO = echocardiography; ED = emergency department; ETT = exercise treadmill test; SPECT = single photon emission computed tomography.

In patients with suspected ACS, there was no difference in hospitalization between CCTA and functional testing across studies, regardless of comparator, at 1 to 6.5 months after index testing (9 RCTs, 3.0 vs. 3.9 per 100 patients, pooled RR 0.76, 95% CI 0.49 to 1.1, I^2=18%).[37,47,84,85,109,143,145,161,171] Similarly, there was no difference between testing arms at ≥12 months (6 RCTs 14.9 vs. 17.4 per 100 patients, pooled RR 0.90, 95% CI 0.77 to 1.03, I^2=0%),[96,111,138,140,143,248] (Figure 12 and Figure 13).

Figure 12. Comparison of CCTA and functional testing: Hospitalization in patients with suspected ACS 1 to 6.5 months after index testing

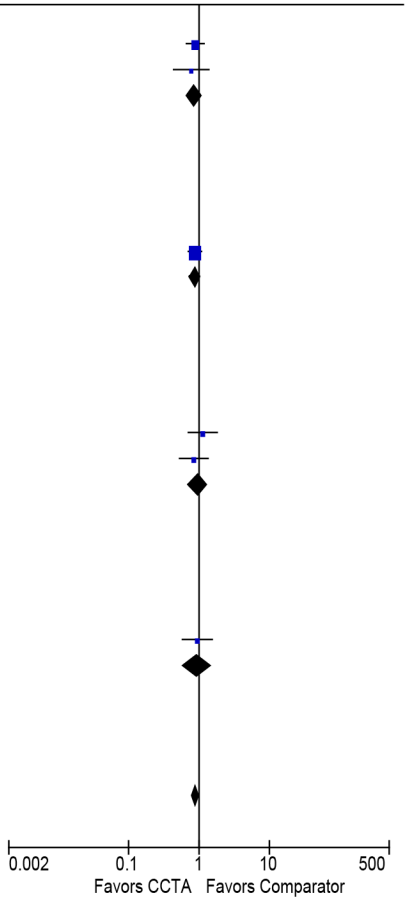
Study or Subgroup	CCTA Events	CCTA Total	Comparator Events	Comparator Total	Weight	Risk Ratio [95% CI]
CCTA vs. Any Functional						
Litt 2012	28	889	11	456	18.5%	1.31 [0.66, 2.60]
Miller 2011	6	30	16	30	15.1%	0.38 [0.17, 0.83]
Hoffmann 2012	7	501	7	499	9.7%	1.00 [0.35, 2.82]
Chang 2008	0	133	1	133	1.2%	0.33 [0.01, 8.11]
Dedic 2016	7	245	14	245	12.6%	0.50 [0.21, 1.22]
Linde 2013	7	285	11	291	11.6%	0.65 [0.26, 1.65]
Subtotal (95% CI)		2083		1654	68.8%	0.69 [0.44, 1.09]
Total events	55		60			
Heterogeneity: Tau² = 0.08; Chi² = 6.80, df = 5 (P = 0.24); I² = 26%						
Test for overall effect: Z = 1.60 (P = 0.11)						
CCTA vs SPECT						
Goldstein 2007	1	99	4	98	2.5%	0.25 [0.03, 2.17]
Goldstein 2011	3	330	1	297	2.4%	2.70 [0.28, 25.82]
Nabi 2016	24	283	27	300	26.3%	0.94 [0.56, 1.59]
Subtotal (95% CI)		712		695	31.2%	0.91 [0.44, 1.87]
Total events	28		32			
Heterogeneity: Tau² = 0.10; Chi² = 2.29, df = 2 (P = 0.32); I² = 13%						
Test for overall effect: Z = 0.26 (P = 0.79)						
Total (95% CI)		2795		2349	100.0%	0.76 [0.49, 1.10]
Total events	83		92			
Heterogeneity: Tau² = 0.05; Chi² = 9.78, df = 8 (P = 0.28); I² = 18%						
Test for overall effect: Z = 1.54 (P = 0.12)						
Test for subgroup differences: Chi² = 0.39, df = 1 (P = 0.53), I² = 0%						



ACS = acute coronary syndrome; CCTA = coronary computed tomography angiography; CI = confidence interval; ETT = exercise treadmill test; SPECT = single photon emission computed tomography.

Figure 13. Comparison of CCTA and functional testing: Hospitalization in patients with suspected ACS ≥12 months after index testing

Study or Subgroup	CCTA Events	CCTA Total	Comparator Events	Comparator Total	Weight	Risk Ratio [95% CI]
CCTA vs. Any Functional						
Hollander 2016	109	843	63	432	23.9%	0.89 [0.66, 1.18]
Linde 2015	19	285	25	291	6.0%	0.78 [0.44, 1.38]
Subtotal (95% CI)		1128		723	29.9%	0.86 [0.67, 1.12]
Total events	128		88			
Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 1 (P = 0.68); I² = 0%						
Test for overall effect: Z = 1.12 (P = 0.26)						
CCTA vs SPECT						
Levksy 2015	86	200	98	200	43.5%	0.88 [0.71, 1.09]
Subtotal (95% CI)		200		200	43.5%	0.88 [0.71, 1.09]
Total events	86		98			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.20 (P = 0.23)						
CCTA vs Stress ECHO						
Levksy 2018	32	201	28	199	9.0%	1.13 [0.71, 1.81]
Uretsky 2017	28	206	33	205	9.1%	0.84 [0.53, 1.34]
Subtotal (95% CI)		407		404	18.2%	0.98 [0.70, 1.36]
Total events	60		61			
Heterogeneity: Tau² = 0.00; Chi² = 0.76, df = 1 (P = 0.38); I² = 0%						
Test for overall effect: Z = 0.14 (P = 0.89)						
CCTA vs ETT						
Hamilton-Craig 2014	33	322	26	240	8.4%	0.95 [0.58, 1.54]
Subtotal (95% CI)		322		240	8.4%	0.95 [0.58, 1.54]
Total events	33		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.22 (P = 0.82)						
Total (95% CI)		2057		1567	100.0%	0.90 [0.78, 1.04]
Total events	307		273			
Heterogeneity: Tau² = 0.00; Chi² = 1.35, df = 5 (P = 0.93); I² = 0%						
Test for overall effect: Z = 1.53 (P = 0.13)						
Test for subgroup differences: Chi² = 0.43, df = 3 (P = 0.93), I² = 0%						



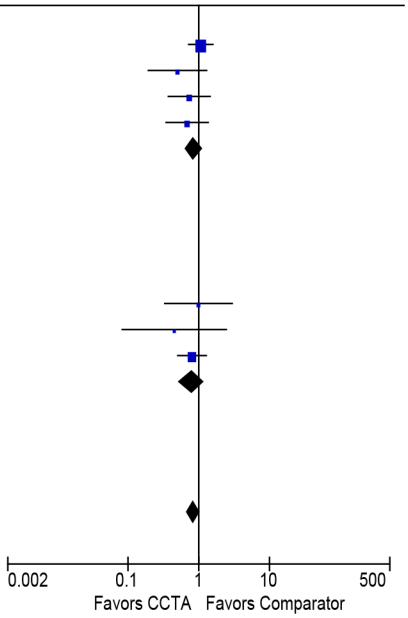
ACS = acute coronary syndrome; CCTA = coronary computed tomography angiography; CI = confidence interval; ECHO = echocardiography; ETT = exercise treadmill test; SPECT = single photon emission computed tomography.

6.1.2.5 Subsequent emergency department visits in patients with suspected ACS

In patients with suspected ACS, there was no difference in emergency department visits after index testing between CCTA and functional testing across studies, regardless of comparator, at 1 to 6.5 months after index testing (7 RCTs, 5.9 vs.6.7 per 100 patients, pooled RR 0.84, 95% CI 0.66 to 1.06, I^2=0%).[47,84,85,109,145,161,171] Exclusion of two poor RCTs[85,161] had little impact on the effect estimates (5 RCT, pooled RR 0.86, 95% CI 0.62 to 1.11). Similarly, at there was no difference between testing arms ≥12 months (5 RCTs, 30.5 per 30.8 per 100 patients, pooled RR 1.06, 95% CI 0.93 to 1.56, I^2=16%),[96,111,138,140,192] (Figure 14 and Figure 15).

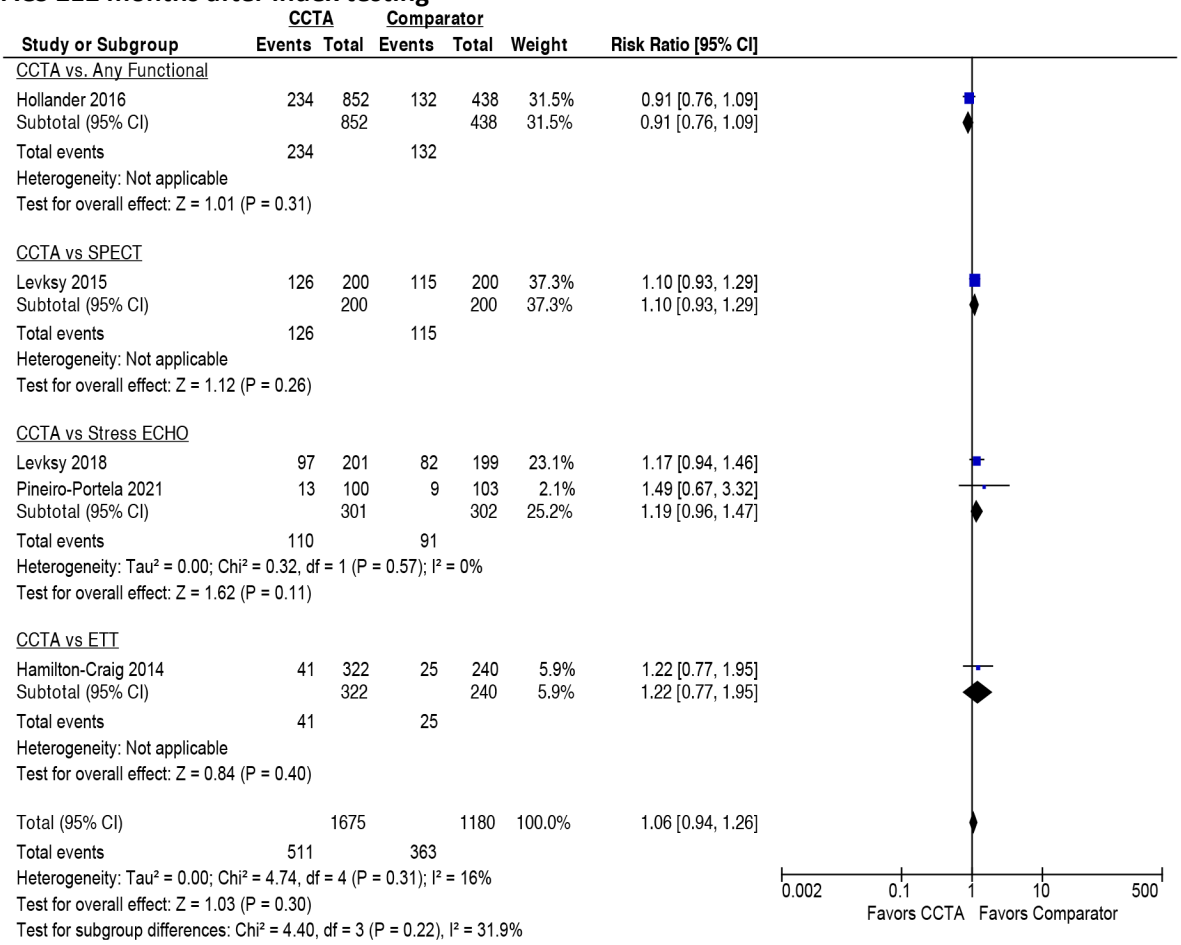
Figure 14. Comparison of CCTA and functional testing: Subsequent ED visits in patients with suspected ACS 1 to 6.5 months after index testing

Study or Subgroup	CCTA Events	CCTA Total	Comparator Events	Comparator Total	Weight	Risk Ratio [95% CI]
CCTA vs. Any Functional						
Litt 2012	71	885	34	452	36.5%	1.07 [0.72, 1.58]
Miller 2011	5	30	10	30	6.3%	0.50 [0.19, 1.29]
Hoffmann 2012	14	501	19	499	12.2%	0.73 [0.37, 1.45]
Dedic 2016	13	245	19	245	12.1%	0.68 [0.35, 1.35]
Subtotal (95% CI)		1661		1226	67.1%	0.85 [0.64, 1.15]
Total events	103		82			
Heterogeneity: Tau² = 0.00; Chi² = 3.05, df = 3 (P = 0.38); I² = 2%						
Test for overall effect: Z = 1.06 (P = 0.29)						
CCTA vs SPECT						
Goldstein 2007	6	99	6	98	4.7%	0.99 [0.33, 2.96]
Goldstein 2011	2	330	4	297	2.0%	0.45 [0.08, 2.44]
Nabi 2016	28	283	37	300	26.2%	0.80 [0.50, 1.27]
Subtotal (95% CI)		712		695	32.9%	0.80 [0.53, 1.21]
Total events	36		47			
Heterogeneity: Tau² = 0.00; Chi² = 0.59, df = 2 (P = 0.74); I² = 0%						
Test for overall effect: Z = 1.07 (P = 0.29)						
Total (95% CI)		2373		1921	100.0%	0.84 [0.66, 1.06]
Total events	139		129			
Heterogeneity: Tau² = 0.00; Chi² = 3.72, df = 6 (P = 0.71); I² = 0%						
Test for overall effect: Z = 1.47 (P = 0.14)						
Test for subgroup differences: Chi² = 0.07, df = 1 (P = 0.80), I² = 0%						



ACS = acute coronary syndrome; CCTA = coronary computed tomography angiography; CI = confidence interval; ED = emergency department; ETT = exercise treadmill test; SPECT = single photon emission computed tomography.

Figure 15. Comparison of CCTA and functional testing: Subsequent ED visits in patients with suspected ACS ≥12 months after index testing



ACS = acute coronary syndrome; CCTA = coronary computed tomography angiography; CI = confidence interval; ECHO = stress echocardiography; ED = emergency department; ETT = exercise treadmill test; SPECT = single photon emission computed tomography.

6.1.2.6 Medication changes (Appendix O, Table O27 and O28)

Across populations and within populations, CCTA was not consistently associated with initiation of, discontinuation of or changes to medications. Results across trials for mediations were mixed. Evidence is insufficient to draw firm conclusions about the impact of testing on medication decisions.

In stable outpatients, initiation, discontinuation or change in medication use are briefly outlined below

- **Aspirin, statin, and beta-blocker use**: One large, good-quality RCT[135] reported that CCTA was associated with changes in use of these medications compared with functional testing with a higher proportion of CCTA recipients initiating them by 60 days. There

didn't appear to be differences in discontinuation. Another small, poor-quality RCT found no differences.[163]

- **ACE inhibitors, ARBs, non-statins**: There were no differences between CCTA and functional tests for the following medications: ACE inhibitors, (Angiotensin converting enzyme inhibitor) or ARBs (Angiotensin receptor blockers) in two RCTs,[135,163] calcium channel blockers or non-statin lipid-lowering mediations.[163]
- **Other medical management**: Two RCTs reported that CCTA was associated with more patients initiating medical management (unspecified) compared with ETT.[115,153,215] The largest of the two RCTs reported that CCTA was associated with both initiation and discontinuation of medications (unspecified) and antianginal medications at 6 weeks and through a median of 4.8 years follow-up.[115,215] (Confidence intervals for discontinuation were large indicating substantial variation.)
- **Lifestyle changes:** The same large good-quality RCT reported no differences between testing groups related to smoking cessation, exercise or changes in overweight/obese status based on changes in BMI.[135]

In patients with suspected ACS, results for initiation, continuation or change in medications are briefly outlined below.

- **Aspirin:** across five RCTs were mixed. Three RCTS found no differences use between CCTA and functional tests[111,138,140,145] while two reported that CCTA was associated with initiation of aspirin (after index visit)[144] or change in use (at median of 48 hours after index).[248]
- **Statins or lipid prescription**: Three trials reported no differences between CCTA and functional tests.[140,143,248] CCTA was associated with higher continued use of statins at 12 months compared with functional testing in the fourth trial[111,145] and with new or increased dose of a lipid prescription in a fifth trial.[138]
- **Antiplatelet drugs**: Only one trial found that CCTA was associated with initiation of antiplatelet therapy following the index visit[143,144] compared with functional testing however a second larger trial found no difference between testing groups for initiation or continuation of such medications at any time frame (up to 12 months following index).[111,145] Two other RCTs comparing CCTA with stress echo also found no differences between testing groups for initiation of or change in these medications.[138,248]
- **Beta-blockers:** Two RCTs reported no difference in initiation or change in use of beta blockers between testing arms.[143,144,248] In contrast, one trial reported that CCTA was associated with initiation of beta blockers compared with stress echo at a median of 2 years follow-up.[138,139]
- **Nitrate**s: Initiation of nitrates was more common following index testing with CCTA versus functional testing in one RCT,[143,144] but there was no difference between testing arms in another trial evaluating change in use.[248]
- **Anti-hypertensive drugs:** CTTA was associated with fewer changes in use in one RCT within 49 hours of index testing compared with stress echo (10% vs. 18%).[248]
- **Diuretics:** These were initiated more frequently following CCTA and the time of index test compared with functional tests in one trial.[143,144]
- **Diabetes medications**: There were no differences between CCTA and stress echo in the percent changes in either insulin or oral hypoglycemics in one trial.[248]

6.1.3 Key Question 3: Safety

6.1.3.1 Test-related Adverse Events

Fourteen trials (across 18 publications; N=21,446)[36,37,47,52,59,83,85,109,111,126,138,140,145,149,153,215,238,257] assessing CCTA provided information on adverse events related to index testing (Table 29). Trials have been previously described and detailed information about each trial can be found in Appendix Q. Briefly, patients had suspected CAD in 7 trials[36,52,59,126,149,153,215,238,257] (N=17,311) and suspected ACS in 7 trials[37,47,83,85,109,111,138,140,145] (N=4,135). Comparator tests included any functional testing in 5 trials [37,47,59,109,111,145,149], SPECT in 4 trials[83,85,126,140,238], exercise ECG in 2 trials[52,215,257], ICA in 2 trials[36,52], and stress echocardiography in 1 trial [138]. In addition, data from one case series was included.[23]

See Appendix F, Table F3 for detailed abstraction of safety-related outcomes by trial.

6.1.3.1.1 Summary of results for test-related adverse events

- Major or serious test-related adverse events/harms are rare for all modalities. Complications reported across studies were minor. For stress testing most reported symptoms are expected responses to the pharmacologic agents used.
- No major complications were observed across three RCTS at time of index test or within 24 hours (SOE Low). The largest RCT in stable outpatients also reported no test-related hospitalization in the CCTA arm and 0.1% (5/4837) in the functional testing arm (SOE Low).
- Minor complications at time of index test or within 24 hours was <4% across treatment arms across five RCTs in stable outpatients and five RCTs in patients with suspected ACS. Two other trials in patients with suspected ACS reported on a broader range of minor complications, one finding that 24% of patients in each testing arm experienced them and the other that 14% of CCTA patients and 6.4% experienced minor complications (1 RCT, RR 2.16, 95% CI 1.12 to 4.14) (SOE Low).
    - Contrast-related events related to CCTA occurred in ≤3% of patients at time of index testing as reported in six RCTs and one case series. Transient creatinine elevation not requiring dialysis were reported in two trials as 0.2% and 1% (SOE Low) and a third RCT reported that no contrast-induced nephropathy occurred (SOE Insufficient). Mild contrast reaction occurred in 0.5% to 2.1% of patients across six RCTs (SOE Low).
    - CCTA was associated with lower risk of chest pain, shortness of breath, or palpitations at the time of index testing compared with stress SPECT (1 RCT, 0.5% vs. 16% RR 0.03, 95% CI 0.004 to 0.24, p<0.001) and stress echo (1 RCT, 0% vs. 3%, p=0.03) in patients with suspected ACS (SOE Low). The symptoms are likely consistent with inducing cardiac stress with pharmacologic agents. One large RCT in stable outpatients reported much lower risk of symptoms related to nuclear stress testing (0.1%) and events related to dipyridamole or adenosine (0.2%) (SOE Low).
    - Arrythmias occurred in ≤ 0.2% in all testing arm across testing arms (SOE Insufficient).

Detailed Results

6.1.3.1.2 Any major or minor test-related complications (Table 30)

No major test-related complications were observed in one RCT[59,149] in stable outpatients (N=9470) with suspected CAD or in two RCTs (N= 800) in patients with suspected ACS[83,138,140] that compared CCTA with functional testing at time of index testing or within 24 hours of index testing. The RCT[59,149] in stable outpatients defined major complications as death, renal failure requiring dialysis, or anaphylaxis requiring emergency respiratory and/or circulatory support within 24 hours of index test. Hospitalization related to testing complications was rare (<1%), occurring in none of patients receiving CCTA and total of 4 patients receiving stress imaging. In supplemental material, authors of this trial report that within 72 hours of index testing, the following occurred in CCTA vs. functional testing groups: stroke 0.02% (1/4996) vs. 0.04% (2/5007), major bleeding in 0.06% (3/4996) vs. 0.06% (3/5007) and no anaphylaxis or renal failure requiring dialysis in either group. It is unclear if these later events were directly related to testing or subsequent treatment. Stroke and cardiac arrest were considered major adverse events as part of MACE in the other two RCTs.[83,138,140]

Test-related complications considered to be minor by trial authors were described in five RCTs[59,126,149,153,215,238,257] in stable outpatients and seven RCTs[37,47,83,85,109,111,138,140,145] in patients with suspected ACS that compared CCTA with functional testing. Examples of complications considered minor included transient elevation of creatinine levels, contrast extravasation, minor contrast reactions (e.g., hives, rash), dizziness, vasovagal reaction, headache, nausea, shortness of breath, and others. Arrhythmias including tachycardia, bradycardia and atrial fibrillation were reported in some trials and occurred in < 0.5% of patients. Description of specific events varied across trials. Complications are listed by trial in Appendix F, Table F3. Commonly described individual minor complications are summarized below and in Table 30. Some of the minor complications reported are specific to the testing modality. For example, those related to iodinated contrast material are specific the CCTA, those related to pharmacologic stress agents are specific to stress echo or stress SPECT. Patients may have experienced more than one minor event. Given these factors, no direct comparisons between testing arms can be made. This, combined with the heterogeneity of outcomes reported precluded pooling across trials.

Risk of any minor test-related complication at time of index test or within 24 hours was <4% across treatment arms across five RCTs[59,126,149,153,215,238,257] in stable outpatients and five RCTs[37,47,85,109,111,145] in patients with suspected ACS. In the largest trial in stable outpatients, CCTA was associated with having a minor complication compared with functional testing but the absolute risks for both testing arms were low (0.8% vs. 0.5%, RR 1.76, 95% CI 1.04 to 2.87). [59,149] Two trials in patients with suspected ACS, however, reported much higher risk of any minor complication and appear to have included a broader range of potential events. One trial[83,140] comparing CCTA with SPECT reported that 24% of patients in each testing arm experienced one or more minor complication, most commonly headache, nausea, dizziness or feeling of warmth. The other trial from the same author group[138], reported that 14% of CCTA patients and 6.4% of stress echo patients had complaints or adverse reactions to imaging (RR 2.16, 95% CI 1.12 to 4.14). They report 17 CCTA (9%) and 6 stress echo (3%) recipients complained about

examination length or positional discomfort and that none of the CCTA group but 3% of the stress echo group complained about shortness of breath or chest pain during imaging.

*6.1.3.1.3 Individual test-related adverse events (*Table 30*)*

Contrast-related adverse events occurring with CCTA occurred in ≤3% of patients at time of index testing as reported in six RCTs[37,47,59,109,149,215,257] and one case series[23]. Transient creatinine elevation not requiring dialysis were reported in two trials as 0.2%[109] and 1%[47] and a third RCT reported that no contrast-induced nephropathy occurred.[37] Extravasation of contrast occurred in 2%[47] to 3%[59,149] of patients in another. Mild contrast reaction occurred in 0.5% to 2.1% of patients across three trials[59,126,149,215,257] in stable outpatient and in 1% to 1.5% of patients across three trials in patients suspected ACS (skin rash, pruritus). [37,47,83,140] Contrast-related allergic reactions were reported in 1.7% of patients in the case series[23] (N=232).

CCTA was associated with lower risk of **chest pain, shortness of breath, or palpitations** at the time of index testing compared with stress SPECT (1RCT, 0.5% (1/186) vs. 16% (30/188), RR 0.03, 95% CI 0.004 to 0.24, p<0.001)[83,140] and stress echo (1 RCT, 0% vs. 3% (5/188). p=0.03)[138] in patients with suspected ACS. Similarly, in one RCT[59,149] in stable outpatients, **dipyridamole or adenosine-related events** were seen in patients receiving nuclear stress testing as were unspecified stress-induced symptoms, however the risks were small (0.2%, [5/3263] and 0.1% [5/3263] respectively). These responses are expected effects of the stressors and not likely minor adverse events. **Arrythmias, hypotension and hemodynamic instability** were rare across testing arms (≤0.2%). (Table 30)

Table 30. Summary table of test-related adverse events reported by CCTA trials

Outcome	Author, year/Trial name	Intervention vs. comparator	F/U	CCTA % (n/N)	Comparator % (n/N)	Effect size or p-value
Suspected CAD						
Any major complication	PROMISE trial (as tested population)*†	CCTA vs. any functional test	24 hours	0% (0/4633)	0% (0/4837)	NR
Any minor complication	PROMISE trial (as tested population)*	CCTA vs. any functional test	24 hours	0.8% (37/4633)	Any functional test: 0.5% (22/4837) - Nuclear Stress: 0.6% (20/3263) - Stress Echo: 0.2% (2/1083) - Exercise ECG: 0% (0/491)	Any functional test: RR 1.76, 95% CI 1.04 to 2.87
	SCOT-HEART trial	CCTA vs. Exercise ECG	Index test	1.7% (31/1778)	NR	NR
	CAPP trial	CCTA vs. Exercise ECG	Index test	0% (0/250)	0% (0/250)	NR
	IAEA-SPECT/CTA trial	CCTA vs. SPECT	Index test	2.1% (3/146)	0% (0/143)	NR
	RESCUE trial	CCTA vs. SPECT	Index test	0.8% (4/473)§§	0% (0/468)	NR
Hypotension	PROMISE trial (as tested population)*	CCTA vs. any functional test	24 hours	0% (0/4633)	- Nuclear Stress: 0.2% (6/3263) - Stress Echo: 0.2% (2/1083) - Exercise ECG: 0% (0/491)	NR
Mild contrast reaction	PROMISE trial (as tested population)*	CCTA vs. any functional test	24 hours	0.5% (22/4633)	Any functional test: 0% (0/4837)	NR
	SCOT-HEART trial	CCTA vs. Exercise ECG	Index test	0.7% (13/1778)	NR	NR
	IAEA-SPECT/CTA trial	CCTA vs. SPECT	Index test	2.1% (3/146)	0% (0/143)	NR
Extravasation of contrast	PROMISE trial as	CCTA vs. any	24	0.3%	Any functional test: 0%	NR

Outcome	Author, year/Trial name	Intervention vs. comparator	F/U	CCTA % (n/N)	Comparator % (n/N)	Effect size or p-value
	tested population)*	functional test	hours	(12/4633)	(0/4837)	
	SCOT-HEART trial	CCTA vs. Exercise ECG	Index test	0.4% (7/1778)	NR	NR
Hemodynamic instability	PROMISE trial (as tested population)*	CCTA vs. any functional test	24 hours	0.1% (3/4633)	Any functional test: 0% (0/4837)	NR
Acute bronchospasm	PROMISE trial (as tested population)*	CCTA vs. any functional test	24 hours	0% (0/4633)	Any functional test: 0% (0/4837)	NR
Vasovagal reactions	SCOT-HEART trial	CCTA vs. Exercise ECG	Index test	0.2% (4/1778)	NR	NR
Headache	SCOT-HEART trial	CCTA vs. Exercise ECG	Index test	0.2% (4/1778)	NR	NR
Other (not otherwise specified)	SCOT-HEART trial	CCTA vs. Exercise ECG	Index test	0.2% (4/1778)	NR	NR
Ventricular tachycardia	PROMISE trial (as tested population)*	CCTA vs. any functional test	24 hours	0% (0/4633)	- Nuclear Stress: 0.2% (5/3263) - Stress Echo: 0% (0/1083) - Exercise ECG: 0% (0/491)	NR
Rapid atrial fibrillation	PROMISE trial (as tested population)*	CCTA vs. any functional test	24 hours	0% (0/4633)	- Nuclear Stress: 0% (0/3263) - Stress Echo: 0% (0/1083) - Exercise ECG: 0% (0/491)	NR
Stress induced symptoms (not otherwise specified)	PROMISE trial (as tested population)*	CCTA vs. any functional test	24 hours	0% (0/4633)	- Nuclear Stress: 0.1% (4/3263) - Stress Echo: 0% (0/1083) - Exercise ECG: 0% (0/491)	NR
Dipyridamole/adenosine-related events	PROMISE trial (as tested population)*	CCTA vs. any functional test	24 hours	0% (0/4633)	- Nuclear Stress: 0.2% (5/3263) - Stress Echo: 0% (0/1083) - Exercise ECG: 0% (0/491)	NR
Hospital admission related to a test complication	PROMISE trial (as tested population)*	CCTA vs. any functional test	24 hours	0% (0/4633)	Any functional test: 0.1% (5/4837) - Nuclear Stress: 0.1%	NR

Outcome	Author, year/Trial name	Intervention vs. comparator	F/U	CCTA % (n/N)	Comparator % (n/N)	Effect size or p-value
					(3/3263) - Stress Echo: 0% (0/4633) - Exercise electrocardiography: 0.2% (1/491)	
Suspected ACS						
Any major complication**	PROSPECT trial	CCTA vs. SPECT	Index test	0% (0/200)	0% (0/200)	p=1.0
	Levsky, 2018	CCTA vs. Stress Echocardiography	Index test	0% (0/201)	0% (0/199)	p=1.0
Any minor complication	Chang, 2008	CCTA vs. any functional test	Index test	1.5% (2/133)	0% (0/133)	NR
	ROMICAT-II trial	CCTA vs. any functional test	Index test	0.2% (1/501)	0% (0/499)	NR
	ACRIN-PA trial	CCTA vs. any functional test	Index test	0.1% (1/908)	0.2% (1/462)	NR
	BEACON trial	CCTA vs. any functional test	Index test	3.6% (9/250)	0.4% (1/250)	NR
	Goldstein, 2007	CCTA vs. SPECT	Index test	0% (0/99)	0% (0/98)	NR
	PROSPECT trial††	CCTA vs. SPECT	Index test	24% (45/186)	24% (46/188)	NR
	Levsky, 2018	CCTA vs. Stress Echo	Index test	14% (26/189)	6.4% (12/188)	RR 2.16, 95% CI 1.12 to 4.14 p=0.03
Skin rash/reaction; pruritus	Chang, 2008	CCTA vs. any functional test	Index test	1.5% (2/133)	0% (0/133)	NR
	BEACON trial	CCTA vs. any functional test	Index test	1% (2/250)	0% (0/250	NR
	PROSPECT trial	CCTA vs. SPECT	Index test	1.5% (3/186)	0% (0/186)	p=0.25
Contrast-induced nephropathy	Chang, 2008	CCTA vs. any	Index	0% (0/133)	0% (0/133)	NR

Outcome	Author, year/Trial name	Intervention vs. comparator	F/U	CCTA % (n/N)	Comparator % (n/N)	Effect size or p-value
		functional test	test			
Transient increase in the creatinine level without the need for dialysis	ROMICAT-II trial	CCTA vs. any functional test	Index test	0.2% (1/501)	0% (0/499)	NR
	BEACON trial	CCTA vs. any functional test	Index test	1% (3/250)	0.4% (1/250)	NR
Extravasation of contrast	BEACON trial	CCTA vs. any functional test	Index test	2% (4/250)	0% (0/250)	NR
Chest pain, shortness of breath, or palpitations	PROSPECT trial	CCTA vs. SPECT	Index test	0.5% (1/186)	16% (30/188)	RR 0.03, 95% CI 0.004 to 0.24 p<0.001
	Levsky, 2018	CCTA vs. Stress Echo	Index test	0% (0/189)	3% (5/188)	p=0.03
Bradyarrhythmia	ACRIN-PA trial	CCTA vs. any functional test	Index test	0.1% (1/908)	0.2% (1/462)	NR

ACS = acute coronary syndrome, CAD = coronary artery disease, CCTA = coronary computed tomography angiography, ECG = electrical echocardiogram, ICA = invasive coronary angiography, NR = not reported, SPECT = single photon emission computed tomography

* 404 patients had no testing and 29 had ICA as a first test; these patients are not included in the as tested population.

† In the PROMISE trial, for both CCTA and functional testing, major complications were defined as death, renal failure requiring dialysis, or anaphylaxis requiring emergency respiratory and/or circulatory support.

‡ In the CONSERVE trial, only major bleeding was reported as an adverse event. Of the four major bleeds in the ICA group of this trial, one also required major transfusion.

§ Of the minor procedural complications in the CCTA group, four occurred after coronary angiography and two after CCTA. The p-value for the difference between groups for all complications, including those from procedures, was 0.014. Only those related to CCTA are reported in the table above.

** Neither the PROSPECT trial nor Levsky 2018, defined major complications. Both trials simply stated that no patients had serious complications from imaging.

†† Of patients in each testing arm experienced one or more minor complication, most commonly headache, nausea, dizziness or feeling of warmth.

‡‡Authors report this as complaints or adverse reactions to imaging; 17 CCTA and 6 stress echo patients complained about examination length or positional discomfort; None of the CCTA group but 3% of the stress echo group complained about shortness of breath or chest pain during imaging

§§ 3 events were rated as possibly due to testing, 1 rated as unlikely to be due to testing

6.1.3.2 Radiation exposure

Sixteen trials[36,37,47,52,59,83,84,96,109,126,138,140,143,144,149,153,163,171,215,257] (across 20 publications; N=21,627) assessing CCTA provided information on radiation exposure. Trials have been previously described and detailed information about each trial can be found in Appendix Q. Thirteen trials[36,37,59,83,84,96,126,138,140,143,144,149,153,163,171,215,257] (N=19,787) provided information on effective radiation dose for the index test only (**Table 31**). Of these 13 trials, 6 trials[36,59,126,149,153,163,215,257] were in patients with suspected CAD (N=16,210) and 7 trials[37,83,84,96,138,140,143,144,171] were in patients with suspected ACS (N=3,577). Ten trials[47,52,59,83,109,126,138,140,143,144,149,163,171] (N=14,324) reported on the cumulative radiation dose from all tests (**Table 32**). Of these 10 trials, 4 trials[52,59,126,149,163] were in patients with suspected CAD (N=10,826) and 6 trials[47,83,109,138,140,143,144,171] were in patients with suspected ACS (N=3,498).

6.1.3.2.1 Summary of results for radiation exposure

Data reported in **Table 31** for the PROMISE trial[59,149] are among the subgroup intended for nuclear stress testing before randomization (n=3146 vs. 3203 as tested); this was the only group with radiation data available for index test only. Additionally, one trial[52], comparing CCTA with ICA reported on radiation from follow-up procedures (ICAs and revascularizations), in addition to testing.

- **Radiation from index tests**: Across six RCTs comparing CCTA specifically with SPECT radiation exposure at index tended to be lower with CCTA (SOE Low). Five RCTs reported that CCTA was associated with a lower effective radiation dose for the index test; a sixth trial reported that CCTA was associated with slightly higher radiation (estimated difference 1.8 mSv). Rough estimates of difference between tests ranged from approximately 1.30 mSv to 11.9 mSv. Stress echocardiography and ETT do not involve ionizing radiation (SOE Low).
- **Cumulative radiation**: Across nine RCTs, results are somewhat mixed, but suggest that cumulative radiation may be higher when CCTA is the initial test (SOE Low). Good- or fair-quality RCTs found that CCTA was associated with higher cumulative radiation compared with functional testing with rough estimates of differences ranging from 1.9 mSv to 9.0 mSv in these trials. It is unclear from included RCTs what tests (e.g., SPECT, ICA) or procedures (e.g., PCI) were included in the estimates. Stress echocardiography does not involve ionizing radiation. It is unclear if some of the differences between arms would impact clinical decision making. CCTA was associated with lower cumulative radiation versus SPECT in two RCTs (estimated range 6 mSv to 15 mSv) and no statistical difference between CCTA and SPECT was reported in a third smaller poor-quality RCT.

Detailed results

6.1.3.2.2 Index test radiation

Three RCTs[59,126,149,163] in stable outpatients and three RCTs[83,84,140,171] in patients with suspected ACS compared index test effective radiation dose for CCTA with SPECT or any nuclear stress testing. Radiation doses in the CCTA arms of these trials ranged varied substantially across trials (means range 10.4 mSv to 12.7 mSv, median ranges 5.0 mSv to 11.5 mSv) (Table 31). Radiation doses in the SPECT/nuclear stress testing arms also varied (means range 10.9 mSv to 14.1 mSv, median ranges 9.3 mSv to 27 mSv). Across five RCTS, CCTA was associated with a lower effective radiation dose than SPECT (or other nuclear stress test) at index test. One large good-quality RCT (N=6,348) in stable outpatients reported a mean difference (MD –3.7 ,95% CI –3.9 to –3.5).[59,149] In contrast index CCTA was associated with higher effective radiation dose in one smaller fair-quality RCT[171] (N=598) in patients with suspected ACS (MD 1.8, 95% CI 0.89 to 2.7) (Table 31). It is unclear whether some of the differences would impact clinical decision making.

The other RCTs either did not report radiation dose for functional tests[37,143,144] or compared CCTA with tests that do not involve ionizing radiation (i.e., ETT or stress echo).[96,138,153,215,257] Across this group of RCTs, the means ranged from 5.1 mSv to 12.5 mSv and medians ranged from 3.8 mSv to 6.4 mSv (Table 31).

Table 31. Summary table of effective radiation dose for index test only reported by CCTA trials

Author Year	N	Intervention test (n)	Comparator test (n)	Intervention group; radiation from index test only	Comparator group; radiation from index test only	MD (95% CI), p-value [calculated] Author provided p-value for Medians
Suspected CAD						
PROMISE trial	6,349*	CCTA* (n=3,146 as tested)	Nuclear stress testing* (n=3203 as tested)	Mean (SD): 10.4 (6.6) mSv Median (IQR): 8.8 (5.3 to 14.6) mSv	Mean (SD): 14.1 (5.6) mSv Median (IQR): 12.6 (11.3 to 14.6) mSv	MD –3.7 (95% CI –3.9 to –3.5), p=0.0001
IAEA-SPECT/CTA trial Karthikeyan 2017	303	CCTA (n=152 as randomized)	SPECT (n= 151 as randomized)	Median (IQR): 5.0 (3.8 to 10) mSv	Median (IQR): 9.3 (8.5 to 9.7) mSv	p<0.001
Min, 2012	180	CCTA (n=91 as randomized)	SPECT (n= 89 as randomized)	Median (IQR): 6.5 (5.1 to 13.3) mSv	Median (IQR): 13.3 (13.1 to 38.0) mSv	p<0.0001
Compared with ECG or Echo						
SCOT-HEART trial	4146	CCTA (n=2073 as randomized)	Exercise ECG (n=2073 as randomized)	Median (IQR): 4.1 (3.0 to 5.6) mSv	NR	N/A
CAPP trial McKavanagh 2015	500	CCTA (n=243 as randomized)	Exercise ECG (n=245 as randomized)	Mean (SD NR): 5.31 mSv	Mean (SD NR): 0.00 mSv	NR
Suspected ACS						

Author Year	N	Intervention test (n)	Comparator test (n)	Intervention group; radiation from index test only	Comparator group; radiation from index test only	MD (95% CI), p-value [calculated] Author provided p-value for Medians
CT-STAT trial Goldstein 2011	749	CCTA (n=361 as randomized)	SPECT (n=338 as randomized)	Median (IQR): 11.5 (6.8 to 16.8) mSv	Median (IQR): 12.8 (11.6 to 13.9) mSv	p=0.02
PROSPECT trial Levsky 2015	400	CCTA (n=200 as randomized)	SPECT (n=200 as randomized)	Median (IQR): 9.6 (6.2 to 23) mSv (n=184)	Median (IQR): 27 (19 to 27) mSv (n=189)	p<0.001
Nabi, 2016	598	CCTA (n=288 as randomized)	SPECT (n=310 as randomized)	Mean (SD): 12.7 (4.9) mSv	Mean (SD): 10.9 (4.4) mSv	MD 1.8 (95% CI 0.89 to 2.7), p=0.0001
Data for comparator NR or compared with ECG or Echo						
Chang 2008	268	CCTA (n=133 as randomized)	Any functional test (n=133 as randomized)	Mean (SD): 12.5 (2.0) mSv	NR	N/A
CATCH trial Linde 2013	600	CCTA (n=299 as randomized)	Any functional test (n=301 as randomized)	Median (IQR): 4.7 (3.8 to 6.0) mSv	NR	N/A
CT-COMPARE trial Hamilton-Craig 2014	562	CCTA (n=322 as randomized)	Exercise ECG (n=240 as randomized)	Median (IQR): 3.8 (3.5 to 4.1) mSv	NR	N/A

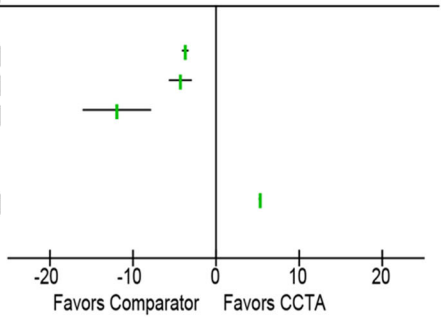
Author Year	N	Intervention test (n)	Comparator test (n)	Intervention group; radiation from index test only	Comparator group; radiation from index test only	MD (95% CI), p-value [calculated] Author provided p-value for Medians
Levsky 2018	400	CCTA (n=201 as randomized)	Stress Echo (n=199 as randomized)	Median (IQR): 6.4 (5.3 to 7.8) mSv	Median (IQR): 0 (0 to 0) mSv	p<0.001

ACS = acute coronary syndrome; CCTA = coronary computed tomography angiography; CI = confidence interval; ECG = electrocardiography; ED = emergency department; ETT = exercise treadmill test; IQR = interquartile range; MD = mean difference; mSv = millisievert; NR = not reported; SPECT = single photon emission computed tomography; Stress Echo = stress echocardiography.

Differences between trials regarding how exposure was reported (means or medians) combined with the substantial heterogeneity across studies precluded pooling of data, however, Figure 16 and Figure 17 provides rough estimates of differences between testing arms and provides a visual representation of the data for studies that reported comparative data. Two of the studies compared CCTA functional tests that do not use ionizing radiations, one with ETT[153] the other with stress echocardiography.[138]

Figure 16. Visual overview of index test radiation exposure in stable outpatients and in patients with suspected ACS

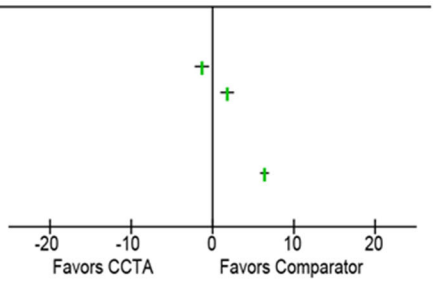
Study or Subgroup	CCTA Effect	CCTA SD	CCTA Total	Comparator Effect	Comparator SD	Comparator Total	Effect Difference [95% CI]
CCTA vs SPECT							
PROMISE trial	10.4	6.6	3146	14.1	5.6	3203	-3.70 [-4.00, -3.40]
Karthikeyan 2017	5	8	152	9.3	0.89	151	-4.30 [-5.58, -3.02]
Min 2012	6.5	6.07	91	18.44	18.44	89	-11.94 [-15.97, -7.91]
CCTA vs ETT							
McKavanagh 2014	5.31	0.0	361	0.0	0.0	338	5.31 [5.24, 5.38]



ACS = acute coronary syndrome; CCTA = coronary computed tomography angiography; CI = confidence interval; ETT = exercise treadmill test; SD = standard deviation; SPECT = single photon emission computed tomography.

Figure 17. Visual overview of index test radiation exposure in patients with suspected ACS

Study or Subgroup	CCTA Effect	CCTA SD	CCTA Total	Comparator Effect	Comparator SD	Comparator Total	Effect Difference [95% CI]
CCTA vs SPECT							
Goldstein 2011	11.5	7.41	361	12.8	1.7	338	-1.30 [-2.09, -0.51]
Nabi 2016*	12.7	4.9	288	10.9	4.4	310	1.80 [1.05, 2.55]
CCTA vs ECHO							
Levksy 2018	6.4	3.26	201	0	0	199	6.40 [5.94, 6.86]



CCTA = coronary computed tomography angiography; CI = confidence interval; ECHO = stress echocardiography; SD = standard deviation; SPECT = single photon emission computed tomography.

6.1.3.2.3 Cumulative Radiation

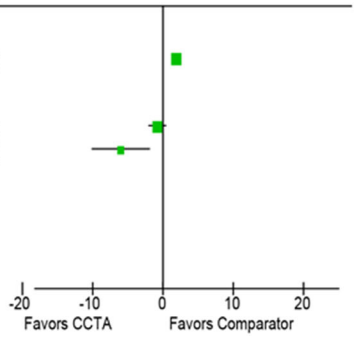
Three RCTs[59,126,149,163] in stable outpatients and 6 trials[47,83,109,138,140,143,144,171] in patients with suspected ACS compared cumulative radiation dose by CCTA versus functional testing as initial testing strategies. It is assumed that the cumulative does includes additional downstream testing. Six RCTs[47,59,109,138,143,144,149,171] found that CCTA was associated with higher cumulative radiation compared with functional testing. CCTA was associated with lower cumulative radiation versus SPECT in two

RCTs[83,126,140] and no statistical difference between CCTA and SPECT was reported in a third smaller poor-quality RCT,[163] (Table 32).

Differences between trials regarding how exposure was reported (means or medians) combined with the substantial heterogeneity across studies precluded pooling of data. Figure 18 and Figure 19 provide rough estimates of differences between arms for a visual overview of differences between testing arms. It is unclear if some differences may impact clinical decision making.

Figure 18. Visual overview of cumulative radiation exposure in stable outpatients

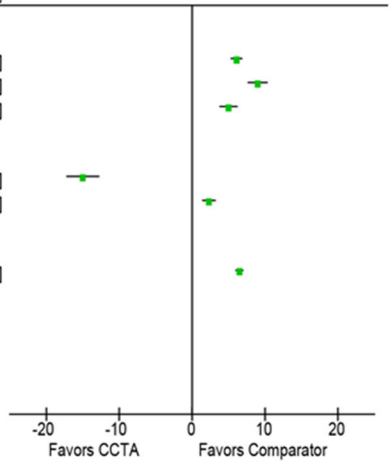
Study or Subgroup	Follow-up	CCTA Effect	CCTA SD	CCTA Total	Comparator Effect	Comparator SD	Comparator Total	Effect Difference [95% CI]
CCTA vs. Any Functional								
PROMISE Trial*	≤3 months	12	8.5	4996	10.1	9	5007	1.90 [1.56, 2.24]
CCTA vs SPECT								
Karthikeyan 2017	12 months	8.8	6.81	152	9.6	2.67	151	-0.80 [-1.96, 0.36]
Min 2012	55 days	7.3	6.37	91	13.3	18.44	89	-6.00 [-10.05, -1.95]



CCTA = coronary computed tomography angiography; CI = confidence interval; SD = standard deviation; SPECT = single photon emission computed tomography.

Figure 19. Visual overview of cumulative radiation exposure in patients with suspected ACS

Study or Subgroup	Follow-up	CCTA Effect	CCTA SD	CCTA Total	Comparator Effect	Comparator SD	Comparator Total	Effect Difference [95% CI]
CCTA vs. Any Functional								
CATCH Trial	4 months	6.1	6.22	299	0	0	301	6.10 [5.39, 6.81]
ROMICAT-II Trial*	1 month	14.3	10.9	501	5.3	9.6	499	9.00 [7.73, 10.27]
BEACON Trial*	1 month	7.3	6.6	250	2.3	6.5	250	5.00 [3.85, 6.15]
CCTA vs SPECT								
PROSPECT Trial	12 month	12	14.52	200	27	5.93	200	-15.00 [-17.17, -12.83]
Nabi 2016*	6.5 months	13.3	5.8	288	11	4.6	310	2.30 [1.46, 3.14]
CCTA vs ECHO								
Levksy 2018	12 months	6.5	3.26	201	0	0	199	6.50 [6.04, 6.96]



CCTA = coronary computed tomography angiography; CI = confidence interval; ECHO = stress echocardiography; SD = standard deviation; SPECT = single photon emission computed tomography.

In stable outpatients, the largest, good-quality RCT (N=10,003 as randomized, 9470 as tested) CCTA was associated with slightly higher cumulative radiation exposure compared with any functional testing within 3 months of testing (MD 1.90 mSv (95% CI 1.6 to 2.2 mSv).[59,149] In contrast, one smaller (N=303) good-quality RCT[126] reported that CCTA was associated with slightly lower cumulative radiation compared with SPECT at 12 months and one small (N=180) poor-quality RCT found no statistically significant difference between CCTA and SPECT (medians 7.3 mSv vs. 13.3 mSv) at a mean of 55 days. [163] (Table 32)

In patients with suspected ACS, in five[47,109,138,143,144,171] of the six RCTs, CCTA was associated with higher cumulative radiation compared with functional testing in general. The largest, fair-quality RCT (N=1000) reported a mean difference of 9mSv (95% CI 7.7 to 10.3 mSv) at 1 month, one good-quality trial[47] (N=500) reported a mean difference of 4.7 mSv (95% CI 3.5 to 5.9) at 1 month and the mean difference in a third fair-quality trial[171] (N=598) was 2.30mSv (95% CI 1.5 to 3.1mSv) at approximately 6.5 months. Median ranges for cumulative radiation reported in the remaining two fair-quality RCTs[138,143,144] were 6.1 to 6.5mSv for CCTA and 0 for functional testing (IQR 0 to 5.7). One of these RCTs compared CCTA with stress echocardiography.[138]

In contrast, in one fair-quality RCT (N=400), CCTA was associated with substantially lower cumulative radiation compared with SPECT at 12 months (median 12mSv vs. 27 mSv) and at a median of approximately 40 months (median 13mSv vs. 27mSv)[83,140] (Table 32).

Table 32. Summary table of cumulative radiation from all tests reported by CCTA trials

Author Year	N	Intervention test (n)	Comparator test (n)	Follow-up time	Intervention group; cumulative radiation from all tests	Comparator group; cumulative radiation from all tests	MD (95% CI), p-value Author provided p-value for Medians
Suspected CAD							
PROMISE trial*	10,003	CCTA (n=4,996 as randomized)	Any functional test (n=5,007 as randomized)	≤3 months	Mean (SD): 12.0 (8.5) mSv Median (IQR): 10.0 (5.6 to 17.2) mSv	Mean (SD): 10.1 (9.0) mSv Median (IQR): 11.3 (0.0 to 13.5) mSv	MD 1.90 (1.6 to 2.2), p=0.0001
	9,470	CCTA (n=4,633 as tested)	Any functional test (n=4,837 as tested)	≤3 months	Mean (SD): 12.5 (8.4) mSv Median (IQR): 10.3 (6.1 to 17.4) mSv	Mean (SD): 10.6 (8.9) mSv Median (IQR): 11.5 (0.0 to 13.8) mSv	MD 1.90 (95% CI 1.6 to 2.3), p=0.0001
IAEA-SPECT/CTA trial Karthikeyan 2017	303	CCTA (n=152 as randomized)	SPECT (n= 151 as randomized)	12 months	Median (IQR): 8.8 (I4.0 to 13.2)	Median (IQR): 9.6 (8.9 to 12.5)	p=0.04
Min, 2012	180	CCTA (n=91 as randomized)	SPECT (n= 89 as randomized)	Mean: 55 days	Median (IQR): 7.3 (5.1 to 13.7) mSv	Median (IQR): 13.3 (13.1 to 38.0) mSv	p=0.31
Suspected ACS							
CATCH trial Linde 2013	600	CCTA (n=299 as	Any functional test	4 months	Median (IQR): 6.1 (4.2 to 12.6)	Median (IQR): 0.0 (0.0 to 5.7)	p<0.0001

Author Year	N	Intervention test (n)	Comparator test (n)	Follow-up time	Intervention group; cumulative radiation from all tests	Comparator group; cumulative radiation from all tests	MD (95% CI), p-value Author provided p-value for Medians
		randomized)	(n=301 as randomized)				
ROMICAT-II trial Hoffmann	1000	CCTA (n=501 as randomized)	Any functional test (n=499 as randomized)	1 month	Mean (SD): 14.3 (10.9) mSv	Mean (SD): 5.3 (9.6) mSv	MD 9.0 (95% CI 7.7 to 10.3), p=0.0001
BEACON trial Dedic 2016	500	CCTA (n=250 as randomized)	Any functional test (n=250 as randomized)	1 month	Mean (SD): 7.3 (6.6) mSv	Mean (SD): 2.6 (6.5) mSv	MD 4.7 (95% CI 3.5 to 5.9), p= 0.0001
PROSPECT trial Levsky 2015	400	CCTA (n=200 as randomized)	SPECT (n=200 as randomized)	12 months	Median (IQR): 12 (6.4 to 26) mSv	Median (IQR): 27 (19 to 27) mSv	p<0.001
				Median: 41.7 (CCTA) and 39.0 (SPECT) months	Median (IQR): 13 (6.9 to 27) mSv	Median (IQR): 27 (19 to 27) mSv	p<0.001
Nabi, 2016	598	CCTA (n=288 as randomized)	SPECT (n=310 as randomized)	Median: 6.5 (CCTA) and 6.4 (SPECT) months	Mean (SD): 13.3 (5.8) mSv	Mean (SD): 11.0 (4.6) mSv	MD 2.30, 95% CI 1.5 to 3.1 p<0.0001
Levsky 2018	400	CCTA (n=201 as randomized)	Stress Echo (n=199 as randomized)	12 months	Median (IQR): 6.5 (5.3 to 9.7) mSv	Median (IQR): 0 (0 to 0)	p<0.001
				Median: 24 months	Median (IQR): 6.5 (5.5 to 10.0) mSv	Median (IQR): 0 (0 to 0)	p<0.001

ACS = acute coronary syndrome, CAD = coronary artery disease, CCTA = coronary computed tomography angiography, CI = confidence interval; ECG = electrical echocardiogram, ICA = invasive coronary angiography, IQR = interquartile range, MD = mean difference, mSv = millisievert, N/A = not applicable, NR = not reported, SD = standard deviation, SPECT = single photon emission computed tomography.

* All PROMISE subjects who had functional testing or CCTA as their first test were included in the as tested population. Patients who had no test or who had invasive coronary angiography (ICA) as their first test were excluded. Computed tomography (CT) protocols commonly include a non-contrast CT for assessment of coronary artery calcium score before contrast-enhanced CCTA to assess coronary artery stenosis. Some sites chose not to proceed with CCTA in patients with a high calcium score; these participants were excluded as the radiation dose from calcium score CT alone is substantially lower than for CCTA.
† Includes radiation from ICAs and revascularizations, in addition to testing.

6.1.3.3 Incidental findings

Four trials[59,83,140,149,215,238,257] (across 7 publications; N=12,671) assessing CCTA reported on incidental and/or extra cardiac findings found on index test (Table 33). Trials have been previously described and detailed information about each trial can be found in Appendix Q. Three trials[59,149,215,238,257] (N=12,295) were in patients with suspected CAD and 1 trial[83,140] was in patients with suspected ACS (N=376). Comparators consisted of SPECT MPI in 2 trials [83,140,238], exercise ECG in 1 trial[215,257], and any functional testing in 1 trial[59,149].

In addition to the four CCTA trials reporting on incidental findings, 2 systematic reviews[72,125] and 4 retrospective single arm studies[24,66,124,200] provided additional information on extracardiac findings found on CCTA (Table 34). One systematic review included 11,703 patients with suspected CAD (unclear if symptomatic or asymptomatic) across 13 studies. The other systematic review included 15,877 mostly with suspected CAD across 19 studies. Karius 2014 included 9 studies that were not included in the Flor 2013 systematic review, and Flor 2013 included 3 studies that were not included in Karius 2014. Across the 4 additional single arm studies, which all included patients with suspected CAD, sample sizes ranged from 1,383 to 3,898 (Total N=9,090). Focus was on total extracardiac findings, clinically significant or major extracardiac findings, malignant extracardiac findings, and the top 5 most commonly reported extracardiac findings in each study.

6.1.3.3.1 Summary of results

- Incidental findings are common with CCTA (28% to 44%) across included RCTs, systematic reviews and nonrandomized studies with pulmonary findings being most common. The proportion that were considered “potentially significant”, “clinically significant” or “required follow-up” ranged from 4.9% to 16% (SOE Low).

Detailed Results

Incidental and/or extra cardiac findings at index testing were commonly seen and variably defined across four CCTA trials[59,83,140,149,215,238,257] that reported on this. Pulmonary-related findings (nodules, masses, granuloma, emphysema or other parenchymal changes) were most commonly reported across trials. (Table 33) In stable outpatients, “potentially significant” incidental findings occurred in 11.6% of patients in the CCTA group versus 0.7% of those receiving stress nuclear testing or 1.9% of patients receiving stress echocardiography ($p<0.001$ for CCTA vs. any functional test) in the largest trial. [59,149] Two other trials in stable outpatients reported frequencies of any incidental findings of 38.1%[215,257] and 32.8%[238], however additional imaging was required in fewer patients, 7.5% and 11.4% respectively. In one trial in patients with suspected ACS incidental findings occurred in 83.4% of patients; 156 of 187 patients had a total of 386 incidental findings.[83,140] The most common were pulmonary (63%), non-coronary cardiac (37%), gastrointestinal (26%) and hepatobiliary (22%) findings. Findings the authors considered potentially serious or life threatening were pericardial effusion (6.4%), aortic dilatation (3.2%), pulmonary embolism (2.1%), pneumonia (1.6%) and congestive heart failure (1.6%).

Across two systematic reviews[72,125], one retrospective database study[124] and three large retrospective case series[24,66,200], the overall frequency of extracardiac findings (ECFs) ranged from 28.4% to 44%. (Table 34) Again, pulmonary findings were most common. The two systematic reviews[72,125] report a pooled prevalence of 16% (95% CI range 9% to 24%) for clinically significant or major ECFs. The frequency of ECFs major and/or requiring follow-up ranged from 2.4% to 6.8% in three retrospective studies[24,66,124] with the fourth study[200] reporting that 4.9% of ECFs were considered significant. The pooled prevalence of acute life-threatening ECFs was 2.2% in one systematic review[125] and the prevalence of ECFs requiring urgent attention was 0.4%in the retrospective database study[124] by the same author group. The prevalence of malignant ECFs ranged from 0.1% to 0.7% across two systematic reviews[72,125], the database study[124] and two case series[24,200].

Resources required to follow-up incidental findings and use of additional testing involving radiation were not described in these studies. The impact of incidental findings and their follow-up on patients (anxiety, cost, time from work, etc.) was not described.

Table 33. Summary table of incidental findings on index test reported by CCTA trials

Outcome	Author, year (trial name)	Intervention vs. comparator	CCTA; % (n/n)	Comparator test; % (n/N)	Effect Size or p-value
Suspected CAD					
Any incidental finding*	Lu, 2017 (PROMISE trial)	CCTA vs. any functional test	11.6% (539/4633)	Any functional test: 0.7% (34/4837)† RR 16.6, 95% CI 11.7 to 23.3 - Nuclear Stress: 0.4% (13/3263) - Stress Echo: 1.9% (21/1083) - Exercise electrocardiography: NR	Any functional test: RR 16.6, 95% CI 11.7 to 23.3 p<0.001 - Nuclear Stress: NR - Stress Echo: NR - Exercise electrocardiography: NR
	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	38.1% (677/1778)‡	NR	NR
	Stillman, 2020 (RESCUE trial)	CCTA vs. SPECT MPI	32.8% (169/516)	1.7% (9/531)	RR 19.32, 95% CI 10.0 to 37.37 NR
Incidental findings requiring additional follow-up imaging	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	7.6% (136/1778)	NR	NR
	Stillman, 2020 (RESCUE trial)	CCTA vs. SPECT MPI	11.4% (59/516)	0.4% (2/531)	RR 03.36, 95% CI 7.45 to 123.6 NR
Coronary anomaly	Lu, 2017 (PROMISE trial)	CCTA vs. any functional test	1.5% (71/4633)	NR	NR
Pulmonary nodule, mass, granuloma	Lu, 2017 (PROMISE trial)	CCTA vs. any functional test	9.4% (437/4633)	NR	NR
	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	11.2% (200/1778)	NR	NR
Pulmonary embolism	Lu, 2017 (PROMISE trial)	CCTA vs. any functional test	0.1% (4/4633)	NR	NR
	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	0.2% (4/1778)	NR	NR
Pneumonia	Lu, 2017 (PROMISE trial)	CCTA vs. any functional test	0.2% (9/4633)	NR	NR
	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	0.8% (15/1778)	NR	NR

Outcome	Author, year (trial name)	Intervention vs. comparator	CCTA; % (n/n)	Comparator test; % (n/N)	Effect Size or p-value
Aortic aneurysm	Lu, 2017 (PROMISE trial)	CCTA vs. any functional test	0.2% (9/4633)	NR	NR
Aortic dissection	Lu, 2017 (PROMISE trial)	CCTA vs. any functional test	0.2% (8/4633)	NR	NR
Hiatal hernia	Lu, 2017 (PROMISE trial)	CCTA vs. any functional test	7.7% (358/4633)	NR	NR
	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	6.8% (121/1778)	NR	NR
Emphysema or other parenchymal changes	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	11.4% (202/1778)	NR	NR
Lung atelectasis/scarring	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	3.5% (63/1778)	NR	NR
Pleural plaque	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	1.6% (29/1778)	NR	NR
Bronchiectasis	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	1.2% (22/1778)	NR	NR
Fibrosis	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	1.0% (17/1778)	NR	NR
Pleural effusion	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	0.2% (3/1778)	NR	NR
Lymphadenopathy	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	1.7% (30/1778)	NR	NR
Calcified lymph nodes	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	1.0% (16/1778)	NR	NR
Aorta atheroma	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	1.5% (26/1778)	NR	NR
Aorta dilation	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	1.0% (17/1778)	NR	NR
Breast nodule	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	0.3% (5/1778)	NR	NR
Liver cysts	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	2.0% (36/1778)	NR	NR
Liver hemangioma	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	0.1% (2/1778)	NR	NR
Fatty infiltration	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	0.1% (2/1778)	NR	NR
Esophagus thickening	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	0.2% (3/1778)	NR	NR
Other§	Williams, 2018 (SCOT-HEART trial)	CCTA vs. exercise ECG	NR	NR	NR
Suspected ACS					
Any incidental finding	Goldman, 2020 (PROSPECT trial)	CCTA vs. SPECT MPI	83.4% (156/187) [386 incidental findings in 156 patients were	0% (0/189)	

Outcome	Author, year (trial name)	Intervention vs. comparator	CCTA; % (n/n)	Comparator test; % (n/N)	Effect Size or p-value
			found among 187 CCTA studies]		
Pulmonary findings	Goldman, 2020 (PROSPECT trial)	CCTA vs. SPECT MPI	63% (118/187)	0% (0/189)	NR
Noncoronary cardiac findings	Goldman, 2020 (PROSPECT trial)	CCTA vs. SPECT MPI	37% (69/187)	0% (0/189)	NR
Gastrointestinal findings	Goldman, 2020 (PROSPECT trial)	CCTA vs. SPECT MPI	26% (49/187)	0% (0/189)	NR
Hepatobiliary findings	Goldman, 2020 (PROSPECT trial)	CCTA vs. SPECT MPI	22% (42/187)	0% (0/189)	NR
Renal findings	Goldman, 2020 (PROSPECT trial)	CCTA vs. SPECT MPI	9% (17/187)	0% (0/189)	NR
Pneumonia**	Goldman, 2020 (PROSPECT trial)	CCTA vs. SPECT MPI	1.6% (3/187)	0% (0/189)	NR
Congestive heart failure**	Goldman, 2020 (PROSPECT trial)	CCTA vs. SPECT MPI	0.5% (1/187)	0% (0/189)	NR
Pericardial effusion**	Goldman, 2020 (PROSPECT trial)	CCTA vs. SPECT MPI	6.4% (12/187)	0% (0/189)	NR
Aortic dilatation**	Goldman, 2020 (PROSPECT trial)	CCTA vs. SPECT MPI	3.2% (6/187)	0% (0/189)	NR
Pulmonary embolism**	Goldman, 2020 (PROSPECT trial)	CCTA vs. SPECT MPI	2.1 %(4/187)	0% (0/189)	NR

ACS = acute coronary syndrome, CAD = coronary artery disease, CCTA = coronary computed tomography angiography, ECG = electrical echocardiogram, ICA = invasive coronary angiography, NR = not reported, SPECT = single photon emission computed tomography.

* Across the trials, incidental findings were defined as "potentially significant incidental findings" (PROMISE trial), "non-cardiac findings" (SCOT-HEART trial), "non-cardiac findings" (RESCUE trial), and "incidental findings" (PROSPECT trial).

† In the functional testing arm, abnormal breast uptake of radiotracer (0.3%, 11/3263) on nuclear stress testing, and mitral regurgitation (1.0%, 11/1083) on stress echocardiography were the most common incidental findings.

‡ In addition, there were 28.2% (501/1778) other cardiac findings identified.

§ To include: anterior mediastinal mass, arteriovenous malformation, Bochdalek hernia, broncocele, duplication cyst, elevated left hemidiaphragm, gallstones, hamartoma, pericardial cyst, sclerotic vertebrae, syndesmophytes, subclavian vein stenosis, splenomegaly, splenic artery aneurysm, vertebral wedge fractures.

** Considered to be potentially serious or life threatening.

Table 34. Summary of extracardiac findings (ECF) identified by CCTA

Author Year	Study design	N	Population	Incidental findings
Karius 2014	SR	11,703 (across 13 studies)*	Suspected CAD (unclear if symptomatic or asymptomatic)	• Pooled prevalence of overall ECFs: 41% (95% CI 27% to 56%), p<0.0001 [Overall ECF were identified in 3794 of 11,186 participants] • Pooled prevalence of clinically significant ECFs: 16.0% (95% CI 9% to 24%, p<0.0001) [Clinically significant ECF were detected in 1989 of 11,703 patients] • Pooled prevalence of acutely life-threatening ECFs in relation to the study cohort: 2.2% (95% CI 1.9% to 2.5%), p<0.0001 • Pooled prevalence of malignant ECFs in relation to the study cohort: 0.3% (95% CI 0.2% to 0.4%), p<0.0001 • Top 5 most commonly reported ECFs in relation to the total number of clinically significant ECFs: - Suspicious pulmonary nodules: 26.6% (575/2160) - Hiatal hernia: 20.8% (450/2160) - Aortic abnormalities: 10.8% (233/2160) - Emphysema: 8.6% (186/2160) - Pulmonary infiltration: 5.5% (11/2160)
Flor 2013	SR	15,877 (across 19 studies)*	Mixed (suspected CAD, healthy subjects, AFIB)	• Pooled prevalence of overall ECFs: 44% (95% CI 35% to 54%), p=0.275 • Pooled prevalence of major ECFs: 16% (95% CI 14% to 20%), p<0.001 • Pooled prevalence of malignant ECFs: 0.7% (95% CI 0.5% to 1.0%), p=NR *Individual event types were not reported by this study.*
Karius 2019	Retrospective database	3,898 (with 4,209 CCTAs performed)	CCTA examinations performed with an indication to rule out CAD. Patients without significant CAD (coronary stenosis < 50%) on CCTA were included.	• Proportion of patients with an ECF: 30.2% (1117/3898) • Proportion of patients with an ECF with a recommended for follow-up: 2.4% (95% CI 2.0% to 2.9%) (94 patients) • Proportion of patients with an urgent ECF: 0.4% (95% CI 0.3% to 0.7%) (16 patients) • Proportion of patients with a malignant ECF: 0.1% (95% CI 0.0% to 0.2%) (3 patients) • Top 5 most commonly reported ECFs in relation to the total number of patients included in the study: - Chronic changes of lung parenchyma and bronchial system: 12.9% (501/3898) - Extensive atherosclerosis: 5.4% (209/3898) - Pulmonary nodule/consolidation: 4.3% (167/3898) - Extensive spinal degradation: 4.1% (159/3898) - Aortic dilation: 2.9% (112/3898)

Author Year	Study design	N	Population	Incidental findings
Bendix 2011	Retrospective case series	1,383	Suspected CAD	• Proportion of patients with an ECF: 28.4% (393/1383) (with 482 ECFs total) • Proportion of patients with a major ECF requiring follow-up: 6.7% (94/1383) (with 1030 ECFs total) • Proportion of patients with a malignant ECF: 0.3% (4/1383) (with 4 ECFs total) • Top 5 most commonly reported ECFs in relation to the total number of ECFs identified: - Adenopathy: 18.0% (87/482) - Hepatic cyst: 12.2% (59/482) - Atelectasis: 8.5% (41/482) - Emphysema: 8.3% (40/482) - Pleural plaque: 5.4% (26/482)
Ramanathan 2019	Retrospective case series	1,713	Suspected CAD†	• Proportion of patients with an ECF: 35.0% (600/1713) (with 812 ECFs total) • Proportion of ECFs that were considered significant: 4.9% (39/812) • Proportion of patients with a malignant ECF: 0.2% (4/812) • Top 5 most commonly located ECFs in relation to the total number of patients included in the study (actual ECF types are NR): - Lungs: 13% (222/1713) - Liver: 11% (189/1713) - Mediastinum: 5% (85/1713) - Bone: 4% (68/1713) - Great vessels: 3% (51/1713)
Erol 2014	Retrospective case series	2,096	Suspected CAD‡	• Proportion of patients with an ECF: 8.1% (170/2096) (with 174 ECFs total) • Proportion of patients with an ECF requiring further follow-up: 6.8% (142/2096) • Top 5 most commonly reported ECFs in relation to the total number of patients included in the study: - Fusiform dilatation of the ascending aorta: 3.2% (67/2096) - Left atrial diverticula: 1.2% (25/2096) - Massive mitral valve annulus calcification: 0.9% (19/2096) - Bicuspid aortic valve: 0.57% (12/2096) - Acute pulmonary embolism: 0.29% (6/2096) - Secundum-type atrial septal defect: 0.29% (6/2096)

AFIB = atrial fibrillation, CAD = coronary artery disease, CAD = coronary artery disease, CCTA = coronary computed tomography, CI = confidence interval, ECF= extra cardiac finding, SR = systematic review.

* Karius 2014 includes 9 studies that are not included in the Flor 2013 SR, and Flor 2013 includes 3 studies that are not included in Karius 2014

† Indications for CCTA included: Acute and chronic chest pain (44%), Dyspnea (8%), Hypertension (15%), Diabetes mellitus (12%), Abnormal or equivocal stress test (8%), Abnormal ECG (3%), Palpitations (2%), Congestive heart failure (30%), Pre operative: assessment (4%)

‡ Indications for CCTA were atypical chest pain, angina pectoris, coronary artery anomalies, and determination of the patency of bypass grafts or stents.

6.1.4 Key Question 4: Differential Efficacy or Safety

6.1.4.1 Summary of results

Three large RCTs comparing CCTA with functional testing reported tests for interaction between subgroups on efficacy and/or safety outcomes. Two RCTs were in stable outpatients (N = 10,003[59] and 4146[215] respectively) and one RCT was in patients with suspected ACS (N=1000)[109]. These trials are described in previous sections. Only one of these pre-specified subgroup analyses and consider this in sample size determinations. All performed multiple analyses for multiple outcomes, including multiple composite outcomes. None of the RCTs specified all outcomes evaluated. None specified hypotheses to be tested or expected direction.

- **Clinical outcomes**: Only one RCT reported on the primary clinical outcomes of interest for this HTA. At a median of 3.2 years, the effect of CCTA did not appear to vary based on anginal classification (non-anginal chest pain, possible anginal chest pain) for MI (SOE Low), all-cause mortality (SOE Insufficient) or death due to CAD (SOE Insufficient). As many of these outcomes appear to be rare, it is possible that this trial was not sufficiently powered to effectively evaluate interaction. The factors, outcomes and hypothesized direction do not appear to have been specified a priori.
- **Downstream testing:** One RCT in patients with suspected ACS found no significant variation in use of downstream testing with CCTA based on sex or race at either the index visit, or 28 day follow up. Downstream testing did vary by diabetes status; more downstream testing occurred with CCTA in patients with diabetes at index visit and by 28-day follow-up (interaction p-values 0.001 and 0.002 respectively). The factors, outcomes and hypothesized direction do not appear to have been specified a priori in this fair-quality trial (SOE Low).
- **ICA referral:** Across two RCTs, one in stable outpatients and the other in patients with suspected ACS the effect of CCTA versus functional testing on ICA referral did not vary by diabetes status (SOE Low). Similarly, there was no effect modification in the trial in patients with suspected ACS by sex or race at index visit or by 28-day follow-up (SOE Low).
- **Revascularization**: Across two RCTs, one in stable outpatients and the other in patients with suspected ACS the effect of CCTA versus functional testing on revascularization did not vary by diabetes status (SOE Low). The effect of CCTA versus functional testing on revascularization was not modified by either sex (1 RCT) or angina classification (1 RCT) (SOE Insufficient).
- **Radiation exposure:** In stable outpatients, CTTA cumulative radiation may vary based on baseline heart rate. Patients with ≥75 beats-per-minute may have higher cumulative radiation with CCTA compared with functional testing. Tests for interaction by age, sex and BMI were not significant (SOE Insufficient). In patients with suspected ACS, there was insufficient evidence to confidently make conclusions about how radiation dose may vary by sex, diabetes status or race for CCTA versus functional testing index testing or within 28 days (SOE insufficient).

Detailed results

Three large RCTs comparing CCTA with functional testing reported tests for interaction between subgroups on efficacy and/or safety outcomes.[5,146,148,175,186,187,204,217,218,245,246] All three reported on multiple patient characteristics or factor for multiple outcomes (Table 35). This section will focus on the primary outcomes of interest to this HTA (MI, all-cause death, cardiac death, stroke, ICA and revascularization referral, safety-related); we will briefly describe analyses on other outcomes, including the various definitions of MACE. Summary tables detail results for factors and outcomes evaluated in these studies are found in greater detail in Appendix O, Tables O7 through O22. Only select tables will be included here.

In stable outpatients, the largest, RCT described pre-specified subgroup analyses and took this into account for sample size determination and during the randomization process[58] based on their protocol. Authors created three cohorts based on specific functional tests (e.g., SPECT, stress echo, ETT) for the pre-specified analyses; in each, half was randomized to the pre-specified functional test and half to CCTA to form paired CCTA-functional test subgroups. The goal was to evaluate subgroups where anatomic testing might be particularly advantageous, or where the question of a benefit from CTA is particularly relevant. While the subgroups/factors were prespecified, the use of multiple composite outcomes for the analyses do not appear to have been. For the other RCT in stable outpatients (N=4146), neither the protocol[176] nor the primary publication[215] specify subgroup analysis in terms of factors or outcomes. Subgroup analyses were reported in a later publication.[5] Multiple composite outcomes were evaluated. Similarly, the fair-quality trial **in patients with suspected ACS** (N=1000) does not specify subgroup analysis in the protocol or primary publication.[109] Their primary trial endpoint was length of stay.

Table 35. Overview of RCTs evaluating differential efficacy and safety

Trial, (N) Quality (ROB)	Factors specified *a priori or not*	Hypothesis direction	Outcome(s)
Stable Outpatients			
PROMISE (Douglas 2015) N=10,003 Good quality	**Specified a priori:** Age, sex, race, comorbidity, cardiovascular risk factors, pre-randomization choice of functional test, and characteristics precipitating symptoms	NR	• Composite (cardiovascular death, MI) • Composite (cardiovascular death, myocardial infarction, and unstable angina hospitalization) • Composite (death from any cause, nonfatal myocardial infarction, hospitalization for unstable angina, or major procedural complication • Composite of the above plus ICA without obstructive CAD • ICA referral • Any revascularization PCI referral • Medication use • test positive rate (≥70% stenosis in at least one epicardial artery or ≥50% stenosis in the left main
SCOT-HEART (2018) N=4146	**Not specified a priori;** Age, sex, 10 year risk,	NR	• MI (fatal, non-fatal, separately, and together) • Composite (MI, stroke)

Trial, (N) Quality (ROB)	Factors specified *a priori or not*	Hypothesis direction	Outcome(s)
Good quality	previous CAD, Diabetes, NICE classification (angina, nonanginal chest pain)		• Composite (Death from CAD or nonfatal MI) at 5 years • All-cause mortality • Cardiac death (CAD) • CABG
Suspected ACS			
ROMICAT-II (Hoffman) N=1000 Fair quality	**Not specified a priori:** Sex, diabetes, race	NR	• MACE (not defined) • Downstream testing • Repeat ED visit or hospitalization for chest pain • ICA • Revascularization, PCI • Index radiation dose • Mean cumulative radiation does • Administrative/Utilization (direct ED discharge, LOS (hours), hospital admission)

CABG = coronary artery bypass graft; CAD = coronary artery disease; ED = emergency department; ICA = invasive coronary angiography; LOS = length of stay; MACE = major adverse cardiac events; MI = myocardial infarction; NICE = National Institute for Health and Care Excellence; PCI = percutaneous coronary intervention; RCT = randomized controlled trial.

6.1.4.2 Primary clinical outcomes

Only one, fair-quality RCT[5] in stable outpatients with suspected CAD reported sub analyses with tests for interaction for the primary clinical outcomes of interest for this HTA. At a median of 3.2 years there was no evidence of differential test effectiveness based on NICE classification of chest pain as non-anginal or possibly anginal for MI, non-fatal stroke, all-cause mortality or death due to CAD. As many of these outcomes appear to be rare, it is possible that this trial was not sufficiently powered to effectively evaluate interaction. The factors, outcomes and hypothesized direction do not appear to have been specified a priori (Table 36).

Table 36. Analyses for impact of NICE classification of chest pain on primary outcomes

Trial name	Follow-up	Subgroup (N)	CCTA, % (n/N))	Exercise ECG, % (n/N)	Author reported HR (95% CI)	Author reported interaction p-value
MI (fatal and nonfatal)						
SCOT-HEART, 2018	Median 3.2 years	NICE classification of non-anginal chest pain*	1.0% (7/712)	1.5% (11/735)	0.65 (0.25 to 1.69)	0.836
		NICE classification of possible anginal chest pain*	1.9% (22/1174)	3.2% (37/1149)	0.58 (0.34 to 0.99)	
Non-fatal stroke						
SCOT-HEART, 2018	Median 3.2 years	NICE classification of non-anginal chest pain*	0.1% (2/712)	0.7% (5/735)	0.21 (0.02 to 1.8)	0.200
		NICE classification of possible anginal chest pain*	0.5% (6/1174)	0.5% (6/1149)	1.01 (0.32 to 3.12)	
All-cause mortality						

SCOT-HEART, 2018	Median 3.2 years	NICE classification of non-anginal chest pain*	1.0% (7/712)	0.5% (4/735)	1.81 (0.53 to 6.18)	0.200
		NICE classification of possible anginal chest pain*	1.5% (18/1174)	1.9% (22/1149)	0.82 (0.44 to 1.53)	
Coronary heart disease death						
SCOT-HEART, 2018	Median 3.2 years	NICE classification of non-anginal chest pain*	0% (0/712)	0.3% (2/735)	0 (0 to Infinity)	0.998
		NICE classification of possible anginal chest pain*	0.3% (3/1174)	0.3% (4/1149)	0.78 (0.17 to 3.48)	

CCTA = coronary computed tomography angiography; CI = confidence interval; ECG = electrocardiography; HR = hazard ratio; MI = myocardial infarction; NICE = National Institute for Health and Care Excellence.
* Participants with non-anginal chest pain had the lowest event rates. Patients with possible angina had a higher and time-varying event rate with increased early hazards. Additionally, study reports third group of patients with known CAD that were already on established preventative therapies which were not reported in this data.

Two trials in stable outpatients reported sub analyses with tests for interaction for composite outcome of cardiovascular death or MI.[175,217,218] Both evaluated whether the presence of diabetes modified the effect of testing for this outcome. Results from the largest trial suggest that diabetes may modify testing for the composite outcome of MI or cardiovascular death, however the other, smaller trial reported no interaction (Table 37).

Table 37. Analyses for impact of diabetes on the composite outcome of MI and cardiovascular death

Trial name	Timing	Subgroup (N)	CCTA, % (n/N)	Comparator, % (n/N)	Author reported effect estimate	Author reported interaction p-value
PROMISE trial	Median follow-up: 25 months	With diabetes (N=NR)	1.1% (10/936)	Any functional test: 2.6% (25/972)	Adj. HR 0.38, 95% CI 0.18 to 0.79*	0.020
		Without diabetes (N=NR)	1.4% (50/3564)	Any functional test: 1.29% (45/3494)	Adj. HR 1.03, 95% CI 0.69 to 1.54*	
SCOT-HEART, 2018	Median 4.8 year follow-up	Diabetes (N=NR)	2.2% (41/1850)	Exercise ECG: 3.5% (64/1852)	HR 0.63 (95% CI 0.43 to 0.94)	0.40
		No diabetes (N=NR)	3.1% (7/223)	Exercise ECG: 7.7% (17/221)	HR 0.36 (95% CI 0.15 to 0.87)	

CI = confidence interval; ECG = electrocardiography; HR = hazard ratio; MI = myocardial infarction; NICE = National Institute for Health and Care Excellence; NR = not reported.

There was no evidence of interaction from additional subanalyses on this composite outcome in the SCOT-HEART trial for any of the following factors (see Appendix O for tables): Age (< 65, ≥65 years), sex, 10-year cardiovascular risk (<15%, ≥15%), previous coronary heart disease, NICE anginal classification (non-anginal, anginal).

Results for other composite outcomes are also found in Appendix O. In general, there was no evidence of differential effectiveness (interaction p-values were not significant) by sex.

6.1.4.3 Downstream testing

In one fair-quality trial[246] in patients with suspected ACS, testing effect appears to be modified by the presence or absence of diabetes. While downstream testing was more common in the CCTA arm for both those with and without diabetes compared with functional testing, those with diabetes had differentially higher rates of downstream testing with CCTA. Neither sex nor race modified the effect of testing (Table 38).

Table 38. Subgroup analyses for any downstream testing in patients with suspected ACS

Trial name	Timing	Subgroup (N)	CCTA, % (n/N)	Functional Testing, % (n/N)	Author reported effect estimate	Author reported interaction p-value
ROMICAT-II trial	Index Visit	Females (N=NR)	16% (37/239)	10% (22/229)	NR	0.08
		Males (N=NR)	30% (79/262)	12% (31/270)	NR	
	28 day follow-up	Females(N=NR)	20% (47/239)	24% (11/229)	NR	0.23
		Males (N=NR)	33% (86/262)	13% (86/270)	NR	
	Index Visit	With diabetes (N=NR)	38% (33/86)	5% (4/87)	NR	0.001
		Without diabetes (N=NR)	20% (83/415)	12% (49/412)	NR	
	28 day follow-up	With diabetes (N=NR)	42% (36/86)	7% (6/87)	NR	0.002
		Without diabetes (N=NR)	23% (97/415)	13% (54/412)	NR	
	Index Visit	White (N=NR)	24% (80/330)	13% (42/329)	NR	0.16
		Black (N=NR)	22% (/141)	6% (9/140)	NR	
	28 day follow-up	White (N=NR)	29% (95/330)	15% (48/329)	NR	0.18
		Black (N=NR)	23% (32/141)	6% (9/140)	NR	

CCTA = coronary computed tomography angiography; NR = not reported.

6.1.4.4 Test positivity rate of index test

Sex and BMI (<35, ≥35) appear to modify the effect of testing on the test positive rate (≥70% stenosis in at least one epicardial artery or ≥50% stenosis) in one trial[186,187] in stable outpatients, based on test for interaction across functional tests. Tests for interaction for age and diabetes status were not significant (Table 39).

Table 39. Subgroup analyses for test positive rate (≥70% stenosis in at least one epicardial artery or ≥50% stenosis in the left main)

Trial name	Timing	Subgroup (N)	CCTA % (n/N)	Comparator % (n/N)	Author reported adjusted OR (95% CI)*	Author reported interaction p-value
PROMISE trial	Index test	Male (N=NR)	16.1% (350/2168)	Any functional test: 14.0% (290/2078)	1.23 (1.04 to 1.47)	CCTA vs. any functional test: <0.001[†]
				Nuclear Stress: 16.9% (230/1362)	1.03 (0.85 to 1.25)	
				Stress Echo: 7.7% (36/465)	2.10 (1.45 to 3.04)	
				Ex ECG: 9.6% (24/251)	1.79 (1.15 to 2.80)	
		Female (N=NR)	7.9% (184/2332)	Any functional test: 11.5% (274/2388)	0.67 (0.55 to 0.82)	
				Nuclear Stress: 12.0% (205/1704)	0.66 (0.53 to 0.82)	
				Stress Echo: 7.7% (39/505)	0.90 (0.63 to 1.30)	
				Ex ECG: 16.8% (30/179)	0.39 (0.25 to 0.61)	
PROMISE trial	Index test	BMI <35 (N=NR)	12.2% (439/3589)	Nuclear Stress: 13.1% (310/2361)	NR	0.003
				Stress Echo: 7.8% (62/795)	NR	
				Ex ECG: 12.8% (47/368)	NR	
		BMI ≥35 (N=NR)	10.3% (90/872)	Nuclear Stress: 18.1% (123/679)	NR	
				Stress Echo: 7.9% (13/165)	NR	
				Ex ECG: 11.7% (7/60)	NR	
PROMISE trial	Index test	Age <65 years (N=NR)	10.1% (328/3249)	Any functional test: 11.2% (350/3129)	1.13 (0.96 to 1.33)	0.20
		Age 65-74 (N=NR)	15.2% (1553/1008)	Any functional test: 15.6% (164/1054)	1.04 (0.82 to 1.33)	
		Age ≥75 (N=NR)	21.8% (53/243)	Any functional test: 17.7% (50/283)	0.74 (0.48 to 1.15)	
PROMISE trial	Index test	With diabetes (N=NR)	14.9% (139/936)	Nuclear Stress: 17.7% (126/711)	NR	0.930
				Stress Echo: 9.2% (17/185)	NR	
				Ex ECG: 9.2% (7/76)	NR	
		Without diabetes (N=NR)	11.1% (395/3564)	Nuclear Stress: 13.1% (309/2355)	NR	
				Stress Echo: 7.4% (58/785)	NR	
				Ex ECG: 13.3% (47/354)	NR	

CCTA = coronary computed tomography angiography; CI = confidence interval; Ex ECG = exercise electrocardiography; NR = not reported; OR = odds ratio; Stress Echo = stress echocardiography.
* Adjusted for age, race, body mass index, coronary artery disease (CAD) equivalent, Framingham risk score, ASCVD score, 2011 Diamond and Forrester score, hypertension, dyslipidemia, diabetes, family history of premature CAD, sedentary lifestyle, smoking, typicality of chest pain, and physician's estimation of likelihood of significant CAD.
† All other tests: p=NR.

6.1.4.5 ICA referral

For ICA referral, there was no evidence of modification/interaction of testing by sex, race or diabetes status across two RCTs, one in stable outpatients[217,218] and the other in patients with suspected ACS[204,245,246] (Table 40).

Table 40. Subgroup analyses for ICA

Trial name	Timing	Subgroup (N)	CCTA, % (n/N)	Functional testing, % (n/N)	Author reported effect estimate	Author reported interaction p-value
PROMISE trial (Stable outpatients)	Within 90 days of index test	With diabetes (N=NR)	15.1% (141/936)	10.2% (99/972)	Adj. OR 2.12 (95% CI 1.50 to 3.00)*	0.596
		Without diabetes (N=NR)	10.9% (388/3564)	7.6% (265/3494)	Adj. OR 1.90 (95% CI 1.56 to 2.33)*	
ROMICAT-II trial (Patients with suspected ACS)	Index Visit	With diabetes (N=NR)	19% (16/86)	6% (5/87)	NR	0.06
		Without diabetes (N=NR)	9% (38/415)	8% (31/412)	NR	
	28 day follow-up	With diabetes (N=NR)	20% (17/86)	7% (6/87)	NR	0.08
		Without diabetes (N=NR)	10% (42/415)	8% (34/412)	NR	
	Index Visit	Females (N=NR)	5% (12/239)	5% (12/229)	NR	0.15
		Males (N=NR)	16% (42/262)	9% (24/270)	NR	
	28 day follow-up	Females (N=NR)	5% (13/239)	5% (12/229)	NR	0.24
		Males (N=NR)	18% (46/262)	10% (28/270)	NR	
	Index Visit	White (N=NR)	13% (44/330)	9% (30/329)	NR	0.83
		Black (N=NR)	5% (7/141)	3% (4/140)	NR	
	28 day follow-up	White (N=NR)	15% (48/330)	10% (34/329)	NR	0.68
		Black (N=NR)	6% (8/141)	3% (4/140)	NR	

ACS = acute coronary syndrome; CCTA = coronary computed tomography angiography; CI = confidence interval; ICA = invasive coronary angiography; NR = not reported; OR = odds ratio.
* Adjusted model controls for noninvasive testing results (positive vs. negative), sex, and age.

6.1.4.6 Revascularization

Diabetes did not modify the effect of testing on revascularization across two RCTs, one in in stable outpatients[217,218] and the other in patients with suspected ACS[245,246]. NICE classification did not modify the testing effect on revascularization in stable outpatients[5] (Table 41). Similarly there was no modification by sex or diabetes status[245,246] or NICE angina classification for the use of PCI[5] or for NICE angina classification for CABG[5] (see Appendix O).

Table 41. Subgroup analyses for any revascularization

Trial name	Timing	Subgroup (N)	CCTA, % (n/N)	Comparator (n/N)	Author reported effect estimate	Author reported interaction p-value
PROMISE trial (Stable outpatients	Within 30 days of ICA	With diabetes (N=NR)	55.7% (78/140)	Any functional test: 38.0% (38/100)	Adj. OR 1.51 (95% CI 0.65 to 3.49)*	0.372
		Without diabetes (N=NR)	49.2% (191/388)	Any functional test: 38.7% (103/266)	Adj. OR 0.95 (95% CI 0.55 to 1.65)*	
ROMICAT-II trial (Suspected ACS)	28 day follow-up	With diabetes (N=NR)	8% (7/86)	Any functional test: 2% (2/87)	NR	0.26
		Without diabetes (N=NR)	6% (25/415)	Any functional test: 4% (18/412)	NR	
ROMICAT-II trial (Suspected ACS)	28 day follow-up	Females (N=NR)	3% (7/239)	Any functional test: 1% (2/229)	NR	0.33
		Males (N=NR)	10% (25/262)	Any functional test: 7% (18/270)	NR	
SCOT-HEART, 2018 (Stable outpatients)	Median 3.2 year follow-up	NICE classification of non-anginal chest pain	2.2% (16/712)	Exercise ECG: 1.0% (14/735)	RR 1.2 (95% CI 0.59 to 2.46)	0.938
		NICE classification of possible anginal chest pain	18.7% (220/1174)	Exercise ECG: 16.5% (170/1149)	RR 1.16 (95% CI 0.95 to 1.41)	

CCTA = coronary computed tomography angiography; CI = confidence interval; ECG = electrocardiography; ICA = invasive coronary angiography; NR = not reported; OR = odds ratio; SD = standard deviation.
* Adjusted model controls for noninvasive testing results (positive vs. negative), sex, and age

6.1.4.7 Medication use

The effect of testing on use of aspirin, statins, beta blockers or angiotensin-converting enzyme inhibitor/angiotensin receptor blockers was not modified by the presence of diabetes in one large trial in stable outpatients (Appendix O).

6.1.4.8 Administrative outcomes in patients with suspected ACS

One fair-quality RCT reported subanalyses for sex, diabetes status and race for administrative outcome. The effect of testing on these outcomes was not modified by diabetes status (Appendix O).

While sex did not appear to modify the testing effect on direct discharge from the emergency department at time of index testing or the composite of repeat ED visit or hospitalization within 28 days of index testing, sex may modify the testing effect for length of stay and hospital admission at the index visit. (Table 42). Race did not modify testing effect for any of the outcomes in the table below (see full tables in Appendix O), with the possible exception of repeat ED visit or hospitalization within 28 days of index testing, where the p-value for the interaction test was 0.049.

Table 42. Subgroup analyses for administrative outcomes

Trial name	Timing	Subgroup (N)	CCTA, % (n/N) or Mean (SD)	Any functional test, % (n/N) or Mean (SD)	Author reported effect estimate	Author reported interaction p-value
Direct ED discharge						
ROMICAT-II trial	Index Visit	Females (N=NR)	55% (132/239)	14% (33/229)	NR	0.22
		Males (N=NR)	41% (107/262)	12% (33/270)	NR	
Hospital length of stay (hours)						
ROMICAT-II trial	Index Visit	Females (N=NR)	17.0 (24.5)	30.7 (24.1)	NR	0.006
		Males (N=NR)	28.8 (44.7)	31.0 (30.9)	NR	
Hospital admission						
ROMICAT-II trial	Index Visit	Females (N=NR)	33% (14/239)	25% (57/229)	NR	0.005
		Males (N=NR)	29% (75/262)	26% (69/270)	NR	
		White (N=NR)	23% (75/330)	25% (82/329)	NR	0.31
		Black (N=NR)	18% (25/141)	26% (36/140)	NR	
Repeat ED visit or hospitalization for chest pain						
ROMICAT-II trial	28 day follow-up	Females (N=NR)	3% (6/239)	1% (2/229)	NR	0.11
		Males (N=NR)	3% (9/262)	6% (17/270)	NR	
		White (N=NR)	2% (8/330)	5% (16/329)	NR	0.049
		Black (N=NR)	4% (6/141)	1% (2/140)	NR	

ED = emergency department; NR = not reported; SD = standard deviation.

6.1.4.9 Safety

Two RCTs comparing CCTA with functional testing reported tests for interaction between subgroups for the outcome of radiation exposures (Table 43).

One large RCT in stable outpatients did not find that the effect of CCTA varied by age (<65 years vs. ≥65 years), sex, or BMI (<30 (<30 kg/m^2 vs. ≥30 kg/m^2), in patients for whom nuclear stress testing was intended at randomization. However, CTTA cumulative radiation may vary based on baseline heart rate. Patients with ≥75 bpm may have higher cumulative radiation with CCTA. In one RCT in patients with suspected ACS, radiation dose at index varied by sex as did mean cumulative radiation dose; doses were higher for men at each time period for CCTA. Mean cumulative radiation dose also varied diabetes status with patients with diabetes receiving higher doses with CCTA. The effect of CCTA on radiation dose did not vary by race.

Table 43. Subgroup analyses for radiation exposure

Trial name	Timing	Outcome	Subgroup	CCTA % (n/N) or Mean (SD)	Functional Test % (n/N) or Mean (SD)	Interaction p-value
PROMISE trial	≤90 days	Cumulative radiation effective dose among those patients intended for nuclear stress testing	<65 years	12.2 (8.1) (N=2178)	15.3 (6.9) (N=2159)	0.072
			≥65 years	12.6 (8.9) (N=968)	15.0 (6.7) (N=1044)	
			Male	13.7 (9.0) (N=1452)	160 (7.4) (N=1694)	0.82
			Female	11.2 (7.5) (N=1694)	14.6 (6.3) (N=1786)	
			Not Obese (<30 kg/m2)	11.1 (8.0) (N=1556)	14.9 (6.9) (N=1537)	0.10
			Obese (≥30 kg/m2)	13.6 (8.5) (N=1570)	15.5 (6.7) (N=1638)	
			Heart rate <75 bpm*	11.9 (8.4)	15.3 (6.9)	0.042
			Heart rate ≥75 bpm*	13.0 (8.3)	15.0 (6.6)	
ROMICATT-II	Index test only	Radiation Dose During the Index Visit	Female	10.8 (8.7)	4.7 (8.1)	0.003
			Male	14.2 (11.2)	4.7 (8.7)	
	28 days	Mean (SD) cumulative radiation dose (mSv)	Female	11.0 (8.9)	6.0 (8.2)	0.002
			Male	14.7 (12.0)	5.6 (10.7)	
			With diabetes	18.4 (14.7)	6.6 (10.4)	0.04
			Without diabetes	13.4 (9.8)	5.1 (9.5)	
			White	Median (IQR) 12.0 (7.9	Median (IQR) 0.0 (0.0 to	0.60

Trial name	Timing	Outcome	Subgroup	CCTA % (n/N) or Mean (SD)	Functional Test % (n/N) or Mean (SD)	Interaction p-value
				to 17.2)	12.4)	
			Black	Median (IQR) 11.7 (8.6 to 16)	Median (IQR) 0.0 (0.0 to 0.0)	

CCTA = coronary computed tomography angiography; IQR = interquartile range; NR = not reported; SD = standard deviation.
* Baseline resting heart rate was recorded at the enrollment physical examination.

6.1.5 Key Question 5: Cost-Effectiveness

Economic studies identified for inclusion primarily compared combinations of testing strategies involving CCTA, stress nuclear imaging (primarily SPECT), stress echocardiography, exercise ECG treadmill testing and invasive coronary angiography, with only few directly comparing one specific test to another. [redacted]. A total of three systematic reviews[243,249,263] and 11 primary studies were included. Eight of the studies (in nine publications) were in stable outpatients with suspected CAD,[8,26,27,91,116,123,136,147,162] and three were in patients with suspected ACS.[82,196,197] Of these, two studies in stable outpatients[123,162] and three studies in patients with suspected ACS were conducted in the United States.[82,196,197] Industry funding was noted and/or author ties to related industries were described in three studies.[82,123,162] Studies reporting changes in risk as the benefit to testing, those comparing different pharmacologic stressors or older versus newer technology were excluded. No full economic studies specific to stress PET imaging were identified.

Full economic studies of diagnostic testing are complex, challenging to perform and challenging to interpret. A variety of assumptions and estimates from diverse sources (which may vary in quality) provide input into any economic model and impact the results of that model. There are a number of additional factors that need to be considered in modeling of the cost-effectiveness of diagnostic testing.[68,131,179,203] Such factors include: the disease prevalence in the population, the pre-test likelihood of disease and spectrum of disease in patients included in the testing strategy (and model estimates), the diagnostic accuracy of index tests, the role of indeterminate tests and follow-up of false positives, consideration of the role of a given test (e.g., as a triage test, add-on test), whether tests are sequential (in what sequence and what is the impact of this on accuracy), the clinical decision-making leading to additional testing or treatment based on test results, treatment options and their impact on patient outcomes. Diagnostic testing's impact on patient clinical outcomes (e.g., MI) is **indirect.** Such outcomes are impacted by the clinical decisions made about treatment(s) and the effectiveness of the treatments. The estimates of treatment provision, adherence and success may be challenging to model and impact the results of any model.

For the diagnosis of CAD specific factors related to the above should be considered when putting the results of cost-effectiveness studies for non-invasive imaging for CAD into context. First, there are multiple scenarios and options for non-invasive testing including index tests, follow-up testing and the sequence of testing in both clinical practice and as recommended by ACC/AHA clinical guidelines. Thus, modeling of a given sequence or pathway may or may not be generalizable to different settings and accuracy of testing in sequential testing may be different from stand-alone testing. A proportion of all non-invasive imaging tests, particularly in low-risk patient populations will be false positives and a proportion of tests will be indeterminant; both situations may require additional testing. Similarly, some tests, particularly CCTA may reveal incidental findings that may or may not require follow-up. The impact of the above on both cost and effectiveness was generally not modeled. The historic "gold standard" for evaluating accuracy of cardiac diagnostic testing has been ICA, however, as described elsewhere, its accuracy is not 100% as assumed in the models. In addition, CCTA as an anatomic test may show better accuracy than functional tests as ICA alone does not provide functional information. As noted in the background, an observation of vessel obstruction does not always correspond to either symptoms or diminished function. Some tests are operator-dependent and/or require special expertise for performance and/or interpretation. This is difficult to model. Finally, various assumptions regarding the effectiveness of treatment were employed across models.

Summary of results:

Most economic models described in the systematic reviews and the primary studies compared testing strategies (i.e., different scenarios for index test and subsequent sequential tests) not individual tests, making it difficult to draw definitive conclusions for specific tests. The results below attempt to focus on findings for specific tests. Variation across studies in data sources, estimation of model parameters, clinical pathways for test sequencing and decision making leading to additional testing and/or treatment make comparison across studies challenging. Evidence was mixed for demonstrating a definitive cost-effective diagnostic approach.

- Results across studies (including systematic reviews) were somewhat mixed.
- Cost-effectiveness and ICERs varied based on testing sequencing, pre-test likelihood of CAD, assumed accuracy of tests across populations. These key drivers were also identified in the prior HTAs.
- In stable outpatients with suspected CAD
    - The U.S. studies generally found CCTA to be the dominant initial testing strategy against comparators/other strategies, which included ICA and functional tests. FFRct in addition to CCTA was consider cost-effective in one industry-funded study.
    - Stress echocardiography and SPECT were found to be cost-effective compared to ICA.
    - Two systematic reviews suggest that stress echo or nuclear stress testing may be more cost-effective than comparators in some settings depending on patient prior probability of CAD and prevalence of CAD. Stress echo may be more cost-effective than SPECT in patients with low to intermediate probability.
- In patients presenting with suspected ACS in an emergency setting

  - CCTA was compared with standard of care (variably defined), ETT, expert consensus based on ACC/AHA guidelines and "do nothing" strategies. CCTA was the dominant or cost-effective approach in most all comparisons.
  - In one poor-quality review of seven studies in patients with acute chest pain. Stress nuclear testing was cost-effective versus traditional strategies involving ECG. However, authors note that stress nuclear testing in the acute setting may not often used in 'real life', due to logistical challenges.
- Common limitations across studies include
  - The assumption that ICA has 100% sensitivity and specificity.
  - Extrapolation of data to lifetime time horizon particularly when RCT data is only available for approximately 2 years for many of the studies. Results from short-term time horizons may differ from those seen at longer term.
  - Lack of or insufficient modeling of indeterminate tests, false positive and false negative results, accuracy based on sequencing of tests, potential adverse events and incidental findings.
  - Some modeled strategies (e.g., some "do nothing" strategies) may not be consistent with clinical practice. Modeling of appropriate "no test" strategies was not done.
  - Models assume the availability of all tests and competence in performing and interpreting them across clinical settings.
  - Lack of information on the potential impact of radiation exposure for index and downstream testing.

Detailed results

6.1.5.1 Outpatients with Stable Chest Pain

The cost-effectiveness of using coronary CT angiography (CCTA), stress nuclear imaging and stress echocardiography (ECHO) for the diagnosis of CAD was considered. A total of three systematic reviews[243,249,263] and eight primary economic studies (in nine publications) met the inclusion criteria.[8,26,27,91,116,123,136,147,162]

Evidence was mixed for demonstrating a definitive cost-effective diagnostic approach; however, multiple studies report common findings and indications for cost-effective alternatives while also delineating areas for further research. Table 44 provides an overview of primary findings.

Eight studies of patients with stable chest pain that analyzed the cost-effectiveness of CCTA, ECHO and SPECT against various comparators (including ICA, ETT and "no imaging") met the inclusion criteria.[8,26,27,91,116,123,136,147,162] The Quality of Health Economic Studies (QHES) instrument was used to systematically assess the quality of each study. Scores ranged from 50 to 94 out of 100. Data for clinical parameters based on government funded clinical studies in some reports. The funding support from government agencies was reported for some studies or in two cases was not reported.[91,116] Of the

remaining six, three appear to have had at least partial industry funding and/or author ties to industry.[82,123,162]

Generally, six of the seven studies that investigated CCTA reported it to be a cost-effective, if not the dominant strategy, against various comparators including ETT and ICA.[8,26,27,123,136,147,162] Of the four studies that reported results for stress ECHO versus ETT or ICA,[26,27,116,147,162] three studies indicated that stress ECHO was the cost-effective approach.[26,27,147,162] In each case, for both the CTTA and ECHO comparisons, the contradicting results came from the same study and that study notably had the lowest QHES score. In general, when SPECT was compared with ICA it was found to be cost-effective, however, CCTA tended to be the preferred alternative. Beyond the base-case results, the primary drivers of cost-effectiveness were the pretest likelihood of CAD, test accuracy and how post-test care was defined. Administering more aggressive post-test care also tended to decrease a test's cost-effectiveness. Detailed data abstraction is found in Appendix K.

Many of the primary studies reviewed drew attention to the large number of influential variables and the intricacy of modeling the cost-effectiveness of diagnostic testing. Consequently, the optimal strategy remained difficult to define. There were several notable limitations that further complicated a conclusive strategy. A high level of variability within studies, as well as between studies, led to uncertainty, which often failed to be thoroughly analyzed in a comprehensive sensitivity analysis. The majority of studies used a model based on a "payer" perspective rather than a more complete societal perspective. A common assumption made to facilitate the analysis was to grant ICA 100% sensitivity and that all positive diagnostic tests resulted in ICA. Studies generally did not consider modeling the impact of indeterminate tests or follow-up of false positive results. Furthermore, some studies had short time horizons or were underpowered to detect significant results. Given that the majority of the studies reviewed were performed outside the United States, the implementation of testing, care provided and relative costs were prone to variability.

Systematic reviews

Three systematic reviews investigated the cost-effectiveness of diagnostic testing for CAD.[243,249,263] Two of the reviews were very poor quality and were narrative in nature.[243,263] They will be only briefly described. The findings of which were consistent with the majority of individual, primary studies reviewed.

The most comprehensive systematic review by van Waardhuizen et al. 2016 included 70 economic studies published between January 1995 to December 2015 (20 years).[249] Confidence in this review was considered moderate based AMSTAR-2 appraisal. Some studies in this review were published prior to the previous HTAs and assumed to have been considered in them. Thirteen studies from our search were included in this SR and will not be described individually. They are listed in Appendix K with the data abstraction. Authors critically appraise included articles; 54% were considered to be at high or moderate risk of bias. Heterogeneity prevented the authors from completing a quantitative meta-analysis. Overall, in patients with low to intermediate prior probability, the optimal diagnostic imaging strategy from a cost-effectiveness perspective was not definitive. However, collectively the studies

revealed several patterns that led the reviewers to conclude that CCTA may be the best as an initial "gatekeeper" test for patients with stable chest pain and low-to-intermediate likelihood of CAD. van Waardhuizen et al. further went on to suggest that ECHO or SPECT to be cost-effective strategies if functional testing is needed in patients with an intermediate prior probability of CAD. When compared directly, ECHO was considered cost-effective versus SPECT in patients with low to intermediate probability. An in-depth assessment of the sensitivity analyses carried out in the 70 studies reviewed highlighted the primary factors determining the cost-effectiveness of the tests. The most common influencing factor was the prior probability of CAD. Of the 51 sensitivity analyses, 26 of them indicated the prior probability of CAD as the most important influence. Testing sensitivity was the next most frequent factor followed by the cost of the diagnostic test, particularly the cost of CCTA testing. In addition to identifying the drivers of cost-effectiveness, the reviewers also noted that many of the studies exhibited similar limitations, which also appeared in the individual studies reviewed here. The main limitation was the heterogeneity of the studies, the range of assumptions and variability of input parameters of the models. Next, the diversity of the country of origin of the studies often made direct comparisons unfeasible (only 13 of the 70 were performed in the U.S. or Canada). Furthermore, the perspectives (healthcare payer or healthcare provider) of many of the analyses were too limited in scope to make fully informed decisions. Short-term time horizons and not reporting the willingness-to-pay threshold were other common limitations.

Another poor-quality systematic review by Zeb et al 2014 looked at the cost-effectiveness of only CCTA and included 42 articles with the goal of assessing CCTA as a "gatekeeper" to ICA.[263] Although authors report a systematic approach to searching for economic studies, inclusion/exclusion criteria were vague, and neither a full list of included studies nor a list of excluded studies with rationale was provided. The narrative description of selected studies and summary tables do not account for all 42 articles. No critical appraisal of individual studies was done and limited data on cost-effectiveness parameters (e.g. ICERs) were provided. Confidence in this review was considered critically low based on AMSTAR-2 appraisal. It is not clear that all studies were full economic studies. Of the 42 articles, 20 looked at CE of CCTA and subsequent downstream testing in stable chest pain patients, 18 articles in patients with acute chest pain presenting to ED and 4 at the cost-effectiveness of CACS as an initial test. The authors found the optimal strategy was dependent on CAD prevalence. CCTA was cost-effective when CAD prevalence was assumed to be between 10% to 50%. When CAD prevalence exceeded 70% ICA was cost-effective.

A third poor-quality review focused on evaluation cost-effectiveness of nuclear stress testing in both patients with stable chest pain, described below and patients presenting with acute chest pain which are discussed with the primary studies for this population.[243] Although authors report using a systematic approach to searching for economic studies, many components of the systematic review were not described, and critical appraisal of individual studies was not done. It was more narrative in nature. A total of 57 studies were reportedly included, however formal lists of included and exclude studies were not provided. Confidence in this review was considered critically low based on AMSTAR-2 appraisal. This is the only review to focus on cost-effectiveness of nuclear stress testing (MPI with SPECT or PET). The review reports findings for three comparisons with MPS in patients with stable chest pain; ETT, ICA and other noninvasive tests. When comparing MPS versus ETT the review assessed 25 studies and found MPS to be more cost-effective than ETT in patients with intermediate likelihood of CAD. The review

included one study that compared initial MPS with selective ICA and direct ICA. MPS reduced the number of ICA by 30% to 41%. MPS was cheaper and equally effective when compared with strategies not using MPS. Lastly, the authors compared MPS with other noninvasive tests. 16 complete studies were included along with four ongoing studies. The results of the cost-effectiveness of MPS over other non-invasive tests, such as CTCA, stress echocardiography, PET, and CMR were conflicting and inconclusive. In patients with suspected stable CAD, ETT was found to be cost-effective as a first line test in patients with low likelihood. However, at higher pretest likelihoods, non-invasive imaging including MPS is more cost-effective than ETT due it its increased accuracy. Overall, MPS was a cost-effective gatekeeper to ICA.

Individual primary studies published subsequent to prior reports and systematic reviews

The individual, primary cost-effectiveness studies, not already included in the systematic reviews, had comparable findings. Two high-quality studies based in the United States were identified. Because of their more direct relevance to this HTA, they will form the focus of the results below. Additional data from these studies and studies outside of the U.S. are found in Appendix K. A summary of the primary findings for all studies in Table 44.

US-Based Studies

Two high-quality studies based in the United States published subsequent to the van Waardhuizen 2016 review are described below.[123,162]

Karady et al. 2020[123]

Overview and Design:

A high-quality study of low-risk, stable chest pain patients that compared CCTA and CCTA combined with CT-derived FFR (FFRct) with functional tests, primarily SPECT as initial tests for diagnosis of CAD A Markov decision-analytic model was populated based on observed outcomes from the PROMISE trial was used as a primary source to simulate changes in health states over time. PROMISE data were combined with assumptions from clinical guidelines, registry data and other sources regarding referral for ICA and treatment options (e.g., medication, PCI) as well as the progression of obstructive and nonobstructive CAD. Data were collected at 6 months and 2 years and costs for testing and subsequent procedures, including ICA with or without revascularization, were recorded. ICERs were calculated for a lifetime time horizon with costs discounted at a rate of 3% to 2014 USD. A societal perspective was stated, however data on indirect costs and other factors usually considered in such analyses were not described; only cost of care appears to have been delineated. Pre-planned subgroup analyses were done based on age and sex. Sensitivity analyses included a probabilistic sensitivity analysis as well as a number of one-way sensitivity analyses ranging from gender to adherence to statin therapy. Authors considered adherence to medical therapy in their modeling. Authors validated their model by comparing it to outcomes as reported in the PROMISE trial through its 2-year follow-up. This economic study was industry-funded (HeartFlow) and multiple authors report relationships with industries related to this study. The PROMISE trial was government-funded. The study scored 90/100 using the QHES.

Key Assumptions:

A mean 53.3% pretest likelihood of CAD was incorporated into the model with an average patient age of 60-years-old; 52.7% of the patients were female and 77.7% white. Diagnostic sensitivity of ETT, CCTA and SPECT were 45-50%, 95-99% and 63-87% respectively while specificity was 85-90%, 64-83% and 63-87% respectively. 25.3% of the sample population had a CAD risk equivalent and 67.6% of patients had a 10-year risk of events of at least 7.5%. FFRct was reportedly done in 31.4% of patients who had 30% to 69% stenosis on CCTA. Models assumed that CCTA and CCTA with FFRct led to more effective selection of patients for ICA and that higher costs for CCTA with FFRct were offset by lower rates of ICA and revascularization compared with CCTA alone.

Results:

[redacted]

[redacted]. Modeling over a patient's lifetime a total of 6 months of good health were gained. The models in this cost-utility analysis for CCTA and functional strategies differ in the proportion of patients requiring additional downstream testing. Meta-analyses across RCTs in this HTA suggest that referral for ICA was associated with CCTA and an initial test but that there were no differences in the use of additional non-invasive testing between CCTA and functional testing strategies.

Driving these improved outcomes was the assumed overall better diagnostic accuracy for obstructive and nonobstructive CAD, which led to greater statin use for those in the anatomic group versus the function group 85.4% and 67.0% respectively. CCTA continued to be cost-effective in both women and men as well as in both older and younger patients [redacted]. CCTA FFRct combined with CCTA was cost-effective in men [redacted] and dominant for all other subgroups explored.

Authors also report sensitivity analysis involving a "do nothing" strategy in which only medical therapy is provided based on their risk-factor profile. As one would expect, the "do nothing" strategy had the lowest costs associated with it and also yielded the fewest quality adjusted life years when compared

with the other strategies. [redacted].

Limitations:

Assumptions regarding diagnostic accuracy were an essential element to the model results, however, uncertainty surrounding these assumptions was a limitation for this study. Furthermore, the authors note gaps in how major adverse cardiovascular events were accounted for and the extent of the effects of medical therapy. Author's objective was to model the cost-effectiveness of patients at low risk of CAD. The population modeled had a substantial cardiovascular risk factor burden and estimated pre-test likelihood of obstructive CAD of 53.3%; it is unclear if results may apply to patients with lower pre-test risk. Modeling of the CCTA strategy appears to assume that only SPECT is used for additional testing in patients with a moderate abnormality on CTTA. Given that costs for stress echocardiography may be less than for SPECT, the impact of modeling of stress echocardiography (and or ETT) may be important to consider. Currently, FFRct is not routinely performed and requires special analysis methods based on CT data. Its role, accuracy and value do not appear to be widely established yet and high-quality evidence of impact on clinical outcomes is sparse.[100] Another potential bias exists when comparing CCTA plus FFRct as some patients were unable to receive FFRct causing a potential imbalance in baseline characteristics across the two groups. Two years of results from the PROMISE trial were available; the model extrapolates to a lifetime. Lastly, the grouping of various functional tests and presentation of results made it difficult to make direct comparisons between specific tests.

Min et al. 2017[162]

Overview and Design:

A well-conducted, but complex study of stable CP patients that explored twelve testing pathways and reported results assuming multiple levels of CAD prevalence. CCTA, ECHO and stress nuclear testing (MPS) were measured against ETT and ICA (among other comparisons). Primary sources for clinical components were from published literature. For modeling treatment, data based on the COURAGE and SYNTAX RCTs were used. The study partially funded by industry, a cardiac imaging institute and reports on data from government-funded research. The lead author reports receiving support from industry. Sensitivity analyses include varying pretest likelihoods from 20% to 50% and to 80% as well as varying post-test treatment plans. A Markov model was used to estimate the costs and assess each test's impact on patients' quality of life from a payer's perspective. The time horizon of the model was over a patient's lifetime. All costs were discounted at a rate of 3%, however, the costing year was not reported. Incremental cost-effectiveness ratios were the primary cost-effectiveness outcome measure. The study scored a 94/100 using the QHES. Funding for this economic study is somewhat unclear; clinical data appear to come from government funding sources. Other funding listed includes the Dalio Institute of Cardiovascular Imaging and an unrestricted educational grant from GE.

Key Assumptions:

The study population consisted of patients of intermediate risk but no prior CAD. A hypothetical cohort of 55-year-old males was considered in the model. The diagnostic sensitivity of ETT, CCTA and ECHO were modeled as 68.0%, 93.7% and 86.7% respectively and specificity ranged from 77% to 84%. Authors provide thresholds for test positivity and categorization of disease. ETT was assumed to be indeterminate 62% of the time while CCTA and ECHO were assumed to be indeterminate in 7% of the tests and depending on the strategy, were referred for either additional downstream non-invasive testing or ICA. All positive test results from noninvasive tests were referred for ICA.

Results:

While the authors found that overall, in patients without known CAD presenting with stable chest pain, a sequence of imaging tests to be the most cost-effective (ETT, followed by ECHO, followed by ICA), [redacted]

This study also investigated the role of varying post-test care as part of the cost-effectiveness modeling. Given the long-term time horizon, slight variability in assumptions regarding the type of care showed a significant impact on both costs and effectiveness. Min et al. report that the cost-effectiveness of each test depends largely on patient characteristics and how treatment approaches are tailored to patient care based upon test findings. Therefore, in addition to the base-case analysis, they also report results for "conservative" post-test care (defined as medical therapy alone for patients with 1–2 vessel CAD and PCI for all patients with 3-vessel or left main CAD) and "aggressive" post-test care (using PCI for all patients with 1–2 vessel CAD and coronary artery bypass surgery for all patients with 3-vessel CAD). When comparing CCTA versus ICA, CCTA changes from being the dominant strategy in conservative cases to ICA being cost-effective [redacted] when more aggressive treatments are employed. Varying post-test treatment approach showed cost-effectiveness contingent on follow-up care post-test. The authors discuss how this serves to underscore the complexity of evaluating the cost-effectiveness of diagnostic testing.

Limitations:

A potential limitation of this study was that all positive diagnostic tests resulted in ICA, which was assumed to have perfect sensitivity and specificity. The impact of false-positive tests was not modeled. It

appears that positive tests at any stage were referred to ICA, including false positives. Authors left some ambiguity surrounds how patients transition between health states within the model. Limited data for some sensitivity analyses were described. PET was not considered in any testing strategy. It remains unclear how reliably or appropriately the sources used for the model inputs can be extended over the course of the model's lifetime time horizon. Additionally, the sensitivity analysis was limited in scope and did not fully explore potential biases or discuss in detail its own potential limitations.

Studies based outside of the U.S.

In addition to the two studies conducted in the United States six international studies not included in the van Waardhuizen systematic review were identified. Three of these were based in Europe and the remainder was comprised of a diverse geographic, socio-economic range from South Korea, Brazil and Iran. Given the differences in healthcare systems between the US and other countries, these studies will only be briefly summarized. Additional detail is found in Appendix K.

Agus et al. 2016[8]

A study conducted alongside an RCT in Northern Ireland and it investigated the cost-effectiveness of CCTA vs ETT. (QHES 64) CCTA was found to be the dominant strategy for patients when a pretest likelihood of less than 30% was assumed. [redacted].

The interpretation of the final results was made difficult because the baseline characteristics across groups were different. Notably, there was imbalanced CAD prevalence across groups, which has been seen as a driving factor for cost-effectiveness in the other studies. Missing data was also an issue when building the model and determining the input parameters. Beyond that, the outcome assessment was not fully blinded from investigators. Also, the sample population excluded BMI greater than 35% and included a low number of diabetic patients. Therefore, it may not be a representative sample. Lastly, the study had a relatively short follow-up time and may not have allowed for all costs and outcomes to occur.

Gurunathan et al 2018[91]

This study was also conducted along with a RCT. It was a relatively poor-quality study (QHES 50/100) carried out in the UK, evaluated the predictive value and costs of stress ECHO and ETT. Its measure of cost-effectiveness was a simple sum of costs and a comparison of the positive predictive value of each test. Authors found ECHO to have a 20% reduction in cost and less downstream testing, hospital visits. ETT yielded a 64% positive predictive value in determining a flow-limiting disease on angiography. Meanwhile, ECHO achieved 100% positive predictions. The cost of ECHO and ETT were £631 and £796 respectively.

A significant limitation from the outset for this study was that it was underpowered to detect most clinical outcomes. It also used an overly simplistic analytic model in which it did not validate or pursue any subgroup or sensitivity analyses.

Lorenzoni et al. 2019[147]

A moderately well-conducted (QHES 84/100) Italian study evaluated several testing strategies. [redacted]. ECHO and SPECT approaches were both found to be a less expensive alternative but yielded fewer correct diagnoses.

Heterogeneity in data relating to sourcing from multiple countries with variation in practices and costs was an issue in this study. It also unrealistically assumed that anyone not receiving ICA was a true negative test result. Adding to that, authors also assumed perfect accuracy of ICA.

Bertoldi et al. 2016/2017[26,27]

A Brazilian study where CCTA appeared to be a cost-effective approach for CAD in this well-conducted study (QHES 94/100). [redacted] SPECT testing strategies were dominated by the other test options. Additionally, sensitivity analysis showed that procedural costs and test sensitivity were significant factors in determining cost-effectiveness.

Many of the potential comparisons were not reported. Furthermore, the authors assumed ICA to have 100% sensitivity and specificity.

Lee et al. 2015[136]

A moderately well-designed study (QHES 77/100) conducted in South Korea that explored the diagnostic accuracy of CCTA and SPECT followed by a brief cost-utility analysis. Its measure of cost-effectiveness was a cost per correct diagnosis. CCTA was shown to be the more accurate, effective and less expensive alternative in the majority of cases. Therefore, CCTA dominated SPECT. For every 1000 patients, CCTA accurately diagnosed 835 while SPECT accurately diagnosed 779 patients. Subgroup analysis by pretest likelihood showed SPECT to perform slightly better with lower pretest probability but CCTA remained cost-effective with the most accepted willingness to pay thresholds.

The baseline characteristics of groups were different, which causes results difficult to interpret. For instance, the SPECT group had significantly older and had a higher pretest likelihood probability. There were also issues with procedural implementation. The CCTA data derived from 2006 when techniques may not have been as developed in Korea.

Jafari et al. 2020[116]

A relatively poorly conducted study (QHES 62/100) conducted in Iran compared several testing options including CCTA, ECHO and SPECT against ETT and ICA among others. It reported its results against a strategy using a combination of tests (that it had found to be optimal). Results reported here are individual testing strategies with stand-alone ETT and ICA testing. The cost-effectiveness measure reported was the cost per diagnosis. In general, it found ETT and ICA to perform better than CCTA and ECHO. [redacted]

[redacted].

The cost data used in this study seems difficult to reconcile to a US setting. Furthermore, there was poor description of patient characteristics with no reporting of demographic information or CAD pretest likelihood. It was also assumed ICA 100% sensitive. Lastly, given the uncertainty involved in the results the sensitivity analysis was very limited.

Table 44. Overview of reported cost-effectiveness (CE) stratified by pretest likelihood, stable CP, assuming a willingness-to-pay WTP of $100,000

Pretest Risk %	Origin	CCTA	ECHO	SPECT
<30%	USA	Min 2017 CCTA dominates ICA	Min 2017 ECHO is CE vs ICA	Min 2017 MPS is CE vs ICA
	Foreign	Lorenzoni 2019 CCTA dominates "no imaging" Bertoldi 2017 CCTA $1420/diagnosis vs ETT Jafari 2020 ETT dominates CCTA Lee 2015 CCTA dominates SPECT	Lorenzoni 2019 ECHO costs €3316/diagnosis vs. "no imaging" Bertoldi 2017 ETT dominates ECHO Jafari 2020 ETT dominates ECHO	Lorenzoni 2019 SPECT costs €2111/diagnosis vs. "no imaging" Bertoldi 2017 CCTA, ECHO dominated SPECT Jafari 2020 SPECT costs $46.74/ diagnosis relative to ETT SPECT costs $11.51/diagnosis relative to ICA
30-60%	USA	Min 2017 CCTA is CE vs ICA Karady 2020 CCTA costs additional [redacted] vs. functional tests	Min 2017 ECHO is CE vs. ICA	Min 2017 MPS is CE vs. ICA

Pretest Risk %	Origin	CCTA	ECHO	SPECT
	Foreign	Agus 2016 CCTA dominates ETT Bertoldi 2017 CCTA costs [redacted] vs. ETT	Gurunathan 2018 ECHO dominates ETT Bertoldi 2017 ECHO [redacted] vs. ETT	Bertoldi 2017 CCTA, ECHO dominated SPECT Lee 2015 SPECT costs additional [redacted] vs. CCTA
>60%	**USA**	Min 2017 CCTA is CE vs. ICA	Min 2017 ECHO is CE vs. ICA	Min 2017 MPS is CE vs. ICA
	Foreign	Bertoldi 2017 CCTA $790/diagnosis vs ETT Lee 2015 CCTA dominates SPECT	Bertoldi 2017 ECHO costs $890/diagnosis vs. ETT	Bertoldi 2017 CCTA, ECHO dominated SPECT

CCTA = coronary computed tomography angiography; CE = cost-effective; ECHO = stress echocardiography; ETT = exercise treadmill test; ICA = invasive coronary angiography; MPS = myocardial perfusions scan; [redacted]; SPECT = single photon emission computed tomography.

6.1.5.2 Patients with suspected ACS (Acute Chest Pain)

One poor-quality review[243] and three US-based economic studies[82,196,197] evaluated the cost-effectiveness of various imaging strategies in patients with suspected ACS or acute chest pain presenting to an emergency department or observational unit.

One systematic review focused on evaluating the cost-effectiveness of nuclear stress testing in both stable chest pain, (described above) and patients presenting with acute chest pain which are discussed here.[243] Authors report that MPI was evaluated in 7 studies of patients with acute chest pain. The review found that MPS was cost-effective when compared with traditional strategies involving ECG. However, authors note that MPS in the acute setting is not very often used in 'real life', due to logistical challenges.

Primary studies published subsequent to prior reports and systematic reviews

Three primary economic studies evaluated testing strategies for patients in emergency departments or observatory units were include and are described below.[82,196,197] Their QHES scores ranged from 69 to 90 out of 100. Table 45 provides an overview of primary findings.

Goehler 2020[82]

Overview and Design:

A study using a well-constructed model of short, intermediate and long-term cost-effectiveness carried out in the United States. CCTA performance was analyzed against three strategies: standard of care, expert consensus following AHA/ACD guidelines and expedited ED discharge with further testing done in an outpatient setting. A Markov model was used to model the cost-effectiveness of the interventions over time. The hypothetical cohort was designed drawing primarily from finding of the ROMICAT II trial, which was subsequently validated using the same trial. Utility values for various chest discomfort classifications were derived from published literature. Initial cost data came from a micro-costing assessment at each ROMICAT-II clinical site while outpatient costs were based on Medicare reimbursements. Long-term cost approximations came from RedBook. Authors assessed outcomes at 28 days, 1 year, 3 years, 10 years and overall lifetime of patients. [redacted] Though not explicitly stated, the perspective assumed was most consistent with a payer's perspective. Costs were discounted at a rate of 3%, however, the costing year was not clearly stated. The trial data used to for the model's parameters ended in 2012 USD. Funding came from grants provided by National Heart, Lung, and Blood Institute, National Institute of Health and the American Heart Association, however, authors also report ties with related industry (imaging companies). Sensitivity analyses looked at varying medical compliance over time and tested the confidence interval bounds of relative risks across interventions. Testing diagnostic sensitivity and specificity were also varied and ICERs recalculated. The study scored 90/100 using the QHES.

Key Assumptions:

A population of emergency department patients with suspected ACS was considered with a mean age of 54.2 years and 53% male. Patients comprised of low-intermediate risk of ACS having an average of 7.5% prevalence of ACS. Diagnostic sensitivity ranged from 85% to 100% while the specificity varied from 50% to 100%. Baseline characteristics of the hypothetical cohort assumed 50.7% of patients had no CAD, 43.0% of patients had non-obstructive CAD and 6.3 presented obstructed CAD.

Results:

Short-term results found CCTA to be both more costly and required more revascularization procedures than all other comparators. Notably, revascularization rates for CCTA were 5.2% versus 2.6 to 3.7% for other strategies. However, in the long-term model, CCTA became cost-effective. Lower mortality (5.06% for CCTA versus 5.21% to 5.36% for other strategies after 10 years) led CCTA to dominate standard of care and ACC/AHA guidelines [redacted] when compared with expedited ED discharge. CCTA was the most effective at identifying obstructive CAD (98% accurate), followed by

expert consensus (75%) and standard of care (69%). Expedited discharged was only 46% accurate at identifying obstructive CAD. Initial costs found CCTA was the most expensive at $2,692. Standard of care costed $2,535, expert consensus following AHA/ACD Guidelines costed $2,501 while expedited ED discharge was the least costly at $1,891. [redacted].

[redacted].

Limitations:

While overall well conducted, there were some limitations. Pretest likelihood of CAD is often a major determining factor to a test's cost-effectiveness. The authors did not incorporate that key aspect. Also not included in the model were repeated visits to the emergency department or the cost of litigation for missed detection of CAD. Additionally, some model input parameters were sourced from older studies which may not reflect current healthcare settings. With regards to presenting the results some useful information was not included such as what scope of the perspective assumed and the costing year that estimates were discounted to.

Powell et al. 2012[196]

Overview and Design:

A moderately well-conducted study comparing CCTA, standard of care and "do nothing" strategies in an observation unit setting. A decision-analytic model was used. The patient population and the strategies' characteristics were derived from data obtained from published literature and from a retrospective cohort review. The time horizon of the model was not made clear. The costing data was reported in 2009 USD and discounted using the Consumer Price Index. [redacted] The source study's funding was not reported. The study scored 69/100.

Key Assumptions:

The study considered patients in an observation unit for the evaluation of low-risk chest pain. Patients were found to have either indeterminate or positive-stress test results. The mean age was 50-year-old and 54% were male. The assumed sensitivity of CCTA 98.9% while the specificity for CCTA was 84%. Given an abnormal stress test result, the probability of that the patient has no CAD was assumed to be 69.5%. The probability of an indeterminate CCTA test was 3.8%.

Results:

Authors found CCTA to have similar effectiveness as the standard of care while being approximately 20% less expensive. The "do nothing" approach was the cheapest, however, also the least effective. [redacted] The marginal cost-effectiveness of standard-of-care as compared with CTCA was $352,651. (CCTA cheaper but marginally less effective).

[redacted]

The standard of care strategy becomes preferable only at extremely high willingness to pay thresholds because it has a slight effectiveness advantage. The do-nothing strategy was preferable at only a very low WTP ($8,306).

Limitations:

The "do-nothing strategy" in which all patients were discharged home after positive- or indeterminate-stress tests without further testing analyzed in this study is likely an unrealistic scenario and does not provide a very valuable comparison. Furthermore, like many other studies, the authors here assumed that ICA 100% sensitive, which also may not be a realistic assumption. It is not entirely clear which costs the authors included in the analysis. They do note that the study does not consider startup costs of a CCTA or additional ED revisits. Additionally, the time horizon of the study is not reported, which potentially has significant implications for interpreting the results. Lastly, given the complexity of the model and degree of uncertainty the scope of the sensitivity analysis was limited.

Priest et al. 2011[197]

Overview and Design:

A fairly well-designed cost-effectiveness study that investigated several testing options in and emergency department including a strategy of doing an initial CCTA followed by confirmatory SPECT for indeterminate CCTA results, CCTA alone, stress ECHO, stress SPECT and ETT. A decision model was implemented with a 12-month time horizon. Estimates were discounted using the Consumer Price Index to 2010 USD. Sensitivity analyses were conducted to compare the differences in the type of stress-based test used (specifically in terms of diagnostic accuracy) and also explore the effect that the rate of incidence of adverse events as well as the costs associated with each test. A payer's perspective was assumed for costs. The study was funded by the National Health and Medical Research Council The study scored 75/100 using the QHES.

Key Assumptions:

Several testing strategies were compared in an emergency department setting with patients having a CAD prevalence of 2–30%. Published literature and a meta-analysis were used to build the model. The sensitivity and specificity of CCTA 2were assumed to be 100% and 80% respectively. The sensitivity and specificity of ETT were assumed to be 67% and 72% respectively. For both ECHO and SPECT, the

estimates varied by to the stress was induced. For stress ECHO, the sensitivity ranged from 72% to 83% while its specificity ranged from 84% to 95%. For stress SPECT, the sensitivity ranged from 84% to 91% while its specificity ranged from 69% to 81%. The procedural costs for ETT, SPEC, ECHO and CCTA were $144, $461, $290, and $374 respectively.

Results:

CCTA with "confirmatory SPECT" was considered the most cost-effective strategy at all prevalence thresholds investigated compared with all other strategies explored. The CCTA with SPECT strategy also had the lowest average cost per patient diagnosed based on the evaluation of diagnostic accuracy. Using the results reported it was possible to compare CCTA, ECHO and SPECT against ETT. ETT was consistently dominated by all three alternative tests at varying levels of CAD prevalence. As the prevalence increase, however, the dominance be narrower. The total 12-month costs with a 5% prevalence of CAD for ETT, SPECT, ECHO, CCTA and CCTA the SPECT were $10,430, $10,799, $7,539, $4,862 and $3,464 respectively. [redacted].

Limitations:

A major limitation found in this study is the short follow-up time. Goehler et al found the comparison of tests' cost-effectiveness to be reversed from the short-term follow-up to the longer-term follow-up. Beyond the insufficient time horizon, when compared to other studies on the topic the model presented is relatively simple and authors indicate a lack of available data to specify the parameters necessary for a more complex model. Specifically, revisits to the emergency department and other complications were not considered. The model also does not include the likely benefits of revascularization or distinguish between varying levels of stenosis. Lastly, as with many other studies, the potential risks and costs associated with radiation exposure from CCTA and SPECT were not factored into the analysis.

Table 45. Overview of reported cost-effectiveness (CE) stratified by pretest likelihood, Acute/ED patients, assuming a willingness-to-pay WTP of $100,000

Pretest Risk %	CCTA	ECHO	SPECT
Standard of Care	Powell 2012 CCTA vs. Standard of care: [redacted] (CCTA cheaper but marginally less effective) Goehler 2020 CCTA dominated Standard of Care	No studies meeting inclusion criteria found	No studies meeting inclusion criteria found
ETT	Priest 2011 CCTA dominates ETT [redacted]	Priest 2011 ECHO dominates ETT [redacted]	Priest 2011 SPECT dominates ETT [redacted]

Pretest Risk %	CCTA	ECHO	SPECT
Do Nothing	Powell 2012 CCTA vs. "Do nothing": [redacted] (CCTA is more expensive and effective)	No studies meeting inclusion criteria found	No studies meeting inclusion criteria found
Expert Consensus (Based on ACC/AHA guidelines)	Goehler 2020 CCTA dominated Expert Consensus	No studies meeting inclusion criteria found	No studies meeting inclusion criteria found
Expedited ED protocol (w/ OP testing)	Goehler 2020 CCTA was CE against [redacted]	No studies meeting inclusion criteria found	No studies meeting inclusion criteria found

ACC/AHA = American College of Cardiology/American Heart Association; CCTA = coronary computed tomography angiography; CE = cost-effective; ECHO = stress echocardiography; ED = emergency department; ETT = exercise treadmill test; ICA = invasive coronary angiography; [redacted] MPS = myocardial perfusions scan; OP = outpatient; [redacted]; SPECT = single photon emission computed tomography.

6.2 CCTA versus ICA

Two randomized control trials compared CCTA with ICA in patients with suspected CAD (N=1,951). (See Appendix F for details.) One trial was conducted exclusively in the outpatient setting[36] and in the other trial,[52] 43% of patients were treated in the outpatient setting and 57% in the inpatient setting. One trial[36] used a 64-slice CT scanner for CCTA imaging and the other trial[52] did not report on this information. Both trials used iodinated contrast agents. One trial included CACS imaging as part of their CCTA protocol.[52]

In both trials, the mean patient age was 60 years and the proportion of females ranged from 44% to 49%. In the one trial reporting race, 87% of patients identified as non-white. Both trials excluded patients with prior MIs and/or revascularizations. One trial excluded patients with known CAD,[36] and in the other trial,[52] 6% of patients had known CAD. In one trial,[52] 100% of patients had chest pain (specific chest pain sub-types included atypical angina in 44% of patients, non-anginal chest pain in 54% of patients, and other chest discomfort in 2% of patients. In the other trial, 72% of patients presented with chest pain (specific sub-types included atypical angina in 40% of patients, typical angina pain in 31% of patients, and non-anginal chest pain in 2% of patients).[36] Eleven percent of patients in the latter trial

were asymptomatic. Neither of the trials reported on the proportion of patients with unstable angina. Across both trials, the proportion of patients reporting diabetes ranged from 28% to 71%; hypertension ranged from 34% to 53%; and current smoking ranged from 14% to 23%. In one trial, 58% of patients had hypertension and 17% presented with dyspnea.[215] Duration of follow-up ranged from 1 to 3.3 years.

One trial was conducted in Germany[52] and the other trial was conducted across multiple countries in North America, East Asia, Europe, and India.[36] One trial received funding from the government[36] and the other trial received funding from a non-profit agency. [52]

One trial was rated good quality[52] and the other was rated fair quality[36] In the good quality trials, blinding of outcome assessors was unclear. Other methodological shortcomings in the fair-quality trial included unclear allocation concealment methods and higher than acceptable attrition at 12 months.

6.2.1 Summary of results (Key questions 1, 2 and 3)

- There was no difference in the risk of all-cause mortality or MI in CCTA versus ICA group at 12 and a median 40 months across one good- and one fair-quality RCT (SOE Low for both). Cardiac mortality was rare (SOE Insufficient).
- Compared with direct referral to ICA, CCTA was associated with a reduced risk of ICA without obstructive CAD (2 RCTs, N=1,019; 22 versus 65 per 100 patients; pooled RR 0.32, 95% CI 0.18 to 0.51, I^2=0%; pooled RD –48.0%, 95% CI –67.0% to –29.2%, I^2=73%) (SOE Moderate) and any revascularization (2 RCTs, N=1,832; 13 vs. 18 per 100 patients; pooled RR 0.71, 95% CI 0.55 to 0.96, I^2=0%; pooled RD –5.0%, 95% CI –8.0% to –2.0%, I^2=0%) (SOE Moderate) to include PCI but not CABG procedures, but an increased risk of additional downstream noninvasive testing (1 fair-quality RCT, N=1,503; 53 vs. 27 per 100 patients; RR 1.96, 95% CI 1.71 to 2.25; RD 26.0%, 95% CI 21.1% to 30.7%) (SOE Moderate). This latter trial found no difference between tests in the risk of cardiac hospitalization (4 vs. 4 per 100 patients) over 12 months (SOE Moderate).
- No major complications were reported in one good-quality trial and only one major complication was reported in the second fair-quality trial, major bleeding, which occurred in two patients (0.4%) in the ICA group; one patient (0.1%) required transfusion (SOE Low).

Detailed results

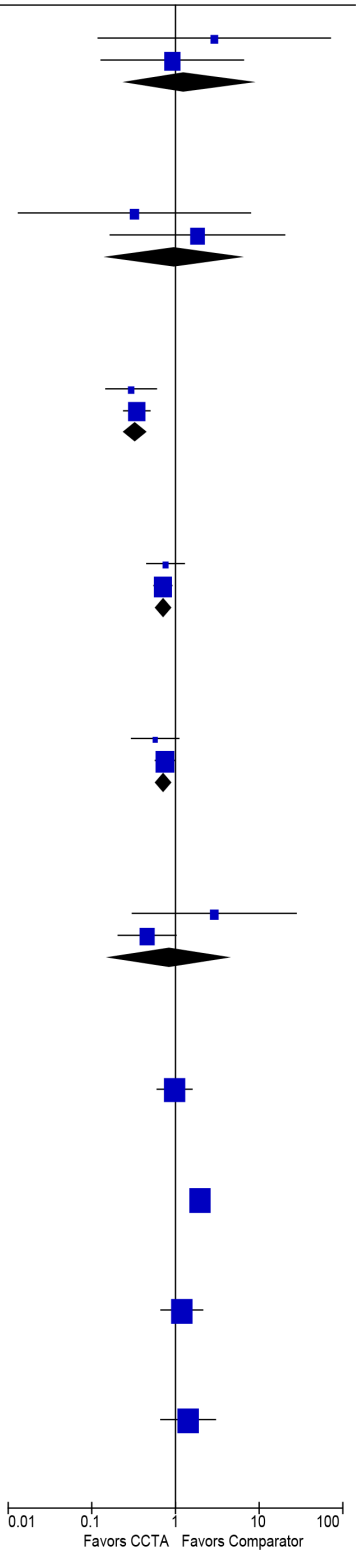
6.2.2 Key Question 1: Primary Outcomes (MI, all-cause mortality, cardiac death)

Myocardial infarction, all-cause mortality and cardiac death

There were no differences between CCTA and ICA in the incidence of MI (0.3 vs. 0.2 per 100 patients; pooled RR 1.26, 95% CI 0.24 to 6.67, I^2=0%) and all-cause mortality (0.2 vs. 0.2 per 100 patients; pooled RR 1.03, 95% CI 0.06 to 11.08, I^2=0%) across 2 RCTs (N=1,832) with follow-up periods of 12 months and a median 40 months (Figure 20).[36,52] One cardiac-related death was reported over a median of 40 months in one trial and it occurred in the ICA group; this death was also counted under all-cause mortality[52].

Figure 20. Clinical outcomes and clinical decision-making outcomes for RCTs comparing CCTA with ICA

Study* or Subgroup	Follow-up	CCTA Events	CCTA Total	Comparator Events	Comparator Total	Weight	Risk Ratio [95% CI]
MI							
Dewey 2016	3.3 years	1	167	0	162	27.3%	2.91 [0.12, 70.93]
Chang 2019	12 months	2	784	2	719	72.7%	0.92 [0.13, 6.49]
Subtotal (95% CI)			951		881	100.0%	1.22 [0.17, 12.90]
Total events		3		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.37, df = 1 (P = 0.54); I² = 0%							
Test for overall effect: Z = 0.27 (P = 0.79)							
Mortality							
Dewey 2016	3.3 years	0	167	1	162	36.1%	0.32 [0.01, 7.88]
Chang 2019	12 months	2	784	1	719	63.9%	1.83 [0.17, 20.18]
Subtotal (95% CI)			951		881	100.0%	1.03 [0.06, 11.09]
Total events		2		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.73, df = 1 (P = 0.39); I² = 0%							
Test for overall effect: Z = 0.02 (P = 0.98)							
ICA Showing No Obstructive CAD							
Dewey 2016	3.3 years	6	24	137	162	21.1%	0.30 [0.15, 0.59]
Chang 2019	12 months	24	114	439	719	78.9%	0.34 [0.24, 0.49]
Subtotal (95% CI)			138		881	100.0%	0.32 [0.18, 0.51]
Total events		30		576			
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.70); I² = 0%							
Test for overall effect: Z = 6.72 (P < 0.00001)							
Revascularization							
Dewey 2016	Index	22	167	28	162	18.3%	0.76 [0.46, 1.28]
Chang 2019	12 months	98	784	127	719	81.7%	0.71 [0.55, 0.90]
Subtotal (95% CI)			951		881	100.0%	0.72 [0.55, 0.96]
Total events		120		155			
Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.80); I² = 0%							
Test for overall effect: Z = 2.96 (P = 0.003)							
PCI							
Dewey 2016	Index	13	167	22	162	13.9%	0.57 [0.30, 1.10]
Chang 2019	12 months	89	784	109	719	86.1%	0.75 [0.58, 0.97]
Subtotal (95% CI)			951		881	100.0%	0.72 [0.48, 0.97]
Total events		102		131			
Heterogeneity: Tau² = 0.00; Chi² = 0.56, df = 1 (P = 0.45); I² = 0%							
Test for overall effect: Z = 2.64 (P = 0.008)							
CABG							
Dewey 2016	Index	3	167	1	162	33.1%	2.91 [0.31, 27.69]
Chang 2019	12 months	9	784	18	719	66.9%	0.46 [0.21, 1.01]
Subtotal (95% CI)			951		881	100.0%	0.56 [0.19, 5.40]
Total events		12		19			
Heterogeneity: Tau² = 0.97; Chi² = 2.31, df = 1 (P = 0.13); I² = 57%							
Test for overall effect: Z = 0.19 (P = 0.85)							
Hospitalizations							
Chang 2019	12 months	33	784	31	719	100.0%	0.98 [0.60, 1.58]
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.10 (P = 0.92)							
NIT (any)							
Chang 2019	12 months	415	784	194	719	100.0%	1.96 [1.71, 2.25]
Heterogeneity: Not applicable							
Test for overall effect: Z = 9.63 (P < 0.00001)							
Stress NIT imaging (any)							
Chang 2019	12 months	26	784	20	719	100.0%	1.19 [0.67, 2.12]
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.60 (P = 0.55)							
NIT (radiation)							
Chang 2019	12 months	17	784	11	719	100.0%	1.42 [0.67, 3.01]
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.91 (P = 0.36)							



Other Outcomes

There were no differences between CCTA and ICA in the incidence of unstable angina, stroke, or MACE across both RCTs (Table 46).

Table 46. Secondary outcomes in trials comparing CCTA vs. ICA in patients with suspected CAD

Outcome	Author, year RCT	Time point	CCTA	ICA	Risk Ratio (95% CI)*
Unstable angina	Dewey, 2016† *CAD-Man*	Median 3.3 years	1.2% (2/167)	0% (0/162)	NC, p=0.16
	Chang, 2019‡ *CONVERSE*	Median 12.3 months	1.1% (9/784)	1.1% (8/719)	1.03 (0.40 to 2.66)
Stroke	Dewey, 2016† *CAD-Man*	Median 3.3 years	0% (0/167)	0.6% (1/162)	NC, p=0.31
	Chang, 2019‡ *CONVERSE*	Median 12.3 months	0.3% (2/784)	0.3% (2/719)	0.92 (0.13 to 6.49)
MACE§	Dewey, 2016† *CAD-Man*	Median 3.3 years	4.2% (7/167)	3.7% (6/162)	1.13 (0.39 to 3.30)
	Chang, 2019‡ *CONVERSE*	Median 12.3 months	4.6% (36/784)	4.6% (33/719)	1.0 (0.63 to 1.59)
Angina-free	Chang, 2019‡ *CONVERSE*	Median 12.3 months	60% (470/784)	62% (446/719)	0.96 (0.89 to 1.05)

adj. = adjusted; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CI = confidence interval; ED = emergency department; HR = hazard ratio; MACE = major adverse cardiac events; MI = myocardial infarction; NR = not reported; RCT = randomized controlled trial; UA = unstable angina.
*Calculated by AAI.
†Patients with stable or unstable angina treated as inpatients (56%) or outpatients (44%)
‡Patients with stable angina treated on an outpatient basis
§MACE definitions:

Dewey: MI, cardiac death, stroke, UA pectoris, re-revascularization or first revascularization more than 2 months after randomization

Chang: death, acute non-fatal MI, UA, cardiac hospitalization, or stroke

6.2.3 Key Question 2: Clinical decision making

Additional testing

Compared with a diagnostic strategy of direct referral to ICA, only 14 per 100 patients (24/167) patients randomized to CCTA in one good-quality trial[52] and 23 per 100 patients (179/784) in one fair-quality trial[36] underwent subsequent ICA over median follow-ups of 12 and 40 months. One of the trials reported that 30 patients in the ICA group (n=719) underwent a second ICA during follow-up[36] (4 per 100 patients). The proportion of patients without obstructive CAD on ICA was significantly lower in patients randomized to index CCTA compared with those randomized to direct ICA in both trials (total N=1,019)[36,52]: 22 versus 65 per 100 patients; pooled RR 0.32 (95% CI 0.18 to 0.51), I^2=0%; pooled RD –48.0% (95% CI –67.0% to –29.2%), I^2=73% (Figure 20). One trial, in mixed stable and acute patients with

atypical chest pain, reported that ICA led to revascularization of obstructive CAD in more CCTA patients (16/24) than ICA patients (23/162) (67 vs. 14 per 100 patients; RR 4.70, 95% CI 2.93 to 7.53; RD 52.5%, 95% CI 32.9% to 72.1%).[52]

Additional downstream noninvasive testing was twice as common following index CCTA compared with direct referral to ICA in one fair-quality trial evaluating stable patients (53 vs. 27 per 100 patients; RR 1.96, 95% CI 1.71 to 2.25; RD 26.0%, 95% CI 21.1% to 30.7%) but there was no difference between groups in the frequency of these tests that required stress testing with imaging or that required radiation (Figure 20).[36] Additional testing (in order of most to least common) included rest echocardiography, exercise ECG, nuclear perfusion, stress echocardiography and CCTA. More CCTA patients underwent subsequent rest echocardiography compared with ICA patients (36 vs. 13 per 100 patients; RR 2.71, 95% CI 2.20 to 3.34; RD 22.6%, 95% CI 18.5% to 26.8%); the frequency of all other tests was similar between groups.

Treatment

When data were pooled across both trials, CCTA was associated with fewer revascularization procedures compared with ICA over median follow-up periods of 12 and 40 months (2 RCTs, N=1,832; 13 vs. 18 per 100 patients; pooled RR 0.71, 95% CI 0.55 to 0.96, I^2=0%; pooled RD –5.0%, 95% CI –8.0% to –2.0%, I^2=0%), Figure 20. Individually, only the larger fair-quality trial (N=1,503) in stable outpatients reported a statistically significant difference between groups over 12 months: 13 versus 18 per 100 patients, RR 0.71 (95% CI 0.55 to 0.90), RD –5.0% (95% CI –9.0% to –2.0%). Results were similar when the frequency of PCI was considered separately but there were no differences in the frequency of CABG between groups (Figure 20). In the trial evaluating both stable and acute patients with atypical chest pain, most patients underwent revascularization following the index visit with similar proportions (re)revascularized more than 2 months after randomization (6/167 vs. 5/162, 4 vs. 3 per 100 patients; adjusted HR 0.89, 95% CI 0.27 to 2.90).[52]

Hospitalization and ED visits

Hospitalization for cardiac causes occurred with similar frequency between the CCTA and ICA groups over a median follow-up of 12 months in one trial evaluating stable patients treated on an outpatient basis: 4 vs. 4 per 100 patients, RR 0.98 (95% CI 0.60 to 1.58)[36]; Figure 20. The other trial, in a mixed stable and acute population with atypical chest pain, did not report hospitalization rates but did report that for those patients hospitalized, CCTA was associated with a shorter hospital length of stay compared with ICA: median 30 (IQR 3.5 to 77.3) versus 52.9 (IQR 49.5 to 76.4) hours.[52]

6.2.4 Key Question 3: Safety

The good-quality trial evaluating both stable and acute patients with atypical chest pain reported that no major complications occurred, i.e., complications that prolonged hospital stay by 24 hours or more.[52] Minor procedural complications were less frequent following CCTA compared with ICA (4 vs. 11 per 100 patients), primarily driven by the rate of hematoma at the puncture site (1 vs. 9 per 100 patients), Table 47. In one fair-quality trial evaluating stable outpatients, only one major complication was reported,

major bleeding, which occurred in two patients (0.4%) in the ICA group; one patient (0.1%) required transfusion[36] (Table 47).

Table 47. Safety data for RCTs comparing CCTA vs. ICA in patients with suspected CAD

Author, year RCT Timepoint	Adverse event	CCTA	ICA	Estimate (95% CI)*
Dewey, 2016* ***CAD-Man*** ≤48 hours after last procedure related to CCTA or ICA	**Any complications prolonging hospital stay by ≥ 24 hours**	0% (0/165)	0% (0/162)	NC, p=NS
	Any minor procedural complication	3.6% (6/165)	10.5% (17/162)	RR 0.35 (0.14 to 0.86) RD –6.9% (–12.4% to –1.3%)
	Hematoma at puncture site	0.6% (1/165)	8.6% (14/162)	RR 0.07 (0.01 to 0.53) RD –8.0% (–12.5% to –3.6%)
	Secondary bleeding at puncture site	0.6% (1/165)	0.6% (1/162)	RR 0.98 (0.06 to 15.56)
	Bradycardia	1.2% (2/165)	0% (0/162)	NC, p=NS
	Angina without infarction	0.6% (1/165)	0% (0/162)	NC, p=NS
	Allergoid reaction to contrast agent	0.6% (1/165)	0% (0/162)	NC, p=NS
	Hypotension requiring treatment	0% (0/165)	0.6% (1/162)	NC, p=NS
	Stent migration	0% (0/165)	0.6% (1/162)	NC, p=NS
Chang, 2019† ***CONSERVE*** Median 12.3 months	**Any major bleeding**	0% (0/784)	0.3% (2/719)	NC, p=NS
	Major bleeding needing transfusion	0% (0/784)	0.1% (1/719)	NC, p=NS

CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CI = confidence interval; NC = not calculable; NS = not statistically significant; RCT = randomized controlled trial.
*Calculated by AAI.
†Patients with stable or unstable angina treated as inpatients (56%) or outpatients (44%)
‡Patients with stable angina treated on an outpatient basis

6.2.5 Key Question 4: Differential Effectiveness or Safety

No trials reported on differential effectiveness or safety.

6.2.6 Key Question 5: Cost-Effectiveness

Given the complexities in how cost-effectiveness was reported in the included studies, cost-effectiveness related to CCTA versus is covered in section 6.1.5 under the comparison of CCTA versus any functional testing.

6.3 CCTA with Fractional Flow Reserve (FFR)

One prospective comparative cohort (across 2 publications), the PLATFORM study, compared CCTA plus Fractional Flow Reserve (FFR) versus any non-invasive testing (N=204) and versus ICA (N=380) in the outpatient setting in patients with suspected CAD who had an intermediate risk of coronary disease.[57,60] Patients were subdivided into two consecutive cohorts based on the evaluation plan decided upon before enrollment (any non-invasive testing or ICA). (See Appendix J for details.) The decision to send patients for noninvasive or invasive testing prior to enrollment was made by the patients' physicians; it is unclear what criteria were used to make this decision, though it is assumed that those patients who were being sent directly to ICA were higher risk than those being sent for noninvasive testing. Among patients originally planned to receive non-invasive testing, 104 were allocated to CCTA (with 64% also receiving FFR) and 100 were allocated to any non-invasive test. Among patients originally planned to receive ICA, 193 were allocated to CCTA (with 69% also receiving FFR) and 187 were allocated to ICA. FFR analyses were performed centrally using HeartFlow when requested by the site (recommended if the CTA revealed ≥30% stenosis or if the patient was referred to ICA), thus not all patients received FFR as indicated previously. CCTA was complete with a 64 slice or greater CT scanner and contrast was used but the type and dose were not reported. CACS was not performed in any patient. For those allocated to the any non-invasive testing arm, tests included stress echocardiogram, SPECT, CMR, CCTA, and other (not further specified).

Patients in the planned ICA cohort were somewhat older than those in the planned non-invasive cohort (mean 62 vs. 59 years); within the planned ICA cohort, patients allocated to receive CCTA with FFR were younger than those allocated to ICA (61 vs. 63 years), Appendix J. The proportion of females ranged from 38% to 40% across the two cohorts. Less than 2% of all patients identified as a racial or ethnic minority. The study excluded patients with previously diagnosed CAD and did not report information on prior revascularizations, myocardial infarctions, or the proportion of patients with dyspnea. Most patients presented with atypical angina (74%); in the planned noninvasive test cohort, fewer patients who were allocated to CCTA with FFR had at atypical angina compared to those who received noninvasive testing (77% vs. 91%). Across all patients, the proportion with hypertension, diabetes, and hyperlipidemia was 54%, 13%, and 71%, respectively, and 54% smoked in the past or presently. In the planned non-invasive test cohort, more patients who were allocated to CCTA with FFR had hypertension (55% vs. 38%) and were taking aspirin (43% vs. 29%) compared with those who received other noninvasive testing. In the planned ICA cohort, fewer patient allocated to CCTA with FFR were taking aspirin (47% vs. 62%). All patients had intermediate likelihood of CAD; mean pretest risk was 45% in the planned noninvasive test cohort and 50.5% in the planned ICA cohort based on the Diamond-Forrester risk model. Follow-up occurred at 3, 6, and 12 months. The study was conducted at 11 sites in Europe and one site in the United States. Authors received funding from industry (HeartFlow, Inc.).

The study quality was rated as good. There were some differences in key characteristics between arms at baseline; however, the authors performed a sensitivity analysis of their primary outcome using propensity score matching (based on age, sex, diabetes, smoking status, and type of angina) to control for these imbalances and the unrandomized nature of the test allocation.

6.3.1 Summary of Results

CCTA with FFR vs. any NIT (planned NIT cohort)

- There was no difference between groups in any outcome over 12 months (SOE Insufficient for all outcomes).
- One MI occurred in the any noninvasive test group (0 vs. 1 per 100 patients). There were no deaths or hospitalizations with urgent revascularization in either group. Given that these are rare events, the study may not have been sufficiently powered to detect a difference.
- Risk of ICA was 21 vs. 16 per 100 patients; of ICA without obstructive CAD was 13 vs. 6 per 100 patients (at 3 months); and of any revascularization was 10 vs. 7 per 100 patients, respectively.

CCTA with FFR vs. ICA (planned ICA cohort)

- There were no differences between groups over 12 months in the risk of MI (1 vs. 1 per 100 patients), all-cause death (0 vs. 1 per 100 patients) or hospitalization with urgent revascularization (1 vs. 0 per 100 patients). Given that these are rare events, the study may not have been sufficiently powered to detect a difference (SOE Insufficient).
- Compared with direct referral to ICA, patients who underwent CCTA with FFR were referred to ICA significantly less often (51 vs. 100 per 100 patients; RR 0.51, 95% CI 0.45 to 0.59) and importantly, there were no events in the 61% of CCTA with FFR patients in whom ICA was cancelled in the planned ICA cohort. The risk of ICA without obstructive CAD was also significantly reduced following CCTA with FFR (39 vs. 100 per 100 patients; RR 0.39, 95% CI 0.33 to 0.47) (SOE Insufficient).
- There was no difference between groups in the risk of any revascularization (SOE Insufficient).

Key Question 3, Safety

- There was one mild contrast reaction from CCTA testing; no other information was provided (SOE Insufficient).
- Patients who received CCTA with FFR had significantly greater cumulative radiation exposure over 12 months compared to those who received any noninvasive test (planned noninvasive test cohort): 9.6 vs. 6.4 mSv, MD 3.1 (95% CI, 0.6 to 5.7); there was no difference for CCTA with FFR versus direct referral to ICA (planned ICA cohort) (SOE Low).

Detailed Results

6.3.2 Key Question 1: Primary clinical outcomes (MI, all-cause mortality, cardiac death)

For both the planned noninvasive test cohort (CCTA with FFR vs. any noninvasive test) and the planned ICA cohort (CCTA with FFR vs. ICA), there were no differences between testing arms in the risk of nonfatal MI (≤1 per 100 patients across all arms) or all-cause mortality (0 per 100 patients in the noninvasive test cohort and <1 per 100 patients in the ICA cohort, across both arms), as well as in the risk of the composite outcomes of MACE or MACE plus vascular complications across 12 months of follow-up (Table 48).[57,60] Importantly, there were no events in the 61% of CCTA with FFR patients in whom ICA was cancelled in the planned ICA cohort. Cardiac mortality was not reported.

6.3.3 Key Question 2: Clinical Decision-making outcomes

Additional testing

In the planned noninvasive cohort, the risk of ICA, as well as the risk of ICA without obstructive CAD, was similar between patients who received CCTA with FFR versus any noninvasive test over 12 months (Table 48).[57,60] In the planned ICA cohort, allocation to CCTA with FFR was associated with a 50% reduction in the risk of ICA over 12 months compared with direct referral to ICA (51 vs. 100 per 100 patients; RR 0.51, 95% CI 0.45 to 0.59; RD –48.7% 95% CI –41.7% to –55.8%). The risk of ICA without obstructive CAD was also significantly reduced in patients who received CCTA with FFR compared with ICA as measured at 3 months (12 vs. 73 per 100 patients; RR 0.17, 95% CI 0.12 to 0.25; RD –60.8%, 95% CI –53.0% to –68.7%). Results from the propensity score matching analysis (n=148 in each arm) were similar (12 vs. 72 per 100 patients).

Over the 12 months after enrollment, in the planned noninvasive testing cohort, CCTA with FFR was associated with fewer total referrals for stress echocardiography (2 vs. 29 per 100 patients) and stress nuclear scans (8 vs. 17 per 100 patients) but a similar frequency of stress ECG and cardiac MRI compared with any noninvasive testing; 62% of patients allocated to the noninvasive testing arm received CCTA over the study duration (Table 48).[57,60] In the noninvasive testing arm, it was unclear which tests patients received at index visit so we could not calculate the proportion of additional noninvasive tests required post-index testing making it difficult to draw conclusions regarding the risk of additional downstream testing for this cohort. In the planned ICA cohort, there was no difference between patients who received CCTA with FFR versus ICA in additional noninvasive testing to include stress ECG, stress echocardiography, stress nuclear, cardiac MRI and CCTA (Table 48).

Additional treatment and hospitalization

There were no differences between test arms in risk of any revascularization or of hospitalization with urgent revascularization over 12 months for both the planned noninvasive test cohort (CCTA with FFR vs. noninvasive testing) and the planned ICA cohort (CCTA with FFR vs. direct referral to ICA), Table 48.[57,60]

Changes in medication use (i.e., aspirin, statins and $P2Y1_{12}$ inhibitors) over 12 months were similar in the two arms of both cohorts except for $P2Y1_{12}$ inhibitors (i.e., clopidogrel, prasugrel, and ticagrelor) in the planned ICA cohort which were greater in the CCTA with FFR arm compared with the ICA arm.[57,60] It is unclear what medication changes were made (e.g., dose increase or decrease, initiation or discontinuation).

Table 48. CCTA FFR versus any noninvasive functional testing and ICA

			Cohort intended for NIT			Cohort intended for ICA		
Author, year RCT	**Outcome**	**Timepoint, cumulative (months)**	**CCTA FFR**	**NIT***	**Estimate (95% CI)**	**CCTA FFR**	**ICA**	**Estimate (95% CI)**
Douglas 2015, 2016 PLATFORM Prospective comparative cohort study Population: - Suspected CAD‡ - Stable, OP - Intermediate pretest risk	**Nonfatal MI**	3	0% (0/104)	0% (0/100)	NC, p=NS	0.5% (1/193)	0% (0/187)	NC, p=NS
		12	0% (0/104)	1.0% (1/100)	NC, p=NS	0.5% (1/193)	0.5% (1/187)	RR 0.97 (0.06 to 15.38)
	All-cause mortality	3	0% (0/104)	0% (0/100)	NC, p=NS	0% (0/193)	0% (0/187)	NC, p=NS
		12	0% (0/104)	0% (0/100)	NC, p=NS	0% (0/193)	0.5% (1/187)	NC, p=NS
	MACE†	3	0% (0/104)	0% (0/100)	NC, p=NS	1.0% (2/193)	0% (0/187)	NC, p=NS
		12	0% (0/104)	1.0% (1/100)	NC, p=NS	1.0% (2/193)	1.1% (2/187)	RR 0.97 (0.14 to 6.81)
	MACE + vascular complication	3	1.0% (1/104)	0% (0/100)	NC, p=NS	3.6% (7/193)	1.1% (2/187)	RR 3.39 (0.71 to 16.12)
		12	1.0% (1/104)	1.0% (1/100)	RR 0.96 (0.06 to 15.17)	3.6% (7/193)	2.1% (4/187)	RR 1.70 (0.50 to 5.70)
	ICA	3	18.3% (19/104)	12.0% (12/100)	RR 1.52 (0.78 to 2.97)	39.4% (76/193)	100% (187/187)	**RR 0.39 (0.33 to 0.47)**
		12	21.2% (22/104)	16.0% (16/100)	RR 1.32 (0.74 to 2.37)	51.3% (99/193)	100% (187/187)	**RR 0.51 (0.45 to 0.59)**
	ICA without obstructive CAD – core lab quantitative	3	12.5% (13/104)	6.0% (6/100)	RR 2.08 (0.82 to 5.27)	12.4% (24/193)	73.3% (137/187)	**RR 0.17 (0.12 to 0.25)**
	ICA without obstructive CAD – site interpretation	3	7.7% (8/104)	5.0% (5/100)	RR 1.54 (0.52 to 4.54)	9.3% (18/193)	56.7% (106/187)	**RR 0.16 (0.10 to 0.26)**
	Any NIT							
	Stress ECG	unclear	8.7% (9/104)	11.0% (11/100)	RR 0.79 (0.34 to 1.82)	9.8% (19/193)	9.1% (17/187)	RR 1.08 (0.58 to 2.02)
	Stress Echo	unclear	1.9% (2/104)	29.0% (29/100)	RR 0.07 (0.02 to 0.27)	3.1% (6/193)	2.7% (5/187)	RR 1.16 (0.36 to 3.75)
	Stress nuclear	unclear	7.7% (8/104)	17.0% (17/100)	RR 0.45 (0.20 to 1.00)	1.6% (3/193)	3.2% (6/187)	RR 0.48 (0.12 to 1.91)
	Cardiac MRI	unclear	2.9% (3/104)	3.0% (3/100)	RR 0.96 (0.20 to 4.65)	1.6% (3/193)	3.2% (6/187)	RR 0.48 (0.12 to 1.91)
	CCTA	unclear	100% (104/104)	62.0% (62/100)	NA	100% (193/193)	0.5% (1/187)	NA
	FFR CT	unclear	57.7% (60/104)§	0% (0/100)	NA	60.6% (117/193)	0% (0/187)	NA
	Revascularization (any)	3	9.6% (10/104)	5.0% (5/100)	RR 1.92 (0.68 to 5.43)	28.5% (55/193)	31.6% (59/187)	RR 0.90 (0.66 to 1.23)

		12	9.6% (10/104)	7.0% (7/100)	RR 1.37 (0.54 to 3.47)	33.7% (65/193)	35.8% (67/187)	RR 0.94 (0.71 to 1.24)
	PCI	3	8.7% (9/104)	3.0% (3/100)	RR 2.88 (0.80 to 10.35)	23.3% (45/193)	22.5% (42/187)	RR 1.04 (0.72 to 1.50)
		12	8.7% (9/104)	5.0% (5/100)	RR 1.73 (0.60 to 4.99)	28.5% (55/193)	26.2% (49/187)	RR 1.09 (0.78 to 1.51)
	CABG	3	1.0% (1/104)	2.0% (2/100)	RR 0.48 (0.04 to 5.22)	5.2% (10/193)	9.1% (17/187)	RR 0.57 (0.27 to 1.21)
		12	1.0% (1/104)	2.0% (2/100)	RR 0.48 (0.04 to 5.22)	5.2% (10/193)	9.6% (18/187)	RR 0.54 (0.26 to 1.14)
	Hospitalization with urgent revascularization	3	0% (0/104)	0% (0/100)	NS	0.5% (1/193)	0% (0/187)	NC, p=NS
		12	0% (0/104)	0% (0/100)	NS	0.5% (1/193)	0% (0/187)	NC, p=NS

ACP = acute chest pain; ACS = acute coronary syndrome; CABG = coronary artery bypass graft; CI = confidence interval; ICA = invasive coronary angiography; MD = mean difference; MI = myocardial infarction; NA = not applicable; NS = not statistically significant; OP= outpatient; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; RR = risk ratio; SD = standard deviation.

*It is unclear what patients received at index testing.

†MACE includes all-cause mortality, non-fatal MI, hospitalization with urgent revascularization.

‡Known/history of CAD was an exclusion criterium.

§Requested in 67 but not completed in 7 due to poor image quality or inadequate acquisition.

6.3.4 Key Question 3: Safety

There was one reported adverse event from CCTA testing, a mild contrast reaction. The authors did not provide any other information or report on any other test-related adverse events.[57,60]

In the planned noninvasive test cohort, CCTA with FFR was associated with greater cumulative radiation exposure compared with the any noninvasive testing arm at both 3 months (8.8 vs. 5.8 mSv; mean difference 3.0, 95% CI 0.6 to 5.4) and 12 months (9.6 vs. 6.4 mSv; mean difference 3.1, 95% CI 0.6 to 5.7). In the planned ICA cohort, there was no difference in cumulative radiation exposure between the CCTA with FFR group and the ICA group (9.9 vs. 9.4 mSv at 3 months and 10.7 vs. 10.4 mSv at 12 months, respectively).

6.3.5 Key Question 4: Differential Effectiveness and Safety

Authors performed analyses on predefined subgroups (age, sex, race, diabetes, pretest risk of CAD) and evaluated interaction to explore differential effects of testing on the finding of no obstructive CAD on ICA within 90 days.[57,60] There was no evidence of differential effectiveness (interaction p-values not statistically significant) by any subgroup for the outcome of ICA without obstructive CAD within 90 days in either the cohort originally planned to receive noninvasive testing or the higher CAD risk cohort originally planned to receive ICA with one exception. In the higher risk cohort, there was a statistically significant test for interaction between subgroups based on pre-test probability of CAD (<50% versus ≥50%) (Appendix O). It appears that the analyses were done on raw data from the respective cohorts that were not adjusted for potential confounding or selection bias. Confounding and selection bias are primary factors which threaten the validity of non-randomized observational studies and causal inference is not possible. Thus, there is insufficient information to draw firm conclusion from these analyses.

6.3.6 Key Question 5: Cost-Effectiveness

Given the complexities in how cost-effectiveness was reported in the included studies, cost-effectiveness related to CCTA with FFR is covered in section 6.1.5 under the comparison of CCTA versus any functional testing.

7 Single Photon Emission Computed Tomography (SPECT) Results

Six trials (across 7 publications) evaluated the effectiveness and/or safety of SPECT compared with stress echocardiography (2 RCTs)[220,241], exercise ECG (2 RCTs)[209,223], clinical assessment only (1 RCT)[142], NICE-guideline directed care (1 RCT)[88], and ICA (1 RCT)[220,241]. One trial included both a stress echocardiography and an ICA comparison arm.[220,241]

7.1 SPECT versus Stress Echocardiography and versus Exercise ECG

Given that the results across the four trials comparing SPECT with stress echocardiography and exercise ECG showed similar results in general, they are summarized together in the bullet points below, in the strength of evidence table, and their results are presented together in the same plots/figures. However, each comparison is described in detail separately in the sections that follow. All figures corresponding to the meta-analyses can be found after the section comparing SPECT versus exercise ECG.

7.1.1 Summary of results

- There was no difference in the risk of MI (SOE Insufficient), all-cause mortality (SOE Low) or cardiac mortality (SOE Insufficient) between SPECT and stress echocardiography (2 trials) or exercise ECG (2 trials) across four trials (N=1,908) with varying populations and follow-up periods. The absolute risk was <2 per 100 patients across all testing arms for all outcomes over follow-up periods ranging from 1 to 24 months. Given that these are rare events, trials may not have been sufficiently powered to detect a difference.
- There was no difference in the risk of ICA (4 trials, N=1,908) (SOE Low) or additional noninvasive testing (N=3 trials, N=1,679) (SOE Insufficient) for SPECT versus stress echocardiography or exercise ECG across all four trials over follow-up periods ranging from 1 to 24 months, however, there was substantial heterogeneity. Individually, only the trials comparing SPECT versus exercise ECG reported statistically significant differences which favored SPECT for both ICA (1 trial) and additional noninvasive testing (2 trials); however, for the latter, the estimates across trials were inconsistent and imprecise. Differences in testing protocols, patient populations and/or pretest risk, and follow-up periods may have played a role in these findings.
- There was no difference in the risk of revascularization (4 trials, N=1,908) (SOE Moderate) or hospitalization (3 RCTs, N=1,451) (SOE Low) between SPECT and stress echocardiography or exercise ECG, or ED visits in 1 trial (N=229) of SPECT vs. echocardiography through 24 months of follow-up (SOE Low).

7.1.2 SPECT versus Stress Echocardiography

Two trials (total N=679)[210,220,241] compared Tc-99m sestamibi SPECT imaging with stress echocardiography in a mixed population of patients with suspected or known CAD, one in stable patients and one in acute patients (See Appendix Q). One trial enrolled patients with stable CAD referred for outpatient angiography (mean age 62 years, 30% female, 27% with prior MI/known CAD). Referral to angiography was based on the results of an exercise ECG complete within 1 month of enrollment, the

results of which were not available to the trial personnel. Patients were considered high risk (69%) or low risk (31%) according to the Pryor risk assessment. Baseline cardiac risk factors included prior cerebrovascular accident (6%), peripheral vascular disease (9%), diabetes (12%), family history of CAD (25%), hypertension (58%), hyperlipidemia (78%), and smoking (43%). Patients were on a variety of cardiovascular related medications at baseline including antiplatelets, statins, and beta-blockers primarily as well as ACE inhibitors, calcium channel blockers, nicorandil, nitrates, diuretics, and angiotensin-II receptor antagonists. The second trial enrolled patients with acute chest pain presenting to the ED[210] and subsequently hospitalized (mean age 57 years, 54% female, 24% known CAD). Baseline cardiac risk factors included prior MI (15%), cerebrovascular disease (8%), diabetes (39%), hypertension (76%), hyperlipidemia (48%), and COPD (10%). Patients were on a variety of cardiovascular related medications at baseline including antihypertensives (beta blockers and other), aspirin, and lipid-lowering medication primarily, as well as diabetes medication, warfarin and clopidogrel. SPECT was performed using adenosine as the stress agent in one trial (the stable outpatient population) and dipyridamole (73%) or treadmill exercise (27%) as the stressor in the other (acute ED population). Stress echocardiography was performed using dobutamine in the stable population and either dobutamine (58%) or exercise (42%) stress in the acute ED population; both trials used contrast to enhance the images. Follow-up was 30 days in the acute ED trial and up to 72 months in the stable outpatient trial. One trial was conducted in the United States and was funded by industry (GE Healthcare)[210] and the other was conducted in the United Kingdom and funded by the National Institute for Health Research.

One trial was considered good quality[220,241] and the other fair quality[210]. The only methodological shortcoming in the good-quality trial was unclear blinding of outcome assessors; in the fair-quality trial, limitations included unclear allocation concealment methods and between-group differences at baseline on a CAD risk factor. See Appendix D for details regarding study quality determination.

Detailed results

7.1.2.1 Key Question 1: Primary Outcomes (MI, all-cause mortality, cardiac death)

Myocardial infarction

Across both trials, the frequency of MI following SPECT versus stress echocardiography was 0.6 versus 1.8 per 100 patients. No events occurred within 30 days in the fair-quality trial evaluating patients hospitalized with acute chest pain.[210] In the good-quality trial evaluating stable outpatients at higher pretest risk, two patients who received SPECT were admitted for acute MI with 18 months of randomization compared with six patients who received dobutamine stress echocardiography; the difference was not statistically significant: 0.9 versus 2.7 per 100 patients; RR 0.34 (95% CI 0.07 to 1.65)[220], Figure 21.

All-cause mortality and cardiac mortality

There was no difference in all-cause mortality between SPECT and stress echocardiography across the two trials, both individually and when pooled (2 RCTs, N=679, 2.4 vs. 3.2 per 100 patients; RR 0.71, 95% CI 0.22 to 4.58, I^2=0%), Figure 22. The good-quality trial in stable outpatients at higher pretest risk

reported a total of seven and 11 deaths, respectively, over 72 months of follow-up (3.1 vs. 4.9 per 100 patients)[241]. The fair-quality trial in acute ED patients reported one death in the SPECT arm over 30 days (0.9 vs. 0 per 100 patients).[210] Cardiac mortality was reported in five SPECT patients and one echocardiography patient at 18 months in the trial evaluating stable outpatients (2.2 vs. 0.4 per 100 patients; RR 5.04, 95% CI 0.59 to 42.84)[220], Figure 23.

Other Outcomes

There was no difference between SPECT and Echo for the composite outcomes of any nonfatal event (admission for chest pain, admission for acute MI, unplanned PCI, unplanned CABG, or other) (10.7 vs. 13.7 per 100 patients; RR 0.78, 95% CI 0.47 to 1.29) and any fatal plus nonfatal event (12.9 vs. 16.4 per 100 patients; RR 0.79, 95% CI 0.50 to 1.24) over 18 months in the good-quality trial evaluating stable outpatients referred for ICA.[220] In this same trial here was no difference in the proportion of patients achieving a clinically significant improvement in CCS angina class at 18 months (42 vs. 34 per 100 patients). Similarly, there were no differences between groups for mean scores on all subscales of the Seattle Angina Questionnaire at 6 and 18 months (See Appendix O for all secondary outcomes).

7.1.2.2 Key Question 2: Clinical decision making

Additional testing

There was no difference in the frequency of ICA between SPECT and stress echocardiography across the two trials, both individually and when pooled (2 RCTs, N=679, 52.1 vs. 51.3 per 100 patients; RR 1.04, 95% CI 0.77 to 1.24, I^2=33%), Figure 24. The good-quality trial in stable outpatients at higher pretest risk reported that 175 and 169 patients, respectively, were referred for ICA over 18 months of follow-up (78 vs. 75 per 100 patients; RR 1.04, 95% CI 0.94 to 1.16)[220] while the fair-quality trial in acute ED patients reported that two and five patients received subsequent ICA within 30 days (1.7 vs. 4.4 per 100 patients; RR 0.39, 95% CI 0.08 to 1.97).[210] In the good-quality trial, one patient in the SPECT arm received additional noninvasive testing (repeat SPECT) compared with no patient in the echocardiography arm (0.4 vs. 0 per 100 patients; RR 3.03, 95% CI 0.12 to 73.90)[220]; the timing of additional noninvasive testing was unclear (Figure 25).

Treatment

There was no difference in the risk of any revascularization for SPECT compared with stress echocardiography across both trials (2 RCTs, N=679, 29 vs. 36 per 100 patients; RR 0.82, 95% CI 0.53 to 1.16, I^2=0%), Figure 26. Individually, the larger, good-quality trial evaluating stable outpatients at higher pretest risk showed an association favoring SPECT (lower risk) over 36 months of follow-up: 43.8 versus 53.5 per 100 patients, RR 0.82 (95% CI 0.67 to 0.99)[241], RD –9.8% (95% CI –19.0% to –0.6%); however, the estimate was just barely statistically significant. The fair-quality trial in acute ED patients reported no difference between diagnostic strategies over 30 days, with only one patient in the stress echocardiography arm undergoing revascularization (PCI) (0 vs. 0.9 per 100 patients).[210] Differences in populations and the length of follow-up periods may have played a role in these findings. When

considered separately, there were no difference between test groups in the risk of PCI (Figure 27) or CABG (Figure 28), though both trials tended to favor SPECT with regarding to PCI (lower risk).

Hospitalization and ED visits

There was no difference in the frequency of hospitalizations due to cardiac causes between SPECT and stress echocardiography across the two trials, both individually and when pooled (2 RCTs, N=679, 7.1 vs. 9.1 per 100 patients; RR 0.76, 95% CI 0.39 to 3.19, I^2=32%), Figure 29. Except for eight acute MIs requiring hospitalization (2 in the SPECT and 6 in echocardiography arm) in the good-quality trial evaluating stable outpatients at higher pretest risk[220], all hospitalizations were due to chest pain. The rate of cardiac hospitalization in the good-quality trial was 9.4 versus 13.3 per 100 patients (RR 0.71, 95% CI 0.42 to 1.20)[220], respectively, over 18 months and in the fair-quality trial evaluating acute ED patients was 2.6 versus 0.9 per 100 patients (RR 2.92, 95% CI 0.31 to 27.68)[210] over 30 days. In the latter trial, three patients (3 per 100) in each group returned to the ED within 30 days. There was no difference between groups in the length of hospital stay in this same trial (Appendix O).

7.1.3 SPECT versus Exercise ECG

Two trials (total N=1,281) compared Tc-99m sestamibi SPECT imaging with exercise ECG in stable patients with suspected CAD (known CAD was an exclusion criteria) treated on an outpatient basis[209,223] (See Appendix Q). Mean patient age was 60 to 63 years. One trial[223] enrolled only women (78% postmenopausal) who were 87% Caucasian while the second trial included 44% women and the population was 52% Caucasian and 40% Indian-subcontinent origin. Most patients across both trials were at intermediate to high pretest risk (100% in the trial enrolling women only[223] and 84% in the other trial[209]); the remaining 16% in the one trial were considered low risk. Regarding cardiac risk factors, there was a similar proportion of patients with hypertension (50% and 53%), diabetes (13% and 17%) and family history of CAD (43% and 47%) in both trials but a greater proportion of patients with smoking history (45% and 14%) in the trial enrolling women only. In the latter trial, presenting symptoms included typical angina (60%), atypical angina (9%), nonspecific angina (28%) and dyspnea (51%). In addition, medications at baseline in this trial included aspirin (35%), statins (32%), gastrointestinal drugs (27%) (39% had coexisting esophageal reflux) primarily as well as beta-blockers, antidepressants, ACE inhibitors, NSAIDs, angiotensin receptor blockers and others. The other trial did not report presenting symptoms (other than chest pain, 100%) or baseline medication use. In the trial enrolling only women, patients in both diagnostic testing arms received exercise stress testing according to Bruce protocol. In the other trial, 62% of patients in the SPECT arm underwent exercise treadmill testing and 38% had pharmacological stressors (dipyridamole or dobutamine) while all patients in the ECG arm underwent exercise using the symptom-limited modified Bruce protocol. Follow-up periods were similar, 24 months and a mean 20 months. One trial was conducted in the United States and the other in the United Kingdom. Both were funded by industry; the United Kingdom trial also received research grants.

Both trials were considered fair quality. The primary methodological shortcoming in both trials included unclear allocation concealment methods and in one, unclear blinding of outcome assessors. See Appendix D for details regarding study quality determination.

Detailed results

7.1.3.1 Key Question 1: Primary Outcomes (MI, all-cause mortality, cardiac death)

Myocardial infarction

Across both trials there were a total of four MIs. One trial reported no difference between SPECT and exercise ECG in the frequency of MI over 24 months (N=457, 0 vs. 0.5 per 100 patients, RR 0.28, 95% CI 0.01 to 6.74)[209]; this was a fatal MI (Figure 21). The other trial reported that there were three nonfatal MIs (0.4 per 100 patients) over a mean of 20 months but did not specify the group to which the patients were randomized.[223]

All-cause mortality and cardiac mortality

There was no difference in all-cause mortality between SPECT and exercise ECG across the two fair-quality trials, both individually and when pooled (2 RCTs, N=1,229, 0.9 vs. 0.7 per 100 patients; RR 1.38, 95% CI 0.27 to 6.44, I^2=0%), Figure 22. There was a total of two cardiac deaths across both RCTs: one fatal MI in the exercise ECG group in one trial (0 vs. 0.5 per 100 patients; RR 0.28, 95% CI 0.01 to 6.74) Figure 23) and one sudden cardiac death (0.1 per 100 patients) in the second trial that enrolled only women, however the authors did not report to which group the patient was randomized.[223]

Other Outcomes

In the trial enrolling women only, the frequency of MACE (composite of cardiac death, nonfatal MI, or hospital admission for an ACS or heart failure) was similar between the SPECT and exercise ECG over 24 months (N=772, 2.3 vs. 1.7 per 100 patients; RR 1.14, 95% CI 0.44 to 2.92).[223] No difference in the frequency of MACE was seen for SPECT versus ECG when women with normal test results and those with abnormal test results were considered separately. Heart failure was reported in one woman (0.1 per 100 patients) and acute coronary syndrome in 12 (1.6 per 100 patients) all of which required hospitalization, but they did not report to which arms the patients were randomized (this data is repeated below in Key Question 2 under Hospitalization). The proportion of women who were angina-free (65 vs. 60 per 100 patients at 24 months) and the median scores across all subscales of the Seattle Angina Questionnaire (data not provided) were also similar between groups during follow-up. The second trial did not report on any secondary outcomes.

7.1.3.2 Key Question 2: Clinical decision making

Additional testing

In one trial, SPECT was associated with an almost 3-fold reduction in referral for ICA compared with exercise ECG over a mean follow-up of 20 months: 16.4 versus 47.3 per 100 patients; RR 0.35 (95% CI 0.25 to 0.47[209]; RD –30.9%, 95% CI –39.2% to –22.7%). The other trial which enrolled only women reported no difference in ICA rates between diagnostic strategies over 24 months (5.5 vs. 6.7 per 100 patients, respectively; RR 0.82, 95% CI 0.47 to 1.43).[223] When the two trials were pooled the difference was not statistically significant and there was substantial heterogeneity (2 RCTs, N=1,229, 9.8 vs. 20.8

per 100 patients; RR 0.50, 95% CI 0.19 to 1.47, I^2=86%), Figure 24. Difference in populations, testing protocols, and treatment algorithms may partially explain the heterogeneity.

In both trials, SPECT was associated with significantly fewer downstream noninvasive tests compared with exercise ECG. In the trial enrolling only women, the risk of subsequent noninvasive testing was 9.4 versus 18.6 per 100 patients, respectively, over 24 months (RR 0.51, 95% CI 0.35 to 0.73), almost all of which were SPECT (9.1 vs. 17.8 per 100 patients); only one SPECT patient and two exercise ECG patients had additional exercise ECG (0.3 vs. 0.5 per 100 patients). In the second trial, no patients randomized to SPECT underwent additional noninvasive testing while 23.2% of patients in the exercise ECG arm received subsequent stress (pharmacological) echocardiography (0 vs. 23.2 per 100 patients; RR 0.01, 95% CI 0.00 to 0.14)[209] over a mean of 20 months. However, when results were pooled across the two trials there was no difference between the two test groups (5.7 vs. 20.0 per 100 patients; RR 0.11, 95% CI 0.00 to 8.87, I^2=93%), likely due to the substantial heterogeneity across the trials (Figure 25).

Treatment

In one trial, SPECT was associated with fewer revascularization procedures compared with exercise ECG over a mean follow-up of 20 months: 10.8 vs. 17.9 per 100 patients, RR 0.60 (95% CI 0.38 to 0.96)[209], RD –7.1% (95% CI –13.6% to –0.6%); however, the difference was only marginally significant. The other trial which enrolled only women reported no difference in revascularization rates between diagnostic strategies over 24 months (2.1 vs. 1.1 per 100 patients, respectively; RR 2.02, 95% CI 0.61 to 6.66).[223] When the two trials were pooled the difference was not statistically significant, however heterogeneity was high (2 RCTs, N=1,229, 5.5 vs. 6.9 per 100 patients; RR 0.71, 95% CI 0.29 to 3.78, I^2=71%), Figure 26. Difference in populations, testing protocols, and treatment algorithms may partially explain the heterogeneity.

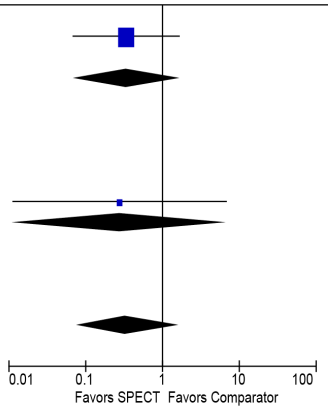
More patients randomized to SPECT versus exercise ECG started aggressive medical therapy (not defined) as a result of the test (83.6 vs. 30.4 per 100 patients; RR 2.75, 95% CI 2.22 to 3.40) in one trial.[209] The other trial enrolling only women reported similar rates of new use or discontinuation of nitrates, beta-blockers, statins and antidepressants between groups (no data provided, p=0.20).[223]

Hospitalization and ED visits

There was no difference between SPECT versus exercise ECG in the frequency of hospitalization for chest pain symptoms over 24 months in the trial enrolling only women (N=772, 3.9 vs. 3.1 per 100 patients; RR 1.26, 95% CI 0.60 to 2.66)[223], Figure 29. This same trial also reported one hospitalization for heart failure (0.1 per 100 patients) and 12 hospitalizations for acute coronary syndrome (1.6 per 100 patients) but they did not report to which arms the patients were randomized (this data is repeated above for Key Question 1 under Other Outcomes).

Figure 21. SPECT vs. stress echocardiography and vs. exercise ECG: Myocardial infarction

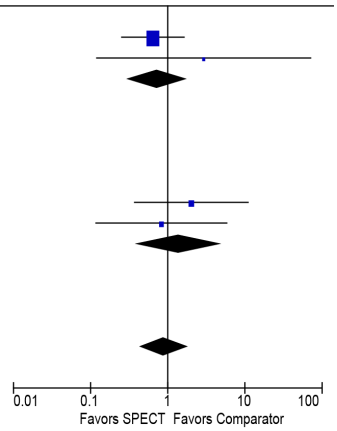
Study or Subgroup	Follow-up	Setting	Population	SPECT Events	SPECT Total	Comparator Events	Comparator Total	Weight	Risk Ratio [95% CI]
SPECT vs ECHO									
Sharples 2007	18 months	OP, Stable	Suspected or known CAD*	2	224	6	226	80.2%	0.34 [0.07, 1.65]
Salame 2018	1 month	ED/Hospital, Acute	Suspected or known CAD*	0	116	0	113		Not estimable
Subtotal (95% CI)					340		339	80.2%	0.34 [0.07, 1.65]
Total events				2		6			
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.34 (P = 0.18)									
SPECT vs. Ex ECG									
Sabharwal 2007	19.6 months	OP, Stable	Suspected CAD†	0	250	1	207	19.8%	0.28 [0.01, 6.74]
Subtotal (95% CI)					250		207	19.8%	0.28 [0.01, 6.74]
Total events				0		1			
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.79 (P = 0.43)									
Total (95% CI)					590		546	100.0%	0.32 [0.05, 1.96]
Total events				2		7			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%									
Test for overall effect: Z = 1.55 (P = 0.12)									
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.91), I² = 0%									



*Sharples: 27% with prior MI/known CAD; population consisted of stable patients referred for outpatient non-emergent angiography. Salame: 24% with known CAD; all patients were subsequently hospitalized following presentation to the ED. †Known/history of CAD was an exclusion criterium.

Figure 22. SPECT vs. stress echocardiography and vs. exercise ECG: All-cause mortality

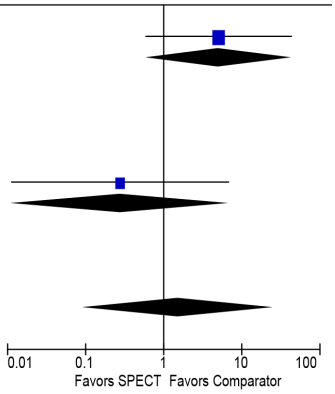
Study or Subgroup	Follow-up	Setting	Population	SPECT Events	SPECT Total	Comparator Events	Comparator Total	Weight	Risk Ratio [95% CI]
SPECT vs ECHO									
Thom 2014	18 months	OP, Stable	Suspected or known CAD*	7	224	11	226	62.0%	0.64 [0.25, 1.63]
Salame 2018	1 month	ED/Hospital, Acute	Suspected or known CAD*	1	116	0	113	5.3%	2.92 [0.12, 71.01]
Subtotal (95% CI)					340		339	67.2%	0.71 [0.22 4.58]
Total events				8		11			
Heterogeneity: Tau² = 0.00; Chi² = 0.80, df = 1 (P = 0.37); I² = 0%									
Test for overall effect: Z = 0.71 (P = 0.48)									
SPECT vs. Ex ECG									
Shaw 2011	24 months	OP, Stable	Suspected CAD†	4	384	2	388	18.7%	2.02 [0.37, 10.97]
Sabharwal 2007	19.6 months	OP, Stable	Suspected CAD†	2	250	2	207	14.1%	0.83 [0.12, 5.83]
Subtotal (95% CI)					634		595	32.8%	1.38 [0.27 6.44]
Total events				6		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.46, df = 1 (P = 0.50); I² = 0%									
Test for overall effect: Z = 0.49 (P = 0.62)									
Total (95% CI)					974		934	100.0%	0.89 [0.42, 2.57]
Total events				14		15			
Heterogeneity: Tau² = 0.00; Chi² = 1.92, df = 3 (P = 0.59); I² = 0%									
Test for overall effect: Z = 0.30 (P = 0.76)									
Test for subgroup differences: Chi² = 0.66, df = 1 (P = 0.42), I² = 0%									



*Thom: 27% with prior MI/known CAD; population consisted of stable patients referred for outpatient non-emergent angiography. Salame: 24% with known CAD; all patients were subsequently hospitalized following presentation to the ED. †Known/history of CAD was an exclusion criterium. Shaw included women only.

Figure 23. SPECT vs. stress echocardiography and vs. exercise ECG: Cardiac mortality

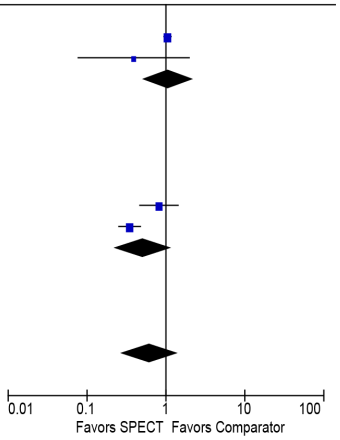
Study or Subgroup	Follow-up	Setting	Population	SPECT Events	SPECT Total	Comparator Events	Comparator Total	Weight	Risk Ratio [95% CI]
SPECT vs ECHO									
Sharples 2007	18 months	OP, Stable	Suspected or known CAD*	5	224	1	226	58.7%	5.04 [0.59, 42.84]
Subtotal (95% CI)					224		226	58.7%	5.04 [0.59, 42.84]
Total events				5		1			
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.48 (P = 0.14)									
SPECT vs. Ex ECG									
Sabharwal 2007	19.6 months	OP, Stable	Suspected CAD†	0	250	1	207	41.3%	0.28 [0.01, 6.74]
Subtotal (95% CI)					250		207	41.3%	0.28 [0.01, 6.74]
Total events				0		1			
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.79 (P = 0.43)									
Total (95% CI)					474		433	100.0%	2.21 [0.05, 35.30]
Total events				5		2			
Heterogeneity: Tau² = 2.29; Chi² = 2.19, df = 1 (P = 0.14); I² = 54%									
Test for overall effect: Z = 0.29 (P = 0.77)									
Test for subgroup differences: Chi² = 2.19, df = 1 (P = 0.14), I² = 54.4%									



*27% with prior MI/known CAD; population consisted of stable patients referred for outpatient non-emergent angiography.
†Known/history of CAD was an exclusion criterium.

Figure 24. SPECT vs. stress echocardiography and vs. exercise ECG: ICA

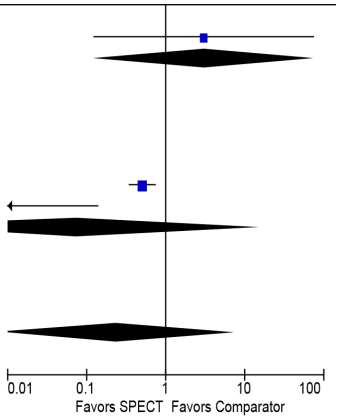
Study or Subgroup	Follow-up	Setting	Population	SPECT Events	SPECT Total	Comparator Events	Comparator Total	Weight	Risk Ratio [95% CI]
SPECT vs ECHO									
Sharples 2007	18 months	OP, Stable	Suspected or known CAD*	175	224	169	226	30.2%	1.04 [0.94, 1.16]
Salame 2018	1 month	ED/Hospital, Acute	Suspected or known CAD*	2	116	5	113	14.1%	0.39 [0.08, 1.97]
Subtotal (95% CI)					340		339	44.3%	1.04 [0.77, 1.24]
Total events				177		174			
Heterogeneity: Tau² = 0.17; Chi² = 1.50, df = 1 (P = 0.22); I² = 33%									
Test for overall effect: Z = 0.32 (P = 0.75)									
SPECT vs. Ex ECG									
Shaw 2011	24 months	OP, Stable	Suspected CAD†	21	384	26	388	26.7%	0.82 [0.47, 1.43]
Sabharwal 2007	19.6 months	OP, Stable	Suspected CAD†	41	250	98	207	29.0%	0.35 [0.25, 0.47]
Subtotal (95% CI)					634		595	55.7%	0.50 [0.19 1.47]
Total events				62		124			
Heterogeneity: Tau² = 0.32; Chi² = 6.92, df = 1 (P = 0.009); I² = 86%									
Test for overall effect: Z = 1.55 (P = 0.12)									
Total (95% CI)					974		934	100.0%	0.64 [0.31, 1.22]
Total events				239		298			
Heterogeneity: Tau² = 0.60; Chi² = 59.39, df = 3 (P < 0.00001); I² = 95%									
Test for overall effect: Z = 1.13 (P = 0.26)									
Test for subgroup differences: Chi² = 0.89, df = 1 (P = 0.34), I² = 0%									



*Sharples: 27% with prior MI/known CAD; population consisted of stable patients referred for outpatient non-emergent angiography. Salame: 24% with known CAD; all patients were subsequently hospitalized following presentation to the ED.
†Known/history of CAD was an exclusion criterium. Shaw included women only.

Figure 25. SPECT vs. stress echocardiography and vs. exercise ECG: Any additional NIT

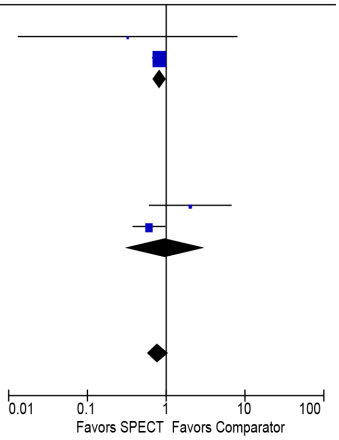
Study or Subgroup	Follow-up	Setting	Population	SPECT Events	SPECT Total	Comparator Events	Comparator Total	Weight	Risk Ratio [95% CI]
SPECT vs ECHO									
Sharples 2007	18 months	OP, Stable	Suspected or known CAD*	1	224	0	226	29.4%	3.03 [0.12, 73.90]
Subtotal (95% CI)					224		226	29.4%	3.03 [0.12, 73.90]
Total events				1		0			
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.68 (P = 0.50)									
SPECT vs. Ex ECG									
Shaw 2011	24 months	OP, Stable	Suspected CAD†	36	384	72	388	39.2%	0.51 [0.35, 0.73]
Sabharwal 2007	19.6 months	OP, Stable	Suspected CAD†	0	250	48	207	31.3%	0.01 [0.00, 0.14]
Subtotal (95% CI)					634		595	70.6%	0.11 [0.00 8.87]
Total events				36		120			
Heterogeneity: Tau² = 13.59; Chi² = 14.27, df = 1 (P = 0.0002); I² = 93%									
Test for overall effect: Z = 0.96 (P = 0.34)									
Total (95% CI)					858		821	100.0%	0.24 [0.01, 8.67]
Total events				37		120			
Heterogeneity: Tau² = 7.82; Chi² = 15.34, df = 2 (P = 0.0005); I² = 87%									
Test for overall effect: Z = 0.82 (P = 0.41)									
Test for subgroup differences: Chi² = 1.37, df = 1 (P = 0.24), I² = 27.2%									



*27% with prior MI/known CAD; population consisted of stable patients referred for outpatient non-emergent angiography.
†Known/history of CAD was an exclusion criterium. Shaw included women only.

Figure 26. SPECT vs. stress echocardiography and vs. exercise ECG: Any revascularization

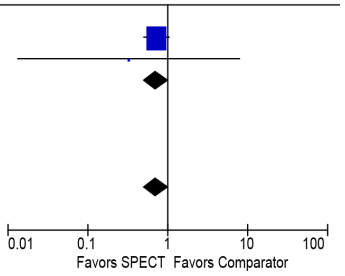
Study or Subgroup	Follow-up	Setting	Population	SPECT Events	SPECT Total	Comparator Events	Comparator Total	Weight	Risk Ratio [95% CI]
SPECT vs ECHO									
Salame 2018	1 month	ED/Hospital, Acute	Suspected or known CAD*	0	116	1	113	0.9%	0.32 [0.01, 7.89]
Thom 2014	36 months	OP, Stable	Suspected or known CAD*	98	224	121	226	63.2%	0.82 [0.67, 0.99]
Subtotal (95% CI)					340		339	64.1%	0.82 [0.53, 1.16]
Total events				98		122			
Heterogeneity: Tau² = 0.00; Chi² = 0.32, df = 1 (P = 0.57); I² = 0%									
Test for overall effect: Z = 2.10 (P = 0.06)									
SPECT vs. Ex ECG									
Shaw 2011	24 months	OP, Stable	Suspected CAD†	8	384	4	388	6.3%	2.02 [0.61, 6.66]
Sabharwal 2007	19.6 months	OP, Stable	Suspected CAD†	27	250	37	207	29.6%	0.60 [0.38, 0.96]
Subtotal (95% CI)					634		595	35.9%	0.71 [0.29 3.78]
Total events				35		41			
Heterogeneity: Tau² = 0.52; Chi² = 3.45, df = 1 (P = 0.06); I² = 71%									
Test for overall effect: Z = 0.05 (P = 0.96)									
Total (95% CI)					974		934	100.0%	0.80 [0.60, 1.09]
Total events				133		163			
Heterogeneity: Tau² = 0.03; Chi² = 4.10, df = 3 (P = 0.25); I² = 27%									
Test for overall effect: Z = 1.52 (P = 0.13)									
Test for subgroup differences: Chi² = 0.09, df = 1 (P = 0.77), I² = 0%									



*Thom: 27% with prior MI/known CAD; population consisted of stable patients referred for outpatient non-emergent angiography. Salame: 24% with known CAD; all patients were subsequently hospitalized following presentation to the ED.
†Known/history of CAD was an exclusion criterium. Shaw included women only.

Figure 27. SPECT vs. stress echocardiography and vs. exercise ECG: PCI

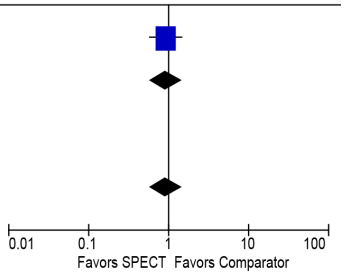
Study or Subgroup	Follow-up	Setting	Population	SPECT Events	SPECT Total	Comparator Events	Comparator Total	Weight	Risk Ratio [95% CI]
SPECT vs ECHO									
Sharples 2007	18 months	OP, Stable	Suspected or known CAD*	40	224	56	226	98.7%	0.72 [0.50, 1.03]
Salame 2018	1 month	ED/Hospital, Acute	Suspected or known CAD*	0	116	1	113	1.3%	0.32 [0.01, 7.89]
Subtotal (95% CI)					340		339	100.0%	0.71 [0.33, 1.31]
Total events				40		57			
Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 1 (P = 0.63); I² = 0%									
Test for overall effect: Z = 1.84 (P = 0.07)									
Total (95% CI)					340		339	100.0%	0.71 [0.33, 1.31]
Total events				40		57			
Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 1 (P = 0.63); I² = 0%									
Test for overall effect: Z = 1.84 (P = 0.07)									
Test for subgroup differences: Not applicable									



*Sharples: 27% with prior MI/known CAD; population consisted of stable patients referred for outpatient non-emergent angiography. Salame: 24% with known CAD; all patients were subsequently hospitalized following presentation to the ED.

Figure 28. SPECT vs. stress echocardiography and vs. exercise ECG: CABG

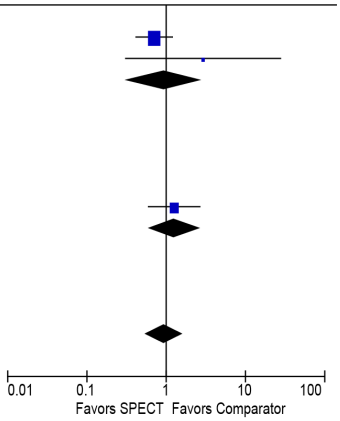
Study or Subgroup	Follow-up	Setting	Population	SPECT Events	SPECT Total	Comparator Events	Comparator Total	Weight	Risk Ratio [95% CI]
SPECT vs ECHO									
Sharples 2007	18 months	OP, Stable	Suspected or known CAD*	30	224	33	226	100.0%	0.92 [0.58, 1.45]
Salame 2018	1 month	ED/Hospital, Acute	Suspected or known CAD*	0	116	0	113		Not estimable
Subtotal (95% CI)					340		339	100.0%	0.92 [0.58, 1.45]
Total events				30		33			
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.37 (P = 0.71)									
Total (95% CI)					340		339	100.0%	0.92 [0.58, 1.45]
Total events				30		33			
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.37 (P = 0.71)									
Test for subgroup differences: Not applicable									



*Sharples: 27% with prior MI/known CAD; population consisted of stable patients referred for outpatient non-emergent angiography. Salame: 24% with known CAD; all patients were subsequently hospitalized following presentation to the ED.

Figure 29. SPECT vs. stress echocardiography and vs. exercise ECG: Cardiac-related hospitalization

Study or Subgroup	Follow-up	Setting	Population	SPECT Events	SPECT Total	Comparator Events	Comparator Total	Weight	Risk Ratio [95% CI]
SPECT vs ECHO									
Sharples 2007	18 months	OP, Stable	Suspected or known CAD*	21	224	30	226	57.1%	0.71 [0.42, 1.20]
Salame 2018	1 month	ED/Hospital, Acute	Suspected or known CAD*	3	116	1	113	5.7%	2.92 [0.31, 27.68]
Subtotal (95% CI)					340		339	62.7%	0.76 [0.39 3.19]
Total events				24		31			
Heterogeneity: Tau² = 0.32; Chi² = 1.46, df = 1 (P = 0.23); I² = 32%									
Test for overall effect: Z = 0.13 (P = 0.90)									
SPECT vs. ECG									
Shaw 2011	24 months	OP, Stable	Suspected CAD†	15	384	12	388	37.3%	1.26 [0.60, 2.66]
Subtotal (95% CI)					384		388	37.3%	1.26 [0.60, 2.66]
Total events				15		12			
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.61 (P = 0.54)									
Total (95% CI)					724		727	100.0%	0.89 [0.54, 2.14]
Total events				39		43			
Heterogeneity: Tau² = 0.06; Chi² = 2.67, df = 2 (P = 0.26); I² = 25%									
Test for overall effect: Z = 0.18 (P = 0.86)									
Test for subgroup differences: Chi² = 0.20, df = 1 (P = 0.65), I² = 0%									



*Sharples: 27% with prior MI/known CAD; population consisted of stable patients referred for outpatient non-emergent angiography. Salame: 24% with known CAD; all patients were subsequently hospitalized following presentation to the ED.
†Known/history of CAD was an exclusion criterium. This trial included women only.

7.2 SPECT versus Clinical Assessment Alone and versus NICE Guideline-Directed Care

Given that the results across the two trials comparing SPECT with clinical assessment alone and with NICE guideline-directed care showed similar results in general, they are summarized together in the bullet points below, in the strength of evidence table, and their results are presented together in the same plots/figures. However, each comparison is described in detail separately in the sections that follow. All figures corresponding to the meta-analyses can be found after the section comparing SPECT versus NICE guideline-directed care.

7.2.1 Summary of results

- There was insufficient evidence to draw conclusions regarding the risk of MI and all-cause mortality in one RCT in stable outpatients (SPECT vs. NICE guideline-directed care) with a median follow-up of 16 months and cardiac death across both RCTs, one in stable and one in acute patients (follow-up range, 1 to median 16 months). The absolute risk was ≤1.3 per 100 patients across both test arms in both trials for all outcomes. Given that these are rare events, the trials may not have been sufficiently powered to detect a difference (SOE Insufficient).
- SPECT was associated with a decreased risk of ICA across both trials (10.2 vs. 21.1 per 100, pooled RR 0.49, 95% CI 0.26 to 0.95, I^2=85%; pooled RD –11.1%, 95% CI –14.4% to –7.8%) (SOE Low); the association was stronger in the trial comparing SPECT versus NICE guideline-directed care, likely due the direct referral to ICA of patients with high pretest risk per the NICE guideline algorithm, and could account for much of the heterogeneity in the pooled estimate. SPECT was also associated with a decreased risk of ICA showing no obstructive CAD (1 RCT, SPECT vs. clinical assessment alone: 21.9 vs. 39.3 per 100 patients; RR 0.56, 95% CI 0.32 to 0.96; RD –17.4%, 95% CI –33.3% to –1.4%) and unnecessary ICA (1 RCT, SPECT vs. NICE guideline-directed care: 7.1 vs. 28.8 per 100 patients; RR 0.25, 95% CI 0.17 to 0.36; RD –21.7%, 95% CI –27.9% to –15.5%) (SOE: Low for both).
- There was no difference between SPECT and clinical assessment alone or NICE guideline-directed care in the risk of any revascularization (2 RCTs, 5.9 vs. 7.0 per 100 patients; RR 0.85, 95% CI 0.57 to 1.28, I^2=0%) (SOE Low).
- SPECT was associated with decreased risk of additional downstream NIT over 12 months (12.1 vs. 68.3 per 100 patients; RR 0.18, 95% CI 0.15 to 0.21; RD –56.2%, 95% CI –60.7% to –51.7%) and hospitalization at the index visit (10.2 vs. 18.5 per 100 patients; RR 0.55, 95% CI 0.42 to 0.71; RD –8.3%, 95% CI –12.2% to –4.4%) compared with clinical assessment alone in one trial (SOE Low for both).

7.2.2 SPECT versus Clinical Assessment Alone

One trial (N=1,508)[142] compared Tc-99m tetrofosmin SPECT imaging (n=1,004) with clinical assessment only (n=504) in acute patients with suspected ACS presenting to the ED (See Appendix Q). All patients first underwent standard observation (continuous 12-lead ECG monitoring and cardiac biomarkers) over

a 6-hour period; only those who had a negative 6-hour observation received their randomly assigned protocol. Mean patient age was 52 years, 41% were female, and 69% were Chinese. A small number of patients had known CAD (4%) or had suffered a prior MI (1%). Patients had the following cardiac risk factors: hypertension (42%), smoker (32%) and diabetes (18%). Stress SPECT was performed using exercise (preferred) or dipyridamole or dobutamine if pharmacological stressors were required. Patients in the clinical assessment group were assessed for the likelihood of ACS by the emergency medicine physician based on patients' characteristics and cardiac risk factors and ECG results; 82% were considered intermediate or high risk and 18% were considered low risk. Patients considered to be at intermediate or high risk per physician assessment were admitted to the hospital. Pretest risk was not reported for those randomized to SPECT. The follow-up period was 12 months. This trial was conducted in Singapore and received government grants.

This trial was considered fair quality; it was unclear if outcome assessors were blinded and attrition at 12 months was unclear. See Appendix D for details regarding study quality determination.

Detailed results

7.2.2.1 Key Question 1: Primary Outcomes (MI, all-cause mortality, cardiac death)

Cardiac mortality

Over 12 months of follow-up, three cardiac deaths were reported, and all occurred in the SPECT arm after 30 days (0.3 vs. 0 per 100 patients), Figure 30. The trial did not report the outcomes of MI and all-cause mortality.

Other outcomes

The incidence of cardiac events (composite outcome defined as cardiac-related death, ventricular fibrillation, MI, cardiogenic shock, or acute pulmonary oedema requiring endotracheal intubation) was similar between SPECT and clinical assessment alone at the end of follow-up (0.7 vs. 1 per 100 patients; RR 0.70, 95% CI 0.22 to 2.20); most events occurred within 30 days (0.4 vs. 0.8 per 100 patients; RR 0.5, 95% CI 0.13 to 2.0).

7.2.2.2 Key Question 2: Clinical decision making

Additional testing

SPECT was associated with fewer referrals for ICA compared with clinical assessment over 12 months: 7.3 versus 11.1 per 100 patients, RR 0.65 (95% CI 0.47 to 0.91), RD –3.8% (95% CI –7.0% to –0.7%), Figure 31. For those who underwent ICA, fewer patients in the SPECT group did not show significant CAD compared to the clinical assessment group: 21.9 versus 39.3 per 100 patients; RR 0.56 (95% CI 0.32 to 0.96), RD –17.4% (95% CI –33.3% to –1.4%). SPECT was also associated with less additional noninvasive testing of any type over 12 months (12.1 vs. 68.3 per 100 patients; RR 0.18, 95% CI 0.15 to 0.21; RD –56.2%, 95% CI –60.7% to –51.7%) as well as noninvasive stress testing requiring imaging (2.6 vs. 32.3 per 100 patients; RR 0.08, 95% CI 0.05 to 0.12; RD –29.8%, 95% CI –34.0% to –25.6%) and requiring radiation

(1.6 vs. 23.8 per 100 patients; RR 0.07, 95% CI 0.04 to 0.11; RD –22.2%, 95% CI –26.0% to –18.4%). The majority of additional testing was resting echocardiography in the SPECT group and equal proportions of SPECT and exercise ECG in the clinical assessment group.

Treatment

There was no difference between the SPECT and clinical assessment groups in the rate of any revascularization procedure over 12 months (4.8 vs. 6.2 per 100 patients; RR 0.78, 95% CI 0.50 to 1.21), Figure 32.

Hospitalization

SPECT was associated with an almost 50% reduction in hospitalization at index testing compared with clinical assessment (10.2 vs. 18.5 per 100 patients; RR 0.55, 95% CI 0.42 to 0.71; RD –8.3%, 95% CI –12.2% to –4.4%). In the clinical assessment arm, 94% of patients admitted to the hospital were considered intermediate or high risk for ACS according to the attending physician. The frequency of subsequent hospitalization following the index visit was not reported.

7.2.3 SPECT versus NICE guideline-directed care

One good-quality trial (N=721)[88] compared Tc-99m tetrofosmin or sestamibi SPECT (n=481) imaging versus NICE guideline-directed care (n=240) in stable patients with suspected CAD treated on an outpatient basis (See Appendix Q). A history of prior MI and prior revascularization were exclusion criteria. Mean patient age was 56 years, 47% of patients were female, and 92% were Caucasian. Patients presented with atypical (67%) and typical angina (33%) and had the following cardiac risk factors: former or current smoker (58%), family history of CAD (55%), dyslipidemia (41%), hypertension (39%), diabetes (13%), cerebrovascular disease (3%) and peripheral vascular disease (3%). Group allocation was stratified by the pretest likelihood of CAD (as well as age, sex, and center) which was determined according to NICE guidelines CG95; the pretest risk was 10% to 29% in 26%, 30% to 60% in 38%, and 61% to 90% in 36% of the population. Patients randomized to the NICE guideline group received specific diagnostic tests based on their pretest risk: those at a pretest risk of 10% to 29% received cardiac CT; 30% to 60% received SPECT; and 61% to 90% proceeded directly to ICA. In the SPECT group, stress imaging was performed using treadmill exercise as the default, with adenosine stress for those who could not exercise. Follow-up was a median 16 months (12 months minimum). This trial was conducted in the United Kingdom and received professional research grants.

See Appendix D for details regarding study quality determination.

Detailed results

7.2.3.1 Key Question 1: Primary Outcomes (MI, all-cause mortality, cardiac death)

Myocardial infarction, all-cause mortality and cardiac mortality

There were no differences between the SPECT and NICE guideline-directed care groups in the incidence of MI (0.4 vs. 0.8 per 100 patients; RR 0.50, 95% CI 0.07 to 3.52), all-cause mortality (0.6 vs. 1.3 per 100 patients; RR 0.50, 95% CI 0.10 to 2.45), and cardiac mortality (0.6 vs. 0.4 per 100 patients; RR 1.50, 95% CI 0.16 to 14.31; Figure 30) over a median follow-up of 16 months.

Other Outcomes

There were no differences between the SPECT and NICE guideline-directed care groups in the incidence of MACE, a composite outcome of cardiovascular death, MI, unplanned revascularization or hospital admission for cardiac causes (3.1 vs. 2.5 per 100 patients; RR 1.24, 95% CI 0.49 to 3.17), heart failure (0.8 vs. 0 per 100 patients), stroke or TIA (0.2 vs. 0 per 100 patients), and arrhythmia (0.6 vs. 0.8 per 100 patients; RR 0.75, 95% CI 0.13 to 4.45) over a median follow-up of 16 months.

7.2.3.2 Key Question 2: Clinical decision making

Additional testing

SPECT was associated with a decreased incidence of ICA compared with NICE guideline-directed care up to 12 months of follow-up: 16.2 versus 42.5 per 100 patients; RR 0.38, 95% CI 0.30 to 0.49; RD –26.3%, 95% CI –33.4% to –19.2% (Figure 31). Unnecessary ICA (as described by the authors) was also less common following SPECT versus NICE guideline-directed care: 7.1 versus 28.8 per 100 patients; RR 0.25, 95% CI 0.17 to 0.36; RD –21.7%, 95% CI –27.9% to –15.5%. The primary reasons cited for an unnecessary ICA included a negative noninvasive test overruled by the attending physician (4.4 per 100 patients) and a false-positive test (2.5 per 100 patients) in the SPECT group, and direct referral to ICA (per algorithm) for patients with high pretest likelihood in the guideline-directed care group (24.6 per 100 patients). This trial did not report on additional noninvasive testing.

Treatment

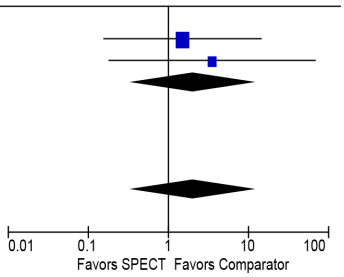
The frequency of any revascularization procedure over 12 months was similar between the SPECT and NICE guideline-directed care groups, respectively, (8.3 vs. 8.8 per 100 patients; RR 0.95, 95% CI 0.57 to 1.57), Figure 32, as was the frequency of PCI (5.6 vs. 5.8 per 100 patients; RR 0.96, 95% CI 0.51 to 1.80) and CABG (2.7 vs. 2.9 per 100 patients; RR 0.93, 95% CI 0.37 to 2.29) specifically. In both groups 0.8% of patients had an unplanned PCI over a median follow-up of 16 months (RR 1.0, 95% CI 0.18, to 5.41). There were no unplanned CABGs performed.

Hospitalization and ED visits

This trial did not report hospitalization or ED visits.

Figure 30. SPECT vs. NICE Guideline/Standard Care: Cardiac mortality

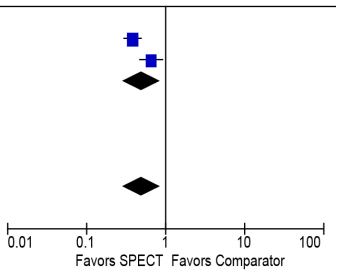
Study or Subgroup	Follow-up	Setting	Population	SPECT Events	SPECT Total	Comparator Events	Comparator Total	Weight	Risk Ratio [95% CI]
SPECT vs. NICE Guideline/Standard Care									
Greenwood 2017	16 months	OP, Stable	Suspected CAD	3	481	1	240	63.2%	1.50 [0.16, 14.31]
Lim 2013	12 months	ED/Hospital, Acute	Suspected ACS	3	1004	0	504	36.8%	3.52 [0.18, 67.96]
Subtotal (95% CI)					1485		744	100.0%	2.04 [0.25, 19.09]
Total events				6		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.65); I² = 0%									
Test for overall effect: Z = 0.78 (P = 0.43)									
Total (95% CI)					1485		744	100.0%	2.04 [0.25, 19.09]
Total events				6		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.65); I² = 0%									
Test for overall effect: Z = 0.78 (P = 0.43)									
Test for subgroup differences: Not applicable									



Greenwood = NICE guideline-directed care; Lim = Clinical assessment only.

Figure 31. SPECT vs. NICE Guideline/Standard Care: ICA

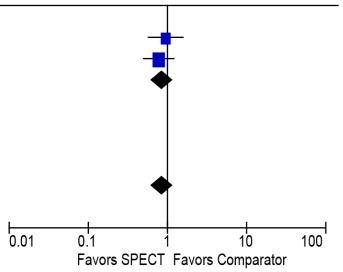
Study or Subgroup	Follow-up	Setting	Population	SPECT Events	SPECT Total	Comparator Events	Comparator Total	Weight	Risk Ratio [95% CI]
SPECT vs. NICE Guideline/Standard Care									
Greenwood 2017	16 months	OP, Stable	Suspected CAD	78	481	102	240	52.1%	0.38 [0.30, 0.49]
Lim 2013	12 months	ED/Hospital, Acute	Suspected ACS	73	1004	56	504	47.9%	0.65 [0.47, 0.91]
Subtotal (95% CI)					1485		744	100.0%	0.49 [0.26, 0.95]
Total events				151		158			
Heterogeneity: Tau² = 0.12; Chi² = 6.55, df = 1 (P = 0.01); I² = 85%									
Test for overall effect: Z = 2.60 (P = 0.009)									
Total (95% CI)					1485		744	100.0%	0.49 [0.26, 0.95]
Total events				151		158			
Heterogeneity: Tau² = 0.12; Chi² = 6.55, df = 1 (P = 0.01); I² = 85%									
Test for overall effect: Z = 2.60 (P = 0.009)									
Test for subgroup differences: Not applicable									



Greenwood = NICE guideline-directed care; Lim = Clinical assessment only.

Figure 32. SPECT vs. NICE Guideline/Standard Care: Any revascularization

Study or Subgroup	Follow-up	Setting	Population	SPECT Events	SPECT Total	Comparator Events	Comparator Total	Weight	Risk Ratio [95% CI]
SPECT vs. NICE Guideline/Standard Care									
Greenwood 2017	16 months	OP, Stable	Suspected CAD	40	481	21	240	43.0%	0.95 [0.57, 1.57]
Lim 2013	12 months	ED/Hospital, Acute	Suspected ACS	48	1004	31	504	57.0%	0.78 [0.50, 1.21]
Subtotal (95% CI)					1485		744	100.0%	0.85 [0.57, 1.28]
Total events				88		52			
Heterogeneity: Tau² = 0.00; Chi² = 0.35, df = 1 (P = 0.56); I² = 0%									
Test for overall effect: Z = 0.98 (P = 0.33)									
Total (95% CI)					1485		744	100.0%	0.85 [0.57, 1.28]
Total events				88		52			
Heterogeneity: Tau² = 0.00; Chi² = 0.35, df = 1 (P = 0.56); I² = 0%									
Test for overall effect: Z = 0.98 (P = 0.33)									
Test for subgroup differences: Not applicable									



Greenwood = NICE guideline-directed care; Lim = Clinical assessment only.

7.3 SPECT versus ICA

One good-quality trial (N=446)[220,241] compared SPECT versus invasive coronary angiography (ICA) in patients with suspected or known (25% with prior MI) stable CAD referred for outpatient angiography (See Appendix Q). Referral to angiography was based on the results of an exercise ECG complete within 1 month of enrollment, the results of which were not available to the trial personnel. Patients in the SPECT arm were randomized to undergo rest and stress 99m Tc sestamibi SPECT with adenosine (or dobutamine if adenosine was contraindicated) while those randomized to the control arm underwent ICA as originally planned. Mean patient age was 61 years, and 69% were male. Patients were considered high-risk (69%) or low-risk (31%) according to the Pryor risk assessment and randomization was stratified based on pretest risk. Baseline cardiac risk factors included prior cerebrovascular accident (5%), peripheral vascular disease (9%), diabetes (12%), family history of CAD (26%), hypertension (56%), hyperlipidemia (75%), and smoking (44%). Patients were on a variety of cardiovascular related medications at baseline including antiplatelets, statins, and beta-blockers primarily as well as ACE inhibitors, calcium channel blockers, nicorandil, nitrates, diuretics, and angiotensin-II receptor antagonists. The primary follow-up period was 18 months. The secondary publication by Thom et al. (focused on cost-effectiveness) provided mortality data out to 72 months and post-index revascularization rates out to 32 months. This trial was conducted in the United Kingdom and funded by the National Institute for Health Research.

See Appendix D for details regarding study quality determination.

7.3.1 Summary of results

- There was insufficient evidence to draw conclusions regarding the risk of MI, all-cause mortality and cardiac mortality between groups. Over 18 months, the absolute risk was ≤2 per 100 patients across both test arms for all outcomes; at 72 months, the absolute risk of all-cause mortality was 3 per 100 patients. Given that these are rare events, the trial may not have been sufficiently powered to detect a difference (SOE Insufficient).
- Compared with ICA, SPECT was associated with a decreased risk of any revascularization after the index visit through 36 months (43.8 vs. 53.2 per 100 patients; RR 0.82, 95% CI 0.68 to 0.99; RD –9.4%, 95% CI –18.6% to –0.2%) (SOE Low). There was no difference in the risk of any hospitalization for chest pain (SOE Low).
- There was insufficient evidence to draw conclusions regarding impact of testing strategies on additional downstream NIT (SOE Insufficient).

Detailed results

7.3.2 Key Question 1: Primary Outcomes (MI, all-cause mortality, cardiac death)

Myocardial infarction, all-cause mortality and cardiac mortality

Two patients randomized to SPECT compared with no patient randomized to ICA were admitted for acute MI over the 18-month follow-up (0.9 vs. 0 per 100 patients; p=0.16)[220], Table 49. There were no differences in the incidence of all-cause (1.8 vs. 1.8 per 100 patients) or cardiac (2.2 vs. 1.4 per 100 patients) mortality between diagnostic strategies by 18 months[220] or for all-cause mortality through 72 months (3.1 vs. 3.2 per 100 patients; RR 0.99, 95% CI 0.35 to 2.78)[241].

Other clinical outcomes

There was no difference between diagnostic strategies for the composite outcomes of any nonfatal event and any fatal plus nonfatal event at 18 months, or in the proportion of patents achieving a clinically significant improvement in Canadian Cardiovascular Society angina class (Table 49). There were no differences between SPECT and ICA on all subscales of the Seattle Angina Questionnaire or on the SF-36 health-related quality of life questionnaire at 6 and 18 months (Appendix Table O6).

7.3.3 Key Question 2: Clinical decision making

Additional testing

Most patients (78%) in the SPECT arm went on to get subsequent ICA during the 18-month follow-up. No patient in the ICA arm required repeat ICA. SPECT was associated with less additional noninvasive testing compared with ICA (0.4 vs. 3.6 per 100 patients; RR 0.12, 95% CI 0.02 to 0.98; RD –3.2%, 95% CI –5.8% to –0.6%)[220], Table 49; all but one additional test was SPECT imaging. The timing of additional noninvasive testing was unclear.

Treatment

Similar proportions of patients received revascularization following index testing with stress echocardiography versus ICA (30.4 vs. 34.2 per 100 patients, respectively; RR 0.89, 95% CI 0.68 to 1.16), to include rates of PCI and CABG.[220] However, SPECT was associated with a lower cumulative rate of revascularization over 36 months versus ICA (43.8 vs. 53.2 per 100 patients; RR 0.82, 95% CI 0.68 to 0.99; RD –9.4%, 95% CI –18.6% to –0.2%)[241], Table 49.

Hospitalization

There was no difference in the proportion of patients admitted for chest pain over 18 months in the stress echocardiography arm versus the ICA arm: 8.5 versus 6.3 per 100 patients, RR 1.35 (0.69 to 2.62)[220], Table 49.

Table 49. SPECT vs. ICA: Summary of primary and clinical decision making outcomes

Author, year RCT	Outcome	Timepoint	SPECT	ICA	Risk Ratio (95% CI)
Sharples 2007 Thom 2014 CECaT Suspected and known CAD Low (21%) and high (69%) risk.	**Admission for acute MI**	18 months	0.9% (2/224)	0% (0/222)	NC, p=0.16
	All-cause mortality	18 months	1.8% (4/224)	1.8% (4/222)	0.99 (0.25 to 3.91)
		72 months	3.1% (7/224)	3.2% (7/222)	0.99 (0.35 to 2.78)
	Cardiac mortality	18 months	2.2% (5/224)	1.4% (3/222)	1.65 (0.40 to 6.83)
	Total nonfatal events*	18 months	10.7% (24/224)	8.6% (19/222)	1.25 (0.71 to 2.22)
	Total nonfatal plus fatal events	18 months	16.4% (29/224)	10.8% (24/222)	1.20 (0.72 to 2.00)
	ICA/additional ICA	18 months	78.1% (175/224)	0% (0/222)	NC, p<0.001
	Additional noninvasive testing	18 months	0.4% (1/224)	3.6% (8/222)	0.12 (0.02 to 0.98)
	SPECT	18 months	0.4% (1/224)	3.2% (7/222)	0.14 (0.02 to 1.14)
	MRI	18 months	0% (0/224)	0.5% (1/222)	NC, p=0.32
	Revascularization (any)	Index Management	30.4% (68/224)	34.2% (76/222)	0.89 (0.68 to 1.16)
		36 months (cumulative)	43.8% (98/224)	53.2% (118/222)	0.82 (0.68 to 0.99)
	PCI	Index Management	17.4% (39/224)	24.8% (55/222)	0.70 (0.49 to 1.01)
	CABG	Index Management	12.9% (29/224)	9.5% (21/222)	1.37 (0.80 to 2.33)
	Unplanned PCI	18 months	0.4% (1/224)	1.8% (4/222)	0.25 (0.03 to 2.20)
	Unplanned CABG	18 months	0.4% (1/224)	1.4% (3/222)	0.33 (0.03 to 3.15)
	Admission for chest pain	18 months	8.5% (19/224)	6.3% (14/222)	1.35 (0.69 to 2.62)
	Significant improvement in CCS angina class (≥2 decrease)	6 months	33% (66/224)	32% (66/222)	0.99 (0.74 to 1.32)
		18 months	42% (87/224)	32% (65/222)	1.33 (1.02 to 1.72)

ACP = acute chest pain; ACS = acute coronary syndrome; Adj = adjusted statistically; CABG = coronary artery bypass graft; CCCS = Canadian Cardiovascular Society; CI = confidence interval; ICA = invasive coronary angiography; MD = mean difference; MI = myocardial infarction; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; SD = standard deviation; SF-36 = Short-Form 36 quality of life questionnaire.
*Includes admission for chest pain or acute MI, unplanned PCI or CABG, and other (other for the SPECT group = 1 post-CABG wound infection, 1 admission for breathlessness, 1 admission for ICD implant, 1 admission for suspected MI found to be muscular pain, 1 seen in A&E with chest pain in SPECT; and for the ICA group = 1 CVA post-ICA, observed overnight).

7.3.4 Key Question 3: Safety

Summary of results

- Test-related complications appear to be rare following SPECT in one good-quality trial (SOE Low).
- Data from one fair-quality trial was insufficient to draw conclusions regarding radiation exposure (SOE Insufficient). Mean exposure following SPECT was 14 mSv; exercise ECG does not use radiation.
- Adverse events from stress agents are relatively common and ranged from 2% to 13% of patients (5% to 37% of events) for dipyridamole and from 4% to 53% for regadenoson; the most

common events included headache, dyspnea, GI upset/nausea and dizziness or lightheadedness (SOE Low). Most reported symptoms are expected responses to the pharmacologic agents used.

Safety data were poorly reported by the included RCTs evaluating SPECT imaging as a first line diagnostic test. One fair-quality trial comparing SPECT with exercise ECG in a population of only women with stable angina and suspected CAD reported mean ionizing radiation exposure following index SPECT testing which was 14 mSv.[223] A second, good-quality trial comparing SPECT with NICE-guideline directed care reported that five test-related medical complications occurred, but none were following SPECT imaging.[88] The complications included one case of mild urticarial reaction following cardiac MRI, one vasovagal episode following cardiac CT, and one each of ventricular tachycardia, pseudo-aneurysm and popliteal deep venous thrombosis, and right coronary artery spasm and transient ST elevation following ICA. No further information was provided.

Given the lack of safety data reported by the included RCTs, additional studies reporting test-specific adverse events related to SPECT were evaluated for inclusion and are summarized below. See Appendix O for detailed results tables.

Adverse events related to Regadenoson and Dipyridamole

Three studies were identified that evaluated regadenoson or dipyridamole as stressor agents for SPECT MPI in patients with suspected or known CAD: two case series (one of regadenoson[134] and one of dipyridamole[158]) and one retrospective comparative cohort study comparing regadenoson versus dipyridamole.[13] For the purposes of this report, each arm of the comparative cohort was treated as a case series.

Across the two studies[13,158] reporting AEs following dipyridamole use for SPECT (N=284 patients in one study and N=604 adverse events in the other), the most common events included headache (13% of patients in one study; 37% of all AEs in the other), gastrointestinal upset/nausea (8% of patients; 11% of all AEs), chest pain (4% of patients; 12% of all AEs), dizziness or lightheadedness (6% of patients; 5% of all AEs), flushing (4% of patients; 8% of all AEs), and dyspnea (2% of patients; 5% of all AEs).

Across the two studies[13,134] reporting AEs following regadenoson use for SPECT (N=96 and 284), the most common events included dyspnea (30% and 53%), gastrointestinal upset/nausea (28% and 3%), chest pain (9% and 16%), dizziness or lightheadedness (8% and 13%), headache (7% and 12%), and flushing (4% and 6%).

Most reported symptoms are expected responses to the pharmacologic agents used. All reported side effects can be found in Appendix O, Table O26.

7.3.5 Key Question 4: Differential Effectiveness and Safety

None of the included trials evaluating SPECT versus stress echocardiography, exercise ECG, clinical assessment alone or NICE-guideline directed care reported safety or differential effectiveness or safety.

8 Positron Emission Tomography (PET) Results

8.1 PET versus SPECT

Two trials (total N=540) evaluated the effectiveness of PET compared with SPECT across different patient populations.

One trial (N=210)[168] randomized stable patients with a mixed of suspected (70%) or known (30%) CAD to initial diagnostic testing with PET versus SPECT in an outpatient setting. The mean patient age was 64 years, and 50% of patients were female. Presenting symptoms included any chest pain in 37%, shortness of breath in 16% and atypical angina in 15%. Baseline risk factors included high blood pressure in 49%, a family history of CAD in 19%, high cholesterol in 13% and congestive heart disease in 3%; in addition, 13% had undergone prior coronary angiography and 11% had a prior MI. PET imaging was performed using Rb-chloride for the radioactive tracer; all patients received dipyridamole as the stressor. SPECT imaging was performed using TI-chloride and Tc-labeled Sestamibi for radioactive tracers (dual-isotope technique); 94% of patients received dipyridamole as the stressor and 6% received dobutamine. Follow-up was a mean of 9 months (range, 6 to 12 months). This trial was conducted in the United States and funding was provided, in part, by industry (Bracco Diagnostics, Positron Corporation). This trial was rated as poor quality. Methodological limitations included unclear randomization and allocation concealment methods, lack of independent or blinded outcomes assessment, difference in sex (a key CAD risk factor) at baseline between treatment groups, and it was unclear whether there was comparable follow-up time between treatment groups.

The second trial (N=322)[189] randomized stable patients with known CAD presenting with new or worsening symptoms to receive PET versus SPECT in an outpatient setting. History of CAD was defined as presence of prior MI or prior coronary revascularization. The mean age of patients was 66 years, and 36% were female. Presenting symptoms included typical chest pain in 33%, atypical chest pain in 27%, non-anginal chest pain in 21%, and shortness of breath in 68%. Baseline cardiac risk factors included hyperlipidemia (99%), hypertension (90%), family history of cerebrovascular disease (43%), diabetes (28%), peripheral vascular disease (27%), smoking (18%), and prior cerebrovascular accident (15%). Sixteen percent of patients had atrial fibrillation. Regarding baseline medications, 89% of patients were taking aspirin, 78% were on 3 or more antianginal medications, 77% were on beta-blocker therapy, and 77% were on a statin. Both PET and SPECT imaging was performed using Tc-99m Sestamibi, RB-82 for the radioactive tracer and all patients in both groups received dipyridamole or regadenoson as the stressor. Follow-up was 12 months. This trial was conducted in the United States and funding was provided by Blue Cross Blue Shield. This trial was considered good quality.

8.1.1 Summary of results

- In the good-quality trial in patients with known CAD and new or worsening symptoms, the absolute risks of MI and all-cause mortality were ≤1 per 100 patients across both the PET and SPECT arms over 12 months, however the evidence was considered insufficient to draw conclusions (SOE Insufficient). There was no difference in the risk of ICA (29 vs. 28 per 100

patients); of diagnostic failure, defined as unnecessary ICA or additional confirmatory noninvasive testing within 2 months (2.0 vs. 2.5 per 100 patients); of any revascularization (16 vs. 15 per 100 patients); and of escalation in antianginal therapy (26 vs. 23 per 100 patients) (SOE Low for all).
- The only outcome reported by the older, poor-quality trial evaluating a mixed population of suspected and known CAD was cardiac mortality (absolute risk 3 vs. 4 in 100 patients over a mean 9 months) (SOE Insufficient).
- Neither trial reported on test safety or on differential effectiveness or safety.

Detailed results

Across both trials, there were no difference in any of the reported outcomes for patients randomized to PET versus SPECT (Table 50).

8.1.2 Key Question 1: Primary Outcomes (MI, all-cause mortality, cardiac death)

In the good-quality trial in patients with known CAD and new or worsening symptoms, the absolute risks of MI and all-cause mortality were ≤1 per 100 patients across both the PET and SPECT arms over 12 months.[189] The only outcome reported by the older, poor-quality trial evaluating a mixed population of suspected and known CAD was cardiac mortality (absolute risk 3 vs. 4 in 100 patients over a mean 9 months).[168] See **Error! Reference source not found.** for data.

8.1.3 Key Question 2: Clinical decision making

Over 12 months, the risk of ICA was 29 versus 28 per 100 patients; of any revascularization was 16 versus 15 per 100 patients; and of escalation in antianginal therapy was 26 versus 23 per 100 patients, for PET versus SPECT, respectively, in the good-quality trial.[189] The risk of diagnostic failure, defined as unnecessary ICA or additional confirmatory noninvasive testing within 2 months, was 2.0 versus 2.5 per 100 patients. See Table 50 for data. There was no difference on any of the SAQ subscales or in the Rose Dyspnea Score between test arms (Appendix H).

Table 50. Summary of primary clinical and decision-making outcomes for comparison of PET with SPECT

Study	Outcome	F/U	PET % (n/N)	SPECT % (n/N)	RR (95% CI)*
Mullani 2000 Mixed suspected or known CAD	Cardiac mortality†	Mean 9 (range 6-12) months	3% (3/105)	4% (4/105)	RR 0.75 (0.17, 3.27)
Patel 2019 Known CAD	MI (not specified)	12 months	0% (0/161)	1.2% (2/161)	NC, p=NS
	All-cause mortality	12 months	1% (1/161)	1.2% (2/161)	RR 0.50 (0.04, 5.46)
	Invasive coronary angiography	3 months	20.5% (33/161)	15.5% (25/161)	RR 1.32 (0.82, 2.11)
		6 months	22.4% (36/161)	18.6% (30/161)	RR 1.20 (0.78, 1.85)

		12 months	28.6% (46/161)	28.0% (45/161)	RR 1.02 (0.72, 1.45)
	Obstructive disease on angiography‡	3 months	15.5% (25/161)	10.6% (17/161)	RR 1.47 (0.83, 2.62)
	Diagnostic failure§	2 months	1.9% (3/161)	2.5% (4/161)	RR 0.75 (0.17, 3.30)
	Revascularization (PCI/CABG)	3 months	11.2% (18/161)	9.9% (16/161)	RR 1.13 (0.60, 2.13)
		6 months	12.4% (20/161)	11.8% (19/161)	RR 1.05 (0.58, 1.90)
		12 months	15.5% (25/161)	14.9% (24/161)	RR 1.04 (0.62, 1.74)
	Late revascularization after 3 months**	3 months	4.3% (7/161)	5.0% (8/161)	RR 0.88 (0.32, 2.36)
	Escalation in anti-anginal therapy††	3 months	25.5% (41/161)	23.0% (37/161)	RR 1.11 (0.75, 1.63)

CAD = coronary artery disease; MI = myocardial infarction; NC = not calculable; PET = positron emission tomography; RR = risk ratio; SPECT = single photon emission computed tomography
*Calculated unless otherwise indicated.
†2 of the deaths occurred in patients with prior history of CAD (3% [1/31] PET vs. 3% [1/31] SPECT), whereas 5 deaths occurred in patients with no prior history of CAD (3% [2/74] PET vs. 4% [3/73] SPECT).
‡Defined as stenosis of ≥ 50% of the left main coronary artery or ≥ 70% of a major epicardial or branch vessel or ≥ 70% of a graft vessel with occluded flow by native circulation for patients with history of coronary bypass graft surgery.
§Defined as unnecessary coronary angiography (i.e. absence of ≥ 50% stenosis in ≥1 vessels should the patient have undergone angiography) or additional confirmatory non-invasive testing such as repeat MPI, stress echo, of CCTA within 60 days of the baseline MPI
**Defined as the cumulative number of patients that had revascularization after 3 months.
††Defined as addition of another anti-anginal medication class or increase in dose or frequency of one or more of existing anti-anginal medications within 3 months post baseline MPI

8.1.4 Key Question 3: Safety

Neither trial reported on adverse events related to the diagnostic tests or radiation exposure.

8.1.5 Key Question 4: Differential Effectiveness and Safety

Neither trial reported differential effectiveness or safety.

9 Stress Echocardiography Results

Six trials (across 8 publications) evaluated the effectiveness and/or safety of stress echocardiography compared with exercise ECG (5 RCTs)[48,91,117,180,211,262], "standard care" (1 RCT)[180], and ICA (1 RCT)[220,241]. One trial included both an exercise ECG and a standard care comparison arm[180].

9.1 Stress Echocardiography versus Exercise ECG

Among the five trials comparing stress echocardiography with exercise ECG, two (total N=543) included stable patients with suspected CAD (known CAD was an exclusion criteria) treated on an outpatient basis (See Appendix Q). Mean patient age was 54 years in both trials. One trial enrolled only women[211] while in the second trial most of the population was male (68%). In the latter trial, patients' pre-test risk was considered low (41%), intermediate (34%), and high (25%); the other trial did not report pre-test risk. Regarding cardiac risk factors, there was a similar proportion of patients with diabetes in both trials (8% and 9%) but a greater proportion of patients with hypertension (49% and 18%), smoking history (21% and 8%), and family history of CAD (23% and 13%) in the trial enrolling women only. The latter trial, 42% of patients had hyperlipidemia and 76% were postmenopausal. Neither trial reported baseline pharmacological treatments. In one trial, patients in both arms underwent treadmill exercise using the standard Bruce protocol; in the echocardiography arm, intravenous contrast (Sonovue) was used as needed in technically difficult patients.[91,262] In the second trial, both treadmill exercise and pharmacological stressor (dobutamine) was used in the echocardiography arm depending on patient capability with no mention of whether contrast was used; treadmill exercise was used in the ECG arm. Mean follow-up periods were 28 and 36 months. One trial was conducted in the United Kingdom and the other in Canada. Both were funded by clinical research grants.

The remaining three trials (total N=854) comparing stress echocardiography with exercise ECG included patients with acute symptoms presenting to the ED or hospital (See Appendix Q). One RCT included low-risk patients with suspected ACS[180], one included patients with suspected or known CAD (27% with known ischemic heart disease) at primarily low (21%)-to-intermediate (69%) pretest risk[117], and the third (COSTAMI-II) included patients presenting with uncomplicated acute MIs.[48] Mean patient age ranged from 51 to 60 years across the trials. The majority of patients in all trials were male, with considerably more males in the trial evaluating those with uncomplicated MIs (57% to 61% vs. 87%). Regarding cardiac risk factors, the proportion of patients with prior MI ranged from 3% to 15%, prior revascularization from 3% to 25% (PCI, 2%–14% and CABG, 1%–11% in the 2 trials that reported it), hypertension from 36% to 66%, diabetes from 9% to 24%, and smoking from 44% to 63%. Pharmacological treatment at baseline varied across the populations. In the trial of low-risk patients with suspected ACS, 20% were taking antiplatelets, 13% beta-blockers, 11% calcium channel blockers, and 9% nitrates.[180] In the trial of low-to-intermediate risk patients with suspected or known CAD, 82% were taking aspirin, 52% statins, 41% beta-blockers and clopidogrel, 34% ACE inhibitors, and 23% calcium channel blockers.[117] The trial of uncomplicated MI patients did not report baseline medications. Two trials used dobutamine/atropine in the echocardiography arm while the third used either dobutamine or exercise as the stressor. Treadmill exercise was used in the ECG arms. Follow-up periods

ranged from 2 to 24 months. Two trials were conducted at multiple hospitals across several European countries[117,180] and one was conducted in the United Kingdom. One trial received support from professional societies[48] and the remaining two did not report any sources of funding.

One trial was considered good quality[91,262], one fair-quality[48] and three poor quality.[117,180,211] Methodological shortcomings in the fair quality trial included unclear allocation concealment methods, lack of blinding of outcome assessors and unclear attrition. Additional limitations in the poor-quality trials included unclear randomization sequence, between group differences at baseline on key CAD risk factors, and lack of a prespecified definition for a positive test in one trial. Both good-quality trials were in stable patients with suspected CAD. See Appendix D for details regarding study quality determination.

9.1.1 Summary of results

- There was insufficient evidence to draw conclusions regarding the risk of MI, all-cause mortality and cardiac mortality following stress echocardiography versus exercise ECG across the five trials. The absolute risks of MI and all-cause mortality across four trials were 1.3 vs. 0.9 and 0.6 vs. 0.9 per 100 patients, respectively, across follow-up periods ranging from 2 to 36 months. The absolute risk of cardiac mortality in one RCT was 0.5 vs. 0 at 36 months. Given that these are rare events, the trial may not have been sufficiently powered to detect a difference (SOE Insufficient).
- In stable patients with suspected CAD, stress echocardiography was associated with a reduced risk of ICA (1 good-quality RCT; 6.3 vs. 13.4 per 100 patients; RR 0.47, 95% CI 0.24 to 0.90; RD –7.1%, 95% CI –13.0 to –1.2%) (SOE Low) and additional downstream NIT (2 RCTs, 1 good and 1 poor quality; 5.8 vs. 42.7 per 100 patients; pooled RR 0.15, 95% CI 0.06 to 0.28, I^2=0%; pooled RD –31.6 (95% CI –49.3% to –14.0%, I^2=84%) (SOE Low) compared with exercise ECG over 28 to 36 months. Across the three trials in acute patients with a mix of known or suspected CAD, there was no difference between groups in either outcome, though one fair-quality trial tended to favor echocardiography for ICA (lower risk); heterogeneity was high possibly due to differences in populations, pretest risk and follow-up times (SOE Low for ICA; SOE Insufficient for additional NIT).
- Across trials in both stable (1 RCT) and acute patients (3 RCTs) with varying pretest risks of CAD, there were no differences between testing arms in the risk of revascularization (4 RCTs, 1 good, 2 fair and 1 poor quality) or (re)hospitalization (3 RCTs, 1 good, 1 fair and 1 poor quality) over follow-up periods ranging from 2 to 36 months (SOE Moderate for both).

Detailed results

9.1.2 Key Question 1: Primary Outcomes (MI, all-cause mortality, cardiac death)

9.1.2.1 Suspected CAD (stable, non-emergent, outpatient)

Myocardial infarction

One nonfatal MI occurred in both the stress echocardiography and the exercise ECG arms over a mean follow-up of 36 months in one good-quality trial[91,262] (N=385): 0.5% vs. 0.5 per 100 patients, RR 1.02 (95% CI 0.06 to 16.12), Figure 33. In the other poor-quality trial (n=158), which enrolled only women, there was also a total of two MIs (1.3 per 100 patients) over a mean follow-up of 28 months, however the authors did not report the incidence by study arm.[211]

All-cause and cardiac mortality

The good-quality trial[91,262] reported mortality, with a total of five all-cause deaths, one in the stress echocardiography arm versus four the exercise ECG arm: 0.5 vs. 2.1 per 100 patients; RR 0.25 (95% CI 0.03 to 2.25), Figure 34. The one death in the echocardiography arm was considered a cardiac death since evidence of coronary atherosclerosis was evident at autopsy (but no evidence of MI or acute coronary thrombosis). This patient was initially discharged based on a negative stress echocardiogram, re-admitted for urgent noncardiac surgery, and later died at home.

Other Outcomes

Both trials reported the incidence of MACE, with no difference between the stress echocardiography and the exercise ECG arms, respectively (Table 51). One good-quality RCT (N=385) defined MACE as death, nonfatal MI, late revascularization (>6 months), and hospitalization for chest pain [10.5 vs. 13.4 per 100 patients, mean follow-up 36 months][91,262] and the other poor-quality trial (N=158), in women only, did not define specific clinical events [7.7 vs. 7.4 per 100 patients, mean follow-up 28 months].[211] In the latter trial, the incidence of several other outcomes were reported for the overall population but not by test arm: unstable angina (1.3 per 100 patients), defined as prolonged or accelerating chest pain with EKG changes but no enzyme rise diagnostic of infarction; composite MI or unstable angina (2.5 per 100 patients overall); and acceleration of chest pain syndrome (9.5 per 100 patients), defined as symptoms not fulfilling criteria for MI or UA but resulted in frequency presentation to the clinic or ED. (See Appendix O, Tables O1 and O2 for other outcomes.)

9.1.2.2 Suspected or known CAD and suspected ACS (acute chest pain, ED/similar setting)

Myocardial infarction

There was no difference in the risk of MI across three trials[48,117,180] reporting various lengths of follow-up, both individually and when pooled (3 RCTs, N=707, 1.7 vs. 1.1 per 100 patients, pooled RR 1.52, 95% CI 0.18 to 8.52, I^2=8%), Figure 33. All MIs occurred in the two trials that included patients with either suspected or known CAD. In the poor-quality trial with 27% of patients with known ischemic heart

disease[117], there was one MI in the echocardiography group compared with two in the exercise ECG group over a mean follow-up period of 8.5 months. In the fair-quality trial evaluating uncomplicated MIs[48], nonfatal reinfarction occurred in five versus two patients, respectively, over 12 months (3.8 vs. 1.5 per 100 patients; RR 2.46, 95% CI 0.49 to 12.46). Of note, in the latter trial, four of the five MIs in the echocardiography group and both MIs in the exercise ECG group occurred following negative tests. The third, poor-quality trial in low-risk patients with suspected ACS which reported no MIs followed patients for only 2 months.[180]

All-cause mortality

There was no difference in the risk of all-cause mortality across three trials reporting various lengths of follow-up, both individually and when pooled (3 RCTs, N=707, 0.6 vs. 0.3 per 100 patients, pooled RR 1.60, 95% CI 0.13 to 21.89, I^2=0%)[48,117,180], Figure 34. All deaths occurred in the two trials that included patients with either suspected or known CAD. In the poor-quality trial with 27% of patients with known ischemic heart disease[117], there was one death in each group over a mean follow-up period of 8.5 months. In the fair-quality trial evaluating uncomplicated MIs[48], only one death occurred over 12 months and was in the echocardiography arm (0.8 vs. 0 per 100 patients; RR 2.95, 95% CI 0.12 to 71.88). The causes of death were not reported in either trial. The third, poor-quality RCT in low-risk patients with suspected ACS that reported no deaths followed patients for only 2 months.[180]

Cardiac mortality

None of the trials evaluating patients presenting to the ED or hospital with known or suspected CAD or suspected ACS reported on cardiac mortality.

Other Outcomes

There was no difference between stress echocardiography and exercise ECG in the frequency of MACE across two trials that included patients with either suspected or known CAD (Table 51). In the poor-quality trial with 27% of patients with known ischemic heart disease[117], the rate of the composite outcome of death, MI or revascularization, respectively, was 12.7 versus 16.6 per 100 patients (RR 0.77, 95% CI 0.44 to 1.34) and of death or MI was 1.4 versus 2.0 per 100 patients (RR 0.71, 95% CI 0.12 to 4.18) over a mean follow-up period of 8.5 months. In the fair-quality trial evaluating uncomplicated MIs[48], the frequency of death, nonfatal MI or unstable angina over 12 months was 19.7 versus 13.8 per 100 patients (RR 1.42, 95% CI 0.82 to 2.47). In the latter trial, the frequency of unstable angina requiring admission did not differ between those who received echocardiography versus exercise ECG, 15.2 versus 12.3 per 100 patients (16/130), RR 1.23 (95% CI 0.67 to 2.27). In a third trial[180], in patients with suspected ACS, there was no difference in quality of life at 2 months as measured by the Nottingham Health Profile (Appendix Table O2).

Table 51. MACE frequency in trials comparing stress echocardiography vs. exercise ECG
MACE frequency in trials comparing stress echocardiography vs. exercise ECG

Author, year RCT	Time point	MACE components	Echocardiography	Exercise ECG	Risk Ratio (95% CI)
Suspected CAD, stable outpatient					
Sanfilippo 2005	Mean 28 ± 14.2 months	"Clinical events" (NOS)	7.7% (8/104)	7.4% (4/54)	1.04 (0.33 to 3.29)
		MI or unstable angina	2.5% (4/158)*		NA
Zacharias 2017, Gurunathan 2018	Mean 36 ± 8.4 months	Death, nonfatal MI, late revascularization (>6 months), or hospitalization for chest pain	10.5% (20/191)	13.4% (26/194)	0.78 (0.45 to 1.35)
Suspected or Known CAD, ED/hospital					
Desideri 2005 COSTAMI-II Uncomplicated MI	12 months	Death, non-fatal MI, or unstable angina	19.7% (26/132)	13.8% (18/130)	1.42 (0.82 to 2.47)
Jeetley 2006 Suspected (63%), Known (27%) IHD	Mean 8.5 ± 4.9 months	Death, MI or revascularization	12.7% (18/142)	16.6% (25/151)	0.77 (0.44 to 1.34)
		Death or MI	1.4% (2/142)	2.0% (3/151)	0.71 (0.12 to 4.18)

ACS = acute coronary syndrome; adj. = adjusted; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CI = confidence interval; ED = emergency department; HR = hazard ratio; IHD = ischemic heart disease; MACE = major adverse cardiac events; MI = myocardial infarction; NR = not reported; RCT = randomized controlled trial; UA = unstable angina.
*Not reported by test arm.

9.1.3 Key Question 2: Clinical decision making

9.1.3.1 Suspected CAD (stable, non-emergent, outpatient)

Additional testing

One good-quality trial[91] (N=385) reported that stress echocardiography was associated with a reduction in referral for ICA compared with exercise ECG over a mean of 36 months: 6.3 versus 13.4 per 100 patients, RR 0.47 (95% CI 0.24 to 0.90), RD –7.1% (95% CI –13.0 to –1.2), Figure 35; most ICAs occurred within 4 months as a direct consequence of the initial test [4.7 vs. 9.8 per 100 patients, RR 0.48 (95% CI 0.22 to 1.04)]. The second, poor-quality trial in women only did not report ICA rates.[211]

In both trials, compared with exercise ECG, stress echocardiography was associated with a reduction in any downstream noninvasive testing (i.e., stress echocardiography, cardiac MRI, SPECT or exercise ECG) (2 RCTs, N=543, 5.8 vs. 42.7 per 100 patients; pooled RR 0.15, 95% CI 0.06 to 0.28, I^2=0%, Figure 36; pooled RD –31.6%, 95% CI –49.3% to –14.0%, I^2=84%); results were similar for any downstream noninvasive testing requiring stress or imaging (i.e., stress echocardiography, cardiac MRI, SPECT) (2

RCTs, N=543, 5.4 vs. 40.7 per 100 patients, pooled RR 0.15, 95% CI 0.06 to 0.28, I^2=0%; pooled RD –30.7%, 95% CI –46.3% to –15.1%, I^2=80%), Figure 37. Only the good-quality trial[91] reported downstream noninvasive testing requiring radiation with no difference between the echocardiography and the ECG group, respectively: 0 versus 1.1 per 100 patients, RR 0.20 (95% CI 0.01 to 4.20); both additional tests were SPECT.

Treatment

There was no difference between groups in the subsequent rate of any revascularization in one good-quality trial with a mean follow-up of 36 months (N=385, 5.8 vs. 6.2 per 100 patients; RR 0.93, 95% CI 0.42 to 2.06)[91], Figure 38. The second, poor-quality trial in women only did not report revascularization rates.[211] Neither trial reported change in medication therapy based on initial diagnostic strategy.

Hospitalization and ED visits

One good-quality trial reported no difference between groups in subsequent hospitalization for chest pain over a mean 36 months (N=385, 7.9 vs. 9.8 per 100 patients; RR 0.80, 95% CI 0.42 to 1.53), Figure 39, but fewer ED visits in the stress echocardiography arm [14 (8 overnight stays) vs. 30 (29 overnight stays), p<0.01]; it was unclear from the article if the latter represented patients or events.[91]

9.1.3.2 Suspected or known CAD and suspected ACS (acute chest pain, ED/similar setting)

Additional testing

There was no difference in the frequency of referral to ICA across three trials with follow-up periods ranging from 2 to 12 months (3 RCTs, N=716, 24.4 vs. 28.4 per 100 patients, pooled RR 0.85 95% CI 0.36 to 1.33, I^2=64%)[48,117,180], Figure 35. Individually, only one poor-quality trial[117] showed a reduction in ICA referral favoring echocardiography (14.2 vs. 23.4 per 100 patients; RR 0.61, 95% CI 0.37 to 0.99) over a mean follow-up of 8.5 months, however, the estimate was marginally statistically significant. In this same trial, of those referred to ICA, more patients in the echocardiography versus exercise ECG arm showed significant coronary artery disease though the difference was not statistically significant (72.6 vs. 55.6 per 100 patients; RR 1.37, 95% CI 0.94 to 2.0).

Only poor-quality one trial[180] (N=152), in patients with suspected ACS, reported the frequency of additional noninvasive testing which was similar following stress echocardiography versus exercise ECG over 2 months: 10.3 versus 9.3 per 100 patients; RR 1.11 (95% CI 0.42 to 2.92), Figure 36. Noninvasive tests included primarily exercise ECG followed by transthoracic echocardiography.

Treatment

There was no difference in the incidence of any revascularization between diagnostic strategies across the same three trials, both individually and when pooled (3 RCTs, N=701, 19.1 vs. 20.2 per 100 patients; pooled RR 0.95, 95% CI 0.64 to 1.29, I^2=0%), Figure 38. Results were similar when just the better- (fair) quality trial was considered.[48] Results were similar when PCI and CABG were considered separately in two of these trials[48,180], one fair and one poor quality (Figure 40 and Figure 41).

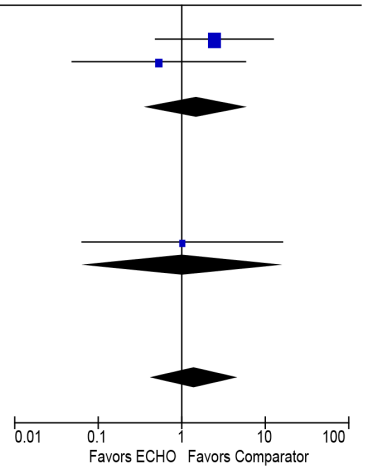
One poor-quality trial in patients with suspected ACS reported pharmacological treatments prescribed at discharge which included nitrates in 14.5% (22/152), beta blockers in 21.7% (33/152), calcium channel blockers in 19.7% (30/152) and antiplatelets in 31.6% (48/152) of the population with similar prescribing patterns between diagnostic testing arms.[180] It was unclear, however, if these constituted only new medications for patients not taking them at baseline or whether/the degree to which patients' medications were discontinued and/or changed.

Hospitalization and length of stay

There was no difference in hospitalization rates across two trials, both individually and when pooled, with follow-up periods of 2 and 12 months (2 RCTs, N=414, 10.5 vs. 10.2 per 100 patients, pooled RR 1.07, 95% CI 0.26 to 2.29, I^2=42%)[48,180], Figure 39. Similarly, length of hospital stay was similar between groups in both trials: mean 9 versus 10 days in one fair-quality trial (patients with uncomplicated MI)[48] and 40 versus 39 hours in the other poor-quality trial (patients with suspected ACS)[180], Appendix O, Table O2.

Figure 33. Stress echocardiography versus exercise ECG: Myocardial infarction

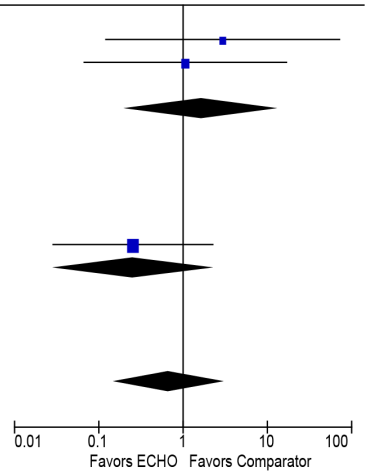
Study or Subgroup	Follow-up	Population	ECHO Events	ECHO Total	Comparator Events	Comparator Total	Weight	Risk Ratio [95% CI]
Acute ED								
Desideri 2005	12 months	Uncomp. MI	5	132	2	130	55.4%	2.46 [0.49, 12.46]
Jeetley 2006	8.5 months	Susp. or known CAD	1	142	2	151	25.5%	0.53 [0.05, 5.80]
Nucifora 2009	2 months	Susp. ACS	0	77	0	75		Not estimable
Subtotal (95% CI)				351		356	80.9%	1.52 [0.18 , 8.52]
Total events			6		4			
Heterogeneity: Tau² = 0.09; Chi² = 1.08, df = 1 (P = 0.30); I² = 8%								
Test for overall effect: Z = 0.55 (P = 0.58)								
Stable CP Outpatient								
Gurunathan 2018	36 months	Susp. CAD	1	191	1	194	19.1%	1.02 [0.06, 16.12]
Subtotal (95% CI)				191		194	19.1%	1.02 [0.06, 16.12]
Total events			1		1			
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.01 (P = 0.99)								
Total (95% CI)				542		550	100.0%	1.41 [0.30, 5.00]
Total events			7		5			
Heterogeneity: Tau² = 0.00; Chi² = 1.15, df = 2 (P = 0.56); I² = 0%								
Test for overall effect: Z = 0.55 (P = 0.58)								
Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.81), I² = 0%								



ACS = acute coronary syndrome; CAD = coronary artery disease; CI = confidence interval; CP = chest pain; ECHO = stress echocardiography; ED = emergency department; MI = myocardial infarction; Susp. = suspected; Uncomp. = uncomplicated.

Figure 34. Stress echocardiography versus exercise ECG: All-cause mortality

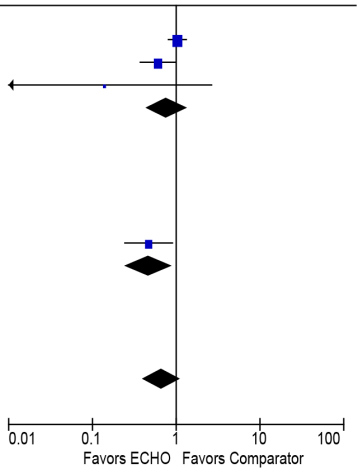
Study or Subgroup	Follow-up	Population	CCTA Events	CCTA Total	Comparator Events	Comparator Total	Weight	Risk Ratio [95% CI]
Acute ED								
Desideri 2005	12 months	Uncomp. MI	1	132	0	130	22.4%	2.95 [0.12, 71.88]
Jeetley 2006	8.5 months	Susp. or known CAD	1	142	1	151	29.8%	1.06 [0.07, 16.84]
Nucifora 2009	2 months	Susp. ACS	0	77	0	75		Not estimable
Subtotal (95% CI)				351		356	52.2%	1.60 [0.13 , 21.89]
Total events			2		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.23, df = 1 (P = 0.63); I² = 0%								
Test for overall effect: Z = 0.47 (P = 0.64)								
Stable CP Outpatient								
Gurunathan 2018	36 months	Susp. CAD	1	191	4	194	47.8%	0.25 [0.03, 2.25]
Subtotal (95% CI)				191		194	47.8%	0.25 [0.03, 2.25]
Total events			1		4			
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.23 (P = 0.22)								
Total (95% CI)				542		550	100.0%	0.65 [0.13, 4.94]
Total events			3		5			
Heterogeneity: Tau² = 0.00; Chi² = 1.70, df = 2 (P = 0.43); I² = 0%								
Test for overall effect: Z = 0.51 (P = 0.61)								
Test for subgroup differences: Chi² = 1.47, df = 1 (P = 0.23), I² = 32.1%								



ACS = acute coronary syndrome; CAD = coronary artery disease; CI = confidence interval; CP = chest pain; ECHO = stress echocardiography; ED = emergency department; MI = myocardial infarction; Susp. = suspected; Uncomp. = uncomplicated.

Figure 35. Stress echocardiography versus exercise ECG: ICA

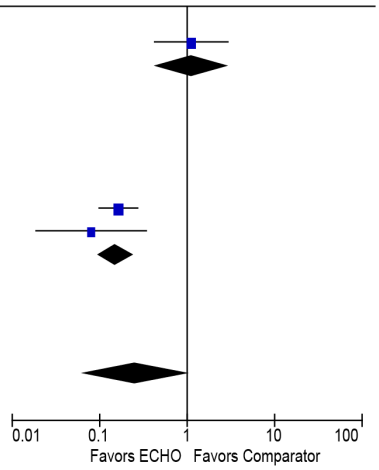
Study or Subgroup	Follow-up	Population	CCTA Events	CCTA Total	Comparator Events	Comparator Total	Weight	Risk Ratio [95% CI]
Acute ED								
Desideri 2005	12 months	Uncomp. MI	66	132	63	130	39.5%	1.03 [0.81, 1.32]
Jeetley 2006	8.5 months	Susp. or known CAD	21	148	36	154	31.5%	0.61 [0.37, 0.99]
Nucifora 2009	2 months	Susp. ACS	0	77	3	75	3.0%	0.14 [0.01, 2.65]
Subtotal (95% CI)				357		359	74.0%	0.85 [0.36 , 1.33]
Total events			87		102			
Heterogeneity: Tau² = 0.14; Chi² = 5.60, df = 2 (P = 0.06); I² = 64%								
Test for overall effect: Z = 0.90 (P = 0.37)								
Stable CP Outpatient								
Gurunathan 2018	36 months	Susp. CAD	12	191	26	194	26.0%	0.47 [0.24, 0.90]
Subtotal (95% CI)				191		194	26.0%	0.47 [0.24, 0.90]
Total events			12		26			
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.27 (P = 0.02)								
Total (95% CI)				548		553	100.0%	0.71 [0.36, 1.11]
Total events			99		128			
Heterogeneity: Tau² = 0.17; Chi² = 9.69, df = 3 (P = 0.02); I² = 69%								
Test for overall effect: Z = 1.49 (P = 0.14)								
Test for subgroup differences: Chi² = 1.27, df = 1 (P = 0.26), I² = 21.4%								



ACS = acute coronary syndrome; CAD = coronary artery disease; CI = confidence interval; CP = chest pain; ECHO = stress echocardiography; ED = emergency department; MI = myocardial infarction; Susp. = suspected; Uncomp. = uncomplicated.

Figure 36. Stress echocardiography versus exercise ECG: Noninvasive Testing

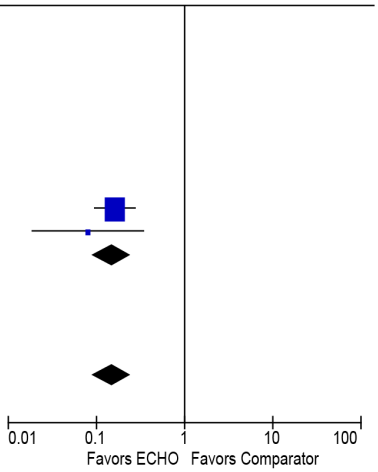
Study or Subgroup	Follow-up	Population	CCTA Events	CCTA Total	Comparator Events	Comparator Total	Weight	Risk Ratio [95% CI]
Acute ED								
Nucifora 2009	2 months	Susp. ACS	8	77	7	75	33.8%	1.11 [0.42, 2.92]
Subtotal (95% CI)				77		75	33.8%	1.11 [0.42, 2.92]
Total events			8		7			
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.22 (P = 0.83)								
Stable CP Outpatient								
Gurunathan 2018	36 months	Susp. CAD	15	191	93	194	38.0%	0.16 [0.10, 0.27]
Sanfilippo 2006	28 months	Susp. CAD	2	104	13	54	28.2%	0.08 [0.02, 0.34]
Subtotal (95% CI)				295		248	66.2%	0.15 [0.06 , 0.28]
Total events			17		106			
Heterogeneity: Tau² = 0.00; Chi² = 0.84, df = 1 (P = 0.36); I² = 0%								
Test for overall effect: Z = 7.72 (P < 0.00001)								
Total (95% CI)				372		323	100.0%	0.26 [0.04, 1.42]
Total events			25		113			
Heterogeneity: Tau² = 1.31; Chi² = 14.15, df = 2 (P = 0.0008); I² = 86%								
Test for overall effect: Z = 1.88 (P = 0.06)								
Test for subgroup differences: Chi² = 13.20, df = 1 (P = 0.0003), I² = 92.4%								



ACS = acute coronary syndrome; CAD = coronary artery disease; CI = confidence interval; CP = chest pain; ECHO = stress echocardiography; ED = emergency department; MI = myocardial infarction; Susp. = suspected; Uncomp. = uncomplicated.

Figure 37. Stress echocardiography versus exercise ECG: Any additional stress imaging NIT

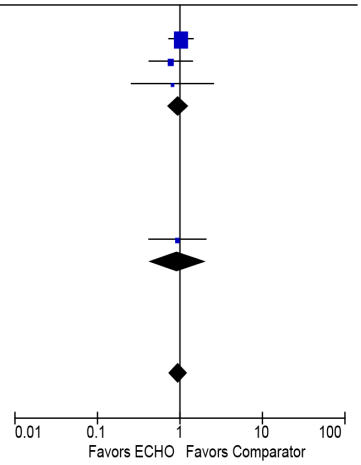
Study or Subgroup	Follow-up	Population	CCTA Events	CCTA Total	Comparator Events	Comparator Total	Weight	Risk Ratio [95% CI]
Acute ED								
Nucifora 2009	2 months	Susp. ACS	0	77	0	75		Not estimable
Subtotal (95% CI)				77		75		Not estimable
Total events			0		0			
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
Stable CP Outpatient								
Gurunathan 2018	36 months	Susp. CAD	14	191	88	194	88.3%	0.16 [0.10, 0.27]
Sanfilippo 2006	28 months	Susp. CAD	2	104	13	54	11.7%	0.08 [0.02, 0.34]
Subtotal (95% CI)				295		248	100.0%	0.15 [0.06 , 0.28]
Total events			16		101			
Heterogeneity: Tau² = 0.00; Chi² = 0.80, df = 1 (P = 0.37); I² = 0%								
Test for overall effect: Z = 7.53 (P < 0.00001)								
Total (95% CI)				372		323	100.0%	0.15 [0.06 , 0.28]
Total events			16		101			
Heterogeneity: Tau² = 0.00; Chi² = 0.80, df = 1 (P = 0.37); I² = 0%								
Test for overall effect: Z = 7.53 (P < 0.00001)								
Test for subgroup differences: Not applicable								



ACS = acute coronary syndrome; CAD = coronary artery disease; CI = confidence interval; CP = chest pain; ECHO = stress echocardiography; ED = emergency department; MI = myocardial infarction; Susp. = suspected; Uncomp. = uncomplicated.

Figure 38. Stress echocardiography versus exercise ECG: Any revascularization

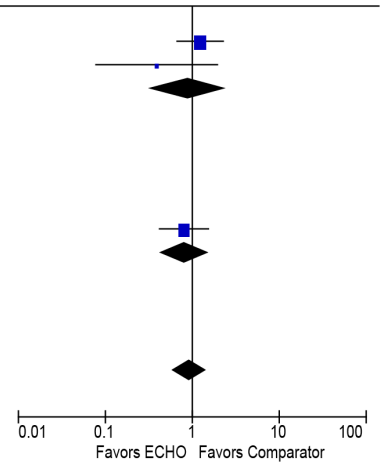
Study or Subgroup	Follow-up	Population	CCTA Events	CCTA Total	Comparator Events	Comparator Total	Weight	Risk Ratio [95% CI]
Acute ED								
Desideri 2005	12 months	Uncomp. MI	46	132	44	130	63.5%	1.03 [0.74, 1.44]
Jeetley 2006	8.5 months	Susp. or known CAD	16	142	22	151	19.7%	0.77 [0.42, 1.41]
Nucifora 2009	2 months	Susp. ACS	5	77	6	75	5.5%	0.81 [0.26, 2.55]
Subtotal (95% CI)				351		356	88.7%	0.95 [0.64 , 1.29]
Total events			67		72			
Heterogeneity: Tau² = 0.00; Chi² = 0.76, df = 2 (P = 0.68); I² = 0%								
Test for overall effect: Z = 0.34 (P = 0.74)								
Stable CP Outpatient								
Gurunathan 2018	36 months	Susp. CAD	11	191	12	194	11.3%	0.93 [0.42, 2.06]
Subtotal (95% CI)				191		194	11.3%	0.93 [0.42, 2.06]
Total events			11		12			
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.18 (P = 0.86)								
Total (95% CI)				542		550	100.0%	0.95 [0.68, 1.25]
Total events			78		84			
Heterogeneity: Tau² = 0.00; Chi² = 0.76, df = 3 (P = 0.86); I² = 0%								
Test for overall effect: Z = 0.38 (P = 0.71)								
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.96), I² = 0%								



ACS = acute coronary syndrome; CAD = coronary artery disease; CI = confidence interval; CP = chest pain; ECHO = stress echocardiography; ED = emergency department; MI = myocardial infarction; Susp. = suspected; Uncomp. = uncomplicated.

Figure 39. Stress echocardiography versus exercise ECG: Hospitalization

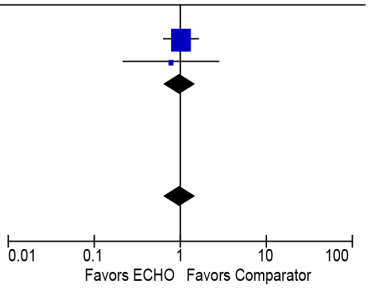
Study or Subgroup	Follow-up	Population	CCTA Events	CCTA Total	Comparator Events	Comparator Total	Weight	Risk Ratio [95% CI]
Acute ED								
Desideri 2005	12 months	Uncomp. MI	20	132	16	130	48.5%	1.23 [0.67, 2.27]
Nucifora 2009	2 months	Susp. ACS	2	77	5	75	7.7%	0.39 [0.08, 1.95]
Subtotal (95% CI)				209		205	56.2%	1.07 [0.26 , 2.29]
Total events			22		21			
Heterogeneity: Tau² = 0.28; Chi² = 1.73, df = 1 (P = 0.19); I² = 42%								
Test for overall effect: Z = 0.23 (P = 0.82)								
Stable CP Outpatient								
Gurunathan 2018	36 months	Susp. CAD	15	191	19	194	43.8%	0.80 [0.42, 1.53]
Subtotal (95% CI)				191		194	43.8%	0.80 [0.42, 1.53]
Total events			15		19			
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.67 (P = 0.50)								
Total (95% CI)				400		399	100.0%	0.94 [0.48, 1.51]
Total events			37		40			
Heterogeneity: Tau² = 0.01; Chi² = 2.14, df = 2 (P = 0.34); I² = 7%								
Test for overall effect: Z = 0.30 (P = 0.77)								
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.87), I² = 0%								



ACS = acute coronary syndrome; CAD = coronary artery disease; CI = confidence interval; CP = chest pain; ECHO = stress echocardiography; ED = emergency department; MI = myocardial infarction; Susp. = suspected; Uncomp. = uncomplicated.

Figure 40. Stress echocardiography versus exercise ECG: PCI

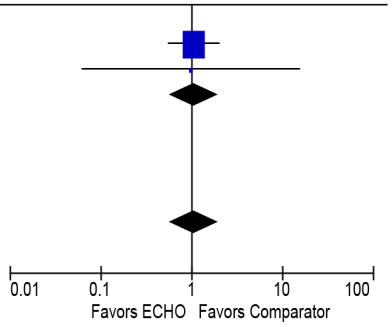
Study or Subgroup	Follow-up	Population	CCTA Events	CCTA Total	Comparator Events	Comparator Total	Weight	Risk Ratio [95% CI]
Acute ED								
Desideri 2005	12 months	Uncomp. MI	29	132	28	130	88.5%	1.02 [0.64, 1.61]
Nucifora 2009	2 months	Susp. ACS	4	77	5	75	11.5%	0.78 [0.22, 2.79]
Subtotal (95% CI)				209		205	100.0%	0.99 [0.51, 1.72]
Total events			33		33			
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.70); I² = 0%								
Test for overall effect: Z = 0.05 (P = 0.96)								
Total (95% CI)				209		205	100.0%	0.99 [0.51, 1.72]
Total events			33		33			
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.70); I² = 0%								
Test for overall effect: Z = 0.05 (P = 0.96)								
Test for subgroup differences: Not applicable								



ACS = acute coronary syndrome; CAD = coronary artery disease; CI = confidence interval; CP = chest pain; ECHO = stress echocardiography; ED = emergency department; MI = myocardial infarction; Susp. = suspected; Uncomp. = uncomplicated.

Figure 41. Stress echocardiography versus exercise ECG: CABG

Study or Subgroup	Follow-up	Population	CCTA Events	CCTA Total	Comparator Events	Comparator Total	Weight	Risk Ratio [95% CI]
Acute ED								
Desideri 2005	12 months	Uncomp. MI	17	132	16	130	94.9%	1.05 [0.55, 1.98]
Nucifora 2009	2 months	Susp. ACS	1	77	1	75	5.1%	0.97 [0.06, 15.29]
Subtotal (95% CI)				209		205	100.0%	1.04 [0.39, 2.71]
Total events			18		17			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.96); I² = 0%								
Test for overall effect: Z = 0.13 (P = 0.90)								
Total (95% CI)				209		205	100.0%	1.04 [0.39, 2.71]
Total events			18		17			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.96); I² = 0%								
Test for overall effect: Z = 0.13 (P = 0.90)								
Test for subgroup differences: Not applicable								



ACS = acute coronary syndrome; CAD = coronary artery disease; CI = confidence interval; CP = chest pain; ECHO = stress echocardiography; ED = emergency department; MI = myocardial infarction; Susp. = suspected; Uncomp. = uncomplicated.

9.2 Stress Echocardiography versus Standard Care

One trial (N=201)[180] compared stress echocardiography with "standard care" in low-risk patients with suspected ACS presenting to the ED (See Appendix Q). Mean patient age was 54 years and 46% were female. Twenty percent of patients presented with atypical ACS. Baseline cardiac risk factors included prior MI (2%), prior unstable angina (2%), prior revascularization (4%), diabetes (11%), hypercholesterolemia (39%), hypertension (42%), and smoking (48%). Pharmacological treatment at admission included antiplatelets (23%), beta-blockers (15%) calcium channel blockers (13%), and nitrates (10%). Patients randomized to echocardiography received dobutamine-atropine stress echocardiography; those with a negative test were immediately discharged. Patients randomized to standard care were hospitalized until a diagnosis was reached according to local protocols; the final diagnosis was achieved using clinical judgment only (i.e., no additional diagnostic examinations) in 71% of patients, exercise treadmill ECG in 13%, stress echocardiography in 11% and ICA in 5%. The follow-up period was 2 months. The trial was conducted across five European countries and did not report any sources of funding.

This trial was considered poor quality due to the following methodological shortcomings: unclear randomization and allocation concealment methods, lack of blinding of outcome assessors, lack of a prespecified definition for a positive test, and high attrition. See Appendix D for details regarding study quality determination.

9.2.1 Summary of results

- Data from one small, poor-quality trial (N=201) in acute patients with suspected ACS are insufficient to draw conclusions regarding the risk of MI, all-cause or cardiac mortality, ICA, additional downstream NIT, any revascularization and rehospitalization for acute chest pain following stress echocardiography versus standard care.
- No MIs and no deaths were reported in either test arm. Stress echocardiography resulted in fewer referrals for ICA and additional NITs, and fewer rehospitalizations for acute chest pain, but no difference in revascularization rates (SOE Insufficient).

Detailed results

9.2.2 Key Question 1: Primary Outcomes (MI, all-cause mortality, cardiac death)

No MIs and no deaths were reported over the 2-month follow-up period, Table 52.

9.2.3 Key Question 2: Clinical decision making

Compared with standard care, stress echocardiography was associated with fewer referrals to ICA (0% vs. 11%; RR 0.06, 95% CI 0.0 to 0.96; RD –10.9%, 95% CI –19.2% to –2.7%) and fewer additional noninvasive tests (10 vs. 49 per 100 patients; RR 0.21, 95% CI 0.10 to 0.43, RD –38.7%, 95% CI –53.6% to –23.8%) with no statistical difference between groups in revascularization rates (6.5 vs. 3.6 per 100

patients) or pharmacological treatments prescribed at discharge (Table 52). Fewer patients randomized to stress echocardiography were re-hospitalized for ACP over the 2-month follow-up period (3 vs. 15 per 100 patients; RR 0.18, 95% 0.04 to 0.81, RD –12.0%, 95% CI –21.9% to –2.0%) and length of hospital stay was significantly reduced in the echocardiography arm (MD –55 hours, 95% –75 to –35). The latter may in part be due to the design of trial/triage at presentation.

Table 52. Stress echocardiography vs. standard care

Author, year RCT	Outcome	Echocardiography	Standard care	Risk Ratio (95% CI)
Nucifora 2009 ASSENCE Suspected ACS Low risk Follow-up: 2 months	**All-cause mortality**	0% (0/77)	0% (0/55)	NC
	Nonfatal MI	0% (0/77)	0% (0/55)	NC
	ICA	0% (0/77)	11% (6/55)	**0.06 (0.0 to 0.96)**
	Revascularization	7% (5/77)	4% (2/55)	1.79 (0.36 to 8.87)
	PCI	5% (4/77)	2% (1/55)	2.86 (0.33 to 24.87)
	CABG	1% (1/77)	2% (1/55)	0.71 (0.05 to 11.17)
	Additional noninvasive testing	10% (8/77)	49% (27/55)	**0.21 (0.10 to 0.43)**
	Stress echocardiography	0% (0/77)	4% (2/55)	-----
	TE echocardiography	1% (1/77)	22% (12/55)	-----
	Electrocardiogram	9% (7/77)	24% (13/55)	-----
	Medications prescribed at discharge			
	Antiplatelet drugs	30% (23/77)	44% (24/55)	0.68 (0.43 to 1.08)
	Beta-blockers	21% (16/77)	29% (16/55)	0.71 (0.39 to 1.30)
	Calcium channel blockers	21% (16/77)	24% (13/55)	0.88 (0.46 to 1.68)
	Nitrates	13% (10/77)	22% (12/55)	0.59 (0.28 to 1.28)
	Rehospitalization for ACP	3% (2/77)	15% (8/55)	**0.18 (0.04 to 0.81)**
	Hospital length of stay (hours), mean ± SD	40 ± 42	95 ± 74	**MD –55 (–75.1 to –34.9)**

ACP = acute chest pain; ACS = acute coronary syndrome; CABG = coronary artery bypass graft; CI = confidence interval; ICA = invasive coronary angiography; MD = mean difference; MI = myocardial infarction; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; SD = standard deviation.

9.3 Stress Echocardiography versus ICA

One good-quality trial (N=448)[220,241] compared stress echocardiography versus invasive coronary angiography (ICA) in patients with suspected or known (27% with prior MI) stable CAD referred for outpatient angiography (See Appendix Q). Referral to angiography was based on the results of an exercise ECG complete within 1 month of enrollment, the results of which were not available to the trial personnel. Patients in the echocardiography arm were randomized to undergo dobutamine-atropine stress echocardiography with contrast while those randomized to the control arm underwent ICA as originally planned. Mean patient age was 62 years, and 69% were male. Patients were considered high-risk (69%) or low-risk (31%) according to the Pryor risk assessment. Baseline cardiac risk factors included prior cerebrovascular accident (5%), peripheral vascular disease (8%), diabetes (12%), family history of CAD (27%), hypertension (55%), hyperlipidemia (77%), and smoking (45%). Patients were on a variety of cardiovascular related medications at baseline including antiplatelets, statins, and beta-blockers primarily as well as ACE inhibitors, calcium channel blockers, nicorandil, nitrates, diuretics, and

angiotensin-II receptor antagonists. The primary follow-up period was 18 months. The secondary publication by Thom et al. (focused on cost-effectiveness) provided mortality data out to 72 months and post-index revascularization rates out to 32 months. The trial was conducted at a single hospital in the United Kingdom and was funded by the National Institute for Health Research.

See Appendix D for details regarding study quality determination.

9.3.1 Summary of results

- There was insufficient evidence from one good-quality trial to draw conclusions regarding the risk of MI, all-cause mortality and cardiac mortality between groups. Over 18 months, the absolute risk was <3 per 100 patients across both test arms for all outcomes; at 72 months, the absolute risk of all-cause mortality was 4.9 vs. 3.2 per 100 patients. Given that these are rare events, the trial may not have been sufficiently powered to detect a difference (SOE Insufficient).
- There were no differences between stress echocardiography and ICA in the risk of additional downstream NIT (SOE Insufficient), any revascularization and hospitalization for chest pain across one trial (SOE Low for both).

9.3.2 Key Question 1: Primary Outcomes (MI, all-cause mortality, cardiac death)

Myocardial infarction, all-cause mortality, cardiac death

Six patients randomized to stress echocardiography compared with no patient randomized to ICA were admitted for acute MI over the 18-month follow-up (2.7 vs. 0 per 100 patients; p=0.01), Table 53. There were no differences in the incidence of all-cause (2.7 vs. 1.8 per 100 patients) or cardiac (0.4 vs. 1.4 per 100 patients) mortality between diagnostic strategies by 18 months[220] or for all-cause mortality through 72 months (4.9 vs. 3.2 per 100 patients; RR 1.54, 95% CI 0.61 to 3.91).[241]

Other clinical outcomes

There was no difference between diagnostic strategies for the composite outcomes of any nonfatal event and any fatal plus nonfatal event at 18 months, or in the proportion of patents achieving a clinically significant improvement in Canadian Cardiovascular Society angina class (Table 53). There were no differences between stress echocardiography and ICA on all subscales of the Seattle Angina Questionnaire or on the SF-36 health-related quality of life questionnaire at 6 and 18 months (Appendix O).

9.3.3 Key Question 2: Clinical decision making

Additional testing

Most patients (75%) in the stress echocardiography arm went on to get subsequent ICA during the 18-month follow-up. No patient in the ICA arm required repeat ICA. No patient in the stress

echocardiography arm received additional noninvasive testing compared with eight patients in the ICA arm (0 vs. 3.6 per 100 patients, p=0.01), including seven SPECT and one cardiac MRI (Table 53). The timing of additional noninvasive testing was unclear.

Treatment

Similar proportions of patients received revascularization following index testing with stress echocardiography versus ICA (35.4 vs. 34.2 per 100 patients, respectively; RR 1.03, 95% CI 0.80 to 1.33), to include rates of PCI and CABG. The cumulative rates of revascularization remained similar over 36 months (53.5 vs. 53.2 per 100 patients; RR 1.01, 95% CI 0.85 to 1.20), Table 53.

Hospitalization

More patients were admitted for chest pain over 18 months in the stress echocardiography arm versus the ICA arm, however the difference was not significant: 10.6 versus 6.3 per 100 patients, RR 1.68 (0.89 to 3.17), Table 53.

Table 53. Stress echocardiography vs. ICA: Summary of primary clinical and decision-making outcomes

Author, year RCT	Outcome	Timepoint	Echocardiography % (n/N)	ICA % (n/N)	Risk Ratio (95% CI)*
Sharples 2007 **Thom 2014** CECaT Suspected and known CAD Low (21%) and high (69%) risk.	**All-cause mortality**	18 months	2.7% (6/226)	1.8% (4/222)	1.47 (0.42 to 5.15)
		72 months	4.9% (11/226)	3.2% (7/222)	1.54 (0.61 to 3.91)
	Cardiac mortality	18 months	0.4% (1/226)	1.4% (3/222)	0.32 (0.03 to 3.12)
	Admission for acute MI	18 months	2.7% (6/226)	0% (0/222)	NC, p=0.01
	Total nonfatal events†	18 months	13.7% (31/226)	8.6% (19/222)	1.60 (0.93 to 2.75)
	Total nonfatal plus fatal events	18 months	16.4% (37/226)	10.8% (24/222)	1.51 (0.94 to 2.45)
	ICA/additional ICA	18 months	74.8% (169/226)	0% (0/222)	NC, p<0.001
	Revascularization (any)	Index Management	35.4% (80/226)	34.2% (76/222)	1.03 (0.80 to 1.33)
		36 months (cumulative)	53.5% (121/226)	53.2% (118/222)	1.01 (0.85 to 1.20)
	PCI	Index Management	22.7% (51/226)	24.8% (55/222)	0.91 (0.65 to 1.27)
	CABG	Index Management	12.9% (29/226)	9.5% (21/222)	1.36 (0.80 to 2.31)
	Unplanned PCI	18 months	2.2% (5/226)	1.8% (4/222)	1.23 (0.33 to 4.51)
	Unplanned CABG	18 months	1.8% (4/226)	1.4% (3/222)	1.31 (0.30 to 5.79)
	Additional noninvasive testing	18 months	0% (0/226)	3.6% (8/222)	NC, p=0.01
	SPECT	18 months	0% (0/226)	3.2% (7/222)	NC, p=0.01
	MRI	18 months	0% (0/226)	0.5% (1/222)	NC, p=0.31
	Admission for chest pain	18 months	10.6% (24/226)	6.3% (14/222)	1.68 (0.89 to 3.17)
	Significant improvement in CCS angina class (≥2 decrease)	6 months	31% (67/226)	32% (66/222)	1.00 (0.75 to 1.33)
		18 months	34% (70/226)	32% (65/222)	1.06 (0.80 to 1.40)

ACP = acute chest pain; ACS = acute coronary syndrome; CABG = coronary artery bypass graft; CI = confidence interval; ICA = invasive coronary angiography; MD = mean difference; MI = myocardial infarction; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; SD = standard deviation.
*Calculated by AAI
†Admission for chest pain or acute MI, unplanned PCI or CABG, and other (1 transient ischemic attack in echocardiography group; 1 cerebrovascular accident post-ICA, observed overnight in ICA group)

9.3.4 Key Question 3: Safety

Summary of results

- Data from one poor-quality trial is insufficient to draw conclusions regarding test-related complications.
- Across 11 case-series, the risk of major or life-threatening adverse events (e.g., death, MI, unstable angina, cerebrovascular accident, acute pulmonary edema) as a result of pharmacologic stress agents appears to be low: for dobutamine, ≤0.1% across all outcomes, and for dipyridamole and adenosine, no major adverse events were reported. Minor transient events (e.g., arrhythmias, chest pain, headache, dyspnea, nausea/vomiting) were not uncommon (SOE low for all); most reported symptoms are expected responses to the pharmacologic agents used.
- Definite or suspected contrast related adverse events and allergic reactions appear to be rare (≤2% across all studies/outcomes) (SOE Low)

Across all included trials and comparisons (stress echocardiography versus exercise ECG, "standard care" and ICA), only one trial comparing stress echocardiography with exercise ECG mentioned safety outcomes, the COSTAMI-II trials in patients with uncomplicated MIs presenting to the ED; the authors stated that no complications occurred during either test.[48]

Given the lack of safety data reported by the included RCTs, additional studies reporting test-specific adverse events related to stress echocardiography were evaluated for inclusion and are summarized below. Most identified studies were case series which are considered low quality (i.e., high risk of bias). See Appendix O (Tables O23-O25) for detailed results tables.

9.3.4.1 <u>Adverse events related to Dobutamine (with or without atropine)</u>

Eleven case series (N range, 86 to 2799), seven prospective and four retrospective, were identified that reported adverse events related to the use of dobutamine (with and without atropine) during stress echocardiography in patients with suspected or known CAD (10 studies)[20,45,87,122,155,164,181,191,193,229] and suspected ACS (one study).[77] The mean maximum dose of dobutamine ranged from 31.6 to 50.0 µg/kg/min. Six studies also used atropine (in 33% to 100% of the populations) to achieve target heart rate.

There were no deaths due to dobutamine as reported by six studies (total N=5512)[45,87,122,191,193,229] and the frequency of acute MI ranged from 0% to 0.1% across seven studies[45,87,122,155,191,193,229] (N range, 122

to 2799). One study reported a single case of unstable angina attributed to dobutamine (0.1%, N=802)[122] and another (N=1012) reported that no cerebrovascular accidents occurred.[45] The incidence of acute pulmonary edema was rare across two studies (0% [N=1012] and 0.1% [N=802]). Chest pain (not otherwise specified) was reported by three studies (N range, 86 to 1118) and ranged from 4.6% to 31.4%.

Arrythmia-related adverse events commonly reported across the studies included any arrhythmias or palpitations in six studies (range, 2.1% to 18.0%; N range, 122 to 1118), supraventricular or ventricular tachycardia in ten (range, 0% to 9.0%; N range, 86 to 2799), atrial or ventricular fibrillation in seven (range, 0% to 1.2%; N range 265 to 2799), and bradycardia in two large studies (≤0.2% in both). The occurrence of hypotension was reported in nine studies (range, 0.1% to 12.5%; N range, 86 to 2799) and hypertension in five studies (range, 0% to 7.5%; N range, 122 to 1118).

Other commonly reported side-effects included nausea and/or vomiting in six studies (range, 3.4% to 20.9%; N range, 86 to 1012), headache in four studies (0.8% to 13.6%; N range 122 to 1012), and dyspnea (range, 0% to 13.6%) and tremors (range, 0.4% to 2.4%) in three studies each (N range, 127 to 1012). Most studies reported that most events were minor and transient.

Most reported symptoms are expected responses to the pharmacologic agents used. All reported side effects can be found in Table O23 of the Appendix.

9.3.4.2 Adverse events related to Dipyridamole (with or without atropine) and Adenosine

Three case series (total N=946)[69,76,165], two prospective and one retrospective, were identified that reported adverse events related to the use of dipyridamole (with and without atropine) during stress echocardiography in patients with suspected or known CAD. In all studies the cumulative dose of dipyridamole was 0.84 mg/kg given over 4 min. No “major”, severe, or life-threatening adverse events, to include death, MI and acute coronary syndrome, were reported by two studies (total N=837). All three studies (N range, 109 to 500) reported the frequency of hypotension/bradycardia which ranged from 0.8% to 6.4%, vomiting and nausea which ranged from 0.2% to 5.5%, and headache which ranged from 2.1% to 43%. Two studies reported the occurrence of arrythmias during stress testing which ranged from 2.7% (N=337) to 10.4% (N=550). Studies reported that most events were minor and transient.

One prospective case series (N=1429)[166] was identified that reported adverse events related to the use of adenosine during stress echocardiography in patients with suspected or known CAD. The most commonly occurring side-effects were hyperpnea (16.7%), atypical chest pain (9.9%), flushing (9.4%) and headache (6.6%).

Most reported symptoms are expected responses to the pharmacologic agents used. All reported side effects can be found in Tables O24 and O25 of the Appendix.

9.3.4.3 Adverse events due to non-iodinated contrast agent

Two retrospective comparative cohort studies (N=6,750)[15,119] and one retrospective non-comparative database study (N=3,071)[4] were identified that reported adverse events related to the use of non-iodinated contrast during stress echocardiography. One of the cohort studies presented results stratified by stable patients with suspected or known CAD and acute patients with suspected ACS[15] while the indications for stress echocardiography in the second cohort study were primarily ischemia assessment (80%) and heart transplantation (12.5%).[119] The database study used medical records to identify patients undergoing their first stress echocardiogram during a specific time period and the indication for the test was unclear. The contrast agents used varied across the studies and included Luminity (54%) and SonoVue (46%) in one cohort[15], Definity (100%) in the second cohort[119], and Definity (86%) and Opstison (14%) in the database study.[4]

One cohort study reported acute MI which was rare in both the contrast and non-contrast groups: 0% vs. 0.1%, respectively.[15] Across both comparative cohorts, the risk of allergic reaction to contrast agent was low and occurred in <0.5% of patients who received stress echocardiography with contrast.[15,119] There was a similar, low risk of arrythmias, hypotension, or severe hypertension between groups in one cohort study[15] while the second cohort study reported an increased risk of chest pain (23% vs. 17%; RR 1.35, 95% CI 1.12 to 1.62) in those who received contrast but a lower risk of palpitations (6% vs. 10%; RR 0.62, 95% CI 0.47 to 0.82) compared with those who did not received contrast; there was no difference between groups in other complications in the latter study.

The noncomparative database study reported definite and suspected contrast-related adverse events in 1.3% (41/3071) and 2.2% (68/3071) of patients[4], respectively. Backache, headache or both were rare (<1% each). Other adverse events that may be indicative of an allergic reaction were very rare and occurred in one patient (0.03%) each: transient wheezing without urticaria, urticaria or hives (limb and thorax) and swelling in the mouth, and throat tingling. Adverse reactions thought to be caused by concomitant infusion of contrast agent and dobutamine included chest pain (0.78%), nausea and vomiting (0.10%), and shivering and tremors (0.16%).

9.3.5 Key Question 4: Differential Effectiveness or Safety

None of the included trials comparing stress echocardiography with exercise ECG, “standard care” or ICA reported differential effectiveness or safety.

10 Strength of Evidence (SOE)

Table 10.1. Key Question 1: Strength of evidence: CCTA versus functional testing, primary clinical outcomes across patient populations

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
Myocardial infarction Cumulative	Up to 58 months following index test	17 RCTs (N =22,328) **Suspected ACS** ACRIN-PA 2012 Hoffman 2012 Chang 2008 Dedic 2016 Goldstein 2007 Goldstein 2011 Hamilton-Craig 2014 Linde 2015 Levsky 2017 Uretsky 2017 Pineiro-Portela 2021 **Stable patients** Douglas 2915 Min 2012 Karthikeyan 2017 Stillman 2020 McKavanagh 2014 SCOT-HEART 2015	Yes (-1)	No	No	No	**CCTA vs. functional testing** Risk: 1.2 vs. 1.8 per 100 persons Pooled estimates (14 RCTs, N= 21,651) RR 0.70, 95% CI 0.56 to 0.89, I^2=0% RD 0.4, 95% CI 0.1 to 0.8 per 100; I^2=19% 3 smaller RCTs (N=667) reported no MI in either testing arm. **Conclusions:** Pooled estimates following exclusion of one trial in stable outpatients (SCOT-HEART) in which 85% of patients in the CCTA group also received functional testing (ETT) bordered the null (13 RCTS RR, 0.75, 95% CI 0.57 to 0.99) suggesting no clear association for reduction of MI with CCTA. Across all 14 trials, CCTA was associated with lower MI risk compared with functional testing based on pooled estimates; the RD (0.4 per 100 patients) was, however, small. Absolute MI risk was < 2 per 100 patients in both testing arms. Patients' pre-test risk across studies was predominately low to intermediate.	⊕⊕⊕◯ MODERATE

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							Smaller trials may not have been sufficiently powered to detect a difference. **In patients with suspected ACS**, there was no difference in MI between tests at the time of index test, or at 1 to 6.5 months or ≥12 months after the index test. MI was most common around the time of index testing and occurred in 1.9 versus 2.8 per 100 patients. **In stable outpatients**, CCTA was associated with decreased risk of MI across 4 RCTS (pooled RR 0.64, 95% CI 0.44 to 0.87 I^2=0%) however following exclusion of the SCOT-HEART, results were no longer significant (3 RCTs pooled RR 0.69, 95% CI 0.27 to 1.14).	
All-cause Mortality Cumulative	Up to 58 months following index test	17 RCTs (N=21,680) **Suspected ACS** ACRIN-PA 2012 (Litt and Holland) Hoffman 2012 Chang 2008 Dedic 2016 Goldstein 2007 Goldstein 2011 Hamilton-Craig 2014 Linde 2015 Levsky 2015 Levsky 2018	Yes (-1)	No	No	No	**CCTA vs. functional testing** Risk: 1.2 vs. 1.3 per 100 persons Pooled estimate: 11 RCTs (N= 18,935) RR 0.99 95% CI 0.40 to 2.68, I^2=0% RD (not calculated, no association) 6 RCTs (N=2746) reported no mortality in either testing arm. **Conclusions:** CCTA was not associated with reduction in all-cause mortality compared with functional testing. The	⊕⊕⊕◯ MODERATE

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
		Uretsky 2017 Pineiro-Portela 2021 **Stable patients** Douglas 2015 Min 2012 Karthikeyan 2017 McKavanagh 2014 SCOT-HEART 2015					absolute risk was 1.2 per 100 patients across testing arms. Patients' pre-test risk across studies was predominately low to intermediate. Smaller trials may not have been sufficiently powered to detect a difference.	
Cardiac Mortality	Up to 58 months following index test	13 RCTs (N=11,647) **Suspected ACS** ACRIN-PA 2012 (Litt and Holland) Hoffman 2012 Goldstein 2007 Goldstein 2011 Nabi 2016 Hamilton-Craig 2014 Linde 2015 Levsky 2018 Uretsky 2017 **Stable patients** Min 2012 Stillman 2020 McKavanagh 2014 SCOT-HEART 2015	Yes (-1)	No	No	Yes (-2)	10 RCTs (N=5559) reported no cardiac mortality in either testing arm. 3 RCTs reported cardiac death **Stable patients:** 1 RCT CCTA 0.28% (5/2073) vs. ETT 0.28% (12/2073), RR 0.42, 95% CI 0.15 to 1.18) **Suspected ACS**: 2 RCTs (N=1942), 2 total events: 1 in CCTA (1 RCT), 1 in functional testing (1 RCT); RR 0.72, 95% CI 0.04 to 13.3) **Conclusions:** Firm conclusions regarding the impact of CCTA or functional testing on cardiac death are not possible. Cardiac death was rare. Sample sizes in individual trials may have been insufficient to detect cardiac death. Populations across trials were generally reported as low to intermediate CAD risk.	⊕◯◯◯ INSUFFICIENT

Reasons for downgrading:

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice;
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies may be downgraded.
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects and may be downgraded once. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

Table 10.2. Key Question 2: Strength of evidence: CCTA versus functional testing; decision-making, additional testing and management

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
ICA referral Cumulative	Up to 58 months	19 RCTs (N=22,335) **Suspected ACS** ACRIN-PA 2012 Hoffman 2012 Chang 2008 Dedic 2016 Goldstein 2007 Goldstein 2011 Hamilton-Craig 2014 Linde 2015 Levsky 2015 Uretsky 2017 Pineiro-Portela 2021 Levsky 2018 Nabi 2016 Miller 2011	Yes (-1)	No	No	No	**CCTA vs. functional testing** **Risk:** 14.4 vs. 12.0 per 100 persons **Pooled estimates** RR 1.25, 95% CI 1.09 to 1.47, I^2=67% RD 2.7, 95% CI 1 to 4 per 100, I^2=59% **Conclusions:** CCTA was associated with more frequent referral to ICA compared with functional testing across patient populations. Sensitivity analyses excluding outliers and poor-quality studies did not alter conclusions. However, in the stable population, exclusion of SCOT-HEART increased the effect size and strengthen the association between CCTA and ICA referral compared with functional testing and substantially reduced the heterogeneity (4 RCTS	⊕⊕⊕◯ MODERATE

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
		Stable patients Douglas 2015 Min 2012 Karthikeyan 2017 McKavanagh 2014 SCOT-HEART 2015					pooled RR 1.57, 95% CI 1.21 to 1.65, I2=0%, RD 4.1, 95% CI 3.0 to 5.2 per 100 patients).	
Any additional noninvasive testing	Up to 58 months	17 RCTs (N= 11,595) **Suspected ACS** ACRIN-PA 2012 Hoffman 2012 Chang 2008 Dedic 2016 Goldstein 2007 Goldstein 2011 Hamilton-Craig 2014 Linde 2015 Levsky 2015 Uretsky 2017 Pineiro-Portela 2021 Levsky 2018 Miller 2011 **Stable patients** Min 2012	Yes (-1)	Yes (-1)	No	Yes (-1)	**<u>CCTA vs. functional testing</u>** **Risk:** 7.2 vs. 7.6 per 100 persons **Pooled estimates** RR 0.82, 95% CI 0.53 to 1.28, I^2=83% RD (not calculated, no association) **<u>Conclusions</u>:** There was no difference in use of additional testing overall between CCTA and functional testing. Exclusion of poor-quality RCTs and outlying studies did not impact this conclusion. Substantial heterogeneity is noted and reasons are unclear.	⊕⊕◯◯ LOW

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
		Karthikeyan 2017 McKavanagh 2014 SCOT-HEART 2015						
Any revascularization	55 days to 58 months	19 RCTs (N=23,124) **Suspected ACS** ACRIN-PA 2012 Hoffman 2012 Chang 2008 Dedic 2016 Goldstein 2007 Goldstein 2011 Hamilton-Craig 2014 Linde 2015 Levsky 2015 Uretsky 2017 Pineiro-Portela 2021 Levsky 2018 Nabi 2016 Miller 2011 **Stable patients** Douglas 2015 Min 2012 Karthikeyan 2017 McKavanagh 2014 SCOT-HEART 2015 Stillman 2020	Yes (-1)	Yes (-1)	No	No	**CCTA vs. functional testing** **Risk:** 9.5 vs. 7.1 per 100 persons **Pooled estimates** RR 1.52, 95% CI 1.26 to 1.90, I^2=66% RD 2.4, 95% CI 1.4 to 3.3 per 100, I^2=46% **Conclusions:** CCTA was associated with more frequent referral for revascularization. The conclusion did not change following exclusion of poor-quality RCTs or one RCT in which 85% of patients in the CCTA arm also received ETT.	⊕⊕⊕◯ MODERATE

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
PCI	Up to 58 months	12 RCTs (N=18,960) **Suspected ACS** Hoffman 2012 Dedic 2016 Miller 2011 Goldstein 2007 Goldstein 2011 Hamilton-Craig 2014 Linde 2015 Uretsky 2017 Levsky 2018 **Stable patients** Douglas 2015 McKavanagh 2014 SCOT-HEART 2015	Yes (-1)	Yes (-1)	No	No	**CCTA vs. functional testing** **Risk:** 8.2 vs. 6.0 per 100 persons **Pooled estimates** RR 1.63, 95% CI 1.22 to 2.35, I^2=74% RD 2.4, 95% CI 1.3 to 3.6 per 100, I^2=51% **Conclusions:** CCTA was associated with more frequent referral for PCI across populations. Exclusion of poor-quality and outlier trials had minimal effect on effect size or heterogeneity. Exclusion of the trial in which 85% of patients received ETT (SCOT-HEART) created a larger difference in risk between treatment groups (5.1 vs. 2.6 per 100 patients), substantially decreased heterogeneity and increased the effect size. (11 RCTs, pooled RR 1.89, 95% CI 1.38 to 2.43, I^2=36%); the conclusion remains the same.	⊕⊕⊕◯ MODERATE
Hospitalization ***Stable Outpatients***	Any	4 RCTs (N=14,810) Min 2012 Douglas 2015 McKavanagh 2014 SCOT-HEART 2015	Yes (-1)	Yes (-1)	No	No	**CCTA vs. functional testing** **Risk:** 4.3 vs. 4.5 per 100 patients, **RR** 1.00, 95% CI 0.29 to 1.75, I^2=77% **Conclusions: T**here was no difference in hospitalization between CCTA and functional testing. Heterogeneity is likely related to one RCTs which reported that CCTA was associated	⊕⊕⊕◯ MODERATE

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							with lower risk of hospitalization compared with ETT	
Hospitalization ***ED Patients with suspected ACS***	Index	8 RCTs (N=4,625) CCTA vs. any functional 4 RCTs (N=3,126) Litt 2012 Hoffman 2012 Chang 2008 Dedic 2016 CCTA vs. SPECT 2 RCTs (N=896) Goldstein 2007 Goldstein 2011 CCTA vs. Stress Echo 2 RCTs (N=603) Levsky 2018 Pineiro-Portela 2021	Yes (-1)	Yes (-2)	NO	No	**<u>CCTA vs. (unspecified) functional tests</u>** 4 RCTs 48 vs. 71 per 100 patients, pooled RR 0.69, 95% CI 0.60 to 0.85, RD –19.6 per 100, 95% CI –31.7 to –7.5 per 100 **<u>CCTA vs. SPECT</u>** 2 RCTs pooled RR 1.49, 95% CI 1.03 to 3.79 (NS) however the larger good-quality RCT (N= 699) in low pre-test risk patients, 27 per 100 patients in the versus 19 per 100 patients who received SPECT (RR 1.43, 95% CI 1.08 to 1.88) **<u>CCTA vs. stress Echo</u>** 2 RCTs (21.9 vs. 18.5 per 100 persons, pooled RR 1.18, 95% CI 0.48 to 3.00, NS). The largest RCT (N=400) CCTA (RR 1.76, 95% CI 1.08 to 2.85 **<u>Conclusion:</u>** Across comparators with CCTA at time of index testing, there is substantial heterogeneity and results are mixed. While 4 RCTs comparing CCTA with any functional test suggest that hospitalization is less common with CCTA, large studies of CCTA vs echocardiography and SPECT suggest	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							that hospitalization may be more common with CCTA	
	1 to 6.5 months after index	9 RCTs (N=5,144) Litt 2012 Hoffman 2012 Chang 2008 Dedic 2016 Goldstein 2007 Goldstein 2011 Linde 2015 Miller 2011 Nabi 2016	Yes (-1)	No	No	No	CCTA vs. functional testing 3.0 vs. 3.9 per 100 patients, pooled RR 0.76, 95% CI 0.49 to 1.1, I^2=18% **Conclusion**: There was no difference in hospitalization visits after index testing between CCTA and functional testing from 1 to 6.5 months post index visit.	⊕⊕⊕⊕ HIGH
	≥12 months after index	6 RCTs (N=3,624) Hollander 2016, Linde 2015 Levsky 2015 Levsky 2018, Uretsky 2017 Hamilton Craig 2014	Yes (-1)	No	No	No	14.9 vs. 17.4 per 100 patients, pooled RR 0.90, 95% CI 0.77 to 1.03, I^2=0%). **Conclusion: T**here was no difference in emergency department visits after index testing between CCTA and functional testing at ≥12 months after index visit	⊕⊕⊕⊕ HIGH
Subsequent ED visits	1 to 6.5 months after index	7 RCTs (N=4,294) **Acute ACS** Litt 2012, Miller 2011 Hoffmann 2012 Dedic 2016 Goldstein 2007 Goldstein 2011 Nabi 2016	Yes (-1)	No	No	No	5.9 vs. 6.7 per 100 patients pooled RR 0.84, 95% CI 0.66 to 1.06, I^2=0% **Conclusion**: There was no difference in emergency department visits after index testing between CCTA and functional testing	⊕⊕⊕⊕ HIGH

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
	≥12 months after index	5 RCTs (N=2,855) **Acute ACS** Hollander 2016 Levsky 2015 Levsky 2018 Pineiro-Portela 2021 Hamilton-Craig 2014	Yes (-1)	No	No	No	30.5 per 30.8 per 100 patients, pooled RR 1.06, 95% CI 0.93 to 1.56, I^2=16% **Conclusion**: There was no difference in emergency department visits after index testing between CCTA and functional testing	⊕⊕⊕⊕ HIGH
Medication changes	Any time	**Stable outpatients** 4 RCTs (N across 3 RCTs = 4,814; N unclear for PROMISE trial) PROMISE (Douglas 2015, Ladapo 2016), Min 2012, McKavanagh 2015 SCOT-HEART (2015, Williams 2018) **Acute ACS** 5 RCTs (N=3,157) Linde 2015, ACRIN-PA (Litt 2012, Hollander 2016), Levsky 2015, Levsky 2018, Uretsky 2017	Yes (-1)	Yes (-2)	No	No	CCTA was not consistently associated with initiation of, discontinuation of or changes in medications and results for many mediations were mixed. Evidence is insufficient to draw firm conclusions about the impact of testing on medication use. Medication use/change was documented differently across trials.	⊕◯◯◯ INSUFFICIENT

Reasons for downgrading:

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice;
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies may be downgraded.
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects and may be downgraded once. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

Table 10.3. Key Question 3: Strength of evidence: CCTA versus functional testing; Safety, harms and consequences of testing

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
Any major test-related AE	Index test up to 24 hours	**3 RCTs (N= 10,270)** Stable outpatients (N=9,470) PROMISE (Douglas 2015) Suspected ACS (N=800) PROSPECT (Levsky 2015) Levsky 2018	Yes (-1)	No	No	Yes (-1)	**CCTA vs. Functional testing** 0% vs. 0% **Conclusion**: No major complications were observed in either arm in 3RCTs. Major complications were defined as death, renal failure requiring dialysis, or anaphylaxis requiring emergency respiratory and/or circulatory support in the PROMISE trial; stroke and cardiac arrest as part of MACE were considered in the other two. The two trials in patients with suspected ACS (N= 400 each) in particular may have been underpowered to detect rare events.	⊕⊕◯◯ LOW

Hospital admission for test-related complication	Index test up to 24 hours	**1 RCT (N=9,470)** **Stable outpatients** PROMISE/Douglas 2015	No	Unknown	No	Yes (-1)	**CCTA vs. any functional test** 0% vs. 0.1% (nuclear stress test)	⊕⊕◯◯ LOW
Any minor test-related AE		**12 RCTs (N=16,762)** **Stable outpatients (5 RCTs, N=12,978)** PROMISE/Douglas 2015, SCOT-HEART 2015 CAPP (McKavanagh 2015) IAEA-SPECT/CT (Karthikeyan 2017) RESCUE (Stillman 2020) **Suspected ACS (7 RCTs, N=3,784)** Chang 2008 ROMICAT-II (Hoffman 2012) ACRIN-PA (Litt 2012) BEACON (Dedic 2016) Goldstein 2007 PROSPECT (Levsky 2015) Levsky 2018	Yes (-1)	Yes (-1)	No	No	**CCTA:** 0% to 24% **Functional Testing:** 0% to 24% **Conclusions:** Risk of any minor test-related complication at time of index test or within 24 hours was <4% across treatment arms (10 RCT) Two RCTs in patients with suspected ACS which reported up to 24% of patients in both testing arms experienced minor events. These RCTs (Levsky 2015 and 2018) report a broader range of minor events including examination length and positional discomfort	⊕⊕◯◯ LOW

Contrast-related AEs Extravasation	Index test up to 24 hours	(CCTA arms only **Stable OP** (N=6,411) PROMISE (Douglas 2015, SCOT-HEART 2015 **Suspected ACS** 1 RCT (N=500) BEACON (Dedic 2016)	Yes (-1)	No	No	Yes (-1)	**CCTA only** **Conclusions:** Extravasation was rare (0.3% to 0.4%) in stable outpatients and 2% in patients with suspected ACS	⊕⊕◯◯ LOW
Nephropathy	Index test	Nephropathy 1 RCT (N=266) Chang 2008	Yes (-1)	unknown	No	Yes (-1)	Authors report that no cases of contrast-induced nephropathy occurred	⊕◯◯◯ **INSUFFICIENT**
Transient creatinine increase	Index test	**Suspected ACS** 2 RCTs (N=1,500) ROMICAT-II (Hoffman 2012) BEACON (Dedic 2016)	Yes (-1)	No	No	Yes (-1)	**CCTA** 0.2% to 1% **Functional test:** 0% to 0.4% **Conclusions:** Transient increases in creatinine not requiring dialysis were rare.	⊕⊕◯◯ LOW

Mild contrast-related reaction, allergic reaction, Skin rash/reaction, pruritis	Index test up to 24 hours	N for CCTA arms only **Stable outpatients** 2 RCTs (N=6,411) PROMISE (Douglas 2015, SCOT-HEART 2015 **Suspected ACS** 3 RCTs (N=596) Chang 2008 BEACON (Dedic 2016) PROSPECT (Levsky 2015	No	Yes	No	Yes (-2)	**CCTA arm only** **Stable outpatients:** **Stable OP**: 0.5% (35/6411) **Suspected ACS:** 1.2% (7/569) **Conclusions:** Contrast-related reactions were rare.	⊕⊕◯◯ LOW
Chest pain (CP), shortness of breath (SOB), or palpitations	Index test up to 24 hours	**2 RCTS (N=751)** **Suspected ACS** PROSPECT (Levsky 2015) Levsky 2018	Yes (-1)	No	No	Yes (-1)	**Suspected ACS (CP, SOB, palpitations)** **CCTA vs. SPECT** 1 RCT, 0.5% vs. 16% RR 0.03, 95% CI 0.004 to 0.24 **CCTA vs. Stress Echo** 1 RCT, 0% vs. 3%, p=0.03 **Conclusions:** CCTA was associated with lower risk of these symptoms, which are likely consistent with inducing cardiac stress	⊕⊕◯◯ LOW

Stress-Related symptoms and events (unspecified) and dipyridamole, adenosine-related events		**1 RCT (N=7,896)** **Stable outpatients** PROMISE (Douglas 2015)	No	Unknown	No	Yes (-1)	**CCTA vs. stress nuclear imaging** Stress-induced symptoms (unspecified) 0% vs. 0.1% Dipyridamole, adenosine related 0% vs. 0.2% **Conclusions:** The risk of symptoms and adverse events related to stress testing were confined to nuclear stress testing and were rare.	⊕⊕◯◯ LOW
Arrythmias: Rapid atrial fibrillation (AF) Ventricular tachycardia Bradyarrhythmia		**Stable outpatients** **1 RCT (N=7,896)** PROMISE (Douglas 2015) **Suspected ACS** **1 RCT (N=1,370)** ACRIN-PA (Litt 2012)	Stable No Suspected ACS Yes (-1)	Unknown	No	Yes (-1)	**CCTA vs. functional testing** **Stable outpatients** Rapid AF 0% vs. 0% Ventricular Tachycardia: 0% vs. 0.2% (nuclear stress test) **Suspected ACS** Bradyarrhythmia: 0.1% vs. 0.2%	⊕◯◯◯ INSUFFICIENT

Radiation exposure	Index Test	**5 RCTs total** **CCTA vs. SPECT** **Stable OP** 3 RCTs (N=6,832) PROMISE (Douglas 2015) IAEA-SPECT/CTA (Karthikeyan 2017) Min 2012 **Suspected ACS** 2 RCTs (N=1,297) CT-STAT (Goldstein 2011) Nabi 2016	Yes (-1)	Yes (-1)	No	No	Across five RCTs comparing CCTA specifically with SPECT, four reported that CCTA was associated with a lower effective radiation dose for the index test (estimated range 1.30 mSv to 11.9 mSv); the fifth trial reported that CCTA was associated with slightly higher radiation (estimated difference 1.8 mSv). **Conclusion:** CCTA may be associated with lower radiation exposure at index test compared with SPECT specifically. It is unclear if some of the differences between arms would impact clinical decision making.	⊕⊕◯◯ LOW

Radiation exposure	Cumulative	9 RCTs total **Stable OP** 3 RCTs (N=10,486) PROMISE (Douglas 2015) IAEA-SPECT/CTA (Karthikeyan 2017) Min 2012 **Suspected ACS** 6 RCTs (N=3,498) CATCH (Linde 2013) ROMICAT-II (Hoffman 2012) BEACON (Dedic 2016) PROSPECT (Levksy 2015) Nabi 2016 Levksy 2018	Yes (-1)	Yes (-1)	No	No	Range of rough estimated differences between arms reported higher for CCTA 1.9 mSv to 9.0 mSv **Conclusions:** Across nine RCTs, results are somewhat mixed, but suggest that cumulative radiation may be higher when CCTA is the initial test. It is unclear if some of the differences between arms would impact clinical decision making.	⊕⊕◯◯ LOW

Incidental findings: "potentially serious" or requiring additional imaging	Any time	3 RCTs (N=12,295) **Stable patients** Lu2017 (PROMISE) Williams 2018 (SCOT-HEART) Stillman 2020 (RESCUE) 2 systematic reviews (N=27,580) Karius 2014 Flor 2013 4 Retrospective cohorts (N=9,090) Karius 2019 Bendix 2011 Erol 2014 Ramanathan 2019	Yes (-2)	Yes (-1)	No	No	**CCTA only** **"**Any" incidental finding range: (28% to 44%) Findings that are "potentially significant" "clinically significant" or "required follow-up" range: 4.9% to 16% **Conclusion**: Incidental findings are common with CCTA with pulmonary findings being most common. There is wide range of findings that were considered potentially important that would likely result in the need to follow-up and/or require additional testing.	⊕⊕◯◯ LOW

Reasons for downgrading:

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice;
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies may be downgraded.
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects and may be downgraded once. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

Table 10.4. Key Question 4: Strength of evidence: CCTA versus functional testing: Differential efficacy or safety for primary outcomes*

Outcome(s)	Subgroups	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Risk, Effect Estimate (95% CI), p for interaction	Quality (SOE)
Primary clinical outcomes								
Myocardial infarction **Median 3.2 years**	NICE classification of chest pain (non-anginal vs. possibly anginal)	1 RCT (N=3,370) **Stable outpatients** SCOT-HEART, 2018	Yes (-2)	Unknown	No	Yes (-1)	**CCTA vs. functional testing** **Nonanginal** 1.0 % vs. 1.5 %, HR 0.65 (95% CI 0.25 to 1.69) **Anginal** 1.9% vs. 3.2%, HR 0.58 (95% CI 0.34 to 0.99) *p=0.836* **Conclusions:** Although the effect of CCTA does not appear to vary based on anginal classification, it is not clear that this study was sufficiently powered for this evaluation.	⊕⊕◯◯ LOW
All-Cause mortality **Median 3.2 years**			Yes (-2)	Unknown	No	Yes (-2)	**CCTA vs. functional testing** **Nonanginal** 0.1% vs. 0.7%, HR 1.81 (95% CI 0.53 to 6.18) **Anginal** 0.5% vs. 0.5%, HR 0.82 (95% CI 0.44 to 1.53) *p=0.200* **Conclusions:** Although the effect of CCTA does not appear to vary based on anginal classification, it is not clear that this study was sufficiently powered for this evaluation. Authors do not state if subgroup analysis was planned a priori or conducted post hoc and do not describe specific hypotheses tested.	⊕◯◯◯ INSUFFICENT
CAD death			Yes (-2)	Unknown	No	Yes (-2)	**CCTA vs. functional testing**	⊕◯◯◯

Outcome(s)	Subgroups	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Risk, Effect Estimate (95% CI), p for interaction	Quality (SOE)
Median 3.2 years							**Nonanginal** 0% vs 0.3%, HR 0 (95% CI 0 to Infinity) **Anginal** 0.3% vs. 0.3%, HR 0.78 (95% CI 0.17 to 3.48) *p=0.998* **Conclusions:** Although the effect of CCTA does not appear to vary based on anginal classification, it is not clear that this study was sufficiently powered for this evaluation. Authors do not state if subgroup analysis was planned a priori or conducted post hoc and do not describe specific hypotheses tested.	INSUFFICENT
Decision making								
Downstream Testing	Diabetes Sex Race	1 RCT (N= 1,000) **Suspected ACS** ROMICAT-II trial (Hoffman 2012)	Yes (-2)	Unknown	No	No	**CCTA vs. functional testing** (no effect sizes provided) ***Index visit*** **Diabetes:** 38% vs. 5% **No diabetes:** 20% vs. 12% *p=0.0001* ***28-day follow-up*** **Diabetes:** 42% vs. 7% **No diabetes:** 23% vs. 13% *p=0.002* **Sex p-value for interaction** Index visit, p=0.08	⊕⊕◯◯ LOW

Outcome(s)	Subgroups	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Risk, Effect Estimate (95% CI), p for interaction	Quality (SOE)
							28-day follow-up, p=0.23 **Race p-value for interaction** Index visit, p=0.16 28-day follow-up, p=0.18 **Conclusions:** Diabetes status may modify the effect of CCTA: more downstream testing occurred with CCTA in patients with diabetes at index visit and by 28-day follow-up Downstream testing. No interaction (differential effect) by sex or race was seen. (See full report)	
ICA referral	Diabetes Sex Race	**Stable OP** 1 RCT (N= 8,966) PROMISE (good quality) **Suspected ACS** 1 RCT (N= 1,000) ROMICAT-II trial (fair quality)	Diabetes Yes (-1) Sex, Race Yes (-2)	No Sex, Race Unknown	No	No	**Conclusions:** Across two RCTs, one in stable outpatients and the other in patients with suspected ACS the effect of CCTA versus functional testing on ICA referral did not vary by diabetes status (p-values 0.596 and 0.06) There was no effect modification in the trial in patients with suspected ACS by sex or race at index visit or by 28-day follow-up. P-values for interaction across all subgroups were not statistically significant. (See full report.)	Diabetes ⊕⊕◯◯ LOW Sex, Race ⊕◯◯◯ INSUFFICIENT
Revascularization	Diabetes Sex Angina classification	Stable OP 2 RCTs PROMISE (N=8,966)	Diabetes Yes (-1)	Diabetes Yes (-1)	No	No	**Diabetes** (2 RCTs, PROMISE, ROMICAT-II) The effect of CCTA versus functional testing on revascularization did not vary by diabetes status within 30 days of ICA (PROMISE) or 28 days of	Diabetes ⊕⊕◯◯ LOW

Outcome(s)	Subgroups	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Risk, Effect Estimate (95% CI), p for interaction	Quality (SOE)
		SCOT-HEART (N=3,770) **Suspected ACS** 1 RCT (N= 1,000) ROMICAT-II trial	Sex Yes (-2) Angina Yes (-1)	Sex, angina Unknown		Sex Yes (-1) Angina Yes (-1)	follow-up (ROMICAT) (p-values, 0.372 and 0.26). **Sex:** (ROMICAT-II) The effect of CCTA versus functional testing on revascularization was not modified by sex (p=0.33) **Angina classification**: (SCOT-HEART) The effect of CCTA versus functional testing on revascularization was not modified by angina classification (p=0.938) See full report	Sex, ⊕◯◯◯ INSUFFICIENT Anginal classification ⊕◯◯◯ INSUFFICIENT
Safety								
Radiation Exposure (mSv) (cumulative) ≤90 days	Age (N=6355) Sex (N=6626) BMI (N=6301) Heart Rate (N=NR)	**Stable OP** 1 RCT (N= 8,966) PROMISE	Yes (-2) (Population subset)	Unknown	No	No	**Age** (<65**,** ≥65 years), p= 0.72 **Sex** (Male, female), p=0.82 **BMI** (<30 kg/m^2, ≥30 kg/m^2), p=0.10 **Heart rate** (<75 bpm, ≥75 bpm), p =0.04 See full report **Conclusion:** CTTA cumulative radiation may vary based on baseline heart rate. Patients with ≥75 bpm may have higher cumulative radiation with CCTA compared with functional testing. Tests for interaction by Age, sex and BMI were not significant.	⊕◯◯◯ INSUFFICIENT
Radiation Exposure (mSv) Index test	Sex	Suspected ACS ROMICAT-II trial (N=NR)	Yes (-2)	Unknown	No	Yes -1	**CCTA vs. functional testing (mSv mean (SD)** **Female** 10.8 (8.7) vs. 4.7 (8.1) **Male**1 14.2 (11.2) vs. 4.7 (8.7) p= 0.003	⊕◯◯◯ INSUFFICIENT

Outcome(s)	Subgroups	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Risk, Effect Estimate (95% CI), p for interaction	Quality (SOE)
							Conclusion: Mean radiation dose at index varied by sex. Doses were higher for men receiving CCTA vs. functional testing.	
Radiation Exposure (mSv) (cumulative) To 28 days	Sex Diabetes Race	Suspected ACS ROMICAT-II trial (N=NR)	Yes (-2)	Unknown	No	Yes -1	**CCTA vs. functional testing (mSv mean (SD)** **Female** 11.0 (8.9) 6.0 (8.2) **Male** 14.7 (12.0) vs. 5.6 (10.7) p= 0.002 **Diabetes** 18.4 (14.7) 6.6 (10.4) **No diabetes** 13.4 (9.8) 5.1 (9.5) P=0.04 Median, IQR **White** 12.0 (7.9 to 17.2) vs 0.0 (0.0 to 12.4) **Black** 11.7 (8.6 to 16 vs. 0.0 (0.0 to 0.0) P=0.60 **Conclusion:** Mean cumulative radiation dose by 28 days varied by sex and diabetes status but not by race for CCTA vs. functional testing. Higher doses in the CCTA groups were seen for men and patients with diabetes. Race did not modify the relationship between testing and dose.	⊕◯◯◯ INSUFFICIENT

*Strength of evidence for evaluation of differential efficacy or safety considers of the overall study risk of bias (study quality) as well as whether subgroup variables and analyses were specified a priori, number of subgroups tested, the hypothesized impact and direction of a subgroup and sample size as evaluation of interaction requires greater sample size.

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice; For HTE evaluation this may be down-graded an additional level based on failure to specify subgroup analysis *a priori* or if the subgroup hypothesis was not one of a smaller number tested and/or not stated (i.e. large number of subgroups tested)
2. Inconsistency: differing estimates of effects across trials

3. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
4. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with TT
5. Imprecise effect estimate for a dichotomous outcome: small sample size, rare outcome
6. Serious risk of bias in evaluation of HTE: the subgroup variables were specified at randomization, however the hypothesized direction was not stated; the subgroup hypothesis was not one of a smaller number tested

Table 10.5. Key Question 1, 2 and 3: Strength of evidence: CCTA vs. ICA

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
Key Question 1: Primary clinical outcomes								
Myocardial infarction Cumulative **Mortality, all-cause** Cumulative **Mortality, cardiac** Cumulative	12 months, median 40 months	2 RCTs (N=1,832) **Chang 2019** Suspected CAD, stable outpatients **Dewey 2016** Suspected CAD, stable and acute, atypical chest pain	No	No	No	Yes (-2)	**MI** Risk: 0.3 vs. 0.2 per 100 patients Pooled estimates (2 RCTs, N=1,832): RR 1.26 (95% CI 0.24 to 6.67), I^2=0% RD (not calculated, no association) **All-cause mortality** Risk: 0.2 vs. 0.2 per 100 patients Pooled estimates (2 RCTs, N=1,832): RR 1.03 (95% CI 0.06 to 11.08), I^2=0% RD (not calculated, no association) **Cardiac mortality** Risk: 0 vs. 0.6 per 100 patients 1 RCT (N=329) **Conclusions:** There was no difference in the risk of MI or all-cause mortality for CCTA vs. ICA, despite difference in populations and follow-up duration across the trials. Firm conclusions	MI, all-cause mortality ⊕⊕◯◯ LOW Cardiac mortality ⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							regarding the impact of CCTA or ICA on cardiac death are not possible. Cardiac death was rare. Sample sizes in individual trials may have been insufficient to detect cardiac death.	
Key Question 2: Clinical Decision-Making Outcomes								
ICA not showing obstructive CAD	12 months, median 40 months	2 RCTs (N=1,832) **Chang 2019** Suspected CAD, stable outpatients **Dewey 2016** Suspected CAD, stable and acute, atypical chest pain	No	No	No	Yes (-1)	Risk: 22 vs. 65 per 100 patients Pooled estimates (2 RCTs, N=1,019): RR 0.32 (95% CI 0.18 to 0.51), I^2=0% RD –48% (95% CI –67% to –29%), I^2=73% **Conclusions:** CCTA was associated with a decreased risk of ICA showing no obstructive CAD compared with direct referral to ICA.	⊕⊕⊕◯ MODERATE
Additional NIT (any)	12 months	1 RCT (N=1,503) **Chang 2019** Suspected CAD, stable outpatients	No	Unknown	No	Yes (-1)	Risk: 53 vs. 27 per 100 patients RR 1.96 (95% CI 1.71 to 2.25) RD 26.0% (95% CI 21.1% to 30.7%) **Conclusions:** CCTA was associated with an increased risk of additional downstream testing compared with direct referral to ICA.	⊕⊕⊕◯ MODERATE
Revascularization (any)	12 months, median 40 months	2 RCTs (N=1,832) **Chang 2019** Suspected CAD,	No	No	No	Yes (-1)	Risk: 13 vs. 18 per 100 patients Pooled estimates (2 RCTs, N=1,832): RR 0.71 (95% CI 0.55 to 0.96), I^2=0% RD –5.0% (95% CI –8.0% to –2.0%),	⊕⊕⊕◯ MODERATE

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
		stable outpatients **Dewey 2016** Suspected CAD, stable and acute, atypical chest pain					I^2=0% **Conclusions:** CCTA was associated with a decreased risk of revascularization compared with direct referral to ICA.	
Hospitalization, cardiac causes	12 months	1 RCT (N=1,503) **Chang 2019** Suspected CAD, stable outpatients	No	Unknown	No	Yes (-1)	Risk: 4 vs. 4 per 100 patients RR 0.98 (95% CI 0.60 to 1.58) RD (not calculated, no association) **Conclusions:** There was no difference in the risk of cardiac hospitalization with CCTA compared with direct referral to ICA.	⊕⊕⊕◯ MODERATE
Key Question 3: Safety								
Major adverse events	≤48 hours, median 12 months	2 RCTs (N=1,832) **Chang 2019** Suspected CAD, stable outpatients **Dewey 2016** Suspected CAD, stable and acute, atypical chest pain	No	No	No	Yes (-2)	**Any complications prolonging hospital stay** Risk: no events in either test arm 1 RCT (N=327) **Major bleeding** Risk: 0 vs. 0.3 per 100 patients 1 RCT (N=1,503) **Conclusions:** There was no difference in the risk of major adverse events between CCTA and ICA. Given that the events are rare, trials may have been	⊕⊕◯◯ LOW

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							under powered to detect a difference.	
Minor adverse events	≤48 hours after last procedure	2 RCTs (N=327) **Dewey 2016** Suspected CAD, stable and acute, atypical chest pain	No	Unknown	No	Yes (-1)	**Any minor procedural complication** Risk: 4 vs. 11 per 100 patients RR 0.35 (0.14 to 0.86) RD –6.9% (–12.4% to –1.3%) **Hematoma at puncture site** Risk: 1 vs. 9 per 100 patients RR 0.07 (0.01 to 0.53) RD –8.0% (–12.5% to –3.6%) **Bradycardia** Risk: 1 vs. 0 per 100 patients **Other minor adverse events** Risk: <1 per 100 patients for each arm: Secondary bleeding at puncture site, angina without MI, allergic reaction to contrast agent, hypotension requiring treatment, stent migration **Conclusions:** CCTA was associated with a reduced risk of any minor procedural adverse event compared with ICA, driven by the frequency of hematoma at the puncture site. There was no difference in the risk of other specific minor events.	⊕⊕◯◯ LOW

Reasons for downgrading:

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice;

2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies may be downgraded.
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects and may be downgraded once. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

Table 10.6. Key Questions 1, 2 and 3: Strength of evidence: CCTA FFR versus any functional and versus ICA

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
Key Question 1: Primary clinical outcomes								
Myocardial infarction cumulative	3, 12 months	1 prospective cohort (N=584) **Planned noninvasive test cohort (N=204)** CCTA FFR vs. any noninvasive test **Planned ICA cohort (N=380)** CCTA FFR vs. ICA	Yes (-1)	Unknown	No	Yes (-2)	**CCTA FFR vs. any noninvasive test** 3 months: No MIs in either arm 12 months: Risk: 0 vs. 1 per 100 patients **CCTA FFR vs. ICA** 3 months: Risk: 1 vs. 0 per 100 patients 12 months: Risk: 1 vs. 1 per 100 patients **Conclusion**: Firm conclusions regarding the impact of CCTA FFR vs. any noninvasive test or vs. ICA on MI are not possible. MI was rare (≤1 per 100 patients [3 MIs total] across both arms of both cohorts through 12 months). The sample size may have been insufficient to detect MI.	⊕◯◯◯ INSUFFICIENT
Mortality, all-cause cumulative	3, 12 months						**CCTA FFR vs. any noninvasive test** 3 and 12 months: No deaths in either arm **CCTA FFR vs. ICA** 3 months: No deaths in either arm 12 months: Risk: 0 vs. 1 per 100 patients	

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							Conclusion: Firm conclusions regarding the impact of CCTA FFR vs. any noninvasive test or vs. ICA on all-cause mortality are not possible. All-cause mortality was rare (1 death [planned ICA cohort] over 12 months across both cohorts). The sample size may have been insufficient to detect all-cause mortality.	
Key Question 2: Clinical Decision-Making Outcomes								
ICA	3, 12 months	1 prospective cohort (N=584) **Planned noninvasive test cohort (N=204)** CCTA FFR vs. any noninvasive test **Planned ICA cohort (N=380)** CCTA FFR vs. ICA	Yes (-1)	Unknown	No	Yes (-1)	**CCTA FFR vs. any noninvasive test** 3 months: Risk: 18 vs. 12 per 100 patients RR 1.52 (0.78 to 2.97) 12 months: Risk: 21 vs. 16 per 100 patients RR 1.32 (0.74 to 2.37) **CCTA FFR vs. ICA** 3 months: Risk: 39 vs. 100 per 100 patients RR 0.39 (0.33 to 0.47) 12 months: Risk: 51 vs. 100 per 100 patients • RR 0.51 (0.45 to 0.59)No events in the 61% of CCTA with FFR patients in whom ICA was cancelled **Conclusion**: Firm conclusions regarding the impact of CCTA FFR vs. any noninvasive test or vs. ICA on referral to ICA are not possible.	⊕◯◯◯ INSUFFICIENT
ICA without obstructive CAD (core lab quantitative analysis)	3 months						**CCTA FFR vs. any noninvasive test** 3 months: Risk: 13 vs. 6 per 100 patients RR 2.08 (0.82 to 5.27) **CCTA FFR vs. ICA**	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							3 months: Risk: 39 vs. 100 per 100 patients RR 0.39 (0.33 to 0.47) **Conclusion**: Firm conclusions regarding the impact of CCTA FFR vs. any noninvasive test or vs. ICA on the frequency of ICA without obstructive CAD are not possible.	
Revascularization (any)	3, 12 months						**CCTA FFR vs. any noninvasive test** 3 months: Risk: 10 vs. 5 per 100 patients RD (not calculated, no association) 12 months: Risk: 10 vs. 7 per 100 patients RR 1.37 (0.54 to 3.47) **CCTA FFR vs. ICA** 3 months: Risk: 29 vs. 32 per 100 patients RR 0.90 (0.66 to 1.23) 12 months: Risk: 34 vs. 36 per 100 patients RR 0.94 (0.71 to 1.24) **Conclusion**: Firm conclusions regarding the impact of CCTA FFR vs. any noninvasive test or vs. ICA on any revascularization are not possible.	⊕◯◯◯ INSUFFICIENT
Hospitalization (with urgent revascularization)	3, 12 months						**CCTA FFR vs. any noninvasive test** 3 and 12 months: No events in either arm **CCTA FFR vs. ICA** 3 and 12 months: Risk: 1 vs. 0 per 100 patients **Conclusion**: Firm conclusions regarding the	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							impact of CCTA FFR vs. any noninvasive test or vs. ICA on hospitalization with urgent revascularization are not possible. There was one hospitalization with urgent revascularization over 12 months across both cohorts which occurred in a patient who received CCTA with FFR rather than being referred directly to ICA (planned ICA cohort). Given that these likely are rare events (there was 1 event in a patient who received CCTA with FFR rather than direct ICA [planned ICA cohort]), the study may not have been sufficiently powered to detect them.	
Key Question 3: Safety								
Test-related AEs	12 months	1 prospective cohort (N=584) **Planned noninvasive test cohort (N=204)** CCTA FFR vs. any noninvasive test **Planned ICA cohort (N=380)** CCTA FFR vs. ICA	Low	Unknown	No	Yes (-2)	One mild contrast reaction from CCTA testing; no other information provided. **Conclusion**: Data are insufficient to draw conclusions.	⊕○○○ INSUFFICIENT
Cumulative radiation exposure (mSv)	12 months						**CCTA FFR vs. any noninvasive test** 3 months: 8.8 vs. 5.8 mSv MD 3.0 (0.6 to 5.4) 12 months: 9.6 vs. 6.4 mSv MD 3.1 (0.6 to 5.7) **CCTA FFR vs. ICA** 3 months: 9.9 vs. 9.4 mSv MD 0.50 (–0.93 to 1.93) 12 months: 10.7 vs. 10.4 mSv MD 0.36 (–1.32 to 2.04)	⊕⊕○○ LOW

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							Conclusion: Patients who received CCTA with FFR had significantly greater cumulative radiation exposure over 12 months compared to those who received any noninvasive test (planned noninvasive test cohort); there was no difference for CCTA with FFR versus direct referral to ICA (planned ICA cohort).	

Reasons for downgrading:

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice;
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies may be downgraded.
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects and may be downgraded once. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

Table 10.7. Key Questions 1 and 2: Strength of evidence: SPECT versus any functional

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
Key Question 1: Primary clinical outcomes								
Myocardial infarction cumulative	30 days to mean 24 months	4 RCTs (N=1,908) **SPECT vs. Echo (Suspected or**	Yes (-1)	No	No	Yes (-2)	Risk: 0.3 vs. 1.3 per 100 patients Pooled estimates (2 RCTs, N=907): RR 0.32 (95% CI 0.05 to 1.96), I^2=0.0% RD (not calculated, no association)	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
		known CAD) 2 RCTs (N=679) Sharples 2007 (stable, OP) Salame 2018 (acute, ED) **SPECT vs. ECG (Suspected CAD)** 2 RCT (N=1,229) Sabharwal 2007 Shaw 2011 (stable, OP)					1 RCT, SPECT vs. Echo (N=229): no events in either group 1 RCT, SPECT vs. ECG (N=772): 0.4 per 100 patients (not reported by test group) **Conclusions:** Firm conclusions regarding the impact of SPECT or functional testing (echocardiography or exercise ECG) on MI are not possible. MI was rare. Sample sizes in individual trials may have been insufficient to detect MI.	
Mortality, all-cause cumulative	30 days to 72 months	4 RCTs (N=1,908) **SPECT vs. Echo (Suspected or known CAD)** 2 RCTs (N=679) Sharples 2007 (stable, OP) Salame 2018 (acute, ED) **SPECT vs. ECG (Suspected CAD)** 2 RCT (N=1,229) Sabharwal 2007 Shaw 2011	Yes (-1)	No	No	Yes (-1)	Risk: 1.4 vs. 1.6 per 100 patients Pooled estimates (4 RCTs, N=1,908): RR 0.89 (95% CI 0.42 to 2.57), I^2=0.0% RD (not calculated, no association) **Conclusions**: There was no difference for SPECT versus stress echocardiography or exercise ECG in the risk of all-cause mortality, despite difference in populations and follow-up duration across the trials. Since this is a rare event, trials may not have been sufficiently powered to detect a difference.	⊕⊕◯◯ LOW

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
		(stable, OP)						
Mortality, cardiac cumulative	18 to 24 months	3 RCTs (N=1,679) **SPECT vs. Echo (Suspected or known CAD)** 1 RCT (N=450) Sharples 2007 (stable, OP) **SPECT vs. ECG (Suspected CAD)** 2 RCT (N=1,229) Sabharwal 2007 Shaw 2011 (stable, OP)	Yes (-1)	Yes (-1)	No	Yes (-1)	1.1 vs. 0.5 per 100 patients Pooled estimates (2 RCTs, N=907): RR 2.21 (95% CI 0.05 to 35.30), I^2=0.0% RD (not calculated, no association) 1 RCT, SPECT vs. ECG (N=772): 0.1 per 100 patients (not reported by test group) **Conclusions:** Firm conclusions regarding the impact of SPECT or functional testing (echocardiography or exercise ECG) on cardiac mortality are not possible. Cardiac mortality was rare. Sample sizes in individual trials may have been insufficient to detect events.	⊕◯◯◯ INSUFFICIENT
Key Question 2: Clinical Decision-Making Outcomes								
ICA	30 days to 24 months	4 RCTs (N=1,908) **SPECT vs. Echo (Suspected or known CAD)** 2 RCTs (N=679) Sharples 2007 (stable, OP) Salame 2018 (acute, ED)	Yes (-1)	Yes (-1)	No	No	Risk: 24.5 vs. 31.9 per 100 patients Pooled estimates (4 RCTs, N=1,908) RR 0.64 (95% CI 0.31 to 1.22), I^2=86.5% RD (not calculated, no association) 1 RCT (N=457), SPECT vs. ECG 16.4 versus 47.3 per 100 patients RR 0.35 (95% CI 0.25 to 0.47) RD –30.9%, 95% CI –39.2% to –22.7%)	⊕⊕◯◯ LOW

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
		SPECT vs. ECG (Suspected CAD) 2 RCT (N=1,229) Sabharwal 2007 Shaw 2011 (stable, OP)					**Conclusion:** There was no difference for SPECT versus stress echocardiography or exercise ECG in the risk of ICA across all 4 trials, however, there was substantial heterogeneity. Individually, only one fair-quality trial comparing SPECT with exercise ECG in stable patients at mixed pretest risk for CAD reported a statistically significant difference which favored SPECT (30% reduction in ICA). Differences in patient populations and/or pretest risk may have played a role in these findings.	
Additional NIT (any)	18 to 24 months	3 RCTs (N=1,679) **SPECT vs. Echo (Suspected or known CAD)** 1 RCT (N=450) Sharples 2007 (stable, OP) **SPECT vs. ECG (Suspected CAD)** 2 RCT (N=1,229) Sabharwal 2007 Shaw 2011	Yes (-1)	Yes (-1)	No	Yes (-1)	Risk: 4.3 vs. 14.6 per 100 patients Pooled estimates (3 RCTs, N=1,679) RR 0.24 (95% CI 0.01 to 8.67), I^2=70.0% RD (not calculated, no association) **SPECT vs. Echo** Risk: 0.4 vs. 0 per 100 patients 1 RCT (N=450) RR 3.03 (95% CI 0.12 to 73.90) RD (not calculated, no association) **SPECT vs. ECG** 5.7 vs. 20.2 per 100 patients Pooled estimate (2 RCTs, N=1,229) RR 0.11 (95% CI 0.00 to 8.87), I^2=93%	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							RD (not calculated, no association) 1 RCT (N=772): Risk: 9.4 vs. 18.6 per 100 patients RR 0.51 (95% CI 0.35 to 0.73) RD –8.2% (95% CI –14.0 to –4.3%) 1 RCT (N=457): Risk: 0 vs. 23.2 per 100 patients RR 0.01 (95% CI 0.00 to 0.14) RD –23.2% (95% CI –29.0 to –17.4%) **Conclusion:** It is difficult to draw firm conclusions across trials due to lack of precision and inconsistency. While both trials comparing SPECT with exercise ECG showed a reduction in risk of downstream NIT with SPECT, heterogeneity was substantial resulting in a pooled estimate that was not statistically significant. Differences in testing protocols, populations (1 trial was in women only), and pre-test risks may partly explain the heterogeneity.	
Revascularization (any)	30 days to 36 months	4 RCTs (N=1,908) **SPECT vs. Echo (Suspected or known CAD)** 2 RCTs (N=679)	Yes (-1)	Yes (-1)	No	No	Risk: 13.7 vs. 17.5 per 100 patients Pooled estimates (4 RCTs, N=1,908): RR 0.80 (95% CI 0.60 to 1.09), I^2=0.0% RD (not calculated, no association) **Conclusion:** There was no difference	⊕⊕⊕◯ MODERATE

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
		Thom 2014 (stable, OP) Salame 2018 (acute, ED) **SPECT vs. ECG (Suspected CAD)** 2 RCT (N=1,229) Sabharwal 2007 Shaw 2011 (stable, OP)					for SPECT versus stress echocardiography or versus exercise ECG in the risk of revascularization, despite difference in populations and follow-up duration across the trials. Two trials in stable patients reported a lower risk of revascularization following SPECT, however, the differences were only marginally significant: 1 good-quality trial comparing SPECT with echocardiography (RR 0.82, 95% CI 0.67 to 0.99) and 1 fair-quality trial comparing SPECT with ECG (RR 0.60 (95% CI 0.38 to 0.96). There were no differences when PCI and CABG were considered separately.	
Hospitalization	30 days to 24 months	3 RCTs (N=1,451) **SPECT vs. Echo (Suspected or known CAD)** 2 RCTs (N=679) Sharples 2007 (stable, OP) Salame 2018 (acute, ED) **SPECT vs. ECG (Suspected CAD)** 1 RCT (N=772)	Yes (-1)	No	No	Yes (-1)	Risk: 5.4 vs. 5.9 per 100 patients Pooled estimates (3 RCTs, N=1,451): RR 0.89 (95% CI 0.54 to 2.14), I^2=0.0% RD (not calculated, no association) **<u>Conclusions</u>:** There was no difference for SPECT versus stress echocardiography or versus exercise ECG in the risk of hospitalization for cardiac causes, despite difference in populations and follow-up duration across the trials.	⊕⊕◯◯ LOW

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
		Shaw 2011 (stable, OP)						
ED revisit	30 days	1 RCT (N=229) **SPECT vs. Echo (Suspected or known CAD)** Salame 2018 (acute, ED)	Yes (-1)	Unknown	No	Yes (-1)	Risk: 2.6 vs. 2.7 per 100 patients RR 0.97 (95% CI 0.20 to 4.73) **Conclusions:** There was no difference for SPECT versus stress echocardiography in the risk of re-presentation to the ED within 30 days.	⊕⊕◯◯ LOW

Reasons for downgrading:

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice;
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies may be downgraded.
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects and may be downgraded once. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

Table 10.8. Key Questions 1 and 2: Strength of evidence: SPECT versus NICE guideline-directed care and versus clinical assessment alone

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
Key Question 1: Primary clinical outcomes								
Myocardial infarction	Median 16 months	1 RCT (N=721)	No	Unknown	No	Yes (-2)	Risk: 0.4 vs. 0.8 per 100 patients, RR 0.50 (95% CI 0.07 to 3.52)	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
cumulative		**NICE guideline-directed care** Greenwood 2017 Suspected CAD (stable, OP)					RD (not calculated, no association) **Conclusions:** Firm conclusions regarding the impact of SPECT or NICE guideline-directed care on MI are not possible. MI was rare. The sample size may have been insufficient to detect MI.	
Mortality, all-cause cumulative							Risk: 0.6 vs. 1.3 per 100 patients, RR 0.50 (95% CI 0.10 to 2.45) RD (not calculated, no association) **Conclusions:** Firm conclusions regarding the impact of SPECT or NICE guideline-directed care on all-cause mortality are not possible. All-cause mortality was rare. The sample size may have been insufficient to detect events.	⊕◯◯◯ INSUFFICIENT
Cardiac mortality cumulative	12, 16 months	2 RCTs (N=2,229) **Clinical assessment alone** Lim 2013 Suspected ACS (acute, ED) **NICE guideline-directed care** Greenwood 2017	Yes (-1)	No	No	Yes (-2)	Risk: 0.4 vs. 0.1 per 100 patients Pooled estimates (2 RCTs, N=2,229): RR 2.04 (95% CI 0.25 to 19.09), I^2=0% RD (not calculated, no association) **Conclusions:** Firm conclusions regarding the impact of SPECT or NICE guideline-directed care or clinical assessment alone on cardiac mortality are not possible. Cardiac mortality was rare. Sample sizes in individual	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
		Suspected CAD (stable, OP)					trials may have been insufficient to detect events.	
Key Question 2: Clinical Decision-Making Outcomes								
ICA	12, 16 months	2 RCTs (N=2,229) **Clinical assessment alone** Lim 2013 Suspected ACS (acute, ED) **NICE guideline-directed care** Greenwood 2017 Suspected CAD (stable, OP)	Yes (-1)	Yes (-1)	No	No	Risk: 10.2 vs. 21.1 per 100 patients Pooled estimates (2 RCTs, N=2,229): RR 0.49 (95% CI 0.26 to 0.95), I^2=85% RD –11.1% (95% CI –14.4% to –7.8%) **SPECT vs. Clinical assessment alone**: 1 RCT, N=1,508 Risk: 7 vs. 11 per 100 patients RR 0.65 (95% CI 0.47 to 0.91) **SPECT vs. NICE guideline-directed care**: 1 RCT, N=721 Risk: 16 vs. 43 per 100 patients RR 0.38 (95% CI 0.30 to 0.49) **Conclusions:** SPECT was associated with a decreased risk of ICA vs. clinical assessment alone and vs. NICE guideline-directed care, however heterogeneity was substantial, driven by the stronger association found for SPECT vs. NICE guideline-directed care due to the direct referral to ICA of patients with high pretest risk per the NICE guideline algorithm.	⊕⊕◯◯ LOW
ICA showing no obstructive CAD	12 months	1 RCT (N=1,508)	Yes (-1)	Unknown	No	No	Risk: 21.9 vs. 39.3 per 100 patients, RR 0.56 (95% CI 0.32 to 0.96)	⊕⊕◯◯ LOW

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
		Clinical assessment alone Lim 2013 Suspected ACS (acute, ED)					RD –17.4% (95% CI –33.3% to –1.4%) **Conclusions:** SPECT was associated with a decreased risk of ICA showing no obstructive disease, compared with clinical assessment alone.	
Unnecessary ICA*	16 months	1 RCT (N=721) **NICE guideline-directed care** Greenwood 2017 Suspected CAD (stable, OP)	No	Unknown	No	Yes (-1)	Risk: 7.1 vs. 28.8 per 100 patients, RR 0.25 (95% CI 0.17 to 0.36), RD –21.7% (95% CI –27.9% to –15.5%) **Conclusions:** SPECT was associated with a decreased risk of unnecessary ICA compared with NICE-guideline directed care.	⊕⊕◯◯ LOW
Additional NIT (any)	12 months	1 RCT (N=1,508) **Clinical assessment alone** Lim 2013 Suspected ACS (acute, ED)	Yes (-1)	Unknown	No	No	Risk: 12.1 vs. 68.3 per 100 patients, RR 0.18 (95% CI 0.15 to 0.21), RD –56.2% (95% CI –60.7% to –51.7%) **Conclusions:** SPECT was associated with a decreased risk of additional downstream NIT compared with clinical assessment alone.	⊕⊕◯◯ LOW
Revascularization (any)	12, 16 months	2 RCTs (N=2,229) **Clinical assessment alone** Lim 2013 Suspected ACS (acute, ED)	Yes (-1)	Unknown	No	No	Risk: 5.9 vs. 7.0 per 100 patients Pooled estimates (2 RCTs, N=2,229): RR 0.85 (95% CI 0.57 to 1.28), I^2=0% RD (not calculated, no association) **Conclusions:** There was no difference between SPECT and clinical assessment alone or NICE guideline-	⊕⊕◯◯ LOW

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
		NICE guideline-directed care Greenwood 2017 Suspected CAD (stable, OP)					directed care in the risk of any revascularization.	
Hospitalization	Index	1 RCT (N=1,508) **Clinical assessment alone** Lim 2013 Suspected ACS (acute, ED)	Yes (-1)	Unknown	No	No	Risk: 10.2 vs. 18.5 per 100 patients, RR 0.55 (95% CI 0.42 to 0.71), RD –8.3% (95% CI –12.2% to –4.4%) **Conclusions:** SPECT was associated with a decreased risk of hospitalization at the index visit compared with clinical assessment alone. Subsequent hospitalization following the index visit was not reported.	⊕⊕◯◯ LOW

*As described by the authors. Primary reasons cited for an unnecessary ICA included negative noninvasive test overruled by the attending physician (4.4 per 100 patients) and a false-positive test (2.5 per 100 patients) in the SPECT group, and direct referral to ICA (per algorithm) for patients with high pretest likelihood in the guideline-directed care group (24.6 per 100 patients).

Reasons for downgrading:

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice;
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies may be downgraded.
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from “mild” to “substantial”. If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for “mild/small” effects and may be downgraded once. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

Table 10.9. Key Questions 1 and 2: Strength of evidence: SPECT versus ICA

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
Primary clinical outcomes								
Myocardial infarction cumulative	18 months	1 RCT (N=446) Sharples 2007/Thom 2017 (Stable OP, suspected CAD)	No	Unknown	No	Yes (-2)	0.9 vs. 0 per 100 patients; all admissions for acute MI **Conclusions:** Firm conclusions regarding the impact of SPECT or ICA on MI are not possible. MI was rare. The sample size may have been insufficient to detect events.	⊕◯◯◯ INSUFFICIENT
All-cause mortality cumulative	72 months						**18 months** 1.8 vs. 1.8 per 100 patients, RR 0.99 (95% CI 0.25 to 3.91) RD (not calculated, no association) **72 months** 3.1 vs. 3.2 per 100 patients, RR 0.99 (95% CI 0.35 to 2.78) RD (not calculated, no association) **Conclusions:** Firm conclusions regarding the impact of SPECT or ICA on all-cause mortality are not possible. All-cause mortality was rare. The sample size may have been insufficient to detect events.	⊕◯◯◯ INSUFFICIENT
Cardiac mortality cumulative	18 months						2.2 vs. 1.4 per 100 patients, RR 1.65 (95% CI 0.40 to 6.83) RD (not calculated, no association) **Conclusions:** Firm conclusions	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							regarding the impact of SPECT or ICA on cardiac mortality are not possible. Cardiac mortality was rare. The sample size may have been insufficient to detect events	
Clinical Decision-Making Outcomes								
Additional NIT (any)	Unclear	1 RCT (N=448) Sharples 2007 (Stable OP, suspected CAD)	No	Unknown	No	Yes (-1)	0.4 vs. 3.6 per 100 patients, RR 0.12 (95% CI 0.02 to 0.98), RD –3.2% (95% CI –5.8% to –0.6%) **Conclusions:** Firm conclusions regarding the impact of SPECT or ICA on additional NITs are not possible.	⊕◯◯◯ INSUFFICIENT
Revascularization (any)	36 months						**Index** 30.4 vs. 34.2 per 100 patients, RR 0.89 (95% CI 0.68 to 1.16) RD (not calculated, no association) **36 months (cumulative)** 43.8 vs. 53.2 per 100 patients, RR 0.82 (95% CI 0.68 to 0.99) RD –9.4% (95% CI –18.6% to –0.2%) **Conclusions:** SPECT was associated with a decreased risk of any revascularization following the index visit through 36 months compared with ICA.	⊕⊕◯◯ LOW
Hospitalization for chest pain	18 months						8.5 vs. 6.3 per 100 patients, RR 1.35 (95% CI 0.69 to 2.62) RD (not calculated, no association)	⊕⊕◯◯ LOW

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							Conclusions: There was no difference between SPECT and ICA in the risk of hospitalization for chest pain.	

Reasons for downgrading:

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice;
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies may be downgraded.
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects and may be downgraded once. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

Table 10.10. Key Questions 3: Strength of evidence: SPECT

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
Safety								
Test-related adverse events,	Median 16 months,	1 RCT (N=721) Greenwood 2016 Stable	No	Unclear	No	Yes	**Test-related medical complications** SPECT vs. NICE guideline-directed care: • 5 test-related medical complications occurred; none were following SPECT imaging; no other information was provided **Conclusions**: Test-related complications appear to be rare following SPECT in one good-quality trial.	⊕⊕◯◯ LOW

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
Radiation exposure	24 months	1 RCT (N=722) Shaw 2011 (women only) Stable	Yes (-1)	Unclear	No	Yes (-2)	**Radiation exposure** SPECT vs. exercise ECG: • Mean ionizing radiation exposure following index SPECT was 14 mSv **Conclusions**: Insufficient evidence to draw conclusions.	⊕◯◯◯ INSUFFICIENT
AEs related to regadenoson and dipyridamole	NR	3 studies (N=380 patients, 604 adverse events) 1 case series 1 retrospective cohort Amer 2017 Koutsikos 2017 Meyer 2000 Suspected or known CAD	Yes	No	No	Yes	**Dipyridamole** (2 studies, N=284 patients and N=604 events), the most common events included: • Headache (13% of patients; 37% of all AEs), • GI upset/nausea (8% of patients; 11% of AEs) • Chest pain (4% of patients; 12% of AEs) • Dizziness or lightheadedness (6% of patients; 5% of AEs) • Flushing (4% of patients; 8% of AEs) • Dyspnea (2% of patients; 5% of AEs). **Regadenoson** (2 studies; N=96, 284), the most common events included: • Dyspnea (30% and 53%) • GI upset/nausea (28% and 3%) Chest pain (9% and 16%) • Dizziness or lightheadedness (8% and 13%) • Headache (7% and 12%) • Flushing (4% and 6%). **Conclusions:** AE's from stress agents	⊕⊕◯◯ LOW

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							are relatively common and ranged from 2% to 13% of patients (5% to 37% of AEs) for dipyridamole and from 4% to 53% for regadenoson.	

Reasons for downgrading:

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice;
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies may be downgraded.
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects and may be downgraded once. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

Table 10.11. Key Questions 1 and 2: Strength of evidence: Stress echocardiography versus ECG

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
Key Question 1: Primary clinical outcomes								
Myocardial infarction cumulative	2 to 36 months	5 RCTs (N=1,250) **Stable OP (suspected CAD)** 2 RCT (N=543) Gurunathan 2018 Sanfilippo 2006	Yes (-1)	No	No	Yes (-2)	Risk: 1.3 vs. 0.9 per 100 patients Pooled estimate (3 RCTs, N=940): RR 1.41 (95% CI 0.30 to 5.00), I^2=0% RD (not calculated, no association) 1 RCT (N=152) reported no events in either arm	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
		Acute, ED/hospital (known or suspected CAD and suspected ACS) 3 RCTs (N=707) Desideri 2005 Jeetley 2006 Nucifora 2009					1 RCT (N=158) did not report MI by testing arm (Risk: 1.3 per 100 patents) **Conclusions:** There is insufficient evidence to draw conclusions about the risk of MI following echocardiography versus exercise ECG. MI was rare. Except for one newer, good-quality trial in stable outpatients, trials were older and of primarily poor-quality. Smaller trials may not have been sufficiently powered to detect a difference.	
Mortality, all-cause cumulative	2 to 36 months	4 RCTs (N=1,092) **Stable OP (suspected CAD)** 1 RCT (N=385) Gurunathan 2018 **Acute, ED/hospital (known or suspected CAD and suspected ACS)** 3 RCTs (N=707) Desideri 2005 Jeetley 2006 Nucifora 2009	Yes (-1)	No	No	Yes (-2)	Risk: 0.6 vs. 0.9 per 100 patients; Pooled estimate (3 RCTs, N=940): RR 0.65 (95% CI 0.13 to 4.94), I^2=0% RD (not calculated, no association) 1 RCT (N=152) reported no events in either arm **Conclusions:** There is insufficient evidence to draw conclusions about the risk of all-cause mortality following echocardiography versus exercise ECG. All-cause mortality was rare. Except for one newer, good-quality trial in stable outpatients, trials were older and of primarily poor-quality. Smaller trials may not have been sufficiently powered to	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							detect a difference	
Mortality, cardiac cumulative	36 months	1 RCT (N=385) Gurunathan 2018 (Stable OP, suspected CAD)	No	Unknown	No	Yes (-2)	Risk: 0.5 vs. 0 per 100 patients **Conclusions:** There is insufficient evidence from one good-quality trial to draw conclusions regarding the risk of cardiac mortality following echocardiography versus exercise ECG. Cardiac mortality was rare. Smaller sample size may have precluded identification of rare events.	⊕◯◯◯ INSUFFICIENT
Key Question 2: Clinical Decision-Making Outcomes								
ICA	2 to 36 months	4 RCTs (N=1,101) **Stable OP (suspected CAD)** 1 RCT (N=385) Gurunathan 2018 **Acute, ED/hospital (known or suspected CAD and suspected ACS)** 3 RCTs (N=716) Desideri 2005 Jeetley 2006 Nucifora 2009	Yes (-1) Yes (-2)	Unknown No	No No	No No	**Stable patients** Risk: 6.3 vs. 13.4 per 100 patients 1 RCT (N=385): RR 0.47 (95% CI 0.24 to 0.90) RD –7.1% (95% CI –13.0 to –1.2%) **Acute patients** Risk: 24.4 vs. 28.4 per 100 patients; Pooled estimate (3 RCTs, N=716): RR 0.85 (95% CI 0.36 to 1.33), I^2=64.3% RD (not calculated, no association) **Conclusions:** In one good-quality trial in stable patients, echocardiography was associated with a reduced risk of ICA versus exercise ECG over 36	⊕⊕◯◯ LOW

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							months. Across 3 trials in acute patients, there was no difference between groups, though one fair-quality trial tended to favor echocardiography; heterogeneity was high possibly due to differences in populations, pretest risk and follow-up times.	
Additional NIT (any)	2 to 36 months	3 RCTs (N=695) **Stable OP (suspected CAD)** 2 RCT (N=543) Gurunathan 2018 Sanfilippo 2006 **Acute, ED/hospital (known or suspected CAD and suspected ACS)** 1 RCT (N=152) Nucifora 2009	Yes (-1) Yes (-2)	No	No	Yes (-1)	**Stable patients** Risk: 5.8 vs. 42.7 per 100 patients Pooled estimate (2 RCTs, N=543): RR 0.15 (95% CI 0.06 to 0.28), I^2=0% RD –31.6 (95% CI –49.3% to –14.0%), I^2=84% **Acute patients** Risk: 10.4 vs. 9.3 per 100 patients 1 RCT (N=152): RR 1.11 (95% CI 0.42 to 2.92) RD (not calculated, no association) **Conclusions:** In stable patients, but not acute patients, echocardiography was associated with a reduced risk of additional downstream NIT compared with exercise ECG; follow-up was 28 to 36 months. The trial in acute patients was considered poor-quality and only followed patients for 2 months; evidence from this trial was considered insufficient to draw	Stable ⊕⊕◯◯ LOW Acute ⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							conclusions in this population.	
Revascularization (any)	2 to 36 months	4 RCTs (N=1,092) **Stable OP (suspected CAD)** 1 RCT (N=385) Gurunathan 2018 **Acute, ED/hospital (known or suspected CAD and suspected ACS)** 3 RCTs (N=707) Desideri 2005 Jeetley 2006 Nucifora 2009	Yes (-1)	No	No	No	Risk: 14.4 vs. 15.3 per 100 patients Pooled estimate (4 RCTs, N=1,092): RR 0.95 (95% CI 0.68 to 1.25), I^2=0% RD (not calculated, no association) **Conclusions:** There was no difference in the risk of revascularization between the echocardiography and exercise ECG groups.	⊕⊕⊕◯ MODERATE
Hospitalization	2 to 36 months	3 RCTs (N=799) **Stable OP (suspected CAD)** 1 RCT (N=385) Gurunathan 2018 **Acute, ED/hospital (known or suspected CAD**	Yes (-1)	No	No	No	Risk: 9.3 vs. 10.0 per 100 patients Pooled estimate (3 RCTs, N=799): RR 0.94 (95% CI 0.48 to 1.51), I^2=6.5% RD (not calculated, no association) **Conclusions:** There was no difference in the risk of (re)hospitalization between the echocardiography and exercise ECG groups.	⊕⊕⊕◯ MODERATE

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
		and suspected ACS) 2 RCTs (N=414) Desideri 2005 Nucifora 2009						

Reasons for downgrading:

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice;
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies may be downgraded.
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from “mild” to “substantial”. If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for “mild/small” effects and may be downgraded once. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

Table 10.12. Key Questions 1 and 2: Strength of evidence: Stress echocardiography versus standard care

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
Key Question 1: Primary clinical outcomes								
Myocardial infarction, All-cause mortality, Cardiac mortality cumulative	2 months	1 RCT (N=132) Nucifora (suspected ACS, ED)	Yes (-1)	Unknown	No	Yes (-2)	No MIs and no deaths reported in either group. **Conclusions:** There is insufficient evidence from one small, poor-quality trial in low-risk patients to draw conclusions regarding the impact of stress echocardiography or standard care on MI, all-cause mortality, or cardiac mortality. No events were reported. The sample size and follow-up period may have been insufficient to detect events.	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
Key Question 2: Clinical Decision-Making Outcomes								
ICA; Additional NIT (any); Revascularization (any); Rehospitalization for ACP	2 months	1 RCT (N=132) Nucifora (suspected ACS, ED)	Yes (-1)	Unknown	No	Yes (-2)	**ICA**: Risk: 0 vs. 11 per 100 patients RR 0.06 (95% CI 0.0 to 0.96) RD –10.9% (95% CI –19.2% to –2.7%) **Any additional NIT:** Risk: 10 vs. 49 per 100 patients RR 0.21 (95% CI 0.10 to 0.43) RD –38.7% (95% CI –53.6% to –23.8%) **Any revascularization:** Risk: 7 vs. 4 per 100 patients RR 1.79 (95% CI 0.36 to 8.87) RD (not calculated, no association) **Rehospitalization for ACP:** Risk 3 vs. 15 per 100 patients RR 0.18 (95% CI 0.04 to 0.81) RD –12.0% (95% CI –21.9% to –2.0%) **Conclusions:** There is insufficient evidence from one small, poor-quality trial in low-risk patients to draw conclusions regarding the impact of stress echocardiography or standard care on referral to ICA, additional NIT, revascularization or rehospitalization.	⊕◯◯◯ INSUFFICIENT

Reasons for downgrading:

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice;
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies may be downgraded.
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects and may be downgraded once. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

Table 10.13. Key Questions 1 and 2: Strength of evidence: Stress echocardiography versus ICA

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
Key Question 1: Primary clinical outcomes								
Myocardial infarction cumulative	18 months	1 RCT (N=448) Sharples 2007/Thom 2017 (Stable OP, suspected CAD)	No	Unknown	No	Yes (-2)	Risk: 2.7 vs. 0 per 100 patients, p=0.01; all admission for acute MI **Conclusion**: The risk of MI following stress echocardiography appears to be low; however, the evidence is considered insufficient to draw firm conclusions.	⊕⊕⊕◯ INSUFFICIENT
All-cause mortality cumulative	72 months						**18 months** Risk: 2.7 vs. 1.8 per 100 patients, RR 1.47 (95% CI 0.42 to 5.15) RD (not calculated, no association) **72 months** Risk: 4.9 vs. 3.2 per 100 patients, RR 1.54 (95% CI 0.61 to 3.91) RD (not calculated, no association)	

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							Conclusion: The risk of all-cause mortality did not differ between stress echocardiography and ICA; however, the evidence is considered insufficient to draw firm conclusions.	
Cardiac mortality cumulative	18 months						Risk 0.4 vs. 1.4 per 100 patients, RR 0.33 (95% CI 0.03 to 3.12) RD (not calculated, no association) **Conclusion**: The risk of cardiac mortality was low and did not differ between stress echocardiography and ICA; however the evidence is considered insufficient to draw firm conclusions.	
Key Question 2: Clinical Decision-Making Outcomes								
Additional NIT (any)	Unclear	1 RCT (N=448) Sharples 2007 (Stable OP, suspected CAD)	No	Unknown	No	Yes (-2)	Risk: 0 vs. 3.6 per 100 patients, p=0.01 **Conclusion**: Firm conclusions regarding the impact of stress echocardiography or ICA on additional NITs are not possible.	⊕◯◯◯ INSUFFICIENT
Revascularization	36 months						**Index** Risk: 35.4 vs. 34.2 per 100 patients, RR 1.03 (95% CI 0.80 to 1.33) RD (not calculated, no association) **36 months** Risk: 53.5 vs. 53.2 per 100 patients, RR 1.01 (95% CI 0.85 to 1.20) RD (not calculated, no association)	⊕⊕◯◯ LOW

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							Conclusion: There was no difference between stress echocardiography and ICA in the risk of revascularization.	
Hospitalization for chest pain	18 months						Risk: 10.6 vs. 6.3 per 100 patients, RR 1.68 (95% CI 0.89 to 3.17) RD (not calculated, no association) **Conclusion**: There was no difference between stress echocardiography and ICA in the risk of hospitalization for chest pain.	⊕⊕◯◯ LOW

Reasons for downgrading:

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice;
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies may be downgraded.
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects and may be downgraded once. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

Table 10.14. Key Question 3: Strength of evidence: Stress echocardiography

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
Any complication	2 months	1 RCT (N=152)	Yes (-1)	Unknown	No	Yes (-1)	No test-related complications occurred in 1 RCT comparing stress	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
		Nucifora 2009 Uncomplicated MI					echocardiography versus stress ECG. **Conclusions:** Insufficient evidence to draw conclusions.	
Dobutamine-related adverse events		11 case series (N range, 86–2799)* Baudhuin 1993 Dakik 1996 Geleijnse 2000 Gordon 1995 Karabinos 2004 Mertes 1993 Minardi 2007 Poldermans 1994 Picano 1994 O'Driscoll 2014 Sitges 2000 Stable, suspected or known CAD (10 studies) Suspected ACS (1 study)	Yes (-2)	Unknown	No	No	Potentially life threatening, major adverse events • **Mortality** (6 studies, N=5,512): No deaths • **MI** (7 studies, N range 122 to 2,799): range, 0% to 0.1% • **UA** (1 study, N=802): 0.1% • **CVA** (1 study, N=1,012): No CVAs • **Acute pulmonary edema** (2 studies, N=1,012, 802): 0% and 0.1% **Conclusion:** The risk of potentially life-threatening adverse event with dobutamine appears to be low, ≤0.1% across all outcomes.	⊕⊕◯◯ LOW
							Arrythmia-related AEs • **Any arrhythmias or palpitations** (6 studies, N range 122 to 1,118): range, 2.1% to 18.0% • **Supraventricular or ventricular tachycardia** (10 studies, N range 86 to 2,799): range, 0% to 9.0% • **Atrial or ventricular fibrillation** (7 studies, N range 265 to 2,799): range, 0% to 1.2% • **Bradycardia** (2 large studies,	⊕⊕◯◯ LOW

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							N=3,917): ≤0.2% in both. **Conclusion:** The frequency of any arrhythmia (not well defined) and tachycardias ranged from 0% to 18%. Atrial fibrillation and bradycardia appear to be infrequent events.	
							<u>Hypotension and Hypertension</u> • **Hypotension** (9 studies; N range 86 to 2799): range, 0.1% to 12.5% • **Hypertension** (5 studies; N range 122 to 1118): range, 0% to 7.5% **Conclusion:** Hypo- and hypertension were not uncommon with dobutamine for stress echocardiography. The severity of the events was not reported.	⊕⊕◯◯ LOW
							<u>Other, general adverse events</u> • **Chest pain (NOS)** (3 studies, N range 86 to 1,118): range, 4.6% to 31.4% • **Nausea and/or vomiting** (6 studies, N range 86 to 1012): range, 3.4% to 20.9% • **Headache** (4 studies, N range 122 to 1012): 0.8% to 13.6% • **Dyspnea** (3 studies, N range 127 to 1012): range, 0% to 13.6% • **Tremors** (3 studies, N range 127 to 1012): range, 0.4% to 2.4%	⊕⊕◯◯ LOW

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							Conclusions: The frequency of other adverse events, such as chest pain, nausea/vomiting, headache, dyspnea and tremors ranged from 0% to 31%; most authors reported that events were mild and transient.	
Dipyridamole and Adenosine		**Dipyridamole** 3 case series (N=946) Minardi 2002 Ferrara 1991 Gaibazzi 2009 **Adenosine** 1 case series (N=1429) Montisci 2017 Suspected or known CAD for all	Yes (-2)	Unknown	No	No	**Dipyridamole** 2 studies (total N=837): • No "major", severe, or life-threatening adverse events, to include death, MI and ACS 3 studies (N range, 109 to 500): • Hypotension/bradycardia: range, 0.8% to 6.4% • Vomiting and nausea: range, 0.2% to 5.5% • Headache: range, 2.1% to 43% **Adenosine** The most commonly occurring side-effects were hyperpnea (16.7%), atypical chest pain (9.9%), flushing (9.4%) and headache (6.6%). **Conclusions**: There were no major or life-threatening adverse events after dipyridamole administration. Minor adverse events with the use of these stressor agents for echocardiography	⊕⊕◯◯ LOW

Outcome	Follow-up	Studies	Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							are not uncommon and occurred with variable frequency and ranged from 0.2% to 43%.	
Noniodinated contrast		3 studies (N=9,821) 2 comparative cohorts (N=6,750) Anantharam 2009 Jin 2019 1 database study (N=3,071) Abdelmoneim 2009	Yes (-2)	Unknown	No	No	**Definite or suspected contrast-related adverse events** 1 database study: 1.3% (41/3071) and 2.2% (68/3071) **Allergic reaction to contrast** • 2 cohort studies: <0.5% of patients who received stress echocardiography with contrast • 1 database study: 0.03% each for transient wheezing without urticaria, urticaria or hives (limb and thorax) and swelling in the mouth, and throat tingling **Conclusions**: Definite or suspected contrast related adverse events and allergic reactions appear to be rare.	⊕⊕◯◯ LOW

CAD = coronary artery disease; CI = Confidence Interval; ECG = electrocardiography; ED = emergency department; OP = outpatient; RCT = randomized controlled trial; SOE = strength of evidence.

Reasons for downgrading:

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice;
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies may be downgraded.

3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects and may be downgraded once. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

Table 10.15. Key Questions 1 and 2: Strength of evidence: PET vs. SPECT

Outcome	Follow-up	Studies	Study Limitations	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
Key Question 1: Primary clinical outcomes								
Myocardial infarction Cumulative; **Mortality, all-cause** cumulative	12 months	1 RCT (N=322) Patel 2019 Known CAD, new or worsening symptoms	No	Unknown	No	Yes (-2)	**MI:** Risk: 0 vs. 1.2 per 100 patients **All-cause mortality:** Risk: 1 vs. 1.2 per 100 patients RR 0.50 (95% CI 0.04 to 5.46) RD (not calculated, no association) **Conclusion:** Firm conclusions regarding the impact of PET or SPECT on MI and all-cause mortality are not possible. Both outcomes were rare. The sample size may have been insufficient to detect events.	⊕◯◯◯ INSUFFICIENT

Outcome	Follow-up	Studies	Study Limitations	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
Mortality, cardiac cumulative	Mean 9 months	1 RCT (N=210) Mullani 2000 Stable, mixed suspected or known CAD	Yes (-1)	Unknown	No	Yes (-2)	Risk: 3 vs. 4 per 100 patients RR 0.75 (95% CI 0.17 to 3.27) RD (not calculated, no association) **Conclusion:** Data from one poor-quality trial were insufficient to draw conclusions.	⊕◯◯◯ INSUFFICIENT
Key Question 2: Clinical Decision-Making Outcomes								
ICA	3, 6, 12 months	1 RCT (N=322) Patel 2019 Known CAD, new or worsening symptoms	No	Unknown	No	Yes (-1)	**3 months** Risk: 20.5 vs. 15.5 per 100 patients RR 1.32 (95% CI 0.82 to 2.11) RD (not calculated, no association) **6 months** Risk: 22.4 vs. 18.6 per 100 patients RR 1.20 (95% CI 0.78 to 1.85) RD (not calculated, no association) **12 months** Risk: 28.6 vs. 28.0 per 100 patients RR 1.02 (95% CI 0.72 to 1.45) RD (not calculated, no association) **Conclusion:** No difference between PET and SPECT in the risk of ICA at any timepoint.	⊕⊕◯◯ LOW
Revascularization (any)							**3 months** Risk: 11.2 vs. 9.9 per 100 patients RR 1.13 (95% CI 0.60 to 2.13) RD (not calculated, no association) **6 months** Risk: 12.4 vs. 11.8 per 100 patients RR 1.05 (95% CI 0.58 to 1.90) RD (not calculated, no association) **12 months**	⊕⊕◯◯ LOW

Outcome	Follow-up	Studies	Study Limitations	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Conclusion Effect Estimate (95% CI)	Quality (SOE)
							Risk: 15.5 vs. 14.9 per 100 patients RR 1.04 (95% CI 0.62 to 1.74) RD (not calculated, no association) **Conclusion:** No difference between PET and SPECT in the risk of any revascularization at any timepoint.	
Medication change*							Escalation in antianginal therapy* at **3 months** Risk: 26 vs. 23 per 100 patients RR 1.11 (95% CI 0.75, 1.63) RD (not calculated, no association)	

CI = Confidence Interval; NR = Not Reported; NS = Not significant;

*Footnote: Defined as addition of another anti-anginal medication class or increase in dose or frequency of one or more of existing anti-anginal medications within 3 months post baseline MPI

Reasons for downgrading:

1. Serious risk of bias: The majority of studies are fair quality related to the outcome reported may be downgraded once; If the majority of studies are poor quality, this may be downgraded twice;
2. Inconsistency: differing estimates of effects across trials; If point estimates across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies may be downgraded.
3. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from “mild” to “substantial”. If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for “mild/small” effects and may be downgraded once. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.
4. Indirect, intermediate or surrogate outcomes may be downgraded.

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Journal of Nuclear Cardiology (2026) 57, 102619

ASNC POSITION STATEMENT

Clinical indications for positron emission tomography myocardial perfusion imaging and myocardial blood flow quantification: An American Society of Nuclear Cardiology position statement

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INTRODUCTION

Since the publication of the 2016 Position Statement on the Clinical Indications for Myocardial Perfusion PET [1], a growing body of evidence has reinforced the expanding role of positron emission tomography (PET) in the diagnosis and management of coronary artery disease (CAD). This momentum derives from an enhanced understanding of the unique capabilities of PET myocardial perfusion imaging (MPI) and the use of dynamic PET acquisitions to quantify myocardial blood flow (MBF). Extensive and convincing evidence on its excellent diagnostic accuracy and valuable risk stratification has been demonstrated in multiple clinical studies. As a result, major national and international multi-societal clinical guidelines now classify it as the preferred test, if available.

This updated Position Statement expands on the previous indications to now recommend, if available, the use of cardiac PET MPI as the preferred modality for CAD evaluation for all patients who meet criteria for MPI. It reflects a broader international consensus on the value of cardiac PET MPI in routine clinical care, informed by the expanding body of research and clinical experience worldwide. It aims to reaffirm and clarify the role of PET MPI as a powerful and excellent tool for assessment of CAD and related symptoms, supporting broader implementation in clinical practice. This document is not intended to be an extensive scientific review of the literature but to detail the position of the American Society of Nuclear Cardiology (ASNC) regarding the use of cardiac PET MPI and MBF for the assessment of CAD.

MULTI-SOCIETAL GUIDELINE RECOMMENDATIONS

Based on its many advantages and a robust scientific literature, PET MPI with MBF is now prominently and explicitly recommended in major U.S.

Available online 31 December 2025
1071-3581/© 2025 Published by Elsevier Inc. on behalf of American Society of Nuclear Cardiology.
https://doi.org/10.1016/j.nuclcard.2025.102619

ABBREVIATIONS

ASNC	American Society of Nuclear Cardiology
CAC	Coronary artery calcium
CAD	Coronary artery disease
CT	Computed tomography
MPI	Myocardial perfusion imaging
MBF	Myocardial blood flow
PET	Positron emission tomography
SPECT	Single-photon emission computed tomography

and European multi-societal clinical guidelines, including the 2021 Multi-societal Chest Pain Guidelines [2], the 2023 Multi-societal Chronic Coronary Disease Guidelines [3], and the 2024 European Society of Cardiology Guidelines for Chronic Coronary Syndromes [4]. These are mainstream cardiovascular clinical guidelines developed by broad coalitions of societies—not limited to nuclear cardiology organizations—underscoring the growing recognition of PET MPI's clinical value across disciplines.

Across these guidelines, PET MPI is consistently preferred over single-photon emission computed tomography (SPECT) MPI. In the U.S. guidelines [2], this preference is reflected as a class 2a recommendation, while the European guidelines elevate it to class 1—recognizing cardiac PET's superior diagnostic accuracy, risk stratification, image quality, and ability to quantify MBF [3,4]. In both U.S. and European guidelines, PET is favored for the evaluation of intermediate- to -high-risk patients with stable or acute chest pain (Class 1), enhanced risk stratification (Class 1), and microvascular assessment when MBF is included (Class 2A) (Figure 1).

ADVANTAGES OF PET MPI

PET offers numerous important advantages that make it the preferred modality, as extensively documented in the ASNC Model Coverage Policy [5], Table 1.

1. High diagnostic accuracy

PET MPI demonstrates high and, when compared to SPECT MPI, superior sensitivity and specificity for detecting and evaluating obstructive epicardial CAD [5]. Its diagnostic performance has been validated in numerous retrospective and prospective

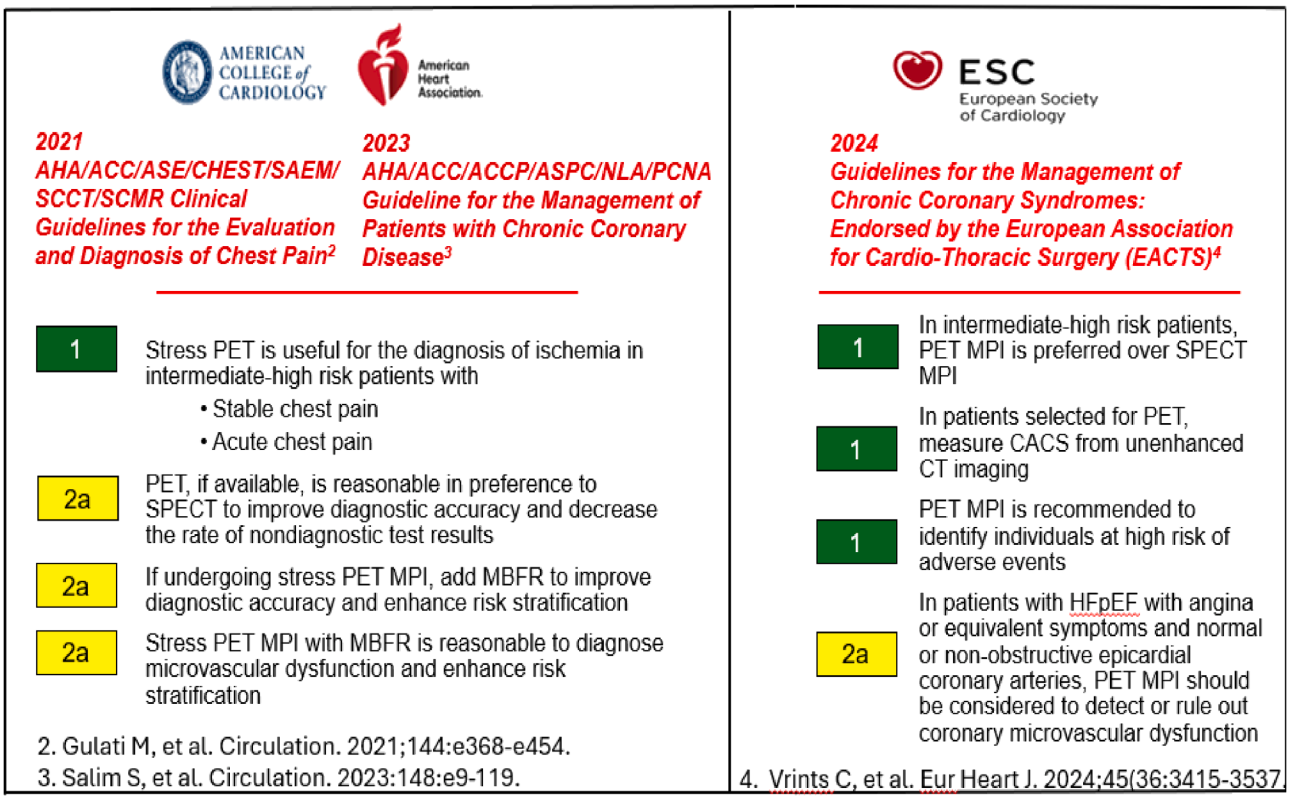

Figure 1. Recommendations for PET MPI in major US and European cardiology guidelines [2–4]. Green box = class 1 recommendation. Yellow box = class 2a recommendation. *MPI*, myocardial perfusion imaging; *PET*, positron emission tomography.

Table 1. Clinical advantages of cardiac PET MPI

Diagnostic accuracy
- ➢ Reduces unnecessary downstream testing.
- ➢ Identifies CAD in absence of perfusion defects.

Risk stratification
- ➢ Perfusion, myocardial-blood-flow, and cardiac function measurements provide independent information about risk.

Robust and reproducible quantification of MBF
- ➢ Requires no additional acquisition time or radiation exposure.
- ➢ Confirms adequacy of vasodilator effectiveness.
- ➢ Enhances diagnostic precision and prognostication.
- ➢ Identifies coronary microvascular dysfunction.

Equitable across diverse patient populations
- ➢ Body habitus, sex, and very high calcium score
- ➢ Arrhythmias, contrast allergies, and implanted devices
- ➢ Feasible in virtually all patients.

Rapid acquisitions
- ➢ Important for patient satisfaction.
- ➢ Minimizes patient motion with associated artifacts.

Low radiation exposure
- ➢ Key consideration for serial imaging.

High image quality
- ➢ Excellent spatial and contrast resolution.
- ➢ High myocardial count density.
- ➢ Superior tracer kinetics.
- ➢ Routine attenuation and scatter correction.

CAD, coronary artery disease; *MBF*, myocardial blood flow; *MPI*, myocardial perfusion imaging; *PET*, positron emission tomography.

studies and confirmed in large meta-analyses [6,7]. The combination of high-quality, high-spatial-resolution perfusion imaging with attenuation correction, rest-and-stress functional assessment (regional/global wall motion and ejection fraction), MBF, MBF reserve, and coronary artery calcium [CAC] when combined with computed tomography [CT] evaluation provides the following:

- Identification of very-low-risk patients, reducing unnecessary downstream testing.
- Identification of coronary-artery-disease in the absence of relative perfusion defects, including microvascular disease.
- More accurate identification of multi-vessel disease-related balanced flow reduction.

2. Improved risk stratification

- Perfusion, blood flow, and function measurements each provide independent information about risk, permitting more precise decisions about medical management and interventions for coronary-artery-disease.

3. Robust and reproducible quantification of MBF

PET is the gold standard, non-invasive modality for the assessment of MBF:

- Performed routinely without added acquisition time or radiation exposure
- Provides confirmation of vasodilator effectiveness
- Enhances diagnostic accuracy and prognostication
- Enables identification of coronary microvascular dysfunction, a key contributor to angina without obstructive CAD [8].
- Identifies the true extent of CAD, enhancing diagnosis of left main or multi-vessel disease and eliminates the concern of false negative perfusion results in the setting of "balanced ischemia" [9,10].

Quantitative assessment of MBF with PET offers substantial added value beyond relative perfusion imaging and gated MPI. By providing absolute measures of perfusion, MBF quantification improves diagnostic accuracy for epicardial CAD and enhances assessment of its extent and severity [9,10]. Myocardial blood flow provides incremental risk stratification information, refining prediction for future cardiovascular events [9,10]. Importantly, MBF quantification provides more informed decision-making to assess the need for coronary revascularization and/or intensified medical therapy [11,12]. In addition, it enables the identification of coronary microvascular dysfunction, in the presence of or in the absence of obstructive epicardial CAD [8]. Quantitative MBF also confirms the effectiveness of pharmacologic stress, adding a layer of confidence to study interpretation. Finally, it is valuable in patients with known CAD, prior PCI or CABG, and cardiac transplant, providing insights into disease progression, response to therapy, and detection of new or evolving disease [9–13].

4. Equitable across diverse patient populations

- Utility unaffected by sex or body habitus or amount of CAC making it equally effective in women, overweight patients, and those with very high CAC scores.
- Feasible in all patients including those capable of exercise, irrespective of cardiac rhythm, implanted devices, iodinated contrast allergy, and virtually all comorbidities.

- Offers robust performance even in those patients with multi-vessel disease or prior revascularization.

5. **Comparatively rapid acquisitions**

- PET acquisitions can be completed quickly, which is important to patient satisfaction, and minimize patient motion with associated artifacts that can erode accuracy.

6. **Low radiation exposure**

- PET MPI protocols typically result in low total-body effective dose, well below current societal recommendations [14]. This is a particularly important consideration for serial imaging in chronic CAD or transplant patients who are likely to undergo numerous radiation-exposing procedures in the course of their disease.

7. **High image quality**

PET MPI provides consistently high-quality images even in challenging patient populations due to:

- Excellent spatial and contrast resolution
- High myocardial count density
- Excellent tracer kinetics
- Routine attenuation and scatter correction

ADDED VALUE OF PET/CT

When available, adjunctive CT should be routinely used to provide additional important anatomic insights, particularly regarding the presence, extent, and severity of CAC. If ECG-gated CT is performed, a CAC score can be measured; in the absence of electrocardiographic gating, visual estimation of CAC remains informative [15]. Detection of CAC has important prognostic implications and can guide preventive and therapeutic medical management. In addition, the CT component may reveal relevant cardiac, vascular, and non-cardiovascular findings that can further inform patient care beyond MPI findings [15].

CONCLUSION

PET MPI with MBF quantification has several strengths that make it ideal for CAD evaluation—high diagnostic accuracy of both epicardial and microvascular disease, low radiation exposure, and powerful risk stratification. Therefore, the ASNC recommends that PET MPI, if available, be the preferred modality for all patients who meet criteria for MPI. There are no clinical scenarios or patient subgroups in which the use of PET MPI should be excluded, given its diagnostic accuracy, risk stratification, and unique quantitative capabilities.

DISCLOSURES

The authors declare the following financial interests/personal relationships, which may be considered as potential competing interests.
Dr. Bateman reports research grants from Bracco, GE HealthCare, and Spectrum Dynamics, is a consultant for GE HealthCare and Synektik, and has ownership in Cardiovascular Imaging Technologies. Dr. Al-Mallah reports research grants from Siemens and GE HealthCare and is a consultant for Jubilant Pharma, Pfizer, Phillips, Medtrace, Synektik, and GE HealthCare. Dr. Arumugam is a speaker for Blue Earth Diagnostics, Ltd. and IBA Radio Pharma Solutions. Dr. Chareonthaitawee is a consultant for GE HealthCare and Synektik is receiving royalty payments from UpToDate. Dr. Di Carli is consultant for Medtrace Pharma, Sanofi, Valo Health, Bitteroot Bio, and IBA Radio Pharma Solutions and reports an institutional research support from Sun Pharma and Gilead Sciences and an in-kind institutional grant from Amgen. Dr. Heller is on the Advisory Board of Molecular Imaging Services. Dr. Soman has received grant support from Pfizer and is receiving consulting fees from Alnylam, Eidos, Pfizer, Spectrum Dynamics, and Synektik is receiving royalty. Dr. Abuzaid is a consultant for BridgeBio. Dr. Osborne is a consultant for WCG Imaging. Dr. Patel reports research grants from the NIH and Jubilant Radiopharma. Dr. Phillips is a consultant for Novo Nordisk. Dr. Sanghani is a consultant and speaker for GE HealthCare.
The following contributors have nothing to disclose: Dr. Alnabelsi, Dr. Calnon, and Dr. Divakaran.

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Section 6.0

2027 CPT code review

2027 CPT Code Review: Lymphovenous Surgery

Plain Language Summary:

Lymphedema is an unusual swelling of the arms or legs, sometimes caused by surgery. Lymphovenous surgery is a procedure done with a microscope to reconnect tiny lymph vessels, helping drain extra fluid out of the limb.

Although lymphovenous surgery looks promising, it hasn't been studied enough. Staff recommend not covering at this time.

This issue summary appeared in the March 19, 2026 meeting materials. No changes have been made to this document.

Staff Analysis Summary:

Significant proposed changes or discussion items:

1) Do not add coverage for lymphovenous surgery as a treatment for lymphedema

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Codes:

*38X03, *38X04 "microvascular anastomosis services; addition of microvascular lymphovenous bypass surgery guidelines"

Similar codes: Previously coded with CPT *1019T Lymphovenous bypass (LVB), including robotic assistance, per extremity

Background:

Lymphedema is a condition in which fluid builds up in the body due to damage to the lymph system. This condition causes swelling and pain in the extremities and can lead to ulcers, infections, limited mobility and other complications. Lymphedema can either be idiopathic (no known cause) or can result from surgeries, typically cancer surgeries that

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involve lymph node removal. Standard treatments include special physical therapy massage, compression garments, and manual drainage. Recently, there has been increasing interest in surgery to connect lymphatic vessels to improve drainage. Types of surgery include lymphovenous bypass that uses microsurgery to connect lymphatic vessels with vein grafts, and lymphaticovenular anastomosis that connects lymphatic vessels directly using microsurgical techniques. This surgery can be done prophylactically, at the time of surgery that removes lymph nodes, or afterwards.

Previous HSC/HERC reviews:

No previous reviews of these procedures have been conducted

Current Prioritized List/Coverage status:

ICD-10-CM I89.0 (Lymphedema, not elsewhere classified) and similar diagnoses are on line 420 LYMPHEDEMA. Line 420 contains procedure codes for PT/OT, and for drainage of lymph collections. Similar conditions and treatments are online 283 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT

[Edits accepted at the January 2026 VBBS/HERC meetings shown in blue/red]

GUIDELINE NOTE 43, LYMPHEDEMA

Lines 283,419

ICD-10-CM I97.89 (Other postprocedural complications and disorders of the circulatory system, not elsewhere classified) is only included on Line 419 for post-operative lymphedema.

Lymphedema treatments (aside from DME) are included on this line when medically appropriate. These services are to be provided by a licensed practitioner who is

1) Certified by Lymphology Association of North America (LANA, http://www.clt-lana.org), OR
2) CLT-LANA eligible (graduates from a minimum 135-hour lymphedema program that meet the LANA eligibility requirements), only if a LANA-certified therapist is not available.

~~Services should be provided by a LANA certified therapist if available.~~

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Treatments for lymphedema are not subject to the visit number restrictions found in Guideline Note 6 REHABILITATIVE AND HABILITATIVE THERAPIES.

~~ICD-10-CM I97.89 (Other postprocedural complications and disorders of the circulatory system, not elsewhere classified) is only included on Line 419 for post-operative lymphedema.~~

For DME: It is the intent of the HERC that compression dressings/garments and other medical equipment needed for the treatment of lymphedema be covered even in the absence of ulcers or other complications.

Evidence:

Treatment of existing lymphedema

1) **Brown 2026** Lymphovenous bypass for the treatment of secondary lymphedema: A meta-analysis of prospective outcomes
    a. N=8 studies (prospective cohort or database design)
        i. N=481 patients undergoing lymphaticovenous bypass (LVB)
    b. Significant limb volume reductions following LVB were observed in four studies. Other studies demonstrated volume reduction as well, although the outcomes did not reach statistical significance
    c. Patient-reported outcomes indicated significant improvements in quality of life (QoL) and symptom relief following LVB in six studies
    d. Four studies reported postoperative reductions in compression garment usage. Weighted pooled analysis across four studies showed that 46.3% (95% CI 24.9–69.1, p=0.002, I 2=79.5%) of patients reduced or discontinued compression therapy following LVB
    e. One study, by Boccardo et al., reported significant reduction (complete cessation of lymphangitis in 79 patients) in cellulitis episodes
    f. Authors conclusions: This meta-analysis consolidates fourteen years of research on LVB, confirming its efficacy in reducing limb volume, improving quality of life, and decreasing cellulitis frequency in patients experiencing lymphedema. The sustained benefits up to three years postoperatively

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support LVB as a viable, long-term treatment option for secondary lymphedema

2) **Hahn 2025** Objectifying Clinical Outcomes After Lymphaticovenous Anastomosis and Vascularized Lymph Node Transfer in the Treatment of Extremity Lymphedema: A Systematic Review and Meta-Analysis
    a. N=52 articles (1920 patients)
        i. 25 retrospective, 23 prospective, two cross-sectional studies, and 2 RCTs (Jonis 2024 lymphovenous anastomosis, Dionyssiou 2016—lymph node transfer)
    b. Of the 1073 extremities that contributed to effect sizes in clinical improvement of upper extremity lymphedema, 528 underwent lymphaticovenous anastomosis (LVA), 496 underwent vascularized lymph node transfer (VLNT), and 49 received a combination of the two procedures. Likewise, of the 847 extremities that contributed to effect sizes in clinical improvement of LEL, 775 underwent LVA, and 72 underwent VLNT.
    c. The clinical improvement of lymphedema was determined based on the rate of postoperative circumference or volume reduction in the affected extremity
    d. A clinical improvement of 29.44% (95% CI: 15.58–43.29) was observed in upper extremities following LVA
    e. Authors conclusions: The clinical improvement in patients with UEL and LEL following microsurgery is estimated to be 36% and 34%, respectively
3) **Jonis 2024** The 6 month interim analysis of a randomized controlled trial assessing the quality of life in patients with breast cancer related lymphedema undergoing lymphaticovenous anastomosis vs. conservative therapy
    a. N=92 patients with 6 month follow up data (46 LVA group, 46 control)
    b. Health related quality of life measured by the lymphedema international classification of functioning (Lymph-ICF) questionnaire (0-100 scale)
        i. In the LVA group the mean difference in the total score of the Lymph ICF between baseline and follow up after three and six months was 8.93 ± 22.71 ($p>0.05$) and 8.57 ± 22.56 ($p>0.05$), respectively. For the domains physical function and mental function a decrease of more than 10 points was observed after 3 and 6 months, representing a statistically significant improvement. In the CDT group there was no

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difference observed in the total score of the Lymph-ICF between baseline and follow up.

ii. The mean difference in the total score of the Lymph-ICF between LVA and control groups was -5.92 (-14.88, 3.04) at 6 months

1. HERC staff unable to find MCID for Lymph-ICF score

c. Volume reduction

i. The excess volume was measured by the difference in affected and non-affected arm. The absolute volume difference was 24.80 ± 179.93 mL (p=0.398) after 3 months and 20.04 ± 196.40 mL (p=0.497) after 6 months for the LVA group. For the CDT group, 13.88 ± 193.36 mL (p=0.640) and 33.98 ± 189.87 mL (p=0.236) after three months and six months, respectively

d. Limb circumference

i. The mean absolute difference in UEL index for the LVA group 3.65 ± 7.24 (p = 0.002) after 3 months and 1.84 ± 14.6, (p = 0.497) after 6 months, for the CDT group the mean absolute difference was respectively 3.3 0± 31.57 (p=0.521) and − 0.84 ± 14.6 (p=0.189) after three and six months

e. Discontinuation of compression garments

i. After 3 months 8 patients (17.0%) in the LVA group completely discontinued the use of compression garments. After 6 months the discontinuation rate increased to 10 patients (21.3%). Furthermore after 3 and 6 months, 10 patients (21.7%) partially discontinued use of compression garments. None of the patients in the CDT group discontinued the use of compression garments in the first 6 months.

f. Author conclusions: Lymphaticovenous anastomosis resulted in improvement of physical and mental function in patients with BCRL. Limb volume and limb circumference did not significantly improve after 6 months in both groups. However, in the LVA group around 40% could completely or partially stopped with the use of compression garments. The current results are promising, however longer follow up is required to assess the long term effect of LVA

4) **Chang 2021** Surgical Treatment of Lymphedema: A Systematic Review and Meta-Analysis of Controlled Trials. Results of a Consensus Conference

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a. N=71 articles reporting on 66 studies
    i. 2 RCTs, 7 prospective cohort studies, 14 retrospective cohort studies, 43 case series
    ii. 8 studies reported on liposuction and compression therapy for treatment of lymphedema; 16 studies reported on lymphovenous bypass and compression therapy; and 17 studies reported on vascular lymph node transplantation and compression therapy. 3 case series reported on combination therapy.
b. Three studies (102 patients) compared lymphovenous bypass to pressure therapy in patients with upper extremity lymphedema or lower extremity lymphedema
    i. Koshima 2000 (retrospective cohort, N=12 LVA, N=12 pressure): arm circumference decreased by a mean 4.1 cm in the lymphovenous bypass group compared to 0.8 cm in the compression therapy group ($p < 0.05$)
    ii. Koshima 2003 (retrospective cohort, N=13 LVA, N=12 pressure): leg circumference decreased by a mean 4.7 cm in the lymphovenous bypass group compared to 0.6 cm in the compression therapy group ($p < 0.05$)
    iii. Engel 2018 (retrospective cohort, N=27 LVA, N=45 LNT, N=52 CDT): 17.3 percent reduction in arm circumference in the lymphovenous bypass group compared to a 9.8 percent reduction in the complex decongestive therapy group (mean difference, 7.50 percent; 95 percent CI, 4.89 to 10.11 percent; $p < 0.00001$
c. 10 studies (134 patients) reported on lymphovenous bypass for reducing limb circumference in patients with stage II to V (Campisi or International Society of Lymphology) upper extremity lymphedema or lower extremity lymphedema. Lymphovenous bypass combined with compression garments significantly reduced circumference by an average of 3.8 cm (95 percent CI, 2.93 to 4.67 cm; $p < 0.00001$; very low-quality evidence)
d. Three case series (14 lower extremity lymphedema and 23 upper extremity lymphedema patients) reported on the mean number of cellulitis infections per year before and after surgery. The incidence of cellulitis before surgery

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was 67 percent (95 of 141) compared to 21 percent (29 of 141) after surgery (OR, 9.11; 95 percent CI, 2.31 to 35.97)

e. Three case series (141 upper or lower extremity lymphedema patients) reported on preoperative and postoperative cellulitis.32,33,51 Cellulitis was significantly reduced after lymphovenous bypass and compression therapy. The incidence of cellulitis before surgery was 67 percent (95 of 141) compared to 21 percent (29 of 141) after surgery (OR, 9.11; 95 percent CI, 2.31 to 35.97)
f. Consensus recommendations
    i. There is evidence to support that lymphaticovenous anastomosis can be effective in reducing severity of lymphedema (grade 1C)
    ii. There is a need for better designed studies that include more objective reporting of outcomes and longer follow-up

Prophylactic surgery

1) **Hinson 2025** Preventing Secondary Lymphedema: A Systematic Review and Meta-Analysis on the Efficacy of Immediate Lymphovenous Anastomosis
    a. N=39 studies (N=3597 patients total)
        i. N=1722 patients receiving immediate LVA
        ii. N=1975 controls
        iii. 1 RCT, 6 prospective cohort, 9 retrospective cohort or case-control, 23 case series
    b. Meta-analysis included 17 studies (917 LVA patients; 1975 controls)
        i. Immediate LVA was associated with a 69% lower risk of secondary lymphedema compared to the control group (RR: 0.31, 95% CI: 0.23–0.42, $p < 0.00001$). A total of 78 patients developed secondary lymphedema in the LVA group out of 917 patients (8.51%), compared to 692 patients in the control group out of a total of 1975 patients (35.04%).
    c. Authors conclusions: This systematic review and meta-analysis provide compelling evidence that immediate LVA significantly reduces secondary lymphedema risk across oncological indications, with the most pronounced benefit observed in breast cancer patients

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Submitted literature:

None received to date

Expert guidelines:

1) **NICE 2024** Lymphovenous anastomosis during axillary or inguinal node dissection for preventing secondary lymphoedema
    a. Lymphovenous anastomosis during axillary dissection for preventing secondary lymphoedema in adults with breast cancer can be used in the NHS while more evidence is generated. It can only be used with special arrangements for clinical governance, consent, and audit or research
2) **International Society of Lymphology 2023** THE DIAGNOSIS AND TREATMENT OF PERIPHERAL LYMPHEDEMA: 2023 CONSENSUS DOCUMENT OF THE INTERNATIONAL SOCIETY OF LYMPHOLOGY
    a. Microsurgical procedures can be medically necessary to treat lymphedema in properly selected patients

Other payer policies:

1) Wellpoint 2025
    a. Microsurgical procedures for the *treatment* of lymphedema (including mastectomy related lymphedema) are considered **medically necessary** when **all** of the following criteria (A, B, C *and* D) are met:
        i. The individual has a diagnosis of lymphedema based on clinical findings and appropriate diagnostic testing; **and**
        ii. The individual has one or more of the following (1, 2 *or* 3):
            1. Physical function impairment (e.g., difficulty ambulating, performing activities of daily living); **or**
            2. History of chronic or recurrent skin conditions (e.g. cellulitis, ulcerations); **or**
            3. Significant pain or weakness in the affected extremity; **and**
        iii. Lymphedema persists or worsens despite at least 3 months of optimal conservative management; **and**
        iv. **One** of the following procedures are used:

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1. Lymphovenous anastomoses; **or**
2. Lymphatic reconstruction techniques (for example, lymphatic-lymphatic bypass); **or**
3. Vascularized lymph node transfer.

v. Microsurgery for the *prevention* of lymphedema, or immediate lymphatic reconstruction, is considered **not medically necessary.**

2) United Healthcare 2026: Surgical procedures for the prevention or treatment of Lymphedema are unproven and not medically necessary due to insufficient evidence of safety and/or efficacy
3) Aetna 2025
   a. Considers the following experimental:
      i. Microsurgical treatments (microsurgical lymphatico-venous anastomosis, lymphatic-capsular-venous anastomosis, lymphovenous bypass) for the treatment of members with chronic obstructive lymphedema
4) Premara BCBS 2026
   a. The following surgical treatments to treat lymphedema (eg, upper or lower extremities or genitalia) are considered investigational:
      i. Lymphatic physiologic microsurgery
         1. Lymphatico-lymphatic bypass
         2. Lymphovenous bypass
         3. Lymphaticovenous anastomosis
         4. Autologous lymph node transplantation
         5. Vascularized lymph node transfer
      ii. Lymphatic physiologic microsurgery performed during nodal dissection or breast reconstruction to prevent lymphedema (including, but not limited to, the Lymphatic Microsurgical Preventing Healing Approach [LYMPHA]) in individuals who are being treated for breast cancer is considered investigational.
5) Cigna 2025
   a. EITHER of the following procedures is considered medically necessary for the treatment of lymphedema:

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i. microsurgical treatment (e.g., microsurgical lymphatico-venous anastomosis, lymphaticcapsular-venous anastomosis [LCVA], lymphovenous bypass, lymph node-to-vein anastomosis [LVNA])
ii. vascularized lymph node transfer

b. When an individual meets ALL of the following criteria:
   i. ONE of the following signs and symptoms:
      1. physical function impairment (e.g., difficulty ambulating, performing activities of daily living)
      2. history of chronic or recurrent skin conditions (e.g. cellulitis, ulcerations)
      3. significant pain or weakness in the affected extremity
   ii. ONE of the following quantitative measurements:
      1. volumetry differential (circumferential measurements and/or perometry differential) >10% (if affected extremity dominant extremity) or >7% (affected extremity is non-dominant extremity)
      2. lymphoscintigraphy results show delayed transit time to first-level lymph nodes or a dermal back flow pattern
   iii. lack of response to at least three consecutive months of medical management (e.g., compression garments, manual lymphatic drainage)
   iv. postoperatively will continue to wear compression garments as instructed to maintain the benefits of treatment

c. The following surgical procedures for the prevention of lymphedema are considered experimental, investigational or unproven:
   i. immediate lymphatic reconstruction (e.g., lymphatic microsurgical preventing healing approach [LYMPHA]), microsurgical lymphatico-venous anastomosis, lymphatic- capsularvenous anastomosis, lymphovenous bypass)

Expert input:

None received to date

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HERC staff summary:

Lymphovenous anastomosis (LVA) or lymphovenous bypass (LVB) microsurgery for existing lymphedema has been studied mostly in retrospective cohort studies and case series without control groups. A recent systematic review of 8 prospective cohort studies without control groups of patients undergoing lymphovenous bypass found significant limb volume reductions with surgeries in half of the studies, improved quality of life in 75% of studies, reduction in use of compression garments and in infections. Another recent systematic review of both retrospective and prospective studies included various lymph surgeries also found clinical improvement in upper limb size with LVA.

A more accurate evaluation of a surgical intervention requires comparison of the surgery to a standard of care control group. One RCT exists that compares LVA to standard compression garment therapy. This study of 92 patients found improvements in the quality of life scores, although it appears to be non-significant between groups at 6 months. Limb volume reduction and circumference change were not significantly different between groups. Approximately 20% of LVA patients were able to stop compression garments compared to no control patients. A recent systematic review identified three retrospective cohort studies that compared LVA to compression therapy. All three found reduced limb circumference in the surgery group compared to controls.

A recent systematic review was found that examined 39 studies of prophylactic LVA surgery, generally for breast cancer patients. This review found 1 RCT and the remainder were generally retrospective cohort studies or case series. Immediate LVA was found to have a lower risk of lymphedema (9% compared to 35% of patients).

Private insurers are mixed on coverage for lymphovenous anastomosis surgery for existing lymphedema. None cover prophylactic surgery. NICE also conducted a recent review and recommended against routine coverage of prophylactic lymphovenous surgery. The international lymphedema society supports lymphedema surgery in appropriate patients.

Based on the comparative studies, LVA/LVB appears to be promising as a treatment for existing lymphedema. However, the only RCT available did not show significant differences in most outcomes. Larger, better designed RCTs are needed in this area. The evidence is much more sparse for lymphovenous surgery as a prophylactic surgery. Based

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on this review, HERC staff recommends against coverage of lymphevenous surgery for either existing lymphedema or as a prophylactic surgery at this time.

HERC staff recommendations:

1) Add an entry for lymphovascular surgery to Excluded Services Guideline E2 as shown below
    a. Replace the temporary CPT code in this entry with the 2027 CPT codes when they become available

EXCLUDED SERVICES GUIDELINE E2, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

The following Interventions are unproven, have no clinically important benefit or have harms that outweigh benefits and should be excluded from coverage

Procedure Code	Intervention Description	Rationale	Last Review
*1019T	Lymphovenous bypass (LVB), including robotic assistance, per extremity	Insufficient evidence of benefit	March 2026

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Breast Cancer Research and Treatment (2026) 215:42
https://doi.org/10.1007/s10549-025-07867-4

REVIEW

Lymphovenous bypass for the treatment of secondary lymphedema: A meta-analysis of prospective outcomes

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Received: 15 July 2025 / Accepted: 17 November 2025 / Published online: 15 December 2025
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Abstract

Background Despite the increasing popularity of microsurgical techniques for the treatment of lymphedema, there is a lack of high-level, prospective, long-term data and standardized outcome metrics. The purpose of this study was to analyze the long-term outcomes of Lymphovenous Bypass (LVB) surgery throughout the past two decades.

Methods We conducted a systematic review of PubMed, Embase, and Web of Science databases to identify prospective clinical trials investigating LVB for lymphedema treatment. Reported outcome data included limb volume measurements, number of cellulitis episodes, compression garment use, and the assessment of complications. For studies involving multiple procedures, only outcomes from the respective LVB cohorts were analyzed. Retrospective data analyses were excluded.

Results Eight prospective studies (2009–2023) were included in the meta-analysis, comprising a total of 431 patients undergoing LVB with a mean follow-up of 21.8 ± 7.7 months. An average of 3.4 ± 1.0 anastomoses were performed per patient. LVB was associated with a 14.26% mean reduction in limb volume (95% CI 6.63–21.88; $p < 0.0001$) at one-year, and 46.3% (95% CI 24.9%-69.1%; $p < 0.01$) reduction/discontinuation of compression therapy following surgery. Patients also reported subjective symptom relief and reduced cellulitis episodes.

Conclusions This systematic review provides the most comprehensive synthesis to date of long-term outcomes following LVB surgery for lymphedema. The findings support LVB as a safe and effective microsurgical intervention, with consistent reductions in limb volume, cellulitis episodes, and reliance on compression therapy.

Keywords Lymphedema · Breast cancer · Lymphovenous bypass

Introduction

Lymphedema is a chronic and progressive condition caused by impaired lymphatic drainage, resulting in the accumulation of lymphatic fluid in the interstitial tissues, most commonly affecting the extremities [1, 2]. It can lead to significant physical discomfort, limb swelling, functional limitations, and recurrent infections [3]. Cancer-related lymphedema is a lifelong and currently incurable condition with global prevalence estimates of 140 to 250 million people worldwide [4]. In developed countries, secondary lymphedema most commonly follows cancer treatment, particularly breast cancer, with incidence rates after axillary lymph node dissection reported between 15 and 40% [1, 4].

Lymphovenous bypass (LVB), a microsurgical technique designed to improve lymphatic drainage, has gained increasing attention over the past two decades. Originally described decades ago, LVB has benefited from significant technical

Stav Brown and Yizhuo Shen contributed equally to the present work.

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advances that allow for the anastomosis of smaller-caliber lymphatic vessels to adjacent veins [5]. The procedure involves creating functional lymphatic-venous anastomoses (LVAs) to divert lymphatic fluid into the venous circulation, reducing fluid accumulation in the affected limb [6]. These refinements in technique have led LVB to be an increasingly popular choice for lymphedema treatment [5, 7].

Prospective and randomized studies consistently demonstrate that LVB can lead to improvements in limb volume, quality of life, and reduction in cellulitis episodes in selected patients with lymphedema [8–10]. However, the magnitude and durability of these benefits vary. Some studies report significant limb volume reduction, while others find improvements primarily in quality of life and infection rates without consistent objective volume changes [8, 9, 11].

The literature highlights substantial heterogeneity in patient populations, surgical techniques, outcome measures, and follow-up periods, which complicates direct comparison and generalizability of results [5, 12]. There is no consensus on the ideal timing of LVB, the most appropriate candidates, or the long-term durability of benefit, as most studies have limited follow-up and are underpowered to detect late recurrences or complications [5]. Recent consensus recommendations from the American Association of Plastic Surgeons also emphasize these ongoing uncertainties and the need for further high-quality, long-term studies to refine patient selection and optimize outcomes [5].

To address these gaps, we conducted a systematic review and meta-analysis of prospective clinical trials published over the past two decades. We aimed to provide a comprehensive synthesis of long-term outcomes following LVB for the treatment of lymphedema, using standardized and clinically meaningful outcome measures.

Methods

Search strategy and inclusion criteria

A systematic review was conducted on PubMed/MEDLINE, Embase, and Web of Science to identify prospective clinical trials investigating LVB for secondary lymphedema treatment according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. The systematic review included articles published on or before February 21st, 2025. The search strategies were initially developed on PubMed and adapted for other databases (Table 1).

Original studies in which LVB was performed as the sole surgical intervention, with or without adjunctive conservative treatment, specifically for secondary lymphedema, were included. Studies had to report at least one of the following outcomes following LVB: limb volume or circumference, patient-reported outcome measures (PROMs), compression garments usage, and frequency of cellulitis. Only prospective studies with post-operative follow-up of 12 months or longer were included.

Non-English publications, animal studies, review articles, expert opinions, case reports, and descriptive studies focusing solely on surgical techniques were excluded. Studies with duplicate data were also excluded. Additionally, we excluded studies where LVB was used to treat primary lymphedema or where LVB was performed in conjunction with other surgical procedures. For research groups with multiple publications potentially containing overlapping patient populations, only the most comprehensive and relevant study was included, as determined by at least two of the authors.

Table 1 Search strategy used for systematic review

Database	Search strategy
PubMed/MEDLINE	("lymphovenous bypass" OR "LVB" OR "lymphaticovenous" OR "lymphatico-venous" OR "lymphovenous anastomosis" OR "LVA" OR "supermicrosurgery" OR "lymphovenous" OR ((lymph* AND vein*) AND (anastom* OR "bypass"))) AND (treat* OR manag* OR interv* OR "treatment outcome"[MeSH] OR "surgical procedures, operative"[MeSH]) AND ("lymphedema" OR "lymphoedema" OR "secondary lymphedema" OR "lymphedema"[MeSH] OR "Breast Cancer Lymphedema"[MeSH])
Embase	('lymphovenous bypass' or LVB or lymphaticovenous or 'lymphatico-venous' or 'lymphovenous anastomosis' or LVA or supermicrosurgery or lymphovenous or (lymph* and vein* and (anastom* or bypass*))).mp. and ((treat* or manag* or interv*).mp. or exp 'treatment outcome'/ or exp 'surgical technique'/ or exp 'reconstructive surgery'/ or exp 'plastic surgery'/) and ((lymphedema' or 'lymphoedema' or 'secondary lymphedema').mp. or exp 'lymphedema'/ or exp 'breast cancer-related lymphedema'/)
Web of Science	((ALL = (("lymphovenous bypass" OR "LVB" OR "lymphaticovenous" OR "lymphatico-venous" OR "lymphovenous anastomosis" OR "LVA" OR "supermicrosurgery" OR "lymphovenous" OR ((lymph* AND vein*) AND (anastom* OR bypass*))))) AND (ALL = (treat* OR manag* OR interv*) OR TS = ("treatment outcome" OR "surgical procedures"))) AND (ALL = ("lymphedema" OR "lymphoedema" OR "secondary lymphedema") OR TS = ("lymphedema" OR "Breast Cancer Lymphedema"))

Data extraction

Each study identified through the database search were independently screened by two of the authors (YS, MN) using Covidence (Veritas Health Innovation, Melbourne, Australia). Risk of bias assessment was conducted using the Risk of Bias in Non-randomized Studies – of Interventions, Version 2 (ROBINS-I V2) [13]. Two independent reviewers (MN and YS) performed these assessments. In cases of disagreement, a third author (SB) resolved disagreements through verbal consensus. Data extraction was performed by two independent reviewers (YS, SB) and included: study design, sample size, patient demographics, follow-up duration, surgical details of LVB, percentage reduction in limb volume, PROs, and frequency of cellulitis episodes. Studies were categorized based on outcome metrics reported one year post-LVB.

Statistical analysis

Meta-analyses were conducted using random-effects models to account for heterogeneity across studies. Pooled estimates included the mean percentage reduction in limb volume compared to preoperative measurements, mean percentage reduction in excess volume relative to the contralateral (healthy) limb, QOL and compression use. All estimates were reported with 95% confidence intervals (CIs). Heterogeneity was quantified using the I^2 statistic, with values > 50% considered indicative of moderate to high heterogeneity. All statistical analyses were conducted using R (version 4.3.2; R Foundation for Statistical Computing, Vienna, Austria), and a p-value < 0.05 was considered statistically significant.

Results

Study selection and characteristics

After search and de-duplication, 1,733 studies entered the screening process (Fig. 1). The final analysis included eight studies published between 2009 and 2023, all of which employed a prospective database or cohort design with a single LVB intervention group [11, 14–21]. A total of 431 patients underwent LVB, with a mean follow-up duration of 21.8 ± 7.7 months. Sample sizes across studies ranged from 10 to 118 patients (Table 2).

Lymphedema and lymphovenous bypass surgery

The majority of patients had cancer-related lymphedema (419, 97.2%), with breast cancer being the most common underlying cause (209, 48.5%), followed by genitourinary/gynecologic cancers (150, 34.8%) and other or unspecified malignancies (60, 13.9%). Upper and lower extremity lymphedema were nearly equally represented, with 214 cases (49.7%) affecting the upper extremities and 217 cases (50.3%) affecting the lower extremities. On average, patients had experienced lymphedema for 5.46 years (range 1–35 years) before undergoing LVB. The International Society of Lymphology (ISL) staging system was the most commonly reported classification, used in five studies encompassing 294 patients. Among these, 261 patients (88.8%) were classified as stage I or II, while 33 patients (11.2%) had stage III disease.

All studies used dyes (Indocyanine Green (ICG), Blue Patent V, or Methylene Blue) and/or lymphoscintigraphy to visualize lymphatic vessels either pre-operatively or intra-operatively during LVB. Only one study reported two minor complications related to LVB surgery, both due to mild skin irritation from contrast injection [19]. Both end-to-end and end-to-side anastomoses were employed. In most studies, more than one anastomosis was performed per patient, with an average of 3.4 ± 1.0 (Table 3). Studies reported heterogeneous outcome measures, including changes in limb volume, excess volume reductions (EVR), PROMs, subjective symptom improvement, frequency of cellulitis episodes, and compression therapy usage.

Limb volume reduction

Significant limb volume reductions following LVB were observed in four studies [15, 17, 18, 21]. Chang et al. (2013) reported sustained volume reduction over a 3-year follow-up period with decreases of 33%, 36%, and 42% at 3, 6, and 12 months, respectively, and 35% and 38% at 2 and 3 years. Boccardo et al. (2022) demonstrated sustained volume reductions at 1 year (75–90% in early stage II, 60–75% in late stage II, $p < 0.001$), which persisted through 5 years across a cohort with both upper and lower extremity lymphedema [15]. Similarly, mean volume at 1, 3, and 5 years postoperatively remained significantly reduced compared to preoperative measurements ($p < 0.001$). For lower extremity lymphedema specifically, Kwon et al. (2023) observed significant limb volume reductions of 11.0% at 1 month, which were maintained at 6 months (10.4%) and 12 months (11.7%, $p < 0.001$) [18]. Phillips et al. (2019) also reported a significant reduction in unilateral lower extremity lymphedema, with excess volume decreasing by 44.42% ($p = 0.008$) [21]. Other studies demonstrated volume reduction as well, although the outcomes did not reach statistical significance. Damstra et al. (2009) noted a slight, non-significant excess volume reduction at one year (4.8%) [22]. Similarly, Cornelissen et al. (2017) also reported a moderate but non-significant

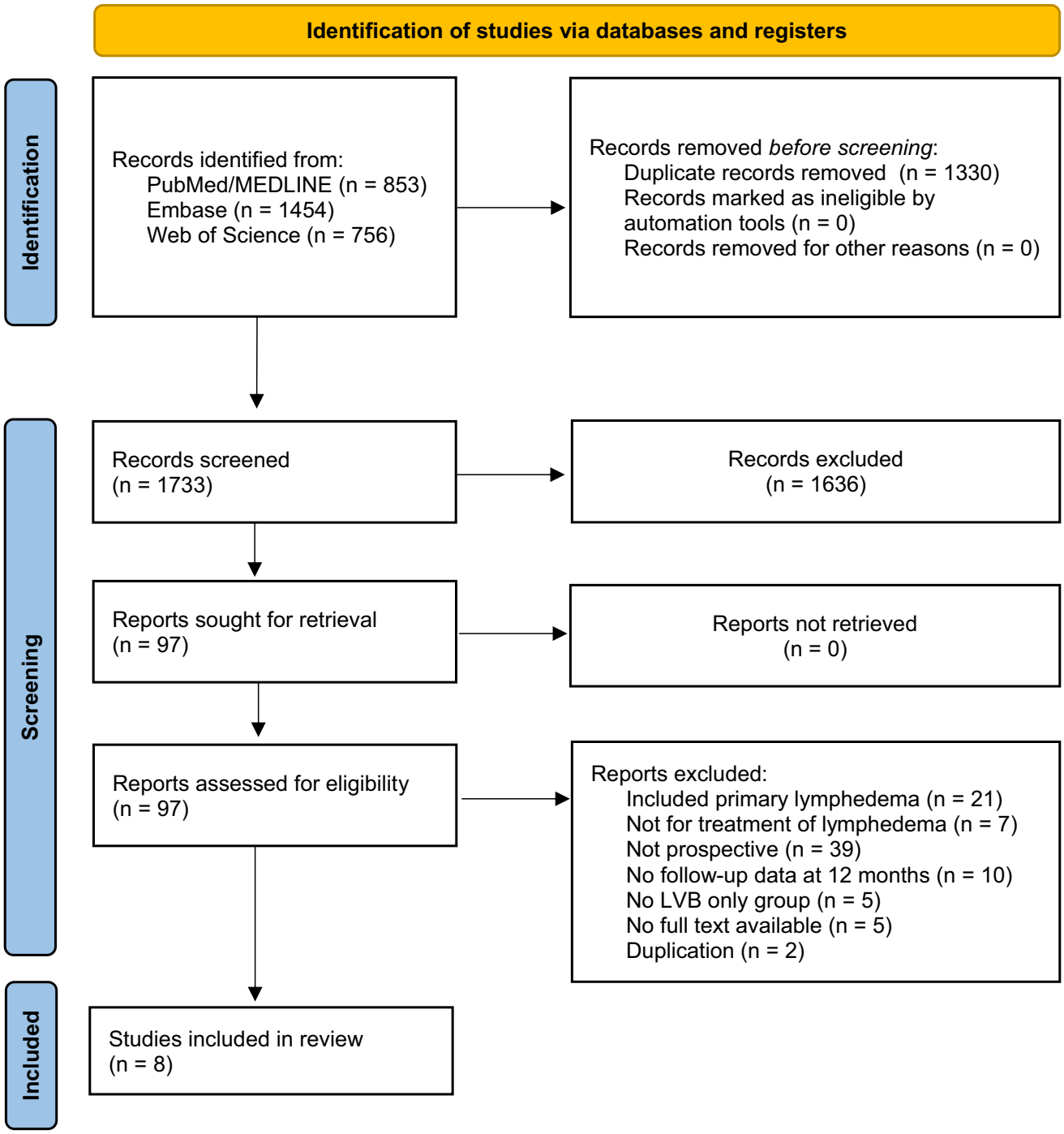

Fig. 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of the study selection process

12.7% decrease in mean limb volume difference ($p = 0.58$) [19]. Khan et al. (2019) reported fluctuating excess volume reductions at different time points (− 14.0 ± 40.7% at 1 month; 2.9 ± 68.4% at 3 months; − 0.6 ± 49.6% at 6 months; 9.2 ± 71.8% at 12 months) [14]. Given that most studies reported either changes in limb volume or EVR, two random effects models were used, respectively, to estimate the pooled effects of LVB using these two measures. Pooled analysis showed that LVB significantly reduced the limb volume by 14.26% (95% CI 6.63–21.88, $p < 0.0001$, $I^2 = 98.6\%$) and the excess volume compared

Table 2 Summary of study characteristics

Author (year)	Country	N	Study design	Follow-up, mean	Outcome measures assessed	Timepoints assessed
Chang (2013)	United States	100	Prospective cohort	Upper (89): 30.4 months (3–84) Lower (11): 18.2 months (1–36)	Limb volume differential by perometer, Subjective symptom improvment	Pre-op 3/6/12 months postoperatively
Kwon (2023)	Korea	118	Prospective cohort	27.3 ± 8.7 months	Quality of Life Measure for Limb Lymphedema (LYMQoL)- lower leg, Limb volume calculated from circumference	Pre-op 1/6/12 months postoperatively
Khan (2019)	United Kingdom	27	Prospective cohort	24 of 27 completed 12 month	Limb volume measured by perometer, Compression garment usage	Pre-op 1/3/6/12 months postoperatively
Damstra (2009)	Netherlands	10	Prospective	8 years	Limb volume with water, Lymphoscintigraphy, Quality of Life with SF-36	Pre-op 3/6/12/24 months postoperatively
Boccardo (2022)	Italy	101	Prospective database	5 years	Limb volume differential, Lymphoscintigraphy, Number of lymphangitis episodes	Pre-op, 1/3/5 years for limb volume 18 months for lymphoscintigraphy
Cornelissen (2017)	Netherlands	20	Prospective cohort	7.8 ± 1.5 months	Lymph-ICF, Discontinuation of compressive stockings, Limb volume using UEL-index,	Pre-op 1/3/6/12 months postoperatively
Phillips (2019)	U.K	29	Prospective	8.9 ± 5.2 months	LYMQOL, Limb volume differential, Compression therapy usage	Pre-op 3/6/12 months postoperatively
Klingelhoefer (2019)	Germany	26	Prospective database	23 months (4 – 54)	Frequency of manual lymphatic drainage, Patient-reported symptoms, Use of compression therapy	Pre-op Post-op (unspecified)

to the contralateral healthy limb by 14.05% (95% CI -53.71–81.80, $p < 0.001$, $I^2 = 88.0\%$) one-year following LVB (Fig. 2, 3).

Patient-reported outcomes

Patient-reported outcomes indicated significant improvements in quality of life (QoL) and symptom relief following LVB in six studies [17–20, 22, 23]. At 6 months, 5 patients (50%) reported subjective symptom relief according to the SF-36 questionnaire (Damstra 2008) [22]. Two studies, Kwon et al. (2023) and Cornelissen et al. (2017), observed significant improvements in all domains and overall scores up to 12 months following LVB assessed by LYMQoL and Lymph-ICF, respectively. [18, 19] Another study by Phillips et al. (2019) also noted improved LYMQoL scores from 71.13 ± 21.43 preoperatively to 87.75 ± 17.52 at the last follow-up visit among the eight patients with > 12-month follow-up, though these did not reach statistical significance [23]. Other studies noted subjective symptom relief in the majority of patients undergoing LVB. In the study by Chang et al., symptoms improved in 96% of patients

Table 3 Patient characteristics

Author (year)	Age, years (Mean, SD)	BMI (Mean, SD)	Gender (n, %)	Diagnosis duration, years (Mean, SD/ range)	Stage of lymphedema, n (%)	Etiology, n (%)	Lymphedema location, n (%)	LVB complications	LVB Techniques	Mean number of Anastomosis
Chang (2013)	UE: 54 LE: 54	UE: 30 (range 20–51) LE: 31 (range 22–42)	Not Specified	UE: 3.5 (range: 1–10) LE: 6.6 (range: 1–25)	MD Anderson staging: Stage 1—4	UE: breast cancer (n = 89) LE: sarcoma (n = 3) melanoma (n = 2) gynecologic cancer (n = 6)	UE: 89 (89%) LE: 11 (11%)	UE: 0 LE: NR	End-to-end (if recipient vein was > > lymphatic vessel: end-to-side)	Stage 1 or 2 (n = 16): 6.5 (4–12) Stage 3 or 4 (n = 14): 4.8 (2–7)
Kwon (2023)	54.4 ± 12.3	24.9 ± 3.9	Female: 109 (92.4%) Male: 9 (7.6%)	**Median (IQR)**: 48 months (70)	ISL staging: I: 5 (4.2%) II early: 45 (38.1%) II late: 37 (31.4%) III: 31 (26.3%)	Cervical cancer: 67 (56.8%) Ovarian cancer: 16 (13.6%) Endometrial cancer: 12 (10.2%) Other malignancy: 14 (11.9%) Trauma: 9 (7.6%)	LE: 118 (100%)	NR	End-to-end: 23 (19.5%) Side-to-end: 63 (53.4%) Combined: 32 (27.1%	3.4 ± 1.3
Khan (2019)	NR	24.8 [range 20.0–38.4]	NR	3.5 [range 0.5–18]	NR	Breast cancer: 27 (100%)	UE: 27 (100%)	NR	End-to-end	3 (range 2–5)
Damstra (2008)	58.7 [range 46–68]	NR	Female: 10 (100%)	5.4 [range 3–14]	Campisi staging: Stage 3: 10 (100%)	Breast cancer: 10 (100%)	UE: 10 (100%)	NR	End-to-side	at least 3–4
Boccardo (2022)	56.94 ± 8.98	NR	UE: Male: 0 (%); Female: 63 (100%) LE: Male: 15 (39.5%); Female: 23 (60.5%)	NR	ISL staging: Early second: 58 (57.4%) Late second: 43 (42.6%)	Breast: 63 (62.4%) Uterus: 14 (13.9%) Prostate: 11 (10.9%) Melanoma: 8 (7.9%) Ovary: 5 (5%)	UE: 63 (62.4%) LE: 38 (37.6%)	NR	Multiple LVA using a sleeve technique	3–6 UE: 3.08 ± 0.27 LE: 4.45 ± 0.79 Early second: 3.76 ± 0.99 Late second: 3.37 ± 0.54
Cornelissen (2017)	55.9 ± 4	25.1 [range 21–30]	Female: 20 (100%)	6 [range 2–30] years	ISL staging: I: 1 (5%) IIA: 19 (95%)	Breast cancer: 20 (100%)	UE: 20 (100%)	2 (10%) skin irritation at contrast injection site	Not Specified	1.5 [range 1–2]

Table 3 (continued)

Author (year)	Age, years (Mean, SD)	BMI (Mean, SD)	Gender (n, %)	Diagnosis duration, years (Mean, SD/range)	Stage of lymphedema, n (%)	Etiology, n (%)	Lymphedema location, n (%)	LVB complications	LVB Techniques	Mean number of Anastomosis
Phillips (2019)	50.2 ± 10.3	Not Reported	Female: 29 (100%)	9.9 ± 8.9 years	ISL stage I or II	Cervical: 15 (51.72%) Endometrial: 4 (13.79%) Melanoma: 3 (10.34%) Other: 7 (24.14%)	LE: 29 (100%) Unilateral: 19 (65.5%) Bilateral: 10 (34.5%)	0	Not Reported	Not Reported
Klingelhoefer (2019)	54.9 (26 –78)	27	Female: 21 (80.8%) Male: 5 (19.2%)	8.4 years (2–35)	ISL Stage I: 7 (26.9%) Stage II: 17 (65.4%) Stage III: 2 (7.7%)	Cancer-related lymphedema: 23 (88.5%) Trauma: 3 (11.5%)	Upper: 5 (19.2%) Lower: 21 (80.8%)	NR	End to end or end to side if mismatch is too large	1.85 (range 1–4)

with upper extremity lymphedema and 57% of patients with lower extremity lymphedema [17]. Klingelhoef et al. (2019) also observed subjective symptom improvement in 50% of patients [20]. Using infection as a proxy for disease burden, Boccardo et al. (2022) reported complete cessation of lymphangitis episodes over 5 years following LVB in all 79 (100%) patients previously experiencing frequent infections (1–3 episodes/year) [15]. Weighted pooled analysis of LYMQoL data from two studies demonstrated an average 46.7% (95% CI 28.3–65.0, $p = 0.593$, $I^2 = 0.0\%$) improvement in patient-reported quality of life after LVB Fig. 4).

Compression use

All patients were on compression therapy before LVB surgery. Four studies reported postoperative reductions in compression garment usage. Weighted pooled analysis across four studies showed that 46.3% (95% CI 24.9–69.1, $p = 0.002$, $I^2 = 79.5\%$) of patients reduced or discontinued compression therapy following LVB (Fig. 5) [14, 19–21]. Khan et al. (2019) observed a significant overall change in compression therapy usage of the entire cohort (27 patients) on contingency analysis ($p = 0.045$), with 10 (37.0%) patients reducing their compression garment therapy, and two discontinuing the use completely [14]. Similarly, Cornelissen et al. (2017) noted that 85% of patients discontinued compressive stockings during a mean follow-up of 7.8 months [19]. Klingelhoef et al. (2019) reported discontinuation of compression therapy and manual lymphatic drainage in 7.7% and 34.6% of patients, respectively. [20] Phillips et al. reported that 4 (13.8%) patients discontinued compression therapy, while 3 (10.3%) reported reduced usage(Table 4) [21].

Patency of lymphovenous anastomosis (LVA)

LVA patency was assessed in two studies using lymphoscintigraphy [15, 22]. Patency rates could not be pooled due to heterogeneity in assessment methods and incomplete reporting; while one study reported a numerical patency rate, others relied on indirect measures or did not quantify patency outcomes. Boccardo et al. (2022) reported a 97% patency rate at 18 months postoperatively [15]. The lymphatic transport index (LyTi) showed a significant decrease from preoperative levels to 18 months post-surgery. Three patients with late-stage II lymphedema demonstrated no patency, corresponding with less volume reduction compared to the rest of the cohort (45%-60% vs. > 60%). Damstra et al. found no significant differences in the Kleinhans transport index between preoperative and one-year post-surgical measurements[22].

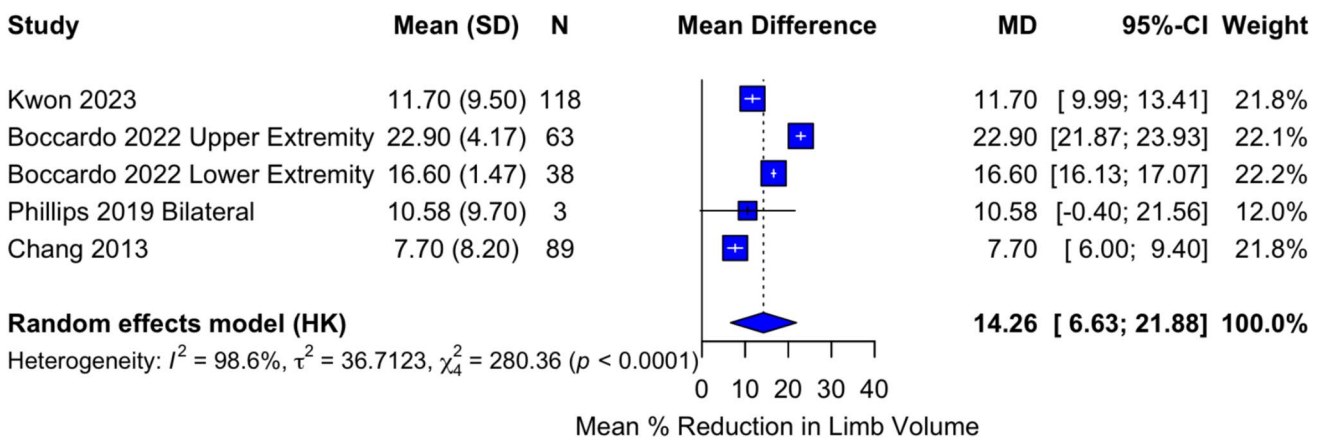

Fig. 2 Mean percentage reduction of limb volume one-year following LVB compared to preoperative limb volume measurement

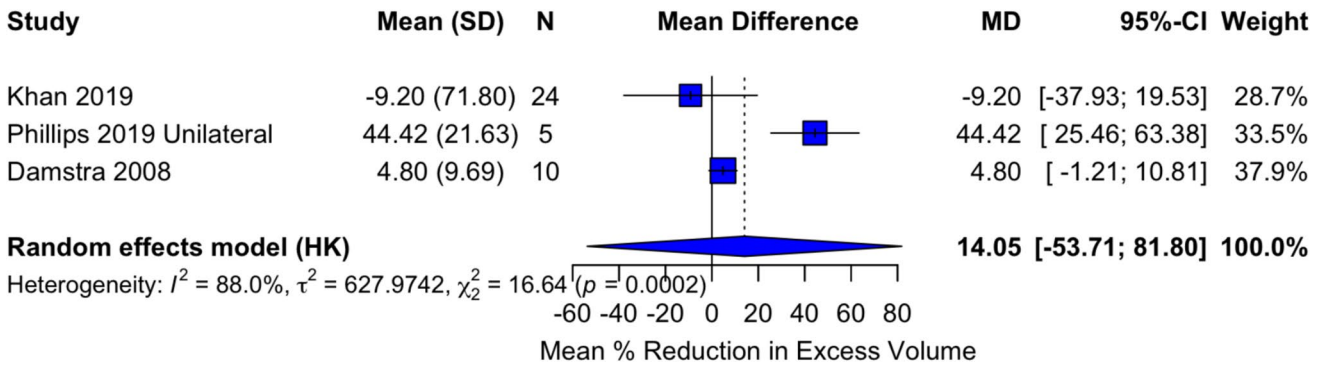

Fig. 3 Mean percentage change of excess volume (to contralateral healthy limb) reduction one-year following LVB compared to preoperative excess volume

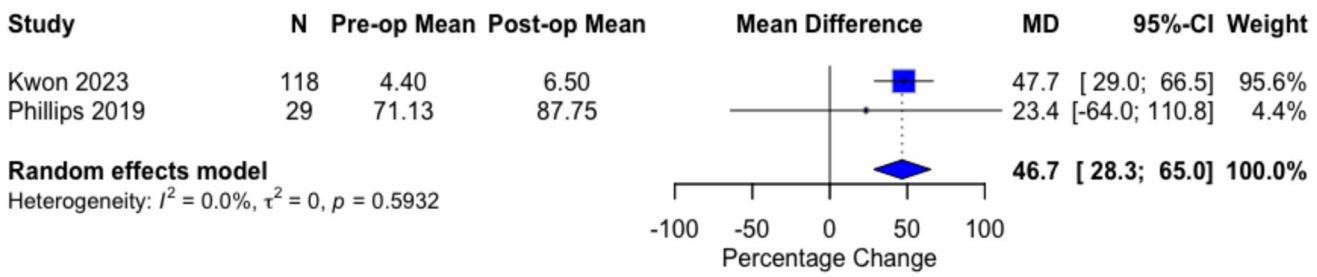

Fig. 4 Pooled percentage improvement in LYMQoL one-year after LVB

Risk of bias assessment

As illustrated in Figs. 6 and 7, the majority of studies demonstrated a low to moderate risk of bias across most domains, and no study was judged to have a critical risk of bias. Overall, the methodological quality of the included studies was deemed acceptable to support the validity of the meta-analysis findings.

Discussion

The most recent meta-analysis evaluating the efficacy of LVB in treating lymphedema was published by Chang et al. in 2021, synthesizing evidence from 10 studies published between 1996 and 2015. Their analysis reported that LVB significantly reduced limb circumference by an average of 3.8 cm. [5] However, most studies included

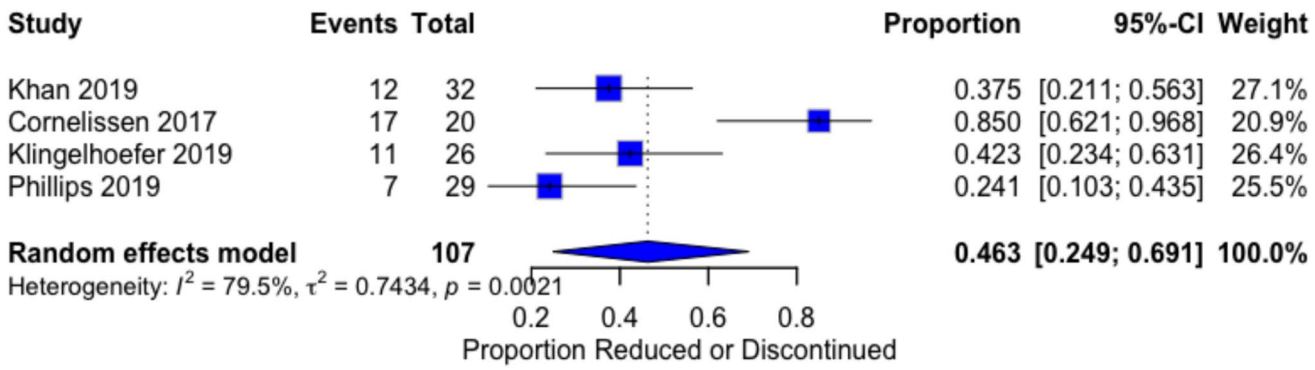

Fig. 5 Pooled proportion of patients who reduced or discontinued compression therapy after LVB

were retrospective, introducing inherent biases. Moreover, the absence of specific exclusion criteria regarding follow-up duration resulted in heterogeneity in the timing of outcome measurements. Since 2021, several prospective studies have been published, providing new data that warrant an updated analysis.

The present study represents the first systematic review and meta-analysis focused on prospective studies evaluating the long-term effect of LVB for secondary lymphedema. We included only studies reporting follow-up data of at least one year post-LVB, with a mean follow-up of 21.8 ± 7.7 months. Our analysis demonstrates that LVB yields sustained benefits beyond one year, including significant reductions in limb volume, improvements in patient-reported quality of life, and decreased compression use. Notably, some studies reported benefits persisting for up to three years, supporting LVB as a durable and effective long-term treatment option for patients with lymphedema [15, 17].

Volume reduction

In our analysis, LVB was associated with a significant mean reduction of 14.26% in absolute limb volume and 14.05% reduction in excess volume relative to the contralateral limb. While both outcomes point to the efficacy of LVB in reducing burden, it is important to interpret the EVR findings with caution. The notably wide confidence interval for EVR suggests a high degree of heterogeneity across studies, which may stem from differences in baseline disease severity, measurement protocols and surgical technique. This underscores the need for greater uniformity in reporting volumetric outcomes and for future studies to adopt standardized methods for EVR assessment.

Quality of life and symptom improvement

Patient-reported outcomes showed significant improvements in quality of life (QoL) and symptom relief following LVB. Our analysis demonstrated a 46.7% improvement in LYMQoL scores and a 46.3% reduction or discontinuation in compression therapy. These findings underscore the value of including psychosocial and functional metrics when evaluating lymphedema interventions. Patients reported enhanced physical mobility, emotional well-being, and social functioning, with many able to discontinue compression garments—highlighting LVB's potential to reduce dependence on lifelong conservative therapy. However, few studies systematically analyzed patients' reasons for discontinuation, which may include both symptomatic improvement and noncompliance or logistical factors. This underscores the need for future studies to capture these motivations more explicitly to better contextualize compression use patterns after surgery. Interestingly, QoL improvements were not closely linked to disease severity or limb volume reduction. For instance, Chang et al. found no significant difference in symptom improvement between early- and advanced-stage patients (16 vs 12, $p = 0.48$) [17], and Kwon et al. reported no correlation between QoL improvement and ISL stage, disease duration, or volume change [18]. Other prospective and randomized studies also showed substantial QoL gains despite minimal objective volume reductions [24]. These findings suggest that LVB may benefit a broader patient population than previously thought, including those with modest anatomical response or advanced-stage disease. The greater improvement in QoL relative to volume reduction indicates that volumetric change may not fully capture clinical benefit. Thus, reliance on volume metrics alone could underestimate LVB's value. [24] Incorporating validated patient-reported outcome measures into clinical trials and routine care is essential to reflect the full impact of surgery. Moreover, the ability to enhance QoL regardless of stage supports timely surgical referral and challenges previous assumptions that limit access based on chronicity or anatomical severity.

Table 4 Outcomes following LVB

Author (year)	Patient-Reported Outcomes	Limb Volume	Cellulitis episodes	Compression Garment Usage
Chang (2013)	**Subjective Symptom Improvement, n (%)** UE: 96% LE: 4 (57%) 30 patients with ICG staging: Stage 1 or 2: 16 (100%) Stage 3 or 4: 12 (86%)	UE: Overall mean volume differential reductions: 3 months: 33%; 6 months: 36%; 12 months: 42% (10 patients) 2 years: 35%; 3 years: 38% Volume compared to pre-op: 3 months: -9.6% ± 9.1%, p = 0.001 6 months: -8.5% ± 11.2%, p = 0.017 12 months: -7.7% ± 8.2%, p = 0.032	NR	NR
Kwon (2023)	**LYMQoL** Function (range) Preoperative: 18.6 ± 0.5 (8–32) 1 month: 16.4 ± 0.5 (8–32), p-value (< 0.0001) 6 months: 15.7 ± 0.6 (8–29), p-value (< 0.0001) 12 months: 15.4 ± 0.6 (8–32), p-value (< 0.0001) Overall p-value: < 0.0001 Appearance (range) Preoperative: 17.8 ± 0.5 (7–28) 1 month: 17.0 ± 0.5 (7–28), p-value (0.0653) 6 months: 16.0 ± 0.6 (7–27), p-value (0.0005) 12 months: 16.0 ± 0.6 (7–28), p-value (0.0015) Overall p-value: 0.0006 Symptoms (range) Preoperative: 11.8 ± 0.3 (5–20) 1 month: 10.0 ± 0.3 (5–20), p-value (< 0.0001) 6 months: 9.4 ± 0.3 (5–18), p-value (< 0.0001) 12 months: 8.9 ± 0.4 (5–20), p-value (< 0.0001) Overall p-value: < 0.0001 Mood (range) Preoperative: 14.5 ± 0.4 (6–24) 1 month: 12.4 ± 0.4 (6–24), p-value (< 0.0001) 6 months: 11.6 ± 0.4 (6–22), p-value (< 0.0001) 12 months: 11.4 ± 0.5 (6–24), p-value (< 0.0001) Overall p-value: < 0.0001 Overall (range) Preoperative: 4.4 ± 0.2 (0–9) 1 month: 5.7 ± 0.2 (1–10), p-value (< 0.0001) 6 months: 6.4 ± 0.2 (1–10), p-value (< 0.0001) 12 months: 6.5 ± 0.3 (1–10), p-value (< 0.0001) Overall p-value: < 0.0001	Volume compared to pre-op: 1 month: -11.0% ± 6.6% 6 months: -10.4% ± 7.5% 12 months: -11.7% ± 9.5% p < 0.001	NR	NR

Table 4 (continued)

Author (year)	Patient-Reported Outcomes	Limb Volume	Cellulitis episodes	Compression Garment Usage
Khan (2019)	NR	Excess volume reduction: 1 month: − 14.0 ± 40·7% 3 months: 2.9 ± 68·4% 6 months: − 0.6 ± 49.6% 12 months: 9.2 ± 71·8% Subgroup analysis: Excess volume reduction (%) 1 month after LVA: Sustained response: -30.8% ± 32.5 Transient response: -12.3% ± 27.5 No response: 37.9% ± 37.9 3 months after LVA: Sustained response: -23.2% ± 43.0 Transient response: 28.4% ± 117.3 No response: 55.3% ± 138.9 6 months after LVA: Sustained response: -20.4% ± 31.7 Transient response: 19.5% ± 74.3 No response: 53.4% ± 26.6 12 months after LVA: Sustained response: -33.2% ± 35.0 Transient response: 102.0% ± 75.7 No response: 52.3% ± 21.4	NR	CGT downgrade: 10 (37.0%) CGT discontinuation: 2 (7.4%)
Damstra (2009)	6 months: 5 (50%) patients had subjective relief of their complaints according to the SF-36 questionnaire	Volume differential: Pre-op: 988 (range 532–1400) 3 months: 841 (range 232–1256) 6 months: 994 (range 500–1789) 12 months: 1075 (range 500–1856) Volume: 4.8% after one year	NR	NR
Boccardo (2022)	NR	*Mean volume at 1, 3, and 5 years after LVB Pre-op: Early second: 5211 ± 3562 Late second: 6181 ± 3845 UE: 2806 ± 460 LE: 10,296 ± 812 Post-op: Early second: 4439 ± 3146 Late second: 4770 ± 3304 UE: 8585 ± 459 LE: 2164 ± 806	Acute lymphangitis with 1–3 episodes/year: 79 patients (29 LE and 50 UE) After surgery: 0	NR

Table 4 (continued)

Author (year)	Patient-Reported Outcomes	Limb Volume	Cellulitis episodes	Compression Garment Usage
Cornelissen (2017)	Physical Function: Pre-op: 48 3 months: 26 6 months: 46 12 months: 13 Mental Function: Pre-op: 42 3 months: 22 6 months: 15 12 months: 11 Household Activities: Pre-op: 52 3 months:42 6 months:33 12 months: 28 Mobility Activities: Pre-op: 41 3 months:36 6 months:33 12 months:11 Life and Social Activities: Pre-op: 41 3 months:39 6 months:28 12 months: 11 Total: Pre-op: 44 3 months: 31 6 months: 30 12 months: 14	Mean volume difference: preop 14.92 ± 8.01 postop 12.99 ± 7.47 P = 0.582	NR	Discontinuation: 17 (85%)
Phillips (2019)	LYMQOL (only on patients with > 12 months follow-up): Preoperative Group: Mean: 71.13 Standard Deviation: 21.43 Postoperative Group: Mean: 87.75 Standard Deviation: 17.52 Paired t-test Results: t-statistic: 2.18 p-value: 0.0655	Unilateral (n = 19): the median pre-operative excess volume was 27% (range 1.4–85%). 15 out of 19 patients showed reduced limb volume post-operatively. The median post-operative excess was 16% (range – 2.3– 63%). The median relative percentage volume reduction was 26% (range – 46.9–267.9, p < 0.005) Bilateral (n = 10): absolute volumetric improvement was seen in 19/20 limbs. Post-operative median absolute percentage improvement in limb volume was 8% (range – 3.4–23.1%)	NR	Discontinue: 4 (13.8%) Reduced usage: 3 (10.3%)
Klingelhoefer (2019)	**Subjective Symptom Improvement at end of follow-up: 23 (50%)**	34.6% patients showed a reduction of circumferential measurement during follow-up	NR	4 (15.4%) stopped conservative therapy 9 (34.6%) stopped manual lymphatic drainage 2 (7.7%) stopped compression therapy

Patency and infection rates

One study, by Boccardo et al., reported significant reduction (complete cessation of lymphangitis in 79 patients) in cellulitis episodes, which suggests that LVB not only addresses physical symptoms of lymphedema but also reduces the risk of infections that commonly affect lymphedema patients. This finding is in alignment with

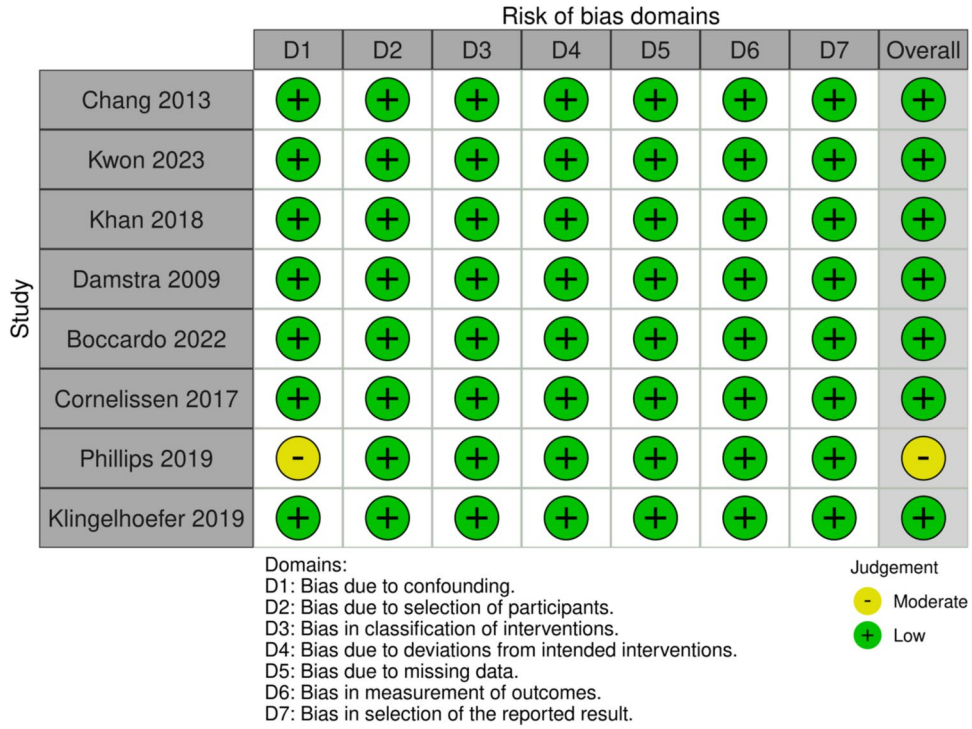

Fig. 6 Risk of bias analysis of included studies (traffic plot)

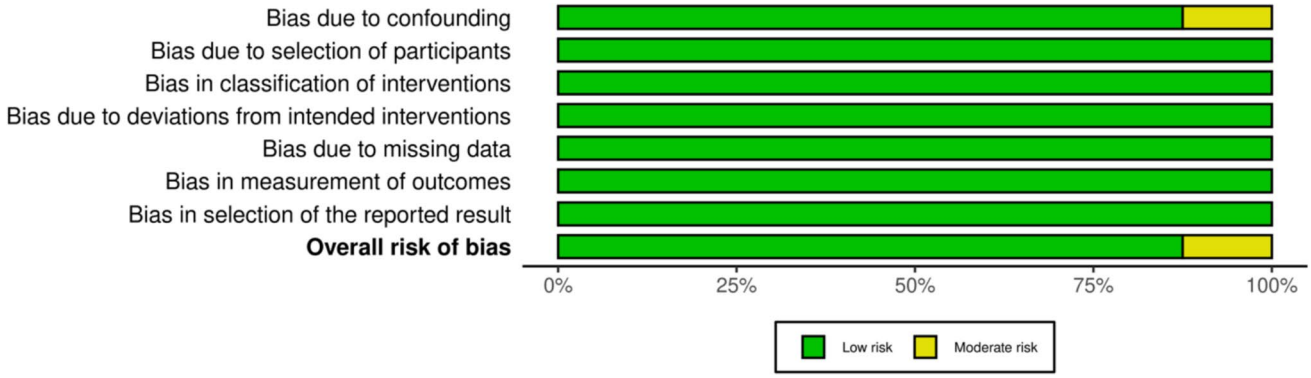

Fig. 7 Summary risk of bias analysis of included studies

previous studies, also showing that LVB leads to a marked decrease in the frequency of cellulitis episodes compared to conservative therapy alone, with reductions sustained over long-term follow-up [12, 25–27]. This reduction in infection risk translates into decreased healthcare utilization, including fewer hospital admissions, reduced need for intravenous and oral antibiotics, and less time off work due to illness. Cost-effectiveness analyses confirm that LVB significantly lowers direct healthcare costs related to cellulitis management, even when accounting for the upfront cost of surgery, and improves quality of life metrics [28].

Patient selection

Although pooled analysis showed significant limb volume reductions following LVB (Fig. 2, 3), individual outcomes varied considerably. Several studies identified early-stage intervention as a critical predictor of success. For example, Chang et al. reported that patients with early-stage lymphedema (MD Anderson stages 1–2) had more anastomoses and significantly greater volume reduction compared to those with advanced-stage disease [17]. Khan et al. found shorter lymphedema duration (< 2 years) was associated with greater excess volume reduction, and the number of anastomoses correlated with improved outcomes [14]. Boccardo et al. found earlier stages linked to

more anastomoses and better lymphatic transport indices [15]. However, Taliat et al. observed that patients with longstanding disease had lymphatic vessel characteristics comparable to those with shorter duration, suggesting duration alone may not predict outcomes [29]. Indeed, only one [30] study used duration as a selection criterion, while most relied on ICG lymphangiography or ISL staging [11, 14–21, 30–32]. This underscores that advanced clinical stage—not disease duration—typically guides surgical candidacy, though the two should not be conflated.

LVB and other surgical interventions

LVB functions as a physiologic bypass that diverts lymph into the venous system and is generally most effective in earlier-stage disease with functioning lymphatics, offering low morbidity and rapid recovery. In contrast, vascularized lymph node transfer (VLNT) may be better suited for more advanced or fibrotic disease through lymphangiogenic and pump mechanisms but involves donor-site morbidity and longer recovery. A recent retrospective cohort study comparing LVB and VLNT showed distinct patterns of reponse, with LVB showing greater but shorter-lasting response peaking within three months after surgery and VLNT showing a delayed but more durable response peaking at three and thirteen months [33]. Debulking techniques, such as liposuction, reduce fibroadipose hypertrophy and limb size but do not restore physiologic lymphatic drainage and often require ongoing compression [5, 10]. Taken together, these approaches may be complementary to LVB: LVB is typically considered first-line for ISL stage I–II disease, VLNT for more advanced or refractory cases (often in combination with LVB), and debulking as an adjunct in patients with significant adipose hypertrophy.

Limitations and future directions

Several limitations should be noted when interpreting these findings. No randomized controlled trials or matched control cohort studies were available for head-to-head comparisons between LVB and conservation therapy or other surgical interventions. Therefore, definitive comparative effectiveness cannot be established. However, the current evidence consistently demonstrates meaningful improvements following LVB in appropriately selected patients. Moreover, the current evidence base is shaped by variability in patient populations, disease severity, surgical techniques, and measurement methodologies. For example, the included studies used different approaches to quantify limb volume, such as percentage reduction, raw volume, raw excess volume, or percentage excess volume, which introduces heterogeneity and challenges to synthesize results across studies. Moderate to high statistical heterogeneity was observed across most pooled analyses, with I^2 values of 88–99% for limb and excess volume reductions (Figs. 2 and 3). Although the presence of heterogeneity warrants cautious interpretation of pooled meta-analysis, the direction and magnitude of effects were consistent across studies, supporting the overall validity of the findings. Future research should adopt standardized protocols for outcome measurement and include longer follow-up periods to conclusively establish the long-term efficacy of LVB.

The paucity of literature highlights the lack of prospective studies with long-term follow-up. Further large-scale, multicenter RCTs are needed to establish standardized guidelines for LVB. To our knowledge, a multicenter RCT, SurLym, was started in 2022 and is currently ongoing to compare the effect of conservative therapy alone to conservative therapy and reconstructive lymphatic surgery [34].

Conclusion

This meta-analysis consolidates fourteen years of research on LVB, confirming its efficacy in reducing limb volume, improving quality of life, and decreasing cellulitis frequency in patients experiencing lymphedema. The sustained benefits up to three years postoperatively support LVB as a viable, long-term treatment option for secondary lymphedema. Given its impact on reducing the physical and psychological burden of lymphedema, LVB holds promise as an important intervention in the management of this condition.

Acknowledgements With support from the Raj and Indra Nooyi Cancer Research Fund and the Yale School of Medicine Fellowship for Medical Student Research. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Yale School of Medicine Fellowship for Medical Student Research.

Author contribution S.B. conceived the manuscript. S.B., Y.S., and S.G.K. wrote the manuscript. Y.S., M.N., and V.S. created the figures. B.P., P.L., and M.G. contributed to the manuscript review. S.H. provided critical revisions and editorial oversight.

Funding The authors received no funding for data collection or preparation of the manuscript.

Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

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REVIEW ARTICLE OPEN ACCESS

Objectifying Clinical Outcomes After Lymphaticovenous Anastomosis and Vascularized Lymph Node Transfer in the Treatment of Extremity Lymphedema: A Systematic Review and Meta-Analysis

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Received: 16 September 2024 | **Revised:** 13 January 2025 | **Accepted:** 3 March 2025

ABSTRACT

Background: Upper extremity lymphedema (UEL) and lower extremity lymphedema (LEL) can develop as a result of lymph node dissection in the treatment of various malignancies. While emerging microsurgical interventions using lymphaticovenous anastomosis (LVA) and vascularized lymph node transfer (VLNT) show promising outcomes for patients with lymphedema, the best approach to implementing the two procedures remains to be defined. This systematic review and meta-analysis provide a comprehensive overview of published literature on the clinical improvement of extremity lymphedema in patients who undergo either LVA, VLNT, or a combined microsurgical procedure.

Methods: From Embase, PubMed, and Web of Science databases, 52 studies were identified that met inclusion criteria. This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The risk of bias was assessed using the Risk Of Bias In Nonrandomized Studies-of Interventions (ROBINS-I) tool and the Cochrane tool for randomized trials (RoB 2).

Results: Random-effects meta-analyses of means estimated a pooled clinical improvement of 36.46% (95% CI: 29.44–43.48) for UEL and 34.16% (95% CI: 23.93–44.40) for LEL. Subgroup analyses revealed differences in clinical improvement according to the microsurgical approach. Clinical improvement of UEL was 29.44% (95% CI: 15.58–43.29) for LVA, 41.66% (95% CI: 34.13–49.20) for VLNT, and 32.80% (95% CI: 21.96–43.64) for combined VLNT + LVA, while the improvement of LEL was 31.87% (95% CI: 18.60–45.14) for LVA and 39.53% (95% CI: 19.37–59.69) for VLNT.

Conclusion: The findings from this study elucidate the clinical improvement in extremity lymphedema from various microsurgical approaches. This knowledge could aid physicians in the shared decision-making process with UEL and LEL patients and better facilitate proper patient selection for microsurgical interventions.

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1 | Introduction

Lymphedema is a condition characterized by the accumulation of interstitial fluid due to impaired lymphatic system function. While primary lymphedema is attributable to congenital abnormalities, secondary lymphedema is often iatrogenic in nature. Upper extremity lymphedema (UEL) typically develops following axillary lymph node irradiation and dissection in breast cancer patients, while lower extremity lymphedema (LEL) stems from inguinal lymph node dissection in the treatment of gynecologic, genitourinary, and dermatological malignancies. Lymphedema has been well documented to contribute to functional disability, pain, and discomfort (Warren et al. 2007; Grada and Phillips 2017). Limitations in the normal range of motion, as well as psychological distress and social isolation, can significantly impact patients' quality of life (Kim et al. 2015; Neuberger et al. 2022).

In contrast to the conservative approach to lymphedema management, emerging microsurgical interventions, such as lymphaticovenous anastomosis (LVA) and vascularized lymph node transfer (VLNT) show promising outcomes for patients with lymphedema (Carl et al. 2017; Ciudad et al. 2022). Microsurgical interventions do not involve the same long-term costs and time-consuming trajectory that physical therapy or compression therapy do, which often weakens patients' compliance (Kerchner et al. 2008; Liao et al. 2012; Masui et al. 2023). Furthermore, LVA and VLNT address the underlying cause of lymphedema by restoring damaged lymphatic draining. LVA facilitates the bypass of obstructed lymphatic vessels through anastomoses to nearby venules, effectively shunting excess lymphatic fluid from the obstructed extremity into the systemic circulation (Chang et al. 2013). VLNT has the potential to restore the physiological function of the affected extremity through the autologous transfer of vascularized lymphatic tissue (Patel et al. 2015).

While both LVA and VLNT have proven effective in alleviating symptoms in patients with lymphedema, the best approach to implementing the two procedures remains to be defined. LVA relies on the presence of patent lymphatic channels and is therefore typically limited to patients with earlier stages of lymphedema (Chang et al. 2020). Because VLNT does not necessitate that patients have complete lymphatic vessel function, the procedure is often reserved for patients with more advanced stages of lymphedema progression (Chang et al. 2020). Combining both procedures has been rationalized as a means to provide patients the immediate improvement in extremity circumference and volume reduction conferred by LVA while also offering the long-term benefits of physiologic function restored by VLNT (Chang 2021). Ultimately, the final decision regarding the type of microsurgical procedure is based on a combination of lymphatic vessel viability and patient preference.

A better understanding of the long-term impact of various microsurgical interventions in the upper and lower extremities could have significant implications for shared decision-making between lymphedema patients and their physicians. Proper selection of those who could benefit from LVA, VLNT, or a combination of the two performed during the same operation could also be improved if physicians were better guided by reported differences in clinical improvement of extremity lymphedema and associated patient characteristics. Furthermore, accurately documented surgical details, such as the number of lymphaticovenous anastomoses and the type of vascularized lymph node flap associated with favorable clinical outcomes could provide clinicians with clarity in determining the appropriate technical approach.

The substantial increase in research within this field in recent years has resulted in the availability of new literature to assess (Nacchiero et al. 2020; Chang et al. 2021; Meuli et al. 2023). Through a systematic review and meta-analysis, this study aims to provide a comprehensive overview of published literature on the clinical improvement in extremity lymphedema and to quantify the pooled effect of circumference and volume changes among patients who undergo either LVA, VLNT, or a combined microsurgical procedure.

2 | Methods

2.1 | Literature Search

A systematic literature review of electronically available publications was performed on June 19, 2024. This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al. 2021), and was registered in the international prospective register of systematic reviews (PROSPERO) under the registration number: CRD42024469481. No amendments were made to the registered protocol during the course of this research. Two reviewers (B.H. and D.K.) performed a search in three online databases (Embase, PubMed, and Web of Science) using a search string developed with the help of a librarian (Supporting Information S1). All studies identified through the search were independently reviewed and included if patients with various etiologies of unilateral secondary lymphedema in the upper or lower extremity received either LVA, VLNT, or a combination of the two performed during the same operation. Only studies that reported clinical improvement in lymphedema, calculated as the percentage change in the pre- and postoperative difference in circumference or volume between affected and healthy extremities, were included. Studies investigating outcomes other than changes in circumference or volume differences in extremities were excluded, as were those that only investigated outcomes in patients treated for primary lymphedema. Articles that investigated outcomes in patients with both primary and secondary lymphedema were included, however, if less than 10% of the study population comprised those with primary lymphedema. Duplicates, conference abstracts, systematic reviews, meta-analyses, case reports, nonclinical studies, and non-English studies were further excluded.

2.2 | Data Extraction

The following variables were extracted from included articles into a standardized spreadsheet: title, authors, year of publication, country of origin, study design, extremity investigated, sample size, age, body mass index (BMI), sex distribution, comorbidities, severity of lymphedema and staging used, type of microsurgical intervention, number of lymphaticovenous

anastomoses or lymph nodes transferred, type and recipient site of VLNT, postoperative care and complications, follow-up period, data collection and lymphedema measurement methods, and clinical improvement in lymphedema. Two reviewers (B.H. and D.K.) independently performed data extraction from articles, figures, and tables. The accuracy of entered data, as well as any uncertainties or disagreements were resolved by a third reviewer.

2.3 | Quality Assessment

The Risk Of Bias In Nonrandomized Studies-of Intervention (ROBINS-I) (Sterne et al. 2016) tool and the Cochrane tool for assessing risk of bias in randomized trials (RoB 2) (Sterne et al. 2019) were used to assess the quality of included studies. Each of the seven domains of bias encompassed in the ROBINS-I tool was addressed using a series of signaling questions that aimed to gather important information about the risk of bias due to confounding, selection of study participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result. Similarly, the RoB 2 tool assessed the risk of bias arising from the randomization process, deviations from the intended intervention, missing outcome data, measurement of the outcome, and selection of the reported result. All domains were taken into consideration before an overall risk of bias judgment for each article was made. Studies were classified as having either a low, moderate, serious, or critical risk of bias. Risk of bias was visualized using the Risk-of-bias VISualization (robvis) tool (McGuinness and Higgins 2021).

2.4 | Statistical Analysis

Random-effects meta-analyses of means were performed on all included studies to quantify the pooled effect of microsurgical interventions on clinical improvement of extremity lymphedema, the primary outcome of interest. Analyses were conducted separately for patients with UEL and LEL, ensuring each study contributed only one effect size even if patient populations in which either extremity was affected were investigated. The restricted maximum likelihood estimator (Viechtbauer et al. 2015) was used to calculate the heterogeneity of variance between studies before employing forest plots to visualize the distribution. Subgroup analyses were performed to investigate secondary outcomes—potential moderators of the overall observed effect size between studies. Studies were pooled into subgroups according to participants' age, BMI, preoperative lymphedema severity, number of lymphaticovenous anastomoses, type of VLNT, follow-up period, edema measurement methods, and study risk of bias. Studies that did not report data for certain variables of interest were excluded from corresponding subgroup analyses. A Q-test was used to determine if clinical improvement of extremity lymphedema differed significantly between various subgroups. All statistical analyses were performed using the meta package (Balduzzi et al. 2019) in R Statistical Software (v4.3.1; R Core Team 2023) (R Core Team 2024). A two-sided $p < 0.05$ was considered significant. The dataset and script used to perform analyses are available at: https://osf.io/nk3sp/?view_only=4478a9a7a16546a5937459cec96f4ee6.

3 | Results

3.1 | Study Characteristics

After removal of duplicates, a total of 2047 original articles were identified in PubMed, Embase, and Web of Science databases. Following initial title/abstract screening, 186 articles underwent full-text review, and 52 articles were included that met all inclusion and exclusion criteria (Agko et al. 2018; Aljaaly et al. 2019; Arrivé et al. 2017; Chung et al. 2022; Ciudad et al. 2017, 2019; Ciudad, Manrique, et al. 2020; Cornelissen et al. 2017; Demiri et al. 2024; Di Taranto et al. 2023; Dionyssiou et al. 2016, 2021; Drobot et al. 2021; Engel et al. 2018; Francis et al. 2022; Furukawa et al. 2011; Fuse et al. 2022; Gennaro et al. 2016; Gharb et al. 2011; Gustafsson et al. 2018; Ho et al. 2018; Jonis et al. 2024; Kim et al. 2021; Knoz et al. 2024; Koshima et al. 2000; Liang et al. 2023; Lin et al. 2009; Liu et al. 2018; Lo Torto et al. 2024; Manrique et al. 2020; Maruccia et al. 2019, 2023; Mousavi et al. 2020; Myung et al. 2023; Ngo et al. 2020; Phillips et al. 2019; Poumellec et al. 2017; Roh et al. 2023; Saaristo et al. 2012; Schaverien et al. 2022; Son et al. 2023; Thomas et al. 2023; Winters et al. 2017, 2019; Yang et al. 2020; Yang, Wu, et al. 2022; Yang, Wang, et al. 2022; Yasunaga et al. 2019, 2020, 2022, 2023). The search string and review methodology are described in the PRISMA flow diagram in Figure 1. Of the 52 articles included, 10 contributed multiple observed effect sizes; nine articles reported outcomes for patient populations who received microsurgery for either UEL or LEL (Agko et al. 2018; Ciudad et al. 2017, 2019; Drobot et al. 2021; Gennaro et al. 2016; Kim et al. 2021; Manrique et al. 2020; Maruccia et al. 2023; Thomas et al. 2023), and one article reported outcomes on two different types of microsurgical reconstructions (Engel et al. 2018).

All included articles were published between 2000 and 2024, and comprised 25 retrospective, 23 prospective, two cross-sectional studies, and two randomized controlled trials across 15 different countries. Clinical outcomes in a total of 1920 extremities were analyzed from 1920 patients who received microsurgical reconstruction (Table S1). Reported mean patient age and BMI ranged from 45 to 71 years old and 22.5 to 33.2 kg/m^2, respectively. Of the 1073 extremities that contributed to effect sizes in clinical improvement of UEL, 528 underwent LVA, 496 underwent VLNT, and 49 received a combination of the two procedures. Likewise, of the 847 extremities that contributed to effect sizes in clinical improvement of LEL, 775 underwent LVA, and 72 underwent VLNT. No studies were included in which patients with LEL underwent a combination of the two microsurgical procedures.

While most of the included studies reported staging of extremity lymphedema prior to surgical intervention, various classifications were used. Lymphedema severity was described according to the International Society of Lymphology (ISL) in 35 studies (Agko et al. 2018; Chung et al. 2022; Ciudad et al. 2017, 2019; Ciudad, Forte, et al. 2020; Cornelissen et al. 2017; Di Taranto et al. 2023; Dionyssiou et al. 2016, 2021; Drobot et al. 2021; Fuse et al. 2022; Gennaro et al. 2016; Gharb et al. 2011; Liu et al. 2018; Manrique et al. 2020; Maruccia et al. 2019, 2023; Myung et al. 2023; Ngo et al. 2020; Phillips et al. 2019; Roh et al. 2023; Thomas et al. 2023; Yang et al. 2020; Yang, Wu, et al. 2022; Yang, Wang, et al. 2022; Yang, Hayashi et al. 2022; Yasunaga

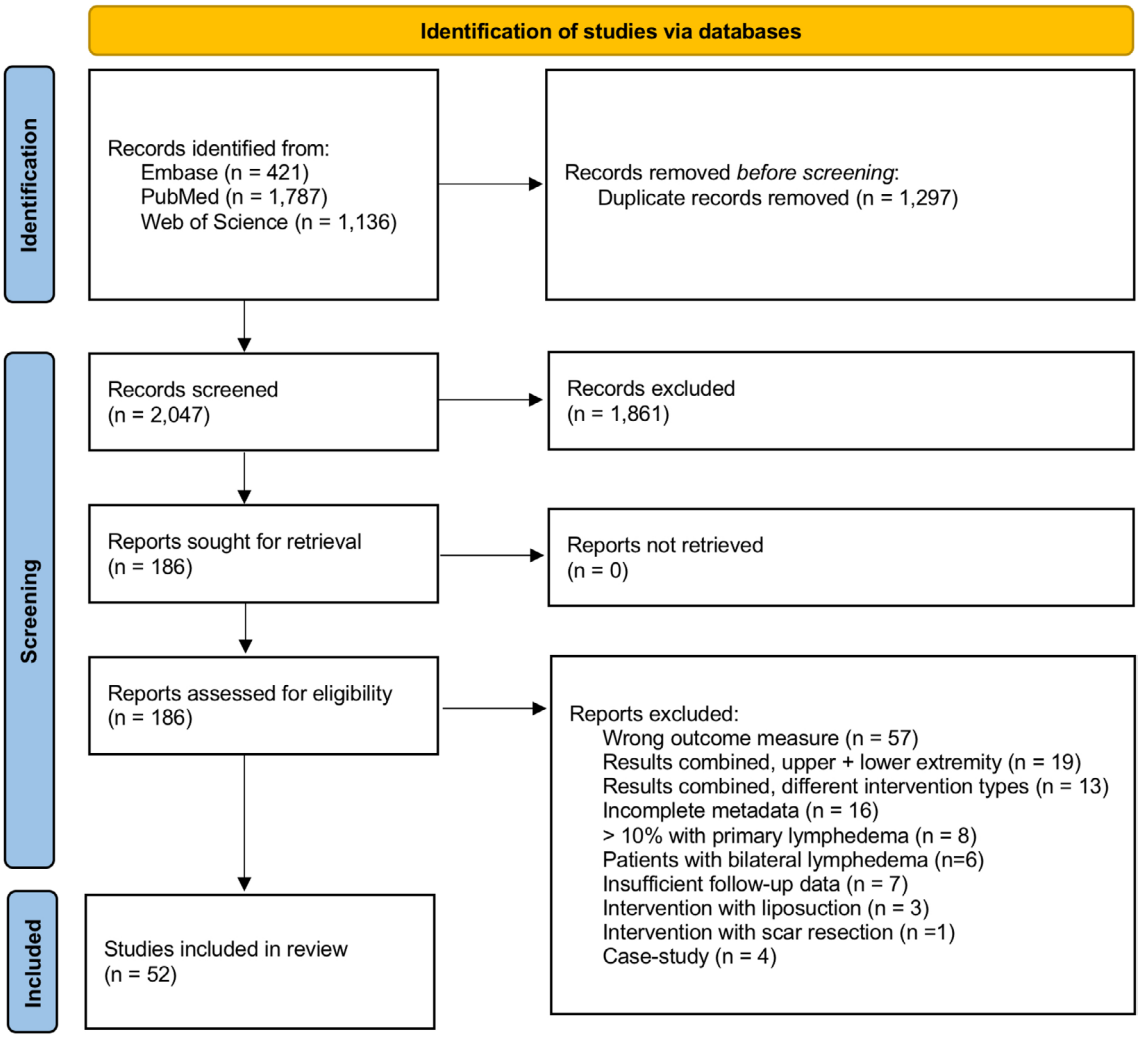

FIGURE 1 | Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of systematic database search.

et al. 2019, 2020, 2022, 2023), Cheng Lymphedema Grade in three studies (Aljaaly et al. 2019; Engel et al. 2018; Francis et al. 2022), Campisi in two studies (Poumellec et al. 2017; Winters et al. 2019), and the M.D. Anderson Cancer Center in one study (Schaverien et al. 2022). Eleven studies did not report preoperative lymphedema severity (Arrivé et al. 2017; Furukawa et al. 2011; Gustafsson et al. 2018; Ho et al. 2018; Kim et al. 2021; Koshima et al. 2000; Lin et al. 2009; Mousavi et al. 2020; Saaristo et al. 2012; Son et al. 2023; Winters et al. 2017). Studies that employed the ISL classification were pooled into groups according to the predominant preoperative lymphedema severity of participants. Effect sizes for patients with UEL were reported in 17 studies in which 50% or more of the population had preoperative ISL Stage II, in two studies with populations primarily in ISL Stages II–III, and in six studies with populations primarily in ISL Stage III. For patients with LEL, effect sizes were reported in eight studies where 50% or more of the population had preoperative ISL Stage II, in seven studies with populations primarily in ISL Stages II–III, and in three studies with populations primarily in ISL Stage III.

Among the studies in which the number of anastomoses performed during LVA was reported, a mean of 3.39 and 4.50 was calculated in patients who received treatment for UEL and LEL, respectively. Studies investigating the effects of VLNT for UEL included donor lymph nodes harvested from the groin ($n = 9$), gastroepiploic ($n = 8$), submental ($n = 1$), jejunal mesenteric ($n = 1$), and a mix of flap types ($n = 5$). Analogously, studies investigating the effects of VLNT for UEL included donor lymph nodes harvested from gastroepiploic ($n = 5$) and submental ($n = 1$) flap types.

The majority of studies outlined care protocols that patients were recommended to follow after surgery, which included either compression therapy ($n = 28$), manual drainage ($n = 8$), or both ($n = 1$). Four studies implemented a restrictive postoperative protocol, in which patients were explicitly instructed to refrain from any compression or physical therapy in the months after surgery. One study allowed patients to adhere to whichever care protocol they were following prior to surgery, and 10 studies did not report any specific postoperative care instructions. Most studies reported outcomes with a follow-up period ≥ 12 months ($n = 39$). Quality assessment of each nonrandomized intervention study using the ROBINS-I tool identified one study with serious risk of bias, nine with moderate risk, and 40 studies with low risk (Figure S1A). The two randomized controlled trials included were assessed as having a low risk of bias using the RoB 2 tool (Figure S1B).

3.2 | Clinical Improvement Extremity Lymphedema

The clinical improvement of lymphedema was determined based on the rate of postoperative circumference or volume reduction in the affected extremity. Circumference of affected and healthy extremities was recorded in 26 studies, while volume was recorded in 26 studies to compare preoperative and postoperative findings. Percentage clinical improvement of extremity lymphedema was defined as the difference between preoperative circumference or volume of the affected and healthy extremities minus the difference between the postoperative measurements of the affected and healthy extremities, divided by the preoperative difference and multiplied by 100. The pooled mean clinical improvement in UEL was 36.46% (95% CI: 29.44–43.48), with a high degree of heterogeneity between studies ($I^2 = 100\%$, $p < 0.001$) attributed in part to differences in outcomes observed by microsurgery type ($p = 0.17$) (Figure 2). A clinical improvement of 29.44% (95% CI: 15.58–43.29) was observed in upper extremities following LVA, 41.66% (95% CI: 34.13–49.20) following VLNT, and 32.80% (95% CI: 21.96–43.64) in the single study that investigated UEL outcomes following a combined VLNT + LVA surgical approach. Similarly, the pooled mean clinical improvement in LEL was 34.16% (95% CI: 23.93–44.40), with a high degree of heterogeneity between studies ($I^2 = 100\%$, $p < 0.001$) also attributed in part to differences in outcomes observed by microsurgery type ($p = 0.59$) (Figure 3). A clinical improvement of 31.87% (95% CI: 18.60–45.14) was observed in lower extremities following LVA, and 39.53% (95% CI: 19.37–59.69) following VLNT.

Subgroup analysis revealed no significant differences in clinical improvement of either UEL or LEL based on patient characteristics, such as mean age, BMI, or preoperative lymphedema severity (Table 1). Among patients with LEL who underwent VLNT, clinical improvement was significantly different according to the donor flap type used during surgery. Lower extremities that received donor flaps containing gastroepiploic lymph nodes had a pooled mean clinical improvement of 43.48% (20.43–66.52), while those that contained submental lymph nodes improved by 19.80% (95% CI: 16.75–22.85) ($p = 0.005$). The postoperative care protocols that patients undergoing treatment for LEL followed also had a significant impact on outcomes. Clinical improvement of LEL reported by studies that outlined a postoperative compression therapy protocol for patients to follow was 34.23% (95% CI: 21.13–47.33), while the study that implemented a restrictive protocol prohibiting patients from actively receiving therapy reported a 19.80% (95% CI: 16.75–22.85) reduction in lymphedema ($p < 0.0001$). The single study without any postoperative standard protocol, in which patients could adhere to the same care they were receiving preoperatively, reported LEL clinical improvement of 46.30% (95% CI: 43.21–49.39). No further statistically significant differences were found between subgroups pooled by the number of lymphaticovenous anastomoses, follow-up period, and edema measurement methods. Statistical significance seen between risk of bias subgroups in patients with UEL did not hold when the single study with serious risk of bias was eliminated from subgroup analysis.

4 | Discussion

This systematic review aimed to provide a comprehensive overview of published literature on the clinical improvement of extremity lymphedema in patients who undergo either LVA, VLNT, or a combined microsurgical procedure. Meta-analyses were designed to further elucidate factors associated with clinical improvement in order to better understand which patients stand to benefit the most from microsurgery. The pooled mean clinical improvement in UEL and LEL was 36.46% (95% CI: 29.44–43.48) and 34.16% (95% CI: 23.93–44.40), respectively. Heterogeneity between studies was attributed in part to differences in outcomes observed by microsurgery type. A clinical improvement of 29.44% (95% CI: 15.58–43.29) was observed in upper extremities following LVA, 41.66% (95% CI: 34.13–49.20) following VLNT, and 32.80% (95% CI: 21.96–43.64) in the single study that investigated UEL outcomes following a combined VLNT + LVA surgical approach. Similarly, clinical improvement of 31.87% (95% CI: 18.60–45.14) was observed in lower extremities following LVA and 39.53% (95% CI: 19.37–59.69) following VLNT. Subgroup analyses revealed no significant differences in clinical improvement of either UEL or LEL based on patient characteristics such as mean age, BMI, or preoperative lymphedema severity. Significant differences in the type of donor flap used in VLNT, as well as the postoperative care protocol followed by patients, were noted. While there was a high degree of heterogeneity between studies regardless of the affected extremity, no statistically significant differences were found in clinical improvement between subgroups pooled by the number of anastomoses performed during LVA, length of follow-up period, and type of edema measurement method used.

4.1 | Differences in Clinical Outcomes by Microsurgical Procedure

For both upper and lower extremities, clinical improvement of lymphedema was greater following VLNT compared to LVA. Although the detailed mechanism by which VLNT alleviates lymphedema remains incompletely understood, recent literature increasingly supports lymphangiogenesis mediated by vascular endothelial growth factor C (VEGF-C) (Alitalo 2011; Nguyen et al. 2017; Cook et al. 2018). When applied in therapeutic settings, VEGF-C has been shown to induce lymphatic capillary growth, which ultimately leads to the differentiation and maturation of functional lymphatic vessels (Alitalo 2011). Using northern blot analysis, Saaristo et al. (Saaristo et al. 2012). compared VEGF-C expression in lymph nodes with other tissue in nine patients who received VLNT for UEL. Results showed that the highest VEGF-C mRNA expression was detected in lymph nodes, further supporting the mechanism that VLNT and the resulting VEGF-C expression may thereby enhance regrowth of the lymphatic network in the transplanted region.

Subgroup analyses conducted on clinical improvement according to the type of donor flap used in VLNT further support this proposed mechanism. Gastroepiploic lymph nodes derived from omentum donor flaps contributed to a 44.27% clinical improvement in UEL and a 43.48% clinical improvement in LEL, the latter of which was statistically significant when compared

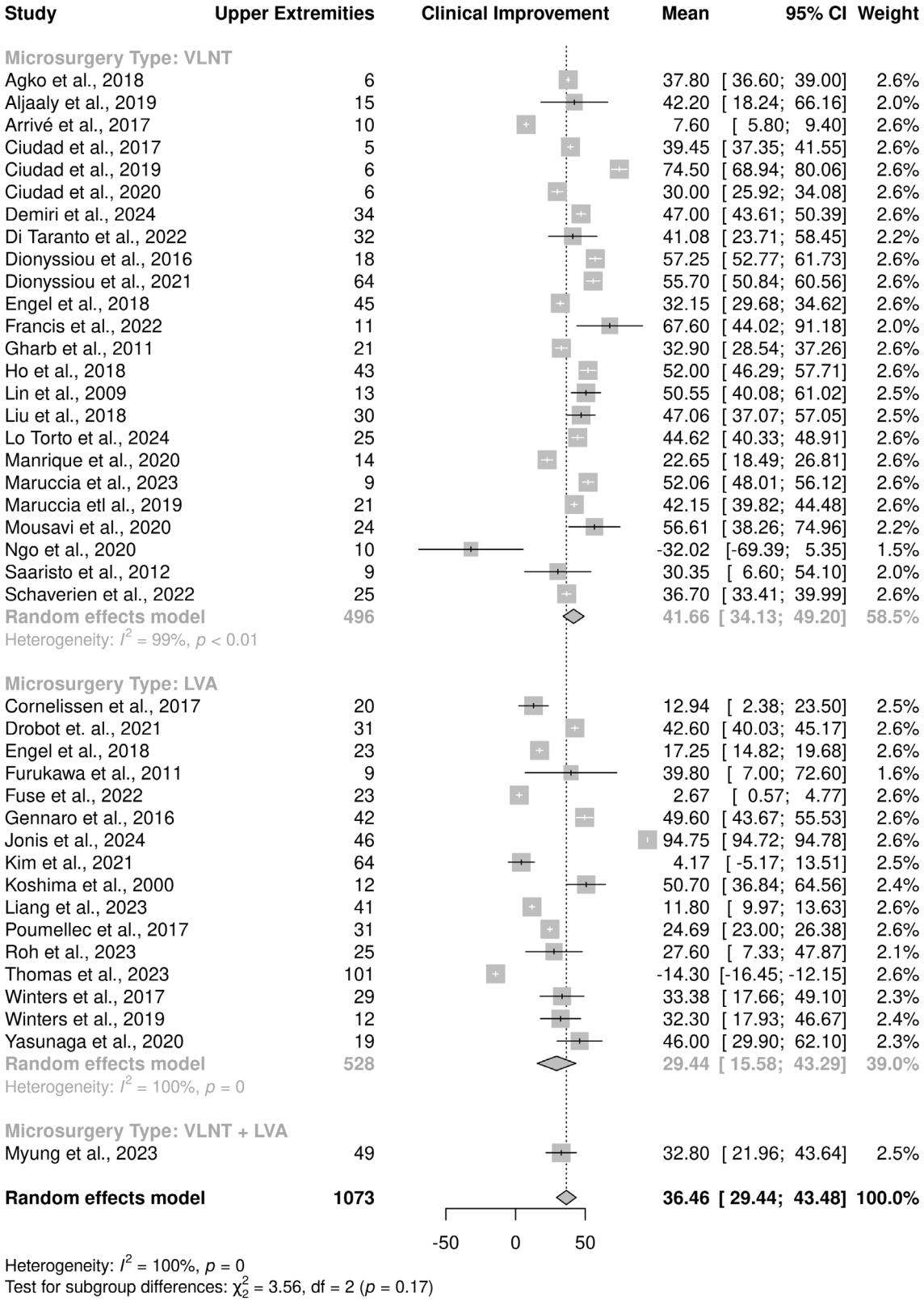

FIGURE 2 | Forest plot of clinical improvement of upper extremity lymphedema (UEL) according to microsurgery type.

with that of submental lymph nodes (19.80%). Not only does the omentum have the highest concentration of VEGF-C compared to that of other tissue, but it is also richly vascularized with an abundant network of lymph nodes (Nguyen et al. 2017; Cook et al. 2018).

Given the potential of VLNT to restore lymphatic vessel function even in cases in which existing vessels are sclerosed or fibrotic, the procedure has often been reserved for patients who present with more advanced stages of lymphedema (Chang et al. 2020). While not statistically significant, subgroup analyses revealed

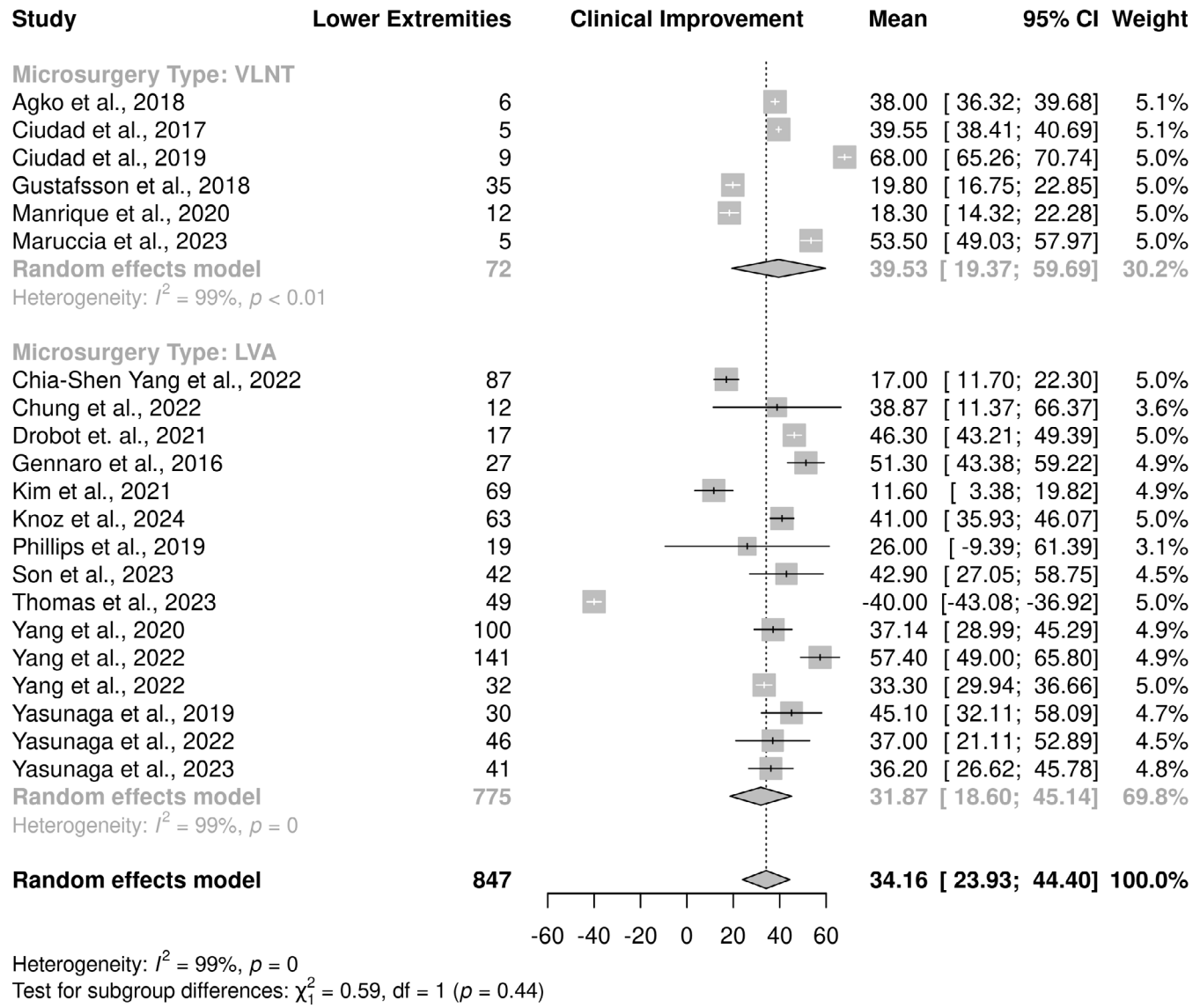

FIGURE 3 | Forest plot of clinical improvement of lower extremity lymphedema (LEL) according to microsurgery type.

that patients with more severe preoperative lymphedema, as determined by ISL stage, showed greater clinical improvement compared to those with lower severity. Not only was this observed in patients undergoing microsurgery for either UEL (32.51%, Stage II; 47.20%, Stage II–III; 45.26%, Stage III) or LEL (24.23%, Stage II; 40.71%, Stage II–III; 52.95%, Stage III), but it was also seen regardless of the type of microsurgery received. This meta-analysis reveals the potential clinical improvement in lymphedema for all patients undergoing LVA, regardless of preoperative severity.

4.2 | Describing Lymphedema Severity and Improvement

Lymphedema staging systems offer an objective paradigm through which the clinical presentation of symptoms can be assessed. The diverse range of classifications available to describe lymphedema severity, however, complicates their reliability in practice. While the majority of studies included in this literature review used the ISL staging system to characterize the severity of preoperative lymphedema, the Campisi staging system ($n = 2$), Cheng Lymphedema Grade ($n = 3$), and the M.D. Anderson Cancer Center staging system were also used ($n = 1$). Eleven studies did not report preoperative lymphedema severity in any of the extremities undergoing microsurgery. Each stage of the ISL system indicates the extent of swelling in the affected extremity, meant to reflect fibrotic soft tissue changes and lymphatic dysfunction (Executive Committee of the International Society of Lymphology 2020). Problematic with the ISL staging system, however, is its incongruence with functional staging that better incorporates the physiologic features of lymphedema. Imaging modalities, such as indocyanine green (ICG) lymphangiography or lymphoscintigraphy, have the ability to scan the layers of the collecting lymphatic channels and visualize lymphatic flow (Imai et al. 2022). Previous studies have demonstrated a weak correlation between ISL and functional imaging staging (Garza et al. 2019), further undermining the sole reliance on ISL for preoperative microsurgical decision-making. The possibility of patients with high ISL staging also having low ICG staging enhances the feasibility of performing LVA due to the potential availability of suitable target vessels.

TABLE 1 | Subgroup analyses.

Extremity	Variable	Subgroup	*N* studies	Mean clinical improvement (%)	95% CI	I^2 (%)	*p* subgroup
Upper	Study design	Randomized control	2	76.07	−162.17 to 314.31	99.6	0.1131
		Cross-sectional	2	43.44	−133.62 to 220.51	85.7	
		Prospective	19	36.09	25.44–46.74	99.3	
		Retrospective	18	31.18	21.92–40.43	98.8	
	Age	> 65 years	2	47.13	−206.93 to 301.18	84.3	0.5839
		< 65 years	39	36.01	28.80–43.21	99.9	
	BMI	Normal (< 30)	28	37.82	29.19–46.46	100.0	0.2680
		Obese (≥ 30)	3	24.10	−26.04 to 74.24	97.7	
	ISL stage, preoperative[a]	Stage II	17	32.51	17.76–47.25	100	0.2044
		Stage II–III	2	47.20	−12.91 to 107.31	93.3	
		Stage III	6	45.26	28.38–62.14	97.2	
	Number of anastomoses, LVA[b]	High	6	36.74	20.10–53.40	98.9	0.9599
		Low	6	37.48	3.47–71.49	99.3	
	Donor flap, VLNT	Gastroepiploic	8	44.27	30.61–57.92	97.6	0.6886
		Submental	1	42.20	18.24–66.16	—	
		Groin	9	41.29	28.93–53.66	99.1	
		Jejunal mesenteric	1	36.70	33.41–39.99	—	
		Mixed	5	35.19	−8.44 to 78.82	94.7	
	Compression, postoperative	Restrictive	3	44.50	−28.12 to 117.11	92.8	0.6559
		No standard of care	1	42.60	40.03–45.17	—	
		Manual drainage	9	38.80	29.55–48.04	97.7	
		Compression	18	36.49	23.02–49.95	99.9	
	Follow-up	≥ 12 months	31	38.40	30.74–46.07	99.1	0.5906
		< 12 months	9	33.34	13.42–53.25	100.0	
	Measurement method	Circumference	25	36.97	29.16–44.78	99.0	0.7962
		Volume	16	34.93	20.19–49.67	99.9	
	Risk of bias	Low	33	36.92	28.59–45.24	99.9	< 0.0001*
		Moderate	7	38.12	24.35–51.89	97.9	
		Serious	1	7.60	5.80–9.40	—	

(Continues)

TABLE 1 | (Continued)

Extremity	Variable	Subgroup	*N* studies	Mean clinical improvement (%)	95% CI	I^2 (%)	*p* subgroup
Lower	Study design	Prospective	9	32.60	8.52–56.68	99.7	0.8275
		Retrospective	12	35.04	26.19–43.89	95.2	
	Age	> 65 years	2	39.82	−42.77 to 122.40	96.8	0.4578
		< 65 years	19	33.54	22.20–44.89	99.4	
	ISL stage, preoperative[a]	Stage II	8	24.23	0.42–48.05	99.6	0.0896
		Stage II–III	7	40.71	28.20–53.22	96.1	
		Stage III	3	52.95	17.04–88.86	99.4	
	Number of anastomoses, LVA[b]	High	6	39.27	24.36–54.18	94.7	0.7042
		Low	7	36.41	24.65–48.17	90.3	
	Donor flap, VLNT	Gastroepiploic	5	43.48	20.43–66.52	99.3	0.0051*
		Submental	1	19.80	16.75–22.85	—	
	Compression, postoperative	No standard of care	1	46.30	43.21–49.39	—	< 0.0001*
		Compression	15	34.23	21.13–47.33	99.4	
		Restrictive	1	19.80	16.75–22.85	—	
	Follow-up	≥ 12 months	13	35.31	18.98–51.64	99.6	0.7352
		< 12 months	8	32.35	21.63–43.06	95.6	
	Measurement method	Circumference	7	40.31	21.75–58.87	99.1	0.3512
		Volume	14	31.10	17.41–44.78	99.5	
	Risk of bias	Low	19	33.90	22.68–45.11	99.5	0.2737
		Moderate	2	42.83	−35.67 to 121.34	0.0	

Note: Studies pooled according to study design, age, BMI, preoperative lymphedema severity, number of anastomoses performed during LVA, donor flap type used during VLNT, postoperative compression protocol, follow-up period, method by which lymphedema was measured, and study risk of bias.
Abbreviations: BMI, body mass index; ISL, International Society of Lymphology; LVA, lymphaticovenous anastomosis; VLNT, vascularized lymph node transfer.
*$p < 0.05$.
[a]Preoperative ISL stage of ≥ 50% of study population.
[b]Mean number of lymphaticovenous anastomoses performed pooled and split into above average ("high") or below average ("low").

More importantly, perhaps, is the limited ability of lymphedema severity staging and imaging to determine and describe patient-reported outcomes following surgery. Studies in this review that reported extremities without any confirmed patent anastomoses or postoperative changes in clinical lymphedema, nevertheless reported improvement in quality of life measures and patients' responsiveness to conservative lymphedema management (Ngo et al. 2020; Thomas et al. 2023; Winters et al. 2017, 2019). Even in the absence of clinical improvement of lymphedema following microsurgery, patients reported either reduced use of compression garments or no longer felt the need to wear them after experiencing attenuation of their complaints. A better understanding of the psychological, physical, and social implications that compression garments have on quality of life is needed. Describing the improvement of lymphedema in relation to the lived experiences of patients burdened by it and its management is imperative to measuring the impact of microsurgical interventions.

4.3 | Strengths and Limitations

While the retrospective nature of the majority of studies included in this review enabled the analysis of large sample sizes across a wide timespan, it also proved to be a significant limitation. The quality and completeness of data recorded for each study participant was heterogeneous. Some studies did not report the BMI of participants, which could have further elucidated the impact of obesity on the clinical improvement of extremity lymphedema following microsurgery. Obesity has been associated with increased chronic inflammation, fibrosis, and adipose deposition that may impair lymphatic clearance. Furthermore, the increased propensity for inflammation in response to injury suggests that obese patients are at higher risk for lymphedema following lymph node dissection (Savetsky et al. 2014; Beesley et al. 2007). While most studies included in this review detailed postoperative care received by patients, such as compression therapy or manual lymphatic

drainage, preoperative interventions were not thoroughly documented. Although available literature on the efficacy of conservative interventions prior to microsurgery remains limited, recent consensus advocates for adequate prehabilitation that could optimize clinical outcomes (Doubblestein et al. 2023; Sacks et al. 2024). The inconsistencies in preoperative data, however, further widen the knowledge gap on which protocols have the potential to enhance response to surgery. Incomplete data on the number of anastomoses created during LVA, as well as the type of and lymph node count within VLNT donor flaps, make it difficult to draw any definitive conclusions on surgical technique. Studies with a moderate or serious risk of bias were evaluated as such with the ROBINS-I tool when complete metadata were not available for all participants who underwent microsurgery, which could have contributed to confounding in reported results. In order to produce the most accurate estimation of clinical improvement in extremity lymphedema, studies should strive to report comprehensive patient and surgical characteristics that could further elucidate any potential impact on outcomes.

This systematic review and meta-analysis provides new insights into the effectiveness of microsurgical options for treating extremity lymphedema. While older systematic reviews similar to this one reach congruent findings, they focus on qualitative outcomes and include fewer studies with quantitative effect sizes (Nacchiero et al. 2020; Chang et al. 2021; Meuli et al. 2023). Furthermore, this study has accounted for the variation in outcome measures rightfully pointed out by Meuli et al. (Meuli et al. 2023). By employing rigorous inclusion criteria and subsequently excluding studies that did not meet these standards. This systematic review and meta-analysis includes additional articles that have not yet been reported on elsewhere, further strengthening the novelty of findings in this study.

5 | Conclusion

The clinical improvement in patients with UEL and LEL following microsurgery is estimated to be 36% and 34%, respectively, with differences attributed in part to the type of microsurgical approach. While VLNT yielded greater improvement in lymphedema compared to LVA, further differences were observed between the type of donor flap used. More comprehensive metadata is needed to elucidate relationships between patient characteristics and outcomes following microsurgery. Furthermore, advances in quality of life may not always directly correspond with changes in extremity volume or circumference. Even in the absence of clinical improvement, patients' reduced reliance on compression therapy may be enough to justify the decision of undergoing microsurgery. Awareness among physicians of these impacts could serve as valuable discussion points to consider during the shared decision-making process with lymphedema patients.

Data Availability Statement

The data that support the findings of this study are openly available in Open Science Framework at https://osf.io/nk3sp/?view_only=4478a9a7a16546a5937459cec96f4ee6.

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Supporting Information

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scientific reports

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The 6 month interim analysis of a randomized controlled trial assessing the quality of life in patients with breast cancer related lymphedema undergoing lymphaticovenous anastomosis vs. conservative therapy

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Breast cancer related lymphedema (BCRL) is a chronic condition with a detrimental impact on psychosocial and physical well-being. Lymphaticovenous anastomosis has shown promising results in alleviating physical symptoms and increasing quality of life in patients with BCRL. The aim of the study is to evaluate the effect on health related quality of life (HrQol) after LVA surgery versus conservative treatment in patients with BCRL. The study is a prospective, multicenter randomized controlled trial. Adult women with unilateral BCRL, with early stage lymphedema and viable lymphatic vessels were included. The primary outcome measure was HrQol measured by the lymphedema functioning disability and health (Lymph-ICF) questionnaire. The secondary outcomes were volume difference measured by the water displacement method; the Upper Extremity Lymphedema (UEL) index; and daily use of the compression garments after 3 and 6 months. For this interim analysis 46 patients per group were included. There was a significant improvement in the domains in physical and mental function in the Lymph-ICF questionnaire in the LVA group after 6 months, (− 16.46 ± 18.5, $p < 0.05$, − 10.12 ± 29.5, $p < 0.05$ respectively). However, there was no statistical difference in the total score of the Lymph-ICF after 6 months in both groups (LVA-group; − 8.57 ± 22.6, $p > 0.05$, CDT-group; − 2.65 ± 18.2, $p < 0.05$). Furthermore, there was no significant volume reduction in both groups (LVA-group: 20.04 ± 196.40, $p = 0.497$, CDT: 33.98 ± 189.87, $p = 0.236$). In the LVA group, 41% partially of completely stopped wearing the compression garments after six months whereas in the CDT group 0% discontinued to use of compression garments. LVA resulted in improvement of the domains physical and mental function of the Lymph-ICF. Limb volume did not significantly improve after 6 months. However, around 42% could completely or partially stopped with the use of compression garments in the LVA group. The current results are promising, however longer follow up is required to assess long term effect of LVA for secondary lymphedema.

Clinical Trial Registration: NCT02790021 registered on 03/06/2016

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Abbreviations

AE	Adverse events
BCRL	Breast cancer related lymphedema
BMI	Body mass index
CDT	Complex decongestive therapy
CI	Confidence interval
HrQoL	Health related quality of life
ICG	Indocyanine green
ISL	International society of lymphology
LVA	Lymphaticovenous anastomosis
Lymph-ICF	Lymphedema functioning, disability and health questionnaire
MLD	Manual lymphatic drainage
NIRF	Near infrared fluoroscopy
RCT	Randomized controlled trial
SAE	Severe adverse events
UEL-index	Upper extremity lymphedema index
VAS	Visual analogue score
WDM	Water displacement method

Breast cancer related lymphedema (BCRL) is a chronic condition, characterized by an aberrant accumulation of lymph fluid due to dysfunction of the lymphatic system[1–3]. It is a well-known consequence of breast cancer treatment and it represents an important survivorship topic in patients after breast cancer[4–7].

BCRL affects approximately 29.4% of breast cancer survivors within 2 years after surgery[1,7]. Axillary lymph node dissection, radiotherapy, mastectomy, number of positive lymph nodes and body mass are all independent risk factors for the development of BCRL[6,8,9].

Nowadays, Health related quality of life (HrQol) is one of the most relevant outcomes after cancer treatment[10,11]. BCRL is known to have a significant negative impact on physical, psychological, and social well-being[5]. Physical morbidities include skin infections, altered sensation, pain, decreased range of motion, strength, and function. In addition, a larger arm sizes requires women to alter daily activities, clothing, sleeping, employment, and sport. Symptoms of anxiety, depression, sexual dysfunction, disturbance of body image, and social avoidance are often associated with BCRL[12–14].

Currently, complex decongestive therapy (CDT) is the gold standard for the treatment of lymphedema, consisting of the use of compression garments and manual lymphatic drainage[5,15]. These treatment modalities however are not curative and require lifelong costly maintenance[16].

The first lymphaticovenous anastomosis (LVA) was described in the 1960 as a novel approach to divert lymphatic fluid through formation of an anastomosis from the lymphatic vessels to adjacent venules[17,18]. The concept was revolutionized by Koshima et al. in the 90 s who introduced the concept of supermicrosurgery in lymphatic surgery[19]. Since then the technique has been refined with the introduction of the microscope and designated supermicrosurgical instruments. LVA surgery has been widely implemented as a surgical treatment of lymphedema and it has shown promising results[20–22]. The aim of this 6-month interim analysis is to show the first results of the first randomized controlled trial (RCT) evaluating HrQol in patients with BCRL undergoing LVA surgery in comparison to conservative treatment.

Methods

From 2018 to 2022, 100 women with BCRL, with stage 1 or 2a, according to the international society of lymphology (ISL) with viable lymphatic vessels and ICG stage II–III according to Narushima measured by near infrared fluoroscopy (NIRF) were included[23,24]. The patients were allocated into two groups, an LVA group and CDT group. The full protocol for the trial has been previously published[25]. The protocol and related documents were approved by the Dutch Medical ethical assessment committee (NL67059.068.18/ METC18-024) registered on 19/12/2018. Clinical Trial Registration: NCT02790021 registered on 03/06/2016. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Design

The trial was an multi-center randomized controlled trial (RCT). Patients were included in the Maastricht University Medical Center + , Radboud University Medical Center, Zuyderland Medical Centre and the Canisius-Wilhelmina Hospital in the Netherlands. All eligible patients were invited to participate in the RCT. Written informed consent was obtained from all participants.

Randomization

Surgeon investigators (S.S.Q, H.T, D.U) determined whether the patients were eligible for surgery. The collection of outcomes was performed at the outpatient clinic (J.W, S.H and Y.J). After inclusion and informed consent, participants were randomly assigned to either the LVA or conservative (CDT) group with a 1:1 allocation as per a computer-generated randomization schedule stratified by site using block randomization. This computer-generated randomization was done within the electronic Case Report Form in CASTOR EDC.

Interventions

CDT

All patients in both groups underwent at least 3 months of CDT prior to inclusion. The patients allocated in the CDT group continued to be treated according to standard protocol known as the 'Verdonkmethod' which is implemented in all patients receiving CDT in the Netherlands[25]. The CDT consisted of two stages, the first phase entailed skincare, MLD, exercises aimed at improvement of mobility/range of motion, and compression therapy. The second phase was focused on maintenance of the achieved limb volume reduction through compression therapy with therapeutic elastic compression garment for the arm. Skincare, mobility exercises and MLD is continued in this phase if needed.

Using this standardized protocol we were able to compare the outcomes within the CDT group. The conservative treatment and the frequency is controlled by the skin therapist. During follow up all changes in conservative therapy were noted by each patient in the patient diary.

LVA

The eligibility for participation in the study was determined with near infrared fluorescence imaging (NIRF) during the outpatient clinic. 0.01 to 0.04 ml of indocyanine green (ICG) (5 mg/ml) was injected into the second and fourth finger webspace intradermally of the lymphedematous limb. Using NIRF the viable lymph vessels were identified, marked, and photographed[23].

The procedure was performed under general or local anesthesia. This was left at the surgeon's discretion. During surgery viable lymphatic collecting vessel and similarly sized adjacent recipient venules were identified in the subdermal plane. Subsequently an anastomosis was performed in an end-to-end fashion with 11–0 suture between the lymphatic collecting vessel and the venule, with the use of a surgical microscope. After the anastomosis was made, the patency was confirmed under the microscope. Between 1 and 5 anastomosis were performed in a lymphedematous arm. The superficial wound was closed using 4–0 Ethilon covered by adhesive plasters.

Two weeks after the surgery the patients were able to continue in the maintenance phase of the CDT protocol.

Outcomes variables

All data was collected according to a standardized protocol. The primary outcome was HrQoL, which was measured by the lymphedema international classification of functioning (Lymph-ICF) questionnaire (Dutch version)[26]. The Lymph-ICF is a validated quality of life questionnaire for patients with upper extremity lymphedema. The questionnaire is divided into five domains: physical function, mental function, household, mobility, life and social activities. A low score on the questionnaire indicates a better quality of life and a higher score indicates of a bad quality of life. A decrease in the sum of scores of more than 10 points, and an increase of more than 9, was considered statistically significant ($p < 0.05$). A decrease in the sum of scores of more than 15 points was considered clinically significant[27].

The secondary outcomes were volume reduction, measured by the water displacement method, circumference reduction measured by the upper extremity lymphedema (UEL) index, the complete or partial discontinuation rate of the use of compression garments, reported through a patient diary. Lastly adverse-, and serious adverse events were reported during follow up[28,29]. The data was collected after 3, 6, 12, 18 and 24 month follow up. The data used for the current article are based on the first six months follow up.

Statistical analysis

We made the following assumptions for the calculation of the sample size to show a statistically significant and clinically relevant difference in quality of life between treatment groups follow-up as measured with the Lymph-ICF questionnaire:

Comparing LVA group to CDT group, the minimal difference in HRQoL that is considered as clinically relevant is 15 points on the Lymph-ICF questionnaire.

To be able to achieve a power of 80%, a total of 45 patients are needed per treatment group, when the SD is 25%, using an alpha of 0.05. If a drop-out rate (loss-to-follow-up and patients with missing data) of 25% is taken into account, a sample size of 60 patients per study group is required and a total of 120 patients will be randomized. Due to the COVID pandemic outpatient clinic at hospitals in the Netherlands were cancelled and there was a lower inclusion rate. In concordance with the ethical committee an amendment was approved to reduce the sample size to 100 patients considering the low dropout rate ($n = 1$).

Continuous variables were reported as mean with standard deviation. Categorical data were reported as frequencies. To examine the effect of LVA, the paired-samples t-test was used to evaluate the changes between baseline, 3 and 6 months within the groups for the Lymph ICF questionnaire, the relative volume difference measured by water displacement and the UEL index. To measure the effect of the LVA between groups the independent-samples t-test was performed for the above-mentioned variables.

Furthermore, a linear regression was used to determine the relationship between the number of LVAs, follow-up months, lymphedema onset, BMI and ICG stage and for the HrQoL and volume reduction (measured by volume displacement). Results were expressed as regression coefficient with a 95% confidence interval (CI). The use of compression garments, adverse and serious adverse events were reported as frequency. All analysis were performed with IBM SPSS version 25 (IBM Corp., Armonk, N.Y).

Ethical approval

The study was carried out in accordance to the declaration of Helsinki. The study was approved by the Ethics Committee of Maastricht University Medical Center on 19 December 2018 (NL67059.068.18/ METC18-024). Written consent has been obtained from all participants.

Results

One hundred consecutive patients with unilateral BCRL were eligible for inclusion. Ninety-two patients finished at least 6 months follow up and were included in the interim analysis. The other eight patients had not finished the 6 month follow up. The patient characteristics are listed in Table 1. Ninety patients had stage 2a lymphedema according to the ISL classification. Eighty-five patients had an ICG stage III lymphedema. After 6 months one patient in the CDT group had discontinued follow up.

Primary outcome

HrQoL

In the LVA group the mean difference in the total score of the Lymph ICF between baseline and follow up after three and six months was 8.93 ± 22.71 ($p > 0.05$) and 8.57 ± 22.56 ($p > 0.05$), respectively. For the domains physical function and mental function a decrease of more than 10 points was observed after 3 and 6 months, representing

	LVA group	CDT group
Number of patients	46	46
BMI (kg/m^2) ± SD	26 ± 3.55	27 ± 5.11
Lymphedema onset (months)* ± SD	78 ± 69	81 ± 67
Affected arm (no., %)		
Left arm	26 (56)	27 (58)
Right arm	20 (44)	19 (41)
ISL stage (no.)	I: 0	I: 2
	II: 46	II: 44
ICG stage (no., %)	I: 0	I: 0
	II: 5 (11)	II: 11 (23)
	III: 40 (87)	III: 35 (77)
Smoking (no., %)	2 (4)	1 (2)
Erysipelas preoperative (no., %)	13 (27)	17 (36)
Breast cancer treatment		
Radiotherapy (no., %)	41 (90)	42 (89)
Radiotherapy in the armpit (no., %)	24 (52.2)	21 (44.7)
Sentinel node procedure (no., %)	40 (89)	40 (89)
Axillary lymph node dissection (no., %)	43 (95)	41 (89)
Chemotherapy (no., %)	42 (91)	44 (96)
Hormone therapy (no., %)	33 (72)	32 (69)
Complications (no., %)	14 (30)	11 (24)
LVA number of anastomoses		
1–2 anastomosis	26	
3–4 anastomosis	19	
5 anastomosis	1	
Water displacement		
Inter limb volume difference (mL)	381.76 ± 227.08	391.59 ± 320.20
UEL index		
Affected arm	118.61 ± 14.13	120.52 ± 17.54
Unaffected arm	103.62 ± 10.90	103.62 ± 9.57
Lymph-ICF		
Physical	46.46 ± 20.83	44.93 ± 24.72
Mental	34.08 ± 26.14	30.59 ± 28.38
Household	44.67 ± 25.71	56.20 ± 26.15
Mobility	42.96 ± 22.87	50.54 ± 20.80
Social	40.74 ± 23.09	48.37 ± 25.69
Total	41.99 ± 17.06	45.75 ± 18.89

Table 1. Demographic and baseline clinical characteristics. *Lymphedema onset: duration of lymphedema since first diagnosis.

a statistically significant improvement ($p < 0.05$). In the CDT group there was no difference observed in the total score of the Lymph-ICF between baseline and follow up. The mean difference in the total score of the Lymph-ICF was 4.57 ± 14.46 ($p > 0.05$) after 3 months and 2.65 ± 18.21 ($p > 0.05$) after 6 months. All data respecting HrQol is presented in Table 2.

When comparing the total score of the Lymph-ICF between the two groups a statistical difference was observed in physical function after 3 ($p = 0.006$) and 6 months ($p = 0.001$), presented in Table 3. No relationship between the total score of the Lymph-ICF and preoperative ICG stage, the amount of anastomosis, lymphedema onset, and BMI was found (see Table 4).

LVA group	0–3 months		0–6 months	
Lymph-ICF	Mean difference ± SD	95% CI	Mean difference ± SD	95% CI
Physical	− 15.24 ± 20.5*[a]	[− 9.16, − 21.33]	− 16.46 ± 18.5*[a]	[− 22.09, − 10.38]
Mental	− 10.10 ± 28.8*	[− 18.65, − 1.56]	− 10.12 ± 29.5*	[− 19.42, − 0.82]
Household	− 4.31 ± 32.4	[− 14.18, 5.54]	− 5.91 ± 32.1	[− 16.05, 4.22]
Mobility	− 5.19 ± 32.2	[− 14.76, 4.38]	− 5.42 ± 30.0	[− 14.88, 4.02]
Social	− 9.21 ± 43.3	[− 18.84, 0.74]	− 5.48 ± 37.2	[− 17.21, 6.24]
Total	− 8.93 ± 22.7	[− 15.68, 2.18]	− 8.57 ± 22.6	[− 15.69, 1.45]
CDT group				
Physical	− 4.93 ± 14.9	[− 9.45, 0.41]	− 0,56 ± 19,1	[− 6.45, 5.31]
Mental	− 3.06 ± 16.2	[− 7.99, 1,85]	− 5.52 ± 22.3	[− 12.38, 1.34]
Household	− 9.15 ± 30.1	[− 17.89, 0.75]	− 7.08 ± 32.0	[− 16.88, 2.77]
Mobility	− 2.27 ± 27.3	[− 10.58, 6.03]	− 2.47 ± 27.3	[− 10.66, 5.71]
Social	2.86 ± 33.0	[− 12.99, 7.28]	3.89 ± 33.3	[− 14.15, 6.36]
Total	− 4.57 ± 14.5	[− 8.98, 0.18]	− 2.65 ± 18.2	[− 8.26, 2.95]

Table 2. The mean difference in Lymph-ICF score between baseline, 3 and 6 months. The mean difference in the score of the Lymph-ICF is calculated using the Paired Samples *T*-Test. Values with * indicate a statistically significant difference ($p < 0.05$). [a]Indicates clinical significant difference. A negative value indicates an improvement in quality of life.

	0–3 months			0–6 months		
CDT vs. LVA	Mean difference	95% CI	P-value	Mean difference	95% CI	P-value
Physical	− 10.69*	[− 18.22, − 3.15]	0.006	− 13.77*	[− 21.84,5.69]	0.001
Mental	− 7.26	[− 17.04, 2.95]	0.146	− 4.06	[− 15.31, 7.19]	0.475
Household	4.64	[− 8.70, 17.98]	0.491	− 0.62	[− 14.71, 13.46]	0.930
Mobility	− 0.33	[− 12.18, 11.52]	0.956	− 4.07	[− 16.09, 7.93]	0.502
Social	− 3.92	[− 6.05, 8.10]	0.518	− 2.93	[− 17.49, 11.62]	0.690
Total	− 3.87	[− 11.74, 4.00]	0.332	− 5.92	[− 14.88, 3.04]	0.192

Table 3. The mean difference between groups after 3 and 6 months. The mean difference between groups is calculated using the Independent Samples *T*-Test. Values with * indicate a statistically significant difference ($p > 0.05$).

	Difference in Lymph-ICF score[a]		
Independent variable	B	95% CI	P
Constant	30.57	[− 148.9, 210.0]	0.732
Anastomosis (count)	− 13.12	[− 27.96, 1.69]	0.081
ICG stage	− 11.75	[− 57.45, 33.96]	0.606
Onset lymphedema	− 0.107	[− 0.317, 0.103]	0.309
BMI	2.39	[− 1.73, 6.53]	0.248

Table 4. Linear regression analysis: using the difference in the Lymph-ICF score as dependent variable. Unstandardized beta (B): Calculated using linear regression analysis. A negative value means a decrease in Lymph-ICF, representing an increase in Quality of Life. [a]Lymph-ICF score difference is calculated by subtracting the post-OR lymph-ICF score from the pre-OR lymph-ICF score.

Secondary outcomes

Volume reduction

The excess volume was measured by the difference in affected and non-affected arm. The absolute volume difference was 24.80 ± 179.93 mL (p = 0.398) after 3 months and 20.04 ± 196.40 mL (p = 0.497) after 6 months for the LVA group. For the CDT group, 13.88 ± 193.36 mL (p = 0.640) and 33.98 ± 189.87 mL (p = 0.236) after three months and six months, respectively. All data respecting volume measurements is presented in Table 5. There was no significant difference observed between the two groups, − 2.82 (p = 0.737) after 6 months.

Furthermore, there was no correlation between volume difference and preoperative ICG stage, the amount of anastomosis, lymphedema onset, and BMI (see Table 6).

Limb circumference

The mean absolute difference in UEL index for the LVA group 3.65 ± 7.24 (p = 0.002) after 3 months and 1.84 ± 14.6, (p = 0.497) after 6 months, for the CDT group the mean absolute difference was respectively 3.30 ± 31.57 (p = 0.521) and − 0.84 ± 14.6 (p = 0.189) after three and six months. The data is presented in Table 7. Furthermore, there is no significant difference in UEL index between the LVA and CDT group, 2.43 (p = 0.458).

Discontinuation of compression garments

After 3 months 8 patients (17.0%) in the LVA group completely discontinued the use of compression garments. After 6 months the discontinuation rate increased to 10 patients (21.3%). Furthermore after 3 and 6 months, 10 patients (21.7%) partially discontinued use of compression garments. None of the patients in the CDT group discontinued the use of compression garments in the first 6 months.

Adverse events (AE)

Within the first 3 months 7 AE's were observed.

In the CDT group one subject had a mild episode erysipelas, treated with oral antibiotics and in one patient moderate erysipelas occurred, where treatment with intravenous antibiotics were required. One patient had COVID, one patient was diagnosed with muscular rheumatism.

	0–3 months			0–6 months		
	WDM					
	Mean absolute difference ± SD	95% CI	P-value	Mean absolute difference ± SD	95% CI	P-value
LVA	24.80 ± 179.93	[− 32.74, 84.34]	0.389	20.04 ± 196.40	[− 38.96, 79.05]	0.497
CDT	13.88 ± 193.36	[− 45.6, 73.39]	0.640	33.98 ± 189.87	[− 23.06, 91.02]	0.236

Table 5. The relative difference in volume measured by the WDM after 0–3 and 0–6 months. The relative difference in volume after 0–3 and 0–6 months is calculated using the Paired Samples T-Test.

	Difference in volume[a]		
Independent variable	B	95% CI	P
Constant	− 346.301	− 1139.4–455.56	0.373
Anastomosis (count)	42.29	− 34.98–96.89	0.204
ICG stage	110.7	− 62.93–344.33	0.253
Onset lymphedema	0.002	− 1.24–0.65	0.131
BMI	− 3.926	− 23.12–13.57	0.657

Table 6. Linear regression analysis: using the difference in volume as dependent variable. Unstandardized beta (B): Calculated using linear regression analysis. [a]The difference in volume measured by WDM and is calculated by subtracting the post-OR volume from the pre-OR volume.

	0–3 months			0–6 months		
	UEL-index					
	Mean absolute difference ± SD	95% CI	P-value	Mean absolute difference ± SD	95% CI	P-value
LVA	3.65 ± 7.24	[1.42, 5.88]	0.002	1.84 ± 9.14	[− 0.94, 4.62]	0.189
CDT	3.30 ± 32.7	[− 6.93, 13.47]	0.521	− 0.84 ± 14.6	[− 5.17,3.49]	0.189

Table 7. The relative difference in circumference after 0–3 and 0–6 months. The relative difference in circumference after 0–3 and 0–6 months is calculated using the Paired Samples *T*-test.

In the LVA group one patient had moderate erysipelas, treated with intravenous antibiotics, one patient had a skin infection and 1 patient had pneumonia.

After 6 months, 5 AEs occurred in the CDT group and 3 AE in the LVA group occurred. In the CDT group 4 patients had erysipelas, in the LVA group 3 patients. All patients received oral antibiotics for the treatment of erysipelas. One patient in the LVA group had an allergic reaction of unknown origin.

Severe adverse events (SAE)

After 3 months no SAE were reported. After six months one patient in the LVA group reported recurrence of her breast cancer but she remained in the study.

Discussion

Previous published studies on the efficacy of the LVA surgery have shown promising results[30–33]. A decrease on subjective complaints and a volume reduction between 0 and 61% have been reported[34–36]. However, most of the studies included a small heterogeneous population and have a retrospective design[28,37–40]. The reported studies did not compare LVA surgery with other conservative treatment modalities and use different assessment tools resulting in disparate results[35,41,42].

To our knowledge, this the first large scale prospective randomized multicenter study assessing the effectiveness of LVA surgery compared with conservative treatment in patients with BCRL with HrQoL as primary outcome. Currently, there is a wide variety of quality of life questionnaires in lymphedema. The Lymph-ICF for the upper extremity has been well rated in regards to content validity, reliability, and construct validity based on good-quality evidence[43].

Intra group analyses demonstrated that physical function and mental function were significantly improved in the LVA group after 3 and 6 months. Moreover, the physical function was significantly improved in the LVA group compared to the CDT group. Indicating that the patients in the LVA group experience a significant improvement in physical symptoms such as heaviness, swelling, weakness, tingling and tightness of the arm as early as 3 months after LVA surgery. Previous studies reported an overall improvement of the subjective symptoms after LVA surgery[21,37,44,45]. However so far, the total score of the Lymph-ICF in the LVA and CDT group showed no statistically significant improvement.

Notwithstanding, the total score of the Lymph-ICF in the LVA group are promising in comparison to the CDT group where smaller differences in total score of the Lymph-ICF were seen. Furthermore, there was a high variability in the overall cohort. Moreover, patients with lymphedema present a wide array of complaints and symptoms. While some patients experience a detrimental effect in the arm volume, other patients experience more loss of mobility, pain and heaviness[5].

After 3 and 6 months no significant changes in arm volume were observed for both groups. Interestingly, after 3 months UEL index significantly improved in the LVA group, however this trend did not persist after 6 months. The volume reductive effect of the LVA treatment could not be evidenced during the first 6 months in the current study. This is concordant with previous studies[21,25,45].

However, the absence of volume reduction does not equate treatment failure. Even though the population had early stage lymphedema a discrepancy was seen between the ISL stage and ICG stage. Most of the cohort had ISL-stage 2a lymphedema, however using NIRF we mostly saw patients with ICG stage 3. Moreover, the patients in our cohort have had lymphedema for an average of ~ 7 years. Altogether this could indicate that even in early stage (ISL stage 2a) lymphedema determined by the ISL classification, the lymph vessels in the subdermal plane could already be nonfunctioning. Furthermore, in ISL stage 2a lymphedema changes in the tissue have been established using Dual Energy X-Ray Absorptiometry, such as lymph vessel dysfunction, fat deposition and, fibrosis. However, little is known about the exact physiological progression of lymphedema over time, which makes it difficult to establish which patients will benefit from LVA surgery[46–49].

Other systematic reviews have demonstrated that limb circumference significantly decreased, however these studies have a smaller patient population, reported heterogeneous assessment modalities and a had longer follow up[39,50]. There are many factors that might influence the outcome of the LVA, however there is a lack of consensus on what these factors are[42,51–53]. A positive correlation between Lymph-ICF and the amount of anastomosis has been reported[21]. As of yet, in our study no correlation was found between Lymph-ICF the amount of anastomosis, ICG stage, BMI and onset of lymphedema. However, in the study by Qiu et al. patients received multiple LVA surgeries and a longer follow up period then our current cohort[21].

In our study there was no correlation shown between volume reduction and the number of anastomosis performed. This concurs with the study conducted by Winters et al. where there was no correlation between the amount of anastomosis and volume reductive effect of the LVA[28]. In the current cohort there was no relationship between the volume, the duration and severity of lymphedema. Concurrently, a meta-analysis conducted by Nacchiero et al. reported that the stage and duration of lymphedema were not dependent on the success of the operation[39,54].

Lastly approximately 42% of the patient population in the LVA group completely of partially discontinued the use of compression garments. The discontinuation rate in our population is line with previously published articles[21,44,45]. Unfortunately, we did not include the reason for discontinuation in our questionnaire, which might be interesting to investigate in the future.

This study is a 6-month interim analysis where 92% of the population completed six-month follow up. At the time of analysis, one patient had dropped out. Because the design of the current study eliminates any form of selection bias, this study more closely resembles results of the general population in comparison to other smaller and retrospective studies. In our study, patients were only able to receive one LVA surgery whereas in other previously published studies patients were able to receive more sessions, and ultimately more LVA's[21,55].

Although the results of the first 6 months may be encouraging, a longer follow up period is required the assess the true effect of the LVA in comparison to CDT for secondary lymphedema.

Conclusion

Lymphaticovenous anastomosis resulted in improvement of physical and mental function in patients with BCRL. Limb volume and limb circumference did not significantly improve after 6 months in both groups. However, in the LVA group around 40% could completely or partially stopped with the use of compression garments. The current results are promising, however longer follow up is required to assess the long term effect of LVA.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Received: 16 March 2023; Accepted: 19 January 2024
Published online: 26 January 2024

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Author contributions

The study conception and design were contributed by S.S.Q., J.W., R.vdH., D.U., H.T., S.H., X.K. Data collection was contributed by J.W., S.H., Y.J. Surgeries were performed by S.S.Q., H.T., D.U. Analysis and interpretation of results were contributed by Y.J. and S.vK. Draft manuscript preparation was contributed by Y.J. All authors refined and contributed of manuscript.

Funding

This work was supported by ZonMw, grant number 80-85200-98-91044.

Competing interests

The authors declare no competing interests.

Additional information

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Surgical Treatment of Lymphedema: A Systematic Review and Meta-Analysis of Controlled Trials. Results of a Consensus Conference

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Chicago, Ill.; New York, N.Y.; Boston, Mass.; London, Ontario, Canada; Barcelona, Spain; Seattle, Wash.; and Palo Alto, Calif.

Background: The goal of this consensus conference, sponsored by the American Association of Plastic Surgeons, was to perform a systematic review and meta-analysis of controlled trials to examine both the benefits and risks of surgical treatment and surgical prevention of upper and lower extremity lymphedema.
Methods: The panel met in Boston for a 3-day, face-to-face meeting in July of 2017. After an exhaustive review of the existing literature, the authors created consensus recommendations using the Grading of Recommendations, Assessment, Development and Evaluation criteria. Important directions for future research were also identified.
Results: There is evidence to support that lymphovenous anastomosis can be effective in reducing severity of lymphedema (grade 1C). There is evidence to support that vascular lymph node transplantation can be effective in reducing severity of lymphedema (grade 1B). Currently, there is no consensus on which procedure (lymphovenous bypass versus vascular lymph node transplantation) is more effective (grade 2C). A few studies show that prophylactic lymphovenous bypass in patients undergoing extremity lymphadenectomy may reduce the incidence of lymphedema (grade 1B). More studies with longer follow-up are required to confirm this benefit. Debulking procedures such as liposuction are effective in addressing a nonfluid component such as fat involving lymphedema (grade 1C). There is a role for liposuction combined with physiologic procedures although the timing of each procedure is currently unresolved (grade 1C).
Conclusions: Many studies seem to support some efficacy of lymphovenous bypass and vascular lymph node transplantation. Many studies show the important role of lymphedema therapy and other procedures such as liposuction and debulking. The management of lymphedema is a challenging field with many promising advances. However, many questions remain unanswered. (*Plast. Reconstr. Surg.* 147: 975, 2021.)

There is no cure for lymphedema and the optimal treatment is unknown. The purpose of this consensus conference was to develop evidence-based consensus statements and recommendations for surgical treatment and prevention of secondary lymphedema by performing a meta-analysis of randomized and nonrandomized clinical trials. The objectives included the following:

1. To assess the effectiveness and safety of surgical treatment of lymphedema. Surgical treatments included lymphovenous bypass, vascular lymph node transplantation, and liposuction. Comparators included surgery (i.e., lymphovenous bypass, vascular lymph node transplantation, or liposuction) and compression therapy.

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Received for publication July 22, 2019; accepted August 28, 2020.
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DOI: 10.1097/PRS.0000000000007783

Disclosure: *None of the authors has a financial interest in any of the products or devices mentioned in this article.*

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2. To assess the effectiveness and safety of surgical treatment to prevent secondary lymphedema. Surgical treatments included lymphovenous bypass. The comparator was no surgery.
3. To develop consensus statements and recommendations for surgical treatment of lymphedema.

PATIENTS AND METHODS

Consensus panel members were selected based on content and methodologic expertise. After considering the evidence, the consensus panel made recommendations regarding surgical treatment for patients with lymphedema and for surgical prevention of lymphedema in high-risk patients. The Grading of Recommendations, Assessment, Development and Evaluation framework was used to assess the overall quality of evidence and the strength of recommendations.[1–3] Randomized trials start as high-quality evidence and nonrandomized studies start as low-quality evidence. Studies may be downgraded because of risk of bias, indirectness, heterogeneity, imprecision, and publication bias. The overall quality of evidence was determined after considering each of these elements and categorized as high, moderate, low, or very low quality. The Grading of Recommendations, Assessment, Development and Evaluation criteria were used to classify recommendations as strong (grade 1) or weak (grade 2).[1] Recommendations were further classified as A, B, or C based on the quality of evidence informing the recommendation. Recommendations to use or not use an intervention are made on the basis of tradeoffs between benefits, risks, and burdens. If the benefits clearly outweigh risks and burdens, a strong recommendation is made. If the benefits, risks, and burdens are finely balanced, or uncertainty exists regarding the extent of benefits or risks, a weak recommendation is made.

Search Methods for Identification of Studies

The MEDLINE, Embase, and Cochrane Library databases were searched from inception to September 20, 2019. (**See Appendix, Supplemental Digital Content 1**, which shows the MEDLINE, Embase, and Cochrane Library search strategy, *http://links.lww.com/PRS/E392*.)

Inclusion Criteria

Randomized controlled trials and observational studies including prospective and retrospective cohort and case-control studies were considered for inclusion. Case series that reported on preoperative and postoperative outcomes of interest were also included.

Adult patients with secondary lymphedema (stages 1, 2, 3, or 4) were considered for inclusion. Surgical interventions for treatment of lymphedema included lymphovenous bypass (lymphaticovenular anastomosis), vascular lymph node transplantation, and liposuction. Studies that used combined procedures (e.g., vascular lymph node transplantation plus liposuction) were also considered for inclusion. The comparison group for surgical treatment studies included surgery and/or compression therapy. Eligible surgical comparators included lymphovenous bypass, vascular lymph node transplantation, and liposuction. Compression therapy could include graduated compression stockings, sequential compression devices, complex decongestive therapy, and physiotherapy.

We were also interested in the effectiveness and safety of surgical treatment to prevent lymphedema. Thus, studies that assessed surgical treatment for prevention of secondary lymphedema in high-risk patients were also considered for inclusion. Surgical interventions for the prevention of lymphedema included lymphaticovenular anastomosis (Lymphatic Microsurgical Preventive Healing Approach technique). The comparison group for surgical prevention studies included a no-surgery control group.

Exclusions

Studies published in abstract form only were excluded. Pediatric patients were excluded. Other types of surgery (e.g., excisional) and microsurgery (e.g., lymph vessel transplant) used for the treatment of lymphedema were excluded.

The primary outcomes for surgical treatment of lymphedema were reduction in limb volume (as a percentage or in milliliters) as measured by a validated system for limb volume measurement (e.g., truncated cone and water displacement) and reduction in limb circumference (as a percentage or in centimeters). The primary outcome for surgical prevention was the proportion of patients who developed lymphedema within 1 year of surgery. Secondary outcomes included surgical complications, ability to discontinue lymphedema interventions (e.g., pressure therapy), and patient-reported outcomes using validated questionnaires (e.g., quality of life).

The Cochrane risk-of-bias tool was used to assess the methodologic quality of randomized controlled trials.[4] The methodologic quality of cohort and case control studies was assessed using the Newcastle-Ottawa Scale.[5]

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Data Extraction and Analysis

Meta-analysis was conducted if the interventions, patient groups, and outcomes were sufficiently similar. We calculated the odds ratio and 95 percent confidence interval for dichotomous outcomes obtained from case-control and cohort studies. For dichotomous outcomes from randomized controlled trials, we calculated the risk ratio and 95 percent confidence interval. For continuous outcomes, we calculated the mean difference and 95 percent confidence interval. Heterogeneity was assessed using the chi-square test. A value of $p = 0.10$ was considered statistically significant. The I^2 statistic was used to quantify heterogeneity.[6] If statistically significant heterogeneity was detected, we visually inspected the forest plots for outliers and conducted sensitivity analyses to explore potential explanations for the heterogeneity. Meta-analysis was carried out using a random-effects model. We planned subgroup analysis by location of lymphedema (i.e., upper extremity lymphedema versus lower extremity lymphedema). We used the software Review Manager (computer program) Version 5.3 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark).

RESULTS

Two hundred fifty-eight studies were excluded. Common reasons for exclusion included lack of usable data, no reporting of prespecified outcomes, ineligible surgical comparators or surgery, and abstract publications. Seventy-one articles reporting the results of 66 studies met the predefined inclusion criteria.[7–77] (**See Figure, Supplemental Digital Content 2**, which shows the study flow chart, *http://links.lww.com/PRS/E393*.) Two studies were randomized controlled trials[13,28]; seven included studies were prospective cohort studies[8,16,17,24,47,52,65]; 14 retrospective cohort studies were included[21,25,29,31,34,40,42,44,60–64,66]; 43 included studies were case series; eight studies reported on liposuction and compression therapy for treatment of lymphedema[7,15,20,26,36,43,57,74]; 16 studies reported on lymphovenous bypass and compression therapy[9–11,14,22,32,33,37–39,46,48,51,58,71,77]; and 17 studies reported on vascular lymph node transplantation and compression therapy.[23,24,27,35,45,49,50,53,56,59,67,69,70,72,73,75,76] Three case series reported on combination therapy.[12,55,68] The characteristics of included studies are described in Table 1 and results are described in Table 2.[7–78]

The risk of bias assessment is summarized. (**See Figure, Supplemental Digital Content 3**, which shows the risk of bias assessment, *http://links.lww.com/PRS/E394*.) The quality assessment of the cohort and case-control studies (Newcastle-Ottawa scale) is reported in Table 3.

Liposuction

A pooled analysis of two studies ($n = 48$ patients) showed that the combination of liposuction and controlled compression therapy was significantly superior to controlled compression therapy for reducing edema volume in patients with stage II (International Society of Lymphology) upper extremity lymphedema.[16,17] On average, patients who had liposuction and controlled compression therapy had a 63.95 percent greater reduction in volume compared to patients who had controlled compression therapy only (95 percent CI, 49.57 to 78.33; very low-quality evidence). [**See Figure, Supplemental Digital Content 4**, which shows the liposuction versus controlled compression therapy; outcome = reduction in limb volume (percent), *http://links.lww.com/PRS/E395*.] Similarly, a pooled analysis of two studies ($n = 69$ patients) showed that the combination of liposuction and controlled compression therapy was significantly superior to controlled compression therapy for reducing the volume of edema (in milliliters) in patients with stage II (International Society of Lymphology) upper extremity lymphedema. On average, patients who had liposuction and controlled compression therapy reduced their lymphedema volume by 895 ml more than controlled compression therapy patients (95 percent CI, −1140.63 to 650.98; very low-quality evidence). [**See Figure, Supplemental Digital Content 5**, which shows the liposuction versus controlled compression therapy; outcome = percentage reduction in limb volume (in milliliters), *http://links.lww.com/PRS/E396*.]

Two case series (163 patients) reported on liposuction for reducing percentage excess limb volume in patients with stage II to III (International Society of Lymphology) lymphedema.[15,20] Liposuction combined with compression therapy significantly reduced excess limb volume by an average 26.59 percent (95 percent CI, 18.64 to 34.54; very low-quality evidence). [**See Figure, Supplemental Digital Content 6**, which shows the liposuction; reduction in excess limb volume (percentage), *http://links.lww.com/PRS/E397*.] This benefit was significant for patients with upper extremity lymphedema (mean difference, 28.68; 95 percent CI, 6.06 to 51.29) and lower extremity lymphedema (mean difference, 29.23; 95 percent CI, 5.56 to 52.90). A high degree of heterogeneity was detected ($I^2 = 91$ percent), which likely

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Table 1. Characteristics of Included Studies

Reference	Methods	No. of Participants/ISL/ Campisi Stage	Interventions	Outcomes	Follow-Up (mo)
Agarwal et al., 1998[7]	Case series; grade 2	8 patients with LEL; compression stockings; physical therapy	Liposuction; circumference (cm)	Volume reduction (ml)	24
Akita et al., 2015[8]	Prospective cohort	46 patients with LEL; I–II (ISL)	LNT ($n = 13$); LVA ($n = 33$); compression stockings	Lymphatic function; hospitalization days; complications; BMI; LEL index	LNT, 15.1; LVA, 18.3
Aljaaly et al., 2019[60]	Retrospective cohort	15 patients with UEL; II–IV (Cheng)	Dorsal wrist: LNT ($n = 7$) Volar wrist: LNT ($n = 8$)	Circumferential difference (%); circumferential reduction rate (%); cellulitis	12
Asuncion et al., 2018[67]	Case series	5 patients with UEL; 10 patients with LEL; stage NR	LNT	Circumferential difference (cm); cellulitis	12
Auba et al., 2012[9]	Case series	4 patients with LEL; 6 patients with UEL; II–V (Campisi)	LVA; compression garments	Circumference (cm)	24
Ayestaray et al., 2013[10]	Case series	20 patients with UEL; II–V (Campisi)	LVA; compression garments	Circumference (cm); volume reduction (%); use of compression	6
Ayestaray and Bekara, 2014[11]	Case series	12 patients with UEL; 8 patients with LEL; II–V (Campisi)	LVA; compression garments	Circumference (cm); volume reduction (%); use of compression	12
Batista et al., 2017[12]	Case series	38 with LEL; stage NR	LNT; physiotherapy; compression stockings; liposuction ($n = 15$)	Volume (ml)	48.6
Boccardo et al., 2011[13]	RCT	49 patients with axillary dissection for breast cancer	LVA, LYMPHA ($n = 23$); no surgery ($n = 23$)	Postoperative lymphedema	18
Boccardo et al., 2014[14]	Case series	7 patients with LEL; stage NR	LVA; compression stockings	Volume (ml); use of compression	12
Boyages et al., 2015[15]	Case series	15 patients with UEL; 6 patients with LEL; II–III (ISL)	Liposuction; compression garments	Excess volume (ml); excess volume (%); PSFS functional/emotional domains; BMI	9
Brorson et al., 1998[18]	Prospective cohort	20 patients with UEL; II (ISL)	Liposuction plus CCT ($n = 11$); CCT ($n = 9$)	Volume (ml); volume reduction (%);	12
Brorson et al., 2006[17]	Prospective cohort	49 patients with UEL; II (ISL)	Liposuction plus CCT ($n = 35$); CCT ($n = 14$)	Volume (ml); volume reduction (%); QoL	12
Campisi et al., 2017[20]	Case series	63 patients with UEL; 83 patients with LEL; IIB–IIIB (Campisi)	Liposuction; compression bandages; compression garments	Volume (ml); volume reduction (%)	12
Casabona et al., 2009[21]	Retrospective cohort	72 patients with sentinel lymph node biopsy for breast cancer	LVA, LYMPHA ($n = 9$); no surgery ($n = 63$)	Postoperative lymphedema	9
Chang et al., 2017[68]	Case series	49 patients with LEL	Liposuction plus LVA	Circumference (cm); volume (ml); cellulitis	12
Chen et al., 2016[22]	Case series	13 patients with UEL; 8 patients with LEL; II–IV (Campisi)	LVA ($n = 18$); LNT ($n = 3$); NR	QoL; UEL index; LEL index	12
Cheng et al., 2012[23]	Case series	7 patients with LEL; II–III (ISL)	LNT	Reduction rate (%); volume differentiation; LYMQOL; cellulitis	8.7
Cheng et al., 2013[24]	Prospective cohort	20 patients with UEL; II (ISL)	LNT ($n = 10$); physical therapy ($n = 10$)	Infection; cellulitis; circumferential reduction; circumferential differentiation; BMI	39.1
Ciudad et al., 2017[25]	Retrospective cohort	41 patients with UEL; 69 patients with LEL; II–III (ISL)	S-LNT ($n = 54$); G-LNT ($n = 20$); O-RG-LNT ($n = 19$); L-RG-LNT ($n = 17$)	Hospital stay; BMI; flap harvest time; complications	S-LNT, 33; G-LNT, 31.4; O-RG, 26.6; RG-LNT, 25.6

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Table 1. ***Continued***

Reference	Methods	No. of Participants/ISL/ Campisi Stage	Interventions	Outcomes	Follow-Up (mo)
Ciudad et al., 2017[61]	Retrospective cohort	30 patients with UEL; 53 patients with LEL; II–III (ISL)	S-LNT (n = 25) G-LNT (n = 13); Gas-LNT (n = 42); A-LNT (n = 1); I-LNT (n = 2)	Circumferential reduction (%); infections; complications	32.8
Ciudad et al., 2017[69]	Case series	4 patients with UEL; 3 patients with LEL; III (ISL)	DG-LNT	Circumferential reduction (%); infections; complications	9.7
Ciudad et al., 2019[70]	Case series	6 patients with UEL; 10 patients with LEL; III (ISL)	LNT plus modified radical reduction; conservative therapy	Circumferential reduction (%); complications; infections; QoL LYMQOL	14.2
Damstra et al., 2009[26]	Case series	37 patients with UEL; stage NR	Liposuction; limb compression; compression garments	Excess volume (ml)	12
De Brucker et al., 2016[27]	Case series	25 patients with UEL; I–II (ISL)	LNT; physiotherapy; compression garments	QoL (ULL-27Q); discontinue physiotherapy	29
Dionyssiou et al., 2016[28]	RCT	36 patients with UEL; II (ISL)	LNT plus physiotherapy (n = 18); physiotherapy (n = 18); compression	Excess volume (%); circumferential differentiation; infection; pain; heaviness; overall function; BMI	18
Engel et al., 2018[62]	Retrospective cohort	124 patients with UEL; I–IV (Cheng)	LVA (n = 27); LNT (n = 45); CDT (n = 52)	Circumferential difference (%); reduction rate (%); cellulitis	19.1
Feldman et al., 2015[29]	Retrospective cohort	32 patients with axillary dissection for breast cancer	LVA, LYMPHA (n = 24); no surgery (n = 8)	Postoperative lymphedema; complications	6
Gentileschi et al., 2017[71]	Case series	16 patients with UEL; IIa, IIb (ISL)	LVA; compression garments	Circumference difference (cm); QoL LYMQOL	12.13
Gharb et al., 2011[31]	Retrospective cohort	21 patients with UEL; II (ISL)	G-LNT (n = 11); I-LNT (n = 10); limb elevation; compression garments; decongestive treatment	Circumference (cm); complications; cellulitis; seroma; necrosis; required further procedures	G-LNT, 46; I-LNT, 40
Gong-Kang et al., 1981[32]	Case series	11 patients with LEL; 2 patients with UEL; stage NR	LVA; bandages; antibiotics	Circumference (cm); cellulitis	6
Huang et al., 1985[33]	Case series	91 patients with LEL; stage NR	LVA; elastic bandages; limb elevation	Excess volume (ml); excess volume (%); cellulitis	24
Granzow et al., 2014[34]	Retrospective cohort; stage NR	26 patients with UEL or LEL; LNT (n = 8); compression garments; lymphedema therapy	Liposuction (n = 10); LVA (n = 8)	Excess volume (ml); cellulitis; need for compression or lymphedema therapy; clinical improvement at 24 mo; complications	25
Gratzon et al., 2017[35]	Case series	50 patients with UEL; I–II (ISL)	LNT; CDT	Volume reduction (%); CDT use; cellulitis; QoL LYMQOL; complications	
Gustafsson et al., 2018[72]	Case series	35 patients with LEL; I–IV (Cheng)	LNT; CDT	Circumferential difference; cellulitis	30.3
Hahamoff et al., 2017[63]	Retrospective cohort	87 patients with axillary dissection for breast cancer	LVA, LYMPHA (n = 8); no surgery (n = 10)	Postoperative lymphedema	15
Ho et al., 2019[73]	Case series	76 patients with UEL (n = 30) or LEL (n = 46); I–IV (Cheng)	LNT; compression	Circumferential difference; excess volume (%)	50.1
Hoffner et al., 2017[36]	Case series	60 patients with UEL; I–III (ISL)	Liposuction plus CCT	Excess volume (ml); QoL: SF-36	12
Hoffner et al., 2018[74]	Case series	105 patients with UEL; stage NR	Liposuction plus CCT; compression garments	Excess volume (ml)	60
Ipsen et al., 1988[37]	Case series	9 patients with LEL; 1 patient with UEL; stage NR	LVA; none	Circumference (cm); subjective symptoms	12

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Table 1. *Continued*

Reference	Methods	No. of Participants/ISL/ Campisi Stage	Interventions	Outcomes	Follow-Up (mo)
Ito et al., 2016[38]	Case series	5 patients with LEL; I–II (Cheng)	LVA; CDT; Compression garments	Circumferential differentiation; cellulitis; compression garment use; BMI	
Koshima et al., 1996[39]	Case series	6 patients with UEL; 8 patients with LEL; moderate/severe	LVA; NR	Excess circumference (cm)	UEL, 25.5; LEL, 23.4
Koshima et al., 2000[40]	Restrospective cohort	24 patients with UEL; severe	LVA plus pressure ($n = 12$); pressure ($n = 12$)	Circumferential differentiation; circumference reduction	12
Koshima et al., 2003[42]	Retrospective cohort	25 patients with LEL; stage NR	LVA plus pressure ($n = 13$); pressure ($n = 12$)	Circumferential differentiation; circumference reduction	55
Lamprou et al., 2017[43]	Case series	41 patients with LEL; III end-stage	Liposuction plus compression	Volume difference	24
Lee et al., 2011[44]	Retrospective cohort	32 patients with LEL; I–III (ISL)	LVA ($n = 19$); LNT ($n = 13$); CDT	Clinical improvement at 12, 24, and 48 mo	48
Leppapuska et al., 2019[64]	Retrospective cohort	48 patients with UEL; I–II	LNT plus liposuction ($n = 21$); LNT ($n = 27$); compression garments	Excess volume (ml); complications; use of compression garments	48.9
Lin et al., 2009[45]	Case series	13 patients with UEL; stage NR	G-LNT; CDT	Circumference reduction (%);Circumference reduction (cm)	56.3
Lin et al., 2019[65]	Prospective cohort	180 patients with UEL; P1–P3, T4–T6 (TLS)	LNT ($n = 100$); CDT ($n = 80$)	Circumferential difference (%);QoL LYMQOL; cellulitis; lymphedema knowledge scale; PHCA seeking	6
Maruccia et al., 2019[66]	Retrospective cohort	39 patients with UEL; II–III (ISL)	LNT plus scar release ($n = 18$); LNT ($n = 21$)	Reduction rate (%);Infectious episodes	LNT plus scar, 29; LNT, 32
Matsubara et al., 2006[46]	Case series	9 patients with LEL; II (ISL)	LVA; physiotherapy; limb elevation; manual lymph drainage; pneumatic compression; compression stocking	Circumference reduction (%);Circumference reduction (cm); cellulitis	68
Montag et al., 2019[75]	Case series	24 patients with UEL; II–III (ISL)	LNT; CDT; Compression	Volume reduction (cm); volume reduction (%); cellulitis	18
Morotti et al., 2013[47]	Prospective cohort	15 patients with vulvar cancer undergoing ILND	LVA, LYMPHA ($n = 8$); no surgery ($n = 7$)	Postoperative lymphedema; Complications	16.7
Mousavi et al., 2019[76]	Case series	24 patients with UEL; stage NR	LNT; compression garments	Circumferential difference; cellulitis	12
Narushima et al., 2010[48]	Case series	12 patients with LEL; 2 patients with UEL; II–IV (Campisi)	LVA; compression garments	Circumference reduction(cm)	8.9
Nguyen et al., 2017[49]	Case series	19 patients with UEL; 24 patients with LEL; III–V (Chang)	O-LNT; CDT	Volume reduction (%);subjective improvement; complications; cellulitis	14
Nicoli et al., 2015[50]	Case series	10 patients with UEL; II (ISL)	S-LNT or G-LNT plus liposuction; arm elevation; compression garments	Circumference (cm)	6
O'Brien et al., 1979[51]	Case series	37 patients with UEL; Stage NR	LVA; elevation; elastic stockings; pumping	Limb volume; subjective improvement; cellulitis	19.9
Orefice et al., 1988[52]	Prospective cohort	114 patients undergoing ilioinguinal dissection for breast cancer	LVA ($n = 30$); no surgery ($n = 84$)	Postoperative lymphedema; hospital stay; complications	29
Patel et al., 2015[53]	Case series	15 patients with UEL; 10 patients with LEL; Late-stage	G-LNT ($n = 13$) or SLNT ($n = 12$)	Excess circumference (%); cellulitis; LYMQOL	UEL, 25.4; LEL, 16.1

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Table 1. *Continued*

Reference	Methods	No. of Participants/ISL/Campisi Stage	Interventions	Outcomes	Follow-Up (mo)
Qi et al., 2009[55]	Case series	11 patients with UEL	LNT plus liposuction; elastic bandage; compression garment	Circumference (cm); cellulitis	26
Saaristo et al., 2012[56]	Case series	9 patients with UEL; stage NR	G-LNT; manual drainage; elastic compression dressing	Circumference (cm)	6
Schaverien et al., 2012[57]	Case series	12 patients with UEL; stage NR	Liposuction; antibiotics; pressure garments	Volume (ml); anxiety; depression;	12
Shi et al., 2015[58]	Case series	11 patients with UEL; moderate/severe	LVA; NR	Circumference (cm)	38.4
Viitanen et al., 2013[59]	Case series	19 patients with UEL; Stage NR	LNT; physiotherapy; elastic compression	Circumference (cm); transport index	27.5
Winters et al., 2017[77]	Case series	29 patients with UEL; Ib-IIa (Campisi)	LVA; compression garment	Excess volume (%);QoL: LYMQOL	12

ISL, International Society of Lymphology; LEL, lower extremity lymphedema; LNT, lymph node transfer; LVA, lymphaticovenular anastomosis; UEL, upper extremity lymphedema; RCT, randomized controlled trial; CCT, controlled compression therapy; QoL, quality of life; ULL-27Q, Upper Limb Lymphedema-27 Questionnaire; LYMQOL, Lymphoedema Quality-of-Life; PSFS, Patient-Specific Functional Scale; BMI, body mass index; S-LNT, supraclavicular lymph node transfer; G-LNT, groin lymph node transfer; O-RG-LNT, open right gastroepiploic lymph node transfer; L-RG-LNT, laparoscopic right gastroepiploic lymph node transfer; Gas-LNT, gastroepiploic lymph node transfer; A-LNT, appendicular lymph node transfer; DG-LNT, double gastroepiploic lymph node transfer; I-LNT, ileocecal lymph node transfer; I-LNT-HP, inguinal lymph nodes with hilar perforators; SF-36, 36-Item Short-Form Health Survey; ILND, inguinofemoral lymph node dissection; O-LNT, omental lymph node transfer; SLNT, submental lymph node transfer; SEKI-LVA, superior edge of knee incision LVA; SE-LVA, side to-end LVA; NR, not reported; CDT, complex decongestive therapy; LDB, leg dermal backflow; ADB, arm dermal backflow; PHCA, professional health care advice.

reflects differences in surgical technique, patients, and lymphedema. Six case series (294 patients) reported on liposuction for reducing excess limb volume (in milliliters) in patients with stage I to III (International Society of Lymphology) upper extremity lymphedema or lower extremity lymphedema.[7,17,26,36,68,74] Liposuction combined with compression therapy significantly reduced excess limb volume by an average 1702.44 ml (95 percent CI, 1558.64 to 1846.23 ml). [**See Figure, Supplemental Digital Content 7**, which shows the liposuction; reduction in volume (in milliliters), *http://links.lww.com/PRS/E398*.] This benefit was significant for patients with upper extremity lymphedema (mean difference, 1666.04 ml; 95 percent CI, 1543.97 to 1788.10 ml) and lower extremity lymphedema (mean difference, 2181.22 ml; 95 percent CI, 1328.00 to 3034.44 ml). A moderate degree of heterogeneity was detected (I^2 = 51 percent). One case series of 10 patients with upper extremity lymphedema and lower extremity lymphedema reported on preoperative and postoperative cellulitis.[34] Cellulitis was significantly reduced after treatment with liposuction and compression therapy. The incidence of severe cellulitis before surgery was 70 percent (seven of 10) compared to 10 percent (one of 10) after surgery (OR, 21.00; 95 percent CI, 1.78 to 248.10).

Lymphovenous Bypass

Three studies (102 patients) compared lymphovenous bypass to pressure therapy in patients with upper extremity lymphedema or lower extremity lymphedema.[40,42,62] Two studies reported significantly higher circumference reduction in lymphovenous bypass patients compared to patients who received compression alone. Koshima et al. reported that leg circumference decreased by a mean 4.7 cm in the lymphovenous bypass group compared to 0.6 cm in the compression therapy group ($p < 0.05$). This corresponded to a 55.6 percent reduction in leg circumference in the lymphovenous bypass group compared to an 8 percent reduction in the compression therapy group.[42] Koshima et al. reported that arm circumference decreased by a mean 4.1 cm in the lymphovenous bypass group compared to 0.8 cm in the compression therapy group ($p < 0.05$). This corresponded to a 47.3 percent reduction in arm circumference in the lymphovenous bypass group compared to a 11.7 percent reduction in the compression therapy group.[40] Engel et al. reported a 17.3 percent reduction in arm circumference in the lymphovenous bypass group compared to a 9.8 percent reduction in the complex decongestive

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Table 2. Results and Methodologic Quality of Included Studies

Reference	No. of Patients/Intervention	Volume Reduction [MD (range) or OR (95% CI)]	Circumference Reduction [MD (range) or OR (95% CI)]	Complications	QoL
Agarwal et al., 1998[7]	8 with LEL; liposuction	2736.6 ml (1767–3706.2 ml)	5 cm (−0.58 to 10.58 cm)	Hyperpigmentation ($n = 2$); cellulitis ($n = 1$)	NR; NR
Akita et al., 2015[8]	46 with LEL; LNT ($n = 13$); LVA ($n = 33$)	NR	NR	LNT ($n = 3$); LVA ($n = 0$); skin paddle congestion ($n = 3$); venus thrombosis ($n = 1$)	NR
Aljaaly et al., 2019[60]	15 with UEL; dorsal LNT ($n = 7$); volar LNT ($n = 8$)	NR	12.1% (−24.05 to 48.25%)	NR	2.0 (1.31–2.69)
Asuncion et al., 2018[67]	5 with UEL; 10 with LEL; LNT	NR	3.2 ± 0.4 cm	NR	4.9 ± 0.3
Auba et al., 2012[9]	4 with LEL; 6 with UEL; LVA	NR	0.70 cm (−4.36 to 5.76 cm)	None	NR
Ayestaray et al., 2013[10]	20 with UEL; LVA	22.8% (7.2–48.8%)	4.2 cm (2.39–6.01 cm)	Partial skin ulceration ($n = 1$)	18/20 had improved QoL at 6 mo
Ayestaray and Bekara, 2014[11]	12 with UEL; 8 with LEL; LVA	504 ml (32.06–975.94 ml); 22.9% (4.9–46.3%)	5 cm (0.71–9.29 cm); 13.1% (3.5–28.1)	Hypertrophic scar ($n = 1$);	19/20 had improved QoL at 12 mo
Batista et al., 2017[12]	38 with LEL; LNT	900 ml (−104.5 to 1904.5 ml)	NR	Complications ($n = 11$); seroma; hematoma; wound dehiscence ($n = 1$)	NR
Boccardo et al., 2011[13]	49 with axillary dissection; LVA ($n = 23$); no surgery ($n = 23$)	NR	NR	Lymphedema; OR, 0.10 (0.01–0.93); LVA, 1/23; no surgery, 7/23	NR
Boccardo et al., 2014[14]	7 with LEL; LVA	1858.6 ml (1721.5–1995.7 ml)	NR	None	NR
Boyages et al., 2015[15]	15 with UEL; 6 with LEL; liposuction	UEL, 40.6% (31.89–49.31%); LEL, 43% (25.55–60.45%)	NR	None	Improved; PSFS
Brorson et al., 1998[18]	20 with UEL; liposuction plus CCT ($n = 11$); CCT ($n = 9$)	61% (38.53–83.47%); −968 ml (−1335.14 to −600.86 ml)	NR	None	NR
Brorson et al., 2006[17]	49 with UEL; liposuction plus CCT ($n = 35$); CCT ($n = 14$)	66% (47.29–84.71%); −838 ml (−1166.53 to −509.47 ml)	NR	None	Improved ROM; symptoms; ADL; NHP; PGWB; HAD
Campisi et al., 2017[20]	63 with UEL; 83 with LEL; liposuction	UEL, 17.51% (14.58–20.44%); LEL, 18.64% (15.96–21.32%); UEL, 261.32 ml (152.0–370.44 ml)	NR	None	NR
Casabona et al., 2009[21]	72 with sentinel lymph node biopsy; LVA, LYMPHA ($n = 9$); no surgery ($n = 63$)	NR	NR	Lymphedema; LVA, 0/9; no surgery, 0/63	NR
Chang et al., 2017[68]	49 with LEL; liposuction plus LVA	1840 ml (1389.98–2290.02 ml)	3.34 cm (2.59–4.09 cm)	NR	NR
Chen et al., 2016[22]	13 with UEL; 8 with LEL; LVA ($n = 18$); LNT ($n = 3$)	NR	NR	Flap congestion ($n = 1$)	MD, 12.80 (7.6–18.00)
Cheng et al., 2012[23]	7 with LEL; LNT	NR	NR	Flap congestion ($n = 1$)	MD, 5.3 (4.60–6.00)
Cheng et al., 2013[24]	20 with UEL; LNT ($n = 10$); physical therapy ($n = 10$)	NR	32.1% (8.39–55.81%)	None	NR

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Table 2. ***Continued***

Reference	No. of Patients/Intervention	Volume Reduction [MD (range) or OR (95% CI)]	Circumference Reduction [MD (range) or OR (95% CI)]	Complications	QoL
Ciudad et al., 2017[25]	41 with UEL; 69 with LEL; S-LNT (*n* = 54); G-LNT (*n* = 20); O-RG-LNT (*n* = 19); L-RG-LNT (*n* = 17)	NR	NR	S-LNT, hematoma (*n* = 1); S-LNT, lymphatic leakage (*n* = 1); G-LNT, lymphatic leakage (*n* = 1); O-RG-LNT, none; L-RG-LNT, none	NR
Ciudad et al., 2017[61]	30 with UEL; 53 with LEL; S-LNT (*n* = 25); G-LNT (*n* = 13); Gas-LNT (*n* = 42); A-LNT (*n* = 1); I-LNT (*n* = 2)	NR; −2.3% (−10.06 to 5.46%); S-LNT vs. Gas-LNT; −4.2% (−10.91 to 2.51%); G-LNT vs. Gas-LNT; −1.9% (−7.52 to 3.72%)	S-LNT vs. G-LNT	Delayed wound healing; lymphatic leak; flap infection; venous congestion; wound infection; flap loss; partial loss of skin graft; hematoma	NR
Ciudad et al., 2019[70]	4 with UEL; 3 with LEL; LNT	NR	43.7 ± 2.5%	None	NR
Ciudad et al., 2019[70]	6 with UEL; LNT	NR	74.5 ± 6.9%	Numbness (*n* = 3); hyperesthesia (*n* = 1); seroma (*n* = 1); lymphatic leakage (*n* = 1)	−4.3 (−5.34 to −3.26)
Damstra et al., 2009[26]	37 with UEL; liposuction	1548 ml (1338.11–1757.89 ml)	NR	None	NR
De Brucker et al., 2016[27]	25 with UEL; LNT	NR	NR	Seroma (*n* = 3); donor-site wound breakdown (*n* = 4); axilla infection and flap loss (*n* = 1)	MD, 18 (8.56–27.44)
Dionyssiou et al., 2016[28]	36 with UEL; LNT (*n* = 18); physiotherapy (*n* = 18)	−15% (−22.03 to −7.97%)	NR	Mild discomfort donor side lower limb (*n* = 2); lymphorrhea at donor site (*n* = 2)	Improved pain, heaviness, overall function
Engel et al., 2018[62]	124 with UEL; LVA (*n* = 27); LNT (*n* = 45); CDT (*n* = 52)	NR	LVA vs. CDT, 5.2% (3.96–6.44%); LNT vs. CDT, 24.2% (21.71–26.69%); LNT vs. LVA, 15.7% (12.73–18.67%)	NR	NR
Feldman et al., 2015[29]	32 with axillary dissection; LVA (*n* = 24); no surgery (*n* = 8)	NR	NR	Lymphedema; OR, 0.14 (0.02–0.90); LVA, 3/24; no surgery, 4/8; no complications	NR
Gentileschi et al., 2017[71]	16 with UEL; LVA	NR	1.80 (0.90–2.70)	NR	Improved QoL; preoperatively, 5.5; postoperatively, 7.9
Gharb et al., 2011[31]	21 with UEL; G-LNT (*n* = 11); I-LNT (*n* = 10)	NR	NR	G-LNT, cellulitis (*n* = 2); seroma (*n* = 2); I-LNT, cellulitis (*n* = 1)	NR
Gong-Kang et al., 1981[32]	11 with LEL; 2 with UEL; LVA	NR	6.2 cm (range, 2.5–11 cm)	Cellulitis (*n* = 1)	NR
Huang et al., 1985[33]	91 with LEL; LVA	703 ± 850 ml; 59.2 ± 29.5%	6.4 cm (range, 1–17 cm)	Cellulitis (*n* = 19)	NR
Granzow et al., 2014[34]	26 with UEL or LEL Liposuction (*n* = 10); LVA (*n* = 8); LNT (*n* = 8)	Liposuction arm, 111% (98–120%) Liposuction leg, 86% (81–97%); LVA, NR; LNT, NR	NR	Liposuction, none; LVA, pulmonary embolus (*n* = 1) Sciatic neurapraxia (*n* = 1); LNT, seroma (*n* = 1); delayed flap healing (*n* = 2)	NR

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Table 2. *Continued*

Reference	No. of Patients/Intervention	Volume Reduction [MD (range) or OR (95% CI)]	Circumference Reduction [MD (range) or OR (95% CI)]	Complications	QoL
Gratzon et al., 2017[35]	50 with UEL; LNT	58.68%	NR	Seroma ($n = 6$); wound dehiscence ($n = 4$); surgical-site infection ($n = 9$); hematoma ($n = 1$); nonhealing wound ($n = 1$); bleeding ($n = 1$)	Improved QoL; function; appearance; symptoms; mood; pain; heaviness
Gustafsson et al., 2018[72]	35 with LEL	NR; LNT	19.8 ± 9.2	Cellulitis	NR
Hahamoff et al., 2017[63]	18 with axillary dissection; LVA ($n = 8$); no surgery ($n = 10$)	NR	NR	Lymphedema; OR, 0.10 (0.01–0.93); LVA, 0/8; no surgery, 4/10	NR
Ho et al., 2019[73]	30 with UEL; 46 with LEL; LNT	8.9% (7.12–10.68%); 13% (11.89–14.11%)	14% (6.47–21.53%); 20.8% (15.00–26.60%)	NR	NR
Hoffner et al., 2017[36]	60 with UEL; liposuction	1578 ml (1419.33–1736.67 ml)	NR	None	Improved; physical functioning; bodily pain; social functioning; mental health; vitality; PCS; MCS
Hoffner et al., 2018[74]	105 with UEL	1761 ml (1624.94–1897.06 ml)	NR	None	NR
Ipsen et al., 1988[37]	9 with LEL; 1 with UEL; LVA	NR	2.2 cm (−2.47 to 6.87 cm)	Erysipelas ($n = 2$); hypoplasia ($n = 1$); thrombophlebitis ($n = 1$)	NR
Ito et al., 2016[38]	5 with LEL; LVA	NR	63.8 ± 20.2%	NR	NR
Koshima et al., 1996[39]	6 with UEL; 8 with LEL; LVA	NR	3.6 cm (0.16–7.04 cm); UEL, 5.3 cm (3.12–7.48 cm); LEL, 2.6 cm (−3.63 to 8.83 cm)	NR	NR
Koshima et al., 2000[40]	24 with UEL; LVA ($n = 12$); pressure ($n = 12$)	NR	LVA, 4.1 cm (47.3%); pressure, 0.8 cm (11.7%)	NR	NR
Koshima et al., 2003[42]	25 with LEL; LVA ($n = 13$); pressure ($n = 12$)	NR	LVA: 4.7 cm, 55.6%; pressure, 0.6 cm (8%)	NR	NR
Lamprou et al., 2017[43]	41 with LEL; liposuction	101%; −38 ml (−1151 to 1135 ml)	NR	Decubitus ulcer ($n = 1$)	NR
Lee et al., 2011[44]	32 with LEL; LVA ($n = 19$); LNT ($n = 13$)	NR	NR; NR	LVA, none; LNT, transient lymphedema in donor limb ($n = 3$)	
Leppapuska et al., 2019[64]	48 with UEL; LNT plus liposuction ($n = 21$); LNT ($n = 27$)	−201.4 ml (−331.55 to −71.25 ml)	NR	Postoperative numbness; wound infection; skin necrosis; seroma	NR
Lin et al., 2009[45]	13 with UEL; G-LNT	NR	3.6 cm (−0.47 to 7.67 cm); 50.6% (35.79–65.41%)	Wound infection ($n = 1$); venous congestion ($n = 1$)	NR

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Table 2. *Continued*

Reference	No. of Patients/Intervention	Volume Reduction [MD (range) or OR (95% CI)]	Circumference Reduction [MD (range) or OR (95% CI)]	Complications	QoL
Lin et al., 2019[65]	180 with UEL; LNT (n = 100); CDT (n =80)	NR	3.7 cm (2.59–4.81 cm)	NR	NR
Maruccia et al., 2019[66]	39 with UEL; LNT plus scar release (n = 18); LNT (n = 21)	NR	LNT plus scar, 51.3 ± 6.3%; LNT, 50.2 ± 5.5%	NR	NR
Matsubara et al., 2006[46]	9 with LEL; LVA;	NR	3.44 cm (0.56–6.32 cm); 37.7% (2.04–73.36%)	None	NR
Montag et al., 2019[75]	24 with UEL; LNT	20.1 ± 44.89%	NR	Cellulitis (n = 3)	NR
Morotti et al., 2013[47]	15 with vulvar cancer had ILND; LVA, LYMPHA (n = 8); no surgery (n = 7)	NR	NR	Lymphedema; OR, 0.36 (0.02–5.11); LVA, 1/8; no surgery, 2/7; LVA, wound dehiscence (n = 1), lymphocele (n = 1), lymphangitis (n = 1); no surgery, DVT (n = 1); lymphangitis (n = 1)	NR
Mousavi et al., 2019[76]	24 with UEL; LNT	NR	20.9% (14.24–27.56%)	NR	NR
Narushima et al., 2010[48]	12 with LEL; 2 with UEL; LVA	NR	3.6 cm (1.56–5.64 cm)	Dehiscence (n = 1)	NR
Nguyen et al., 2017[49]	19 with UEL; 24 with LEL; O-LNT	22% (−35 to 74%)	NR	Flap loss (n = 1); cellulitis (n = 2); hematoma (n = 2); seroma (n = 2)	NR
Nicoli et al., 2015[50]	10 with UEL; S-LNT; or G-LNT plus liposuction	NR	2.4 cm (1.00–3.80 cm)	None	NR
O'Brien et al., 1979[51]	37 with UEL; LVA	15%	NR	Cellulitis (n = 9)	NR
Orefice et al., 1988[52]	114 had ilioinguinal dissection; LVA (n = 30); no surgery (n = 84)	NR	NR	Lymphedema; OR, 0.15 (0.05–0.43); LVA, 7/23; No surgery, 39/52; LVA, lymphocele (n = 7), skin necrosis (n = 5), wound infection (n = 3); no surgery, lymphocele (n = 53), skin necrosis (n = 23), wound infection (n = 3)	NR
Patel et al., 2015[53]	15 with UEL; 10 with LEL; G-LNT (n = 13); S-LNT (n = 12)	NR	UEL, 6% (2.58–9.42%); LEL, 10.1% (−1.87 to 22.07%)	NR	UEL: MD, 3.7 (3.26–4.14) LEL: MD, 4.1 (3.48–5.82)
Qi et al., 2009[55]	11 with UEL; LNT plus liposuction	NR	6.23 cm (4.77–7.69 cm)	Partial wound disruption (n = 2); numbness in fingers (n = 2); dorsal foot edema of donor leg (n = 1); slight edema at medial side of knee (n = 1)	NR

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Table 2. *Continued*

Reference	No. of Patients/Intervention	Volume Reduction [MD (range) or OR (95% CI)]	Circumference Reduction [MD (range) or OR (95% CI)]	Complications	QoL
Saaristo et al., 2012[56]	9 with UEL; G-LNT; 12 with UEL; liposuction	NR; 101% (69–148%); 1381 ml (489–1971 ml)	1.00 cm (−1.18 to 3.18 cm); NR	Seroma ($n = 3$); delayed wound closure ($n = 2$); none	NR; improved anxiety and depression
Seki et al., 2015[78]	30 with LEL; LVA ($n = 15$); EK-LVA ($n = 15$)	NR	NR	NR	NR
Shi et al., 2015[58]	11 with UEL; LVA	NR	3.00 cm (−0.01 to 6.01 cm)	Delayed healing ($n = 1$)	NR
Viitanen et al., 2013[59]	19 with UEL; LNT	NR	1.20 cm (−0.01 to 2.41 cm)	Donor-site infection ($n = 4$); seroma ($n = 5$); delayed wound closure ($n = 5$)	NR
Winters et al., 2017[77]	29 with UEL; LVA	234 ml (43.74–424.26 ml)	NR	None	−1.71 (−2.32 to −1.10)

MD, mean difference; QoL, quality of life; LEL, lower extremity lymphedema; NR, not reported; LNT, lymph node transfer; LVA, lymphaticovenular anastomosis; UEL, upper extremity lymphedema; PSFS, Patient-Specific Functional Scale; CCT, controlled compression therapy; ROM, range of motion; ADL, activities of daily living; NHP, Nottingham Health Profile; PGWB, Psychological General Well-Being Index; HAD, Hospital Anxiety Depression Test; LYMQOL, Lymphoedema Quality-of-Life; BMI, body mass index; S-LNT, supraclavicular lymph node transfer; G-LNT, groin lymph node transfer; O-RG-LNT, open right gastroepiploic lymph node transfer; L-RGLNT, laparoscopic right gastroepiploic lymph node transfer; Gas-LNT, gastroepiploic lymph node transfer; A-LNT, appendicular lymph node transfer; I-LNT, ileocecal lymph node transfer; I-LNT-HP, inguinal lymph nodes with hilar perforators; SF-36, 36-Item Short-Form Health Survey; ILND, inguinofemoral lymph node dissection; O-LNT, omental lymph node transfer; SLNT, submental lymph node transfer; SEKI-LVA, superior edge of knee incision; SE-LVA, side to-end LVA; CDT, complex decongestive therapy; LDB, leg dermal backflow; ADB, arm dermal backflow; EK-LVA, XXX lymphaticovenular anastomosis.

Table 3. Quality Assessment of Cohort and Case-Control Studies (Newcastle-Ottawa Scale)

Reference	Selection	Comparability	Outcomes
Akita et al., 2015[8]	4	0	3
Aljaaly et al., 2019[60]	4	0	2
Brorson et al., 1998[16]	4	1	3
Brorson et al., 2006[17]	4	0	3
Casabona et al., 2009[21]	3	0	2
Cheng et al., 2013[24]	4	0	3
Ciudad et al., 2017[25]	4	0	3
Ciudad et al., 2017[61]	4	0	3
Engel et al., 2018[62]	4	0	2
Feldman et al., 2015[29]	3	0	2
Gharb et al., 2011[31]	4	0	2
Granzow et al., 2014[34]	4	0	2
Hahamoff et al., 2019[63]	4	0	3
Koshima et al., 2000[40]	4	0	2
Koshima et al., 2003[42]	4	0	2
Lee et al., 2011[44]	4	0	2
Leppapuska et al., 2019[64]	4	0	3
Lin et al., 2019[65]	4	1	2
Maruccia et al., 2019[66]	4	0	3
Morotti et al., 2013[47]	3	0	2
Orefice et al., 1988[52]	4	0	2

therapy group (mean difference, 7.50 percent; 95 percent CI, 4.89 to 10.11 percent; $p < 0.00001$).[62]

Ten studies (134 patients) reported on lymphovenous bypass for reducing limb circumference in patients with stage II to V (Campisi or International Society of Lymphology) upper extremity lymphedema or lower extremity lymphedema.[9–11,37,39,40,42,46,48,58] Lymphovenous bypass combined with compression garments significantly reduced circumference by an average of 3.8 cm (95 percent CI, 2.93 to 4.67 cm; $p < 0.00001$; very low-quality evidence) (Fig. 1) after surgery. Two studies[39,71] also reported a significantly reduced circumference difference after lymphovenous bypass combined with compression garments in 29 patients (mean difference, 3.26 cm; 95 percent CI, 0.44 to 6.08 cm; $p = 0.02$). This benefit was significant for patients with upper extremity lymphedema (six patients) (mean difference, 5.30 cm; 95 percent CI, 3.12 to 7.48 cm; $p < 0.00001$) and lower extremity lymphedema (23 patients) (mean difference, 1.82 cm; 95 percent CI, 0.92 to 2.71 cm; $p < 0.0001$). Similarly, Ito et al.[38] found no significant difference in postoperative excess circumference reduction in five patients with lower extremity lymphedema who received lymphovenous bypass with compression garments (mean difference, 3.50 percent; 95 percent CI, −6.89 to 13.89 percent; $p = 0.51$). Ayestaray and Bekara[11] reported a significant reduction in limb volume of 504 ml (95 percent CI, 32.06 to 975.94 ml; $p < 0.05$) after lymphovenous bypass combined with compression garment use in 20 patients with upper and lower

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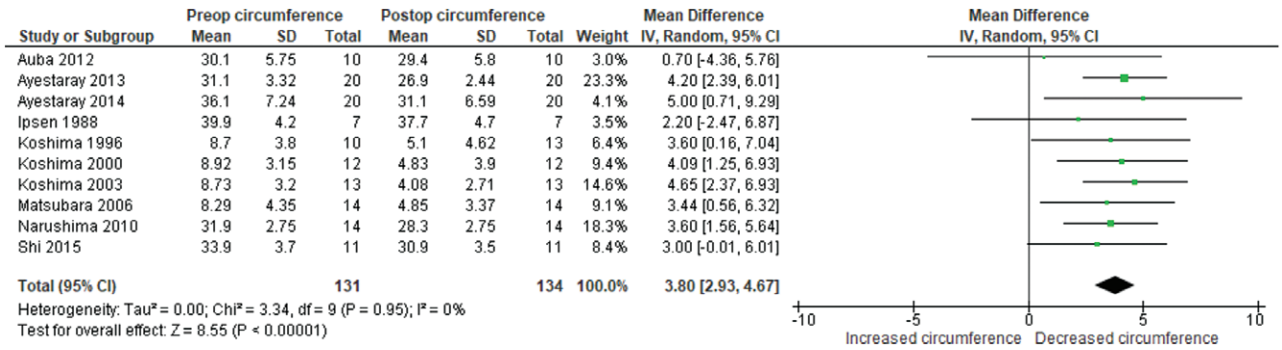

Fig. 1. Lymphovenous bypass; reduction in circumference (in centimeters).

extremity lymphedema. Similarly, Boccardo et al.[14] reported a large and significant excess volume reduction of 1858.6 ml (95 percent CI, 1721.48 to 1995.72 ml; $p < 0.00001$) after lymphovenous bypass combined with compression garment use in seven patients with lower extremity lymphedema. Winters et al.[77] reported a significant volume reduction of 234 ml (95 percent CI, 43.74 to 424.26 ml; $p = 0.02$) after lymphovenous bypass and compression garments in 29 patients with upper extremity lymphedema. Five studies (81 patients) reported on the proportion of patients who were able to discontinue compression garment use postoperatively.[10,11,14,38,77] Although 81 of 81 of patients (100 percent) used compression garments before lymphovenous bypass, 39 of 81 (48 percent) were able to stop using compression garments after surgery (OR, 0.03; 95 percent CI, 0.01 to 0.11; $p < 0.00001$).

Three case series (14 lower extremity lymphedema and 23 upper extremity lymphedema patients) reported on the mean number of cellulitis infections per year before and after surgery.[38,46,62] Mean cellulitis infections were significantly reduced after treatment with lymphovenous bypass and compression therapy (mean difference, 2.57; 95 percent CI, 1.75 to 3.38). Three case series (141 upper or lower extremity lymphedema patients) reported on preoperative and postoperative cellulitis.[32,33,51] Cellulitis was significantly reduced after lymphovenous bypass and compression therapy. The incidence of cellulitis before surgery was 67 percent (95 of 141) compared to 21 percent (29 of 141) after surgery (OR, 9.11; 95 percent CI, 2.31 to 35.97). A high degree of heterogeneity was detected (I^2 = 75 percent), which could reflect differences in surgical technique, patients, and lymphedema stage.

Vascularized Lymph Node Transfer

Four studies (300 patients) reported usable data for the comparison of vascularized lymph node transfer versus physiotherapy.[24,28,62,65] Dionyssiou et al.[28] reported significantly reduced percentage excess arm volume in patients who had vascularized lymph node transfer and physiotherapy compared to physiotherapy alone (mean difference, −15.00 ml; 95 percent CI, −22.0 to −7.97 ml; $p < 0.001$). Similarly, a pooled analysis of two studies showed a significant improvement in both circumferential differentiation (mean difference, 3.99 cm; 95 percent CI, 2.62 to 5.32 cm; 200 patients),[24,65] and circumferential reduction (mean difference, 24.29 percent; 95 percent CI, 21.81 to 26.76 percent; 84 patients),[24,62] in patients who underwent vascularized lymph node transfer and physiotherapy compared to physiotherapy alone. A pooled analysis of two studies (56 patients) shows a nonsignificant reduction in the number of infections per year in patients who underwent vascularized lymph node transfer and physiotherapy compared to physiotherapy alone (mean difference, −0.48; 95 percent CI, −1.25 to 0.29; $p = 0.22$). Patients who underwent vascularized lymph node transfer and physiotherapy had significantly reduced pain (36 patients) (mean difference, −4.00; 95 percent CI, −5.09 to −2.91; $p < 0.00001$) and heaviness (36 patients) (mean difference, −4.17; 95 percent CI, −5.62 to −2.72; $p < 0.00001$) and significantly improved overall function (36 patients) (mean difference, −3.39; 95 percent CI, −5.08 to −1.70; $p < 0.00001$) compared to physiotherapy patients.

Five studies (72 patients) reported on vascularized lymph node transfer for reducing limb circumference in stage II (International Society of Lymphology) upper extremity lymphedema.[31,45,50,56,59] Vascularized lymph node transfer combined with compression garments and complex decongestive therapy significantly reduced circumference by an average of 1.64 cm (95 percent CI, 0.87 to 2.42 cm; $p < 0.0001$; very low-quality evidence) (Fig. 2). Two studies (28 patients with upper extremity lymphedema) reported on circumference difference.[56,59] Circumference

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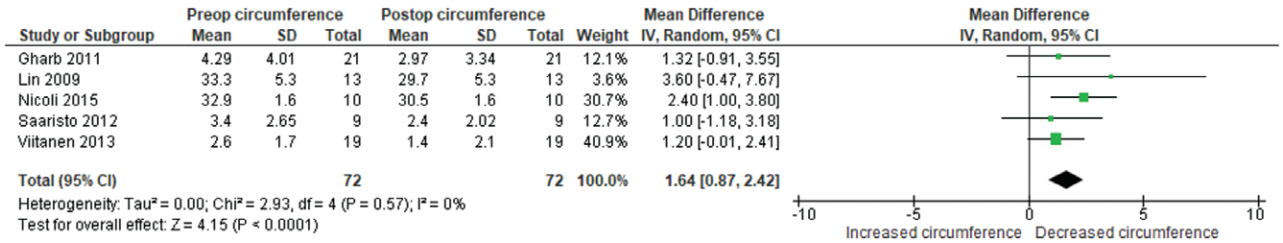

Fig. 2. Lymph node transplantation; reduction in circumference (in centimeters).

difference was significantly lower after vascularized lymph node transfer combined with compression garments and complex decongestive therapy (mean difference, 1.15 cm; 95 percent CI, 0.09 to 2.21 cm; $p = 0.03$). Two studies[53,73] reported on percentage excess volume reduction after vascularized lymph node transfer in 101 patients. Vascularized lymph node transfer significantly reduced excess limb volume by an average 9.60 percent (95 percent CI, 5.98 to 13.22 percent; $p < 0.00001$). This benefit was significant for patients with upper extremity lymphedema (45 patients) (mean difference, 7.83 percent; 95 percent CI, 5.09 to 10.57 percent; $p < 0.00001$) and lower extremity lymphedema (56 patients) (mean difference, 12.98 percent; 95 percent CI, 11.87 to 14.08 percent; $p < 0.00001$). Batista et al.[12] reported on preoperative and postoperative volume (in milliliters) in 15 lower extremity lymphedema patients. Vascularized lymph node transfer combined with physiotherapy and compression stockings reduced leg volume by an average of 900.0 ml (95 percent CI, −104.50 to 1904.50 ml; $p = 0.08$). Some of these patients also received liposuction. Leppapuska et al.[64] reported on preoperative and postoperative excess volume (in milliliters) in 27 upper extremity lymphedema patients. Vascularized lymph node transfer combined with compression stockings reduced arm volume by an average of 112.6 ml (95 percent CI, −81.61 to 306.81 ml; $p = 0.26$). Three studies (175 upper extremity lymphedema patients) reported on the proportion of patients who required physiotherapy and complex decongestive therapy postoperatively.[27,35,65] Although 104 of 175 patients (59 percent) required physiotherapy and complex decongestive therapy before vascularized lymph node transfer, 57 of 175 (33 percent) required physiotherapy and complex decongestive therapy after surgery (OR, 45.37; 95 percent CI, 8.73 to 235.78; $p < 0.00001$).

Eight case series (248 patients) reported on the mean number of cellulitis infections per year before and after surgery.[23,53,60,65–67,72,73] Cellulitis infections were significantly reduced after vascularized lymph node transfer (mean difference, 2.34; 95 percent CI, 1.82 to 2.85; $p < 0.00001$). This benefit was significant for upper extremity lymphedema (181 patients) (mean difference, 2.68; 95 percent CI, 1.94 to 3.41; $p < 0.00001$) and for lower extremity lymphedema (67 patients) (mean difference, 2.01; 95 percent CI, 1.12 to 2.91; $p < 0.001$). Six case series (233 patients with upper extremity lymphedema or lower extremity lymphedema) reported on the proportion of patients with preoperative and postoperative cellulitis.[35,49,61,64,69,75] Cellulitis was significantly reduced after vascularized lymph node transfer. The incidence of cellulitis before surgery was 53 percent (124 of 233) compared to 18 percent (42 of 233) after surgery (OR, 9.37 percent; 95 percent CI, 5.39 to 16.27 percent; $p < 0.0001$). Patel et al.[53] reported on quality of life using the Lymphoedema Quality-of-Life tool. Quality of life improved significantly after vascularized lymph node transfer (25 patients) (mean difference, −3.95; 95 percent CI, −4.33 to −3.57; $p < 0.00001$). This benefit was significant for upper extremity lymphedema (15 patients) (mean difference, −3.70; 95 percent CI, −4.14 to −3.26; $p < 0.00001$) and lower extremity lymphedema (10 patients) (mean difference, −4.10; 95 percent CI, −4.30 to −3.90; $p < 0.00001$).

Vascularized Lymph Node Transfer and Donor Site

Ciudad et al.[25] compared the morbidity of different donor sites for vascularized lymph node transfer in 110 patients with stage II to III (International Society of Lymphology) lymphedema. Donor sites included groin ($n = 20$), supraclavicular ($n = 54$), and right gastroepiploic, where an open ($n = 19$) or laparoscopic approach ($n = 17$) was used. No significant differences in complications were found across donor sites. Ciudad et al.[61] compared the circumference reduction rates across different donor sites for vascularized lymph node transfer in 45 patients with stage II (International Society of Lymphology) lymphedema. Donor sites included groin ($n = 10$), supraclavicular ($n = 10$), and gastroepiploic ($n = 25$).

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No significant differences in circumference reduction rates were found across donor sites.

Lymphovenous Bypass versus Vascularized Lymph Node Transfer

Three studies (161 patients) compared the efficacy and safety of lymphovenous bypass to vascularized lymph node transfer in stage I to III upper extremity lymphedema or lower extremity lymphedema patients.[8,34,44,62] A pooled analysis of two studies[8,44] showed no significant difference in lymphatic function at 12- to 18-month follow-up. Seventeen of 26 patients (65 percent) who underwent vascularized lymph node transfer had improved lymphatic function at 12- to 18-month follow-up compared to 26 of 62 patients (42 percent) who underwent lymphovenous bypass (OR, 1.73; 95 percent CI, 0.29 to 10.15). Similarly, a pooled analysis of two studies,[34,44] showed no significant difference in clinical improvement (lymphatic function) at 24-month follow-up. Fourteen of 21 patients (67 percent) who underwent vascularized lymph node transfer had improved lymphatic function at 24-month follow-up compared to 15 of 27 patients (56 percent) who underwent lymphovenous bypass (OR, 1.57; 95 percent CI, 0.48 to 5.17). Lee et al. also reported 48-month follow-up data.[44] Although the difference was not significant, more patients in the vascularized lymph node transfer group continued to experience improved lymphatic function at 48-month follow-up. Six of 13 patients (46 percent) who underwent vascularized lymph node transfer still had improved lymphatic function at 48 months compared to three of 19 lymphovenous bypass patients (16 percent) (OR, 4.57; 95 percent CI, 0.88 to 23.71; $p = 0.07$). Engel et al.[62] compared circumferential reduction rates, and patients who underwent vascularized lymph node transfer had a 16.7 percent (95 percent CI, 13.32 to 20.08 percent) greater reduction in circumference than patients who underwent lymphovenous bypass.

Two studies reported on postoperative complications.[8,34] Postoperative complications were reported in two of 41 lymphovenous bypass patients (5 percent), compared to six of 21 vascularized lymph node transfer patients (29 percent) (OR, 4.86; 95 percent CI, 0.99 to 23.86 percent; $p = 0.05$). Engel et al. compared cellulitis rates and, on average, patients who underwent vascularized lymph node transfer had 1.2 more episodes of cellulitis per year than patients who underwent lymphovenous bypass (95 percent CI, 0.42 to 1.98; $p = 0.02$). Granzow et al.[34] reported on compression garment use at 24-month follow-up. Six of eight vascularized lymph node transfer patients (75 percent) reported no compression garment use at 24 months compared to three of eight lymphaticovenous anastomosis patients (38 percent) (OR, 5.00; 95 percent CI, 0.58 to 42.80; $p = 0.14$). Akita et al. reported a significantly shorter hospital stay among lymphovenous bypass patients compared to vascularized lymph node transfer patients.[8] The mean hospital stay in the vascularized lymph node transfer group was 15.2 ± 1.6 days compared to 8.9 ± 2.9 days in the lymphovenous bypass group (mean difference, 6.30 days; 95 percent CI, 5.07 to 7.53 days).

Lymphatic Microsurgical Preventive Healing Approach

Three studies (154 patients) reported on the development of lymphedema at greater than 15-month follow-up in cancer patients who underwent lymphovenous bypass for prevention of lymphedema compared to a no-surgery control.[13,47,52,63] Significantly fewer lymphedemas developed in patients who underwent preventive lymphovenous bypass. Nine of 62 patients (14 percent) who underwent lymphovenous bypass developed lymphedema at 15 to 29 months' follow-up compared to 52 of 92 control patients (56 percent) (OR, 0.15; 95 percent CI, 0.06 to 0.35; $p < 0.0001$; very low-quality evidence). (**See Figure, Supplemental Digital Content 8**, which shows the lymphaticovenous anastomosis versus no preventive surgery; outcome = lymphedema at >18-month follow-up, *http://links.lww.com/PRS/E399*.) Two studies (140 patients) reported on complications.[47,52] Patients who had lymphovenous bypass and lymph node dissection were not at increased risk of developing complications compared to patients who only had lymph node dissection.

DISCUSSION

Limitations of Meta-Analysis

This meta-analysis has several limitations. Only two randomized controlled trials were included. The majority of included studies were observational studies, which are at high risk of bias, and the conclusions that can be drawn from these studies are limited. It was difficult to report a meta-analysis on these studies because of the variation in outcome measurements and lack of reported standard deviations. Although there was a lack of standardization in outcomes measurements, the magnitude of limb volume reduction was large for some procedures, particularly for liposuction.

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Physiologic Surgery (Lymphovenous Bypass and Vascularized Lymph Node Transfer)

A lymphedema therapist is recommended for patients undergoing lymphatic surgery. However, the failure of conservative management is not a prerequisite for physiologic surgery. This is based on a plurality of studies demonstrating that patients with earlier stage disease have better outcomes.

There is level I evidence demonstrating vascularized lymph node transfer and 6 months of compression and physiotherapy was more effective in reducing limb volume (grade 1B) and incidence of cellulitis than compression and physiotherapy alone.[28] Further studies that provide a nonsurgical control group are needed in this field. Mapping of the lymphatics is encouraged when harvesting lymph nodes adjacent to the limbs such as reverse lymphatic mapping to avoid lymphatics draining the limb and to minimize the risk of donor-site lymphedema.

A few studies compared lymphovenous bypass to vascularized lymph node transfer, but because of heterogeneous patient populations, there is currently no consensus regarding which procedure is more effective. We understand that patients with more advanced disease who may be offered vascularized lymph node transfer may not be candidates for lymphovenous bypass, and there may be inherent selection bias in these studies.

A few studies show that prophylactic lymphovenous bypass in patients undergoing lymphadenectomy may reduce the incidence of lymphedema. Prophylactic lymphovenous bypass should be avoided in cases of extremity malignancy. Lymphovenous bypass after mastectomy or inguinal dissection may reduce the incidence of lymphedema (grade 1B). The potential for hematogenous spread of extremity malignancies is unknown.

Liposuction

Liposuction is indicated for moderate to advanced lymphedema with a significant component of fat hypertrophy (grade 1C). Evidence of fat hypertrophy of the limb can be provided either by physical examination or by imaging. There is sufficient evidence that liposuction is safe with a large benefit in terms of limb volume reduction (grade 1C). There is a role for liposuction combined with physiologic procedures, although the timing of each procedure is currently unresolved.

Unresolved Questions

Is there a body mass index cutoff for offering physiologic procedures given the correlation with elevated body mass index and impaired lymphatic function? What is the role of scar release? Do physiologic procedures respond better in patients with preserved lymphatic architecture/early stage? Do physiologic procedures work better in upper extremity lymphedema or lower extremity lymphedema? We agree that the International Society of Lymphology staging system is a limited staging system that does not incorporate physiologic measures but is useful in communicating in general terms with the patient population.

CONSENSUS AND RECOMMENDATIONS

- There is evidence to support that lymphaticovenous anastomosis can be effective in reducing severity of lymphedema (grade 1C). A plurality of studies demonstrates that patients with earlier stage disease have better outcomes. There is no evidence that lymphovenous bypass can cure lymphedema.
- There is evidence to support that vascularized lymph node transfer can be effective in reducing the severity of lymphedema (grade 1B). There is no evidence that vascularized lymph node transfer can cure lymphedema.
- Currently, there is no consensus on which procedure (lymphovenous bypass versus vascularized lymph node transfer) is more effective (grade 2C).
- A few studies show that prophylactic lymphovenous bypass in patients undergoing extremity lymphadenectomy may reduce the incidence of lymphedema (grade 1B). More studies with longer follow-up are required to confirm this benefit.
- Debulking procedures such as liposuction are effective in addressing nonfluid component such as fat involving lymphedema (grade 1C).
- There is a role for liposuction combined with physiologic procedures, although the timing of each procedure is currently unresolved (grade 1C).
- Lymphatic procedures are highly complex, and anyone contemplating performing lymphatic surgery is encouraged to visit a high-volume center. To decrease the incidence of complications, microsurgical training is encouraged.
- A consensus on staging of lymphedema and preoperative and postoperative evaluation would be helpful.

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- There is a need for more quantitative methods for measuring fat, fluid, and physiologic measures and immunologic function.
- There is a need for better designed studies that include more objective reporting of outcomes and longer follow-up.

CONCLUSIONS

The role of surgery in the treatment of lymphedema has evolved from debulking procedures to those that aim to counteract the pathophysiology of lymphedema using microsurgical techniques. Many studies seem to support some efficacy of lymphovenous bypass and vascularized lymph node transfer. Many studies show the important role of lymphedema therapy and other procedures such as liposuction and debulking. The management of lymphedema is a challenging field with many promising advances. However, many questions remain unanswered.

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ACKNOWLEDGMENTS

The Consensus Panel acknowledges the support of the American Association of Plastic Surgeons, and Aurelie Alger and Rebecca Bonsaint, for their substantial contribution to this project. The authors appreciate additional data that were kindly provided by Håkan Brorson, M.D., Ph.D., and John Boyages, M.D., Ph.D.

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Journal of Surgical Oncology

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RESEARCH ARTICLE OPEN ACCESS

Preventing Secondary Lymphedema: A Systematic Review and Meta-Analysis on the Efficacy of Immediate Lymphovenous Anastomosis

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Received: 23 May 2025 | **Accepted:** 7 July 2025

Funding: The authors received no specific funding for this work.

Keywords: immediate lymphovenous anastomosis | lymph node surgery | lymphatic bypass | lymphedema | microsurgery | oncologic reconstruction | supermicrosurgery

ABSTRACT

Background: Secondary lymphedema is a debilitating condition following oncologic lymphadenectomy. Despite advancements in rehabilitation and microsurgical interventions, there is no cure for lymphedema. Performing a lymphovenous anastomosis (LVA) at the time of a regional node dissection has been purported to reduce the risks of secondary lymphedema; however, there are conflicting studies and no clear consensus about the routine use of LVA for preventing lymphedema after lymphadenectomy. The present study aims to perform a comprehensive review and meta-analysis on immediate LVA for the prevention of secondary lymphedema.

Methods: A systematic review and literature search were performed using PubMed, Embase, Web of Science, and Cochrane databases. Studies evaluating primary or immediate LVA in oncologic surgery were included. Studies with a control group were included in the meta-analysis.

Results: Overall, 39 studies, including 3697 patients (1,722 LVA; 1975 control), met inclusion criteria. Seventeen of the studies were included in the meta-analysis. Pooled analysis across all studies revealed a secondary lymphedema incidence of 7.1% in the LVA cohort versus 35.0% in controls. Meta-analysis demonstrated a significant reduction in lymphedema risk with immediate LVA (RR: 0.31). Subgroup analysis confirmed strong protective effects in breast cancer patients (RR: 0.28) and a significant but lesser benefit in dermatologic malignancies (RR: 0.35).

Conclusion: Based on the current literature, immediate LVA at time of lymphadenectomy significantly reduces the risk of secondary lymphedema in patients undergoing oncologic treatment. Given these findings, patients undergoing multimodal oncologic treatment including radiation and surgical lymphadenectomy should be considered candidates for immediate LVA.

1 | Introduction

Oncologic reconstruction is an essential component of comprehensive cancer care, restoring both form and function following surgical resection. Patients undergoing treatment for breast, dermatological, and gynecologic malignancies often require complex reconstructive procedures to optimize esthetic and functional outcomes. However, these surgeries frequently involve lymph node dissection and radiation therapy, both of which significantly disrupt the lymphatic system and place patients at risk for secondary lymphedema [1–4]. Secondary lymphedema is a progressive and often debilitating condition characterized by

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impaired lymphatic drainage, leading to chronic limb swelling, fibrosis, inflammation, recurrent infections, and reduced quality of life [5, 6]. The incidence of secondary lymphedema varies by cancer type and surgical intervention, with rates reported as high as 40% following axillary lymph node dissection for breast cancer and around 20% following inguinal lymphadenectomy for melanoma and gynecologic malignancies [7–9]. Despite advances in microsurgery and rehabilitation strategies, there is no cure for lymphedema which underscores need for preventative strategies.

The lymphovenous anastomosis (LVA) is a supermicrosurgical procedure that aims to restore lymphatic drainage by creating bypasses between lymphatic vessels and nearby venules, allowing lymphatic fluid to drain directly into the venous circulation [10]. LVA is a well-documented surgical treatment for lymphedema proven to have a significant benefit in volume reduction, decreased incidence of infection, reduced dependency on compression garments, and improvements in quality of life [11, 12]. More recently, interest has grown in the application of immediate LVA at the time of lymphadenectomy, where lymphatic vessels that are ligated during a nodal dissection are repaired to an adjacent vein to preserve the lymphatic drainage [13, 14]. While a number of modalities exist, all techniques utilize a dye that permits identification of the lymphatic vessels to be repaired [15]. Preliminary studies have suggested promising outcomes, with some reports indicating a significant reduction in lymphedema rates following immediate LVA [16–18].

Despite these promising early outcomes, immediate LVA or immediate lymphatic reconstruction is not yet considered the standard of care in oncological reconstruction when the lymph system is dissected. While many studies have demonstrated a significant reduction in the risk of lymphedema, others have reported contradictory results. Similarly, previous meta-analysis have been limited by inconsistency or short follow-up periods. Many meta-analyses are also outdated given the recent increase in new publications examining the efficacy of immediate LVA. This study aims to provide a comprehensive review of the current literature and perform an in-depth analysis to establish the true value of immediate LVA in mitigating the risks of secondary lymphedema following lymphadenectomy in oncological reconstruction.

2 | Materials and Methods

2.1 | Strategy

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. Our protocol for this review was registered on PROPSERO and is accessible at https://www.crd.york.ac.uk (Record: CRD42025642808).

2.2 | Search and Data Sources

A literature review was performed using PubMed, Embase, Web of Science, and Cochrane. No time constraints were placed on the search. The predetermined search terms utilized included "primary" OR "prophylactic" OR "immediate" AND "lymphaticovenous anastomosis" OR "lymphovenous bypass" OR "lymphatic-venous anastomosis" OR "lymphovenous anastomosis" OR "lymphedema prevention" OR "lymphatic reconstruction" AND "lymphedema" OR "lymphoedema" OR "secondary lymphedema" OR "postoperative lymphedema." Appendix 1 contains the full search terms for each database.

2.3 | Selection Criteria

The Covidence platform (Veritas Health Innovation, Melbourne, Australia) was used for screening. The screening was performed independently by two investigators (C.H. and M.S.); first by title and abstract and then by full-text review. A third investigator (A.O.) resolved conflicts. Studies were eligible if they included patients undergoing immediate LVA at time of lymphadenectomy and reported on secondary lymphedema. Studies that did not focus on immediate LVA or did not report secondary lymphedema were excluded.

2.4 | Data Extraction

The variables extracted from the studies included publication year, lead author, study design, patient sample size, age, body mass index (BMI), area of lymph node dissection, number of lymph nodes removed, number of LVAs performed, frequency of radiotherapy treatment, frequency of secondary lymphedema, and follow-up period. Weighted means and frequencies along with pooling of secondary lymphedema data were performed using Microsoft Excel (Redmond, WA; College Station, TX).

2.5 | Definition of Treatment and Comparison Groups

The treatment group consisted of patients who underwent immediate LVA at the time of lymphadenectomy, which could be at or before oncological resection such as mastectomy or dermatological excision. Additionally, all LVAs, both regionally at site of lymphadenectomy or distally, were included; however, all patients included in the study had LVAs regionally to the lymphadenectomy. The control group included patients who underwent the same types of oncological surgery without immediate LVA. Studies that included patients who had therapeutic LVA for established lymphedema were excluded. There was no strict age cutoff for patient inclusion; however, pediatric patients were not included in the reviewed studies given the rarity of cancer-related lymph node dissection in this population. Studies that were case reports, case series with less than five patients, systematic reviews, and meta-analysis were excluded. Case series with five patients or greater were included only for pooling rates of secondary lymphedema after LVA use; however, they were not included in the meta-analysis.

2.6 | Definition of Outcomes

The immediate outcome assessed was the incidence of secondary lymphedema following lymphadenectomy and oncologic surgery, comparing patients who underwent immediate LVA to those who did not. While each study utilized different

techniques to assess lymphedema, it was defined for this study as an increase in extremity circumference with patient reported symptoms including extremity swelling, feeling of heaviness or tightness in an extremity, skin changes such as thickening or redness, or extremity discomfort or aching. A subgroup analyses was performed based on the type of malignancy. Specifically, secondary lymphedema incidence was stratified by breast and dermatological malignancies that required lymphadenectomy. This analysis aimed to determine whether immediate LVA had differential efficacy based on malignancy type.

2.7 | Statistical Analysis

Meta-analysis was performed using Cochrane Review Manager RevMan 5.4 (London, United Kingdom). Weighted means and frequency were calculated for patient characteristics of both cohorts (LVA cohort and control). Total incidence for lymphedema was calculated along with risk ratios (RR) with 95% confidence intervals (CI). Statistical differences were noted as a $p < 0.05$.

2.8 | Risk of Bias

Two investigators (C.H. and M.S.) independently conducted a quality and bias assessment using a data extraction form, following the Downs and Black (D&B) checklist. The quality of each study was evaluated based on the established criteria for the D&B score, categorized as excellent (≥ 26), good (20–25), fair (15–19), or poor (≤ 14). Additionally, a level of evidence score was assigned to each study according to the American Society of Plastic Surgeons (ASPS) Level of Evidence (LOE) Rating Scale for Therapeutic Studies.

3 | Results

3.1 | Search Results

Our initial search identified 1024 citations (Figure 1). Following the removal of duplicates, 726 citations were screened based on their titles and abstracts. Subsequently, 78 articles were selected for full-text review, resulting in the inclusion of 39 studies (Table S1) [18–55]. Studies were excluded for several reasons: incorrect indications (patients did not receive immediate LVA), inappropriate study design, or incorrect outcome assessment (did not report secondary lymphedema). The inclusion criteria for the meta-analysis component included studies that compared rates of secondary lymphedema between patients who had and had not received LVA, with 17 studies meeting this requirement to be included for meta-analysis.

3.2 | Pooled Baseline Characteristics: Lymphovenous Anastomosis and Control Cohorts

A total of 3697 patients were included in this study with 1722 patients receiving immediate LVAs while the remaining 1975 served as controls. The weighted mean age (standard deviation [SD]) of the LVA cohort was 55.4 (5.76) while for the control cohort it was 56.62 (6.12). Notably, two studies did not provide patient ages. The weighted mean BMI (SD) was 27.10 (1.95) for the LVA cohort and 27.55 (1.66) for the control cohort, with 12 studies not reporting BMI.

Females were the predominant gender in both cohorts, comprising 93.87% of the LVA group (with four studies not reporting gender). The most common oncological pathology treated was breast cancer in both groups, occurring in 79.66% of LVA patients and 81.35% of controls. Melanoma was the second most common pathology, seen in 13.93% of LVA patients and 16.21% of controls, followed by squamous cell carcinoma (2.91%) in the LVA cohort and sarcoma (1.33%) in the control group.

The mean (SD) number of lymph nodes removed during oncological resection was similar between groups: 15.78 (3.52) for the LVA cohort and 15.75 (3.62) for the control cohort. However, 13 studies did not report lymph node counts for the LVA group. The majority of dissections and anastomoses were performed in the axilla (88.92%) for the LVA group, whereas the control cohort predominantly had dissections in the axilla as well (85.94%).

Regarding surgical characteristics, the mean (SD) number of anastomoses created in the LVA group was 2.11 (0.82), though 19 studies did not report the number of anastomoses created. Among anastomotic techniques, end-to-end was the most common (63.48%), followed by intussusception (18.17%) and sleeve (14.13%). Nine studies did not specify the type of anastomosis utilized.

For adjuvant oncologic treatment, 78.92% of LVA patients and 65.94% of control patients received radiotherapy, though 11 studies did not report radiotherapy status. The mean follow-up time (SD) across all studies was 21.34 months (19.72).

Pooling across all studies, the rate of secondary lymphedema was significantly lower in the LVA cohort at 7.14% compared to 35.04% in the control cohort. Table 1 presents the demographics, surgical characteristics, and rates of lymphedema for both groups.

3.3 | Meta-Analysis

The meta-analysis utilized 17 studies and included studies that had both an LVA and control cohort, which directly assesses the impact of LVA on secondary lymphedema across different oncological indications. Immediate LVA was associated with a 69% lower risk of secondary lymphedema compared to the control group (RR: 0.31, 95% CI: 0.23–0.42, $p < 0.00001$) (Figure 2). A total of 78 patients developed secondary lymphedema in the LVA group out of 917 patients (8.51%), compared to 692 patients in the control group out of a total of 1975 patients (35.04%). Heterogeneity was low ($I^2 = 22\%$, $p = 0.20$), suggesting consistent results across studies.

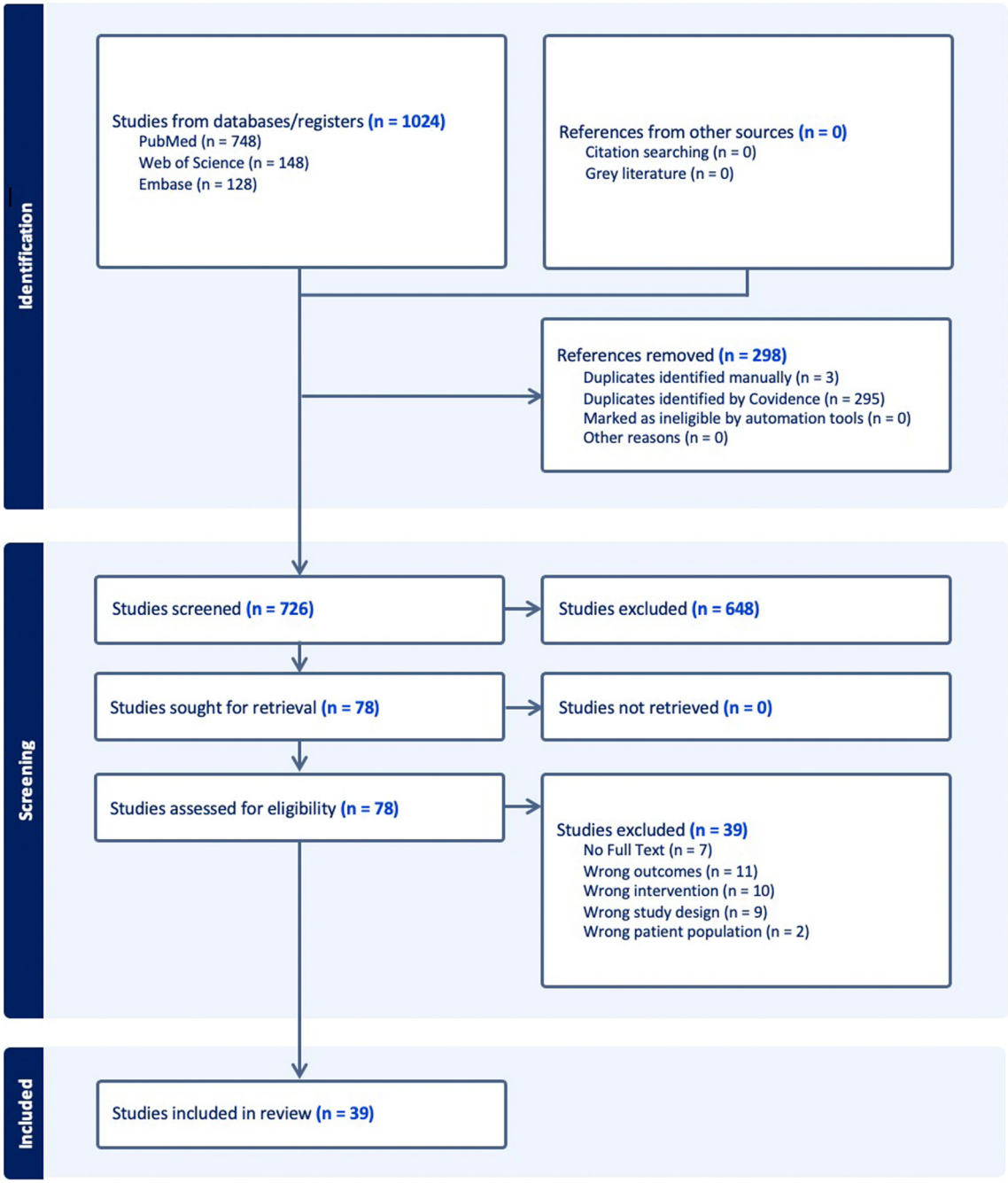

FIGURE 1 | Figure 1 illustrates the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for the study selection process. The initial search identified 1024 records from three databases: PubMed ($n = 748$), Web of Science ($n = 148$), and Embase ($n = 128$). No additional references were obtained through other sources such as citation searching or gray literature. After removing 298 duplicates, 726 studies remained for screening. Of these, 648 studies were excluded based on title and abstract screening, leaving 78 studies for full-text assessment. No studies were unavailable for retrieval. Following eligibility assessment, 39 studies were excluded due to reasons such as lack of full text ($n = 7$), reporting of irrelevant outcomes ($n = 11$), use of the wrong intervention ($n = 10$), incorrect study design ($n = 9$), or an inapplicable patient population ($n = 2$). Ultimately, 39 studies were included in the final systematic review.

3.4 | Subgroup Analysis: Malignancy Type

In subgroup analysis of breast surgery, LVA was associated with a 72% reduction in risk of secondary lymphedema compared to the control group (RR: 0.28, 95% CI: 0.20–0.39, $p < 0.00001$) (Figure 3), A total of 62 patients developed secondary lymphedema out of 778 patients who were in the LVA group (7.97%), compared to 571 patients out of 1596 patients in the control group (35.78%). Heterogeneity was similarly low ($I^2 = 22\%$, $p = 0.23$), indicating a consistent effect across the studies within this subgroup.

For the subgroup analysis of dermatologic malignancies, which includes both melanoma and squamous cell carcinomas, the effect of LVA was slightly less pronounced with a 65% reduction in risk of secondary lymphedema compared to the control group (RR: 0.35,

TABLE 1 | This table presents patient demographics, surgical characteristics, and lymphedema incidence between the prophylactic lymphovenous anastomosis (LVA) cohort and the control cohort. Variables include sample size, mean age, body mass index (BMI), frequency of female patients, number of lymph nodes removed, percentage of upper extremity lymphadenectomy, mean number of anastomoses performed, frequency of radiotherapy, and incidence of secondary lymphedema. Values are reported as mean (standard deviation [SD]) or frequency (%) with corresponding sample sizes provided in brackets.

	LVA cohort	Control cohort
Sample	1722	1975
Age: Mean (SD) [Sample Size]	55.41 (5.76) [1630]	56.62 (6.12) [1975]
BMI: Mean (SD) [Sample Size]	27.20 (1.95) [1271]	27.56 (1.66) [1239]
Female Frequency [Sample Size]	93.87% [1565]	92.90% [1832]
Lymph Nodes Removed: Mean (SD) [Sample Size]	15.78 (3.52) [1195]	15.75 (3.63) [631]
LVA Site: Upper Extremity Frequency [Sample Size]	88.92% [1742]	85.94% [1921]
Anastomosis: Mean (SD) [Sample Size]	2.11 (0.82) [634]	N/A
Radiotherapy: Frequency [Sample Size]	78.92% [1309]	65.94% [869]
Lymphedema: Frequency [Sample Size]	7.14% [1722]	35.04% [1975]

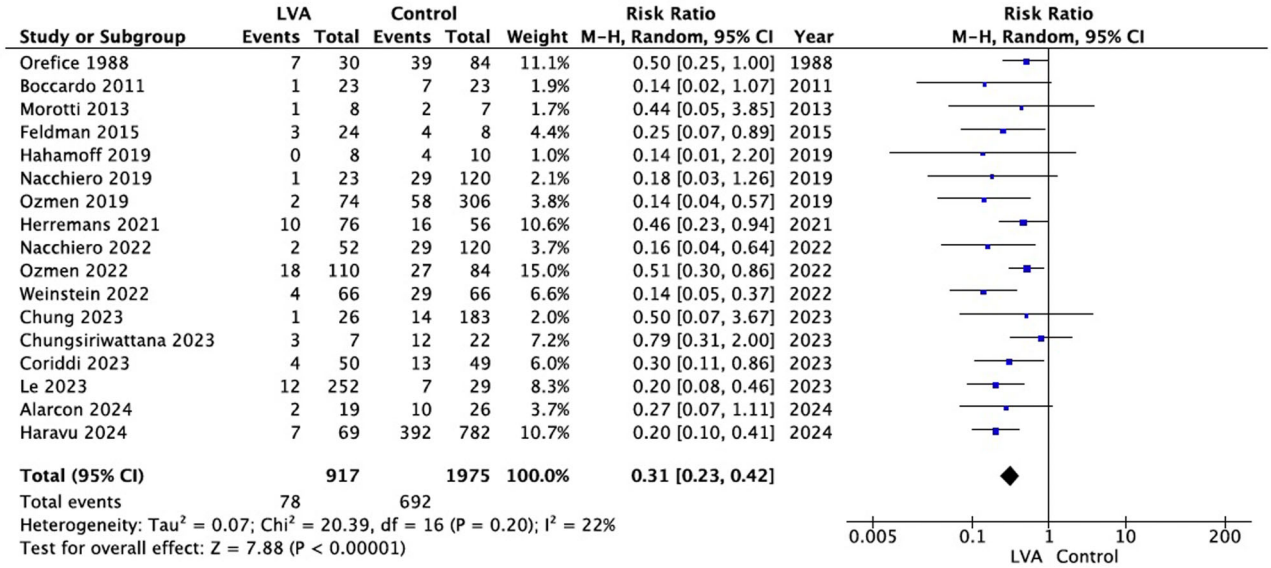

FIGURE 2 | This forest plot illustrates the pooled risk ratio (RR) with 95% confidence intervals (CI) for the incidence of secondary lymphedema in patients undergoing immediate LVA compared to controls. Each included study is represented as a data point, with the horizontal lines indicating the confidence interval and the size of the square reflecting the study weight. The diamond at the bottom represents the overall effect estimate. The meta-analysis demonstrates a significant reduction in secondary lymphedema risk in the LVA cohort (RR: 0.31, 95% CI: 0.23–0.42, $p < 0.00001$), indicating that immediate LVA is associated with a 69% lower risk of developing lymphedema compared to standard oncologic surgery alone. Heterogeneity analysis ($I^2 = 22\%$, $p = 0.20$) suggests low variability among included studies.

95% CI: 0.13–0.98, $p = 0.05$) (Figure 3). There were 7 patients who developed secondary lymphedema out of 90 LVA patients (7.78%), compared to 72 patients in 269 control group patients (26.77%). Heterogeneity was moderate ($I^2 = 46\%$, $p = 0.14$), suggesting some variability among included studies (Figure 4).

3.5 | Risk of Bias and Quality Score

The risk of bias and quality assessment for the included studies were conducted using the D&B checklist. Of the 39 studies evaluated, the mean (SD) D&B score was 19.72 (2.87) (Table S1). This means the average score was "Good" as there was a mix of case series, retrospective, and prospective cohort. The mean ASPS LOE (SD) was 3.31 (0.89). All studies received between 2 and 4 for LOE.

4 | Discussion

Although immediate LVA has garnered recent popularity, the overall effectiveness of this procedure being routinely used in preventing secondary lymphedema remains uncertain. In our meta-analysis, we find that immediate LVA at time of lymphadenectomy was associated with a reduction in the risk of secondary lymphedema across every oncological patient

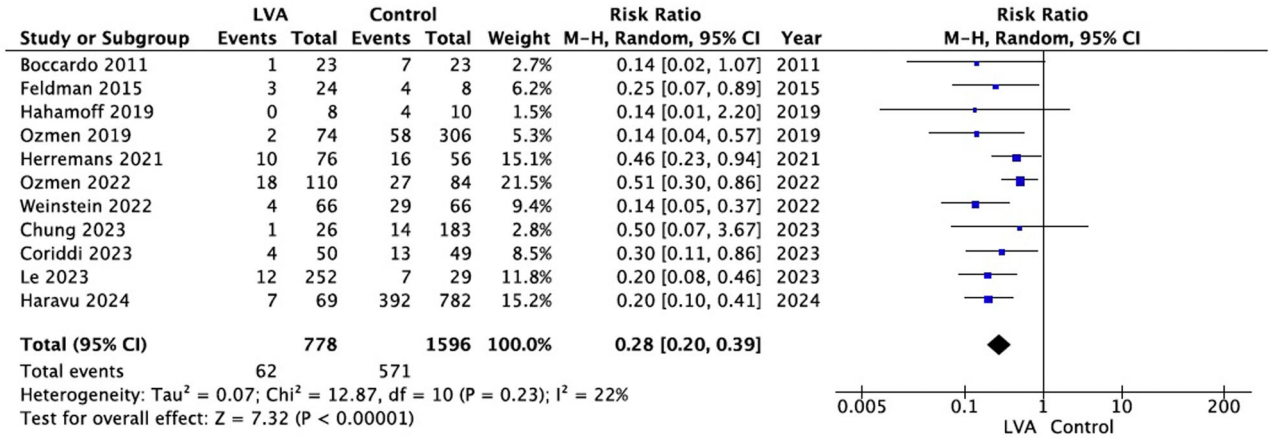

FIGURE 3 | This forest plot presents the pooled risk ratio (RR) with 95% confidence intervals (CI) for the development of secondary lymphedema after mastectomies with immediate lymphovenous anastomosis (LVA) compared to those who did not receive LVA. Each study is represented as a square, with the horizontal lines denoting the confidence interval, while the size of the square reflects the study's weight in the analysis. The diamond at the bottom represents the overall effect estimate. The meta-analysis indicates a significant reduction in lymphedema risk for the LVA cohort (RR: 0.28, 95% CI: 0.20–0.39, $p < 0.00001$), demonstrating a 72% lower risk of developing secondary lymphedema compared to controls. Heterogeneity analysis ($I^2 = 22\%$, $p = 0.23$) suggests a low degree of variability across included studies.

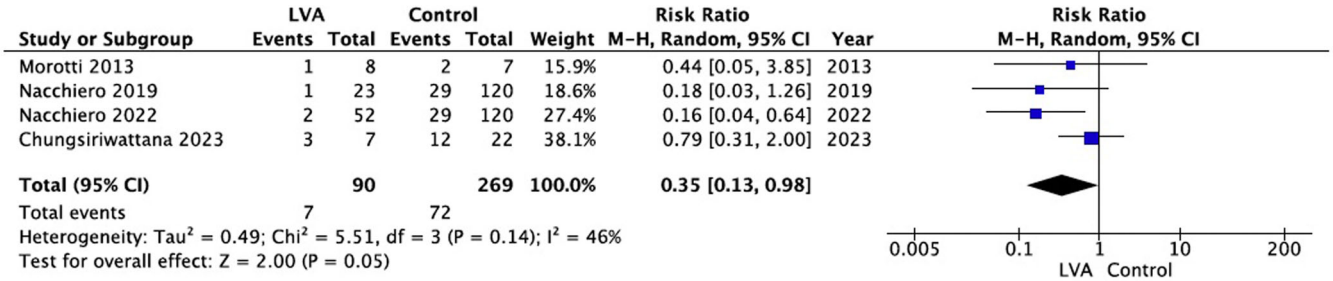

FIGURE 4 | This forest plot displays the pooled risk ratio (RR) with 95% confidence intervals (CI) for the incidence of secondary lymphedema in patients undergoing immediate lymphovenous anastomosis (LVA) following lymphadenectomy for dermatologic malignancies, including melanoma and squamous cell carcinoma. Each included study is represented by a square, with horizontal lines indicating the confidence interval, while the size of the square reflects the study's weight in the analysis. The diamond at the bottom represents the overall effect estimate. The meta-analysis demonstrates a significant reduction in lymphedema risk for the LVA cohort (RR: 0.35, 95% CI: 0.13–0.98, $p = 0.05$), indicating a 65% lower risk of developing secondary lymphedema compared to controls. Heterogeneity analysis ($I^2 = 46\%$, $p = 0.14$) suggests moderate variability among included studies.

population studied. These findings suggest that immediate LVA is beneficial in reducing the risk of secondary lymphedema after surgical treatment of a malignancy.

4.1 | Biologic Rationale for Immediate Lymphovenous Anastomosis

The pathophysiology of secondary lymphedema is driven by the disruption of lymphatic drainage pathways following oncologic lymphadenectomy, leading to chronic fluid stasis, inflammation, and fibrosis [56]. Once fibrosis sets in, lymphatic function is irreversibly compromised, limiting the effectiveness of delayed interventions [57]. Our findings indicate that immediate LVA mitigates this process by establishing direct lymphatic-to-venous bypasses, ensuring uninterrupted lymphatic flow postoperatively. Biologically, LVA prevents lymphatic endothelial apoptosis and vessel regression, mechanisms that contribute to progressive lymphatic failure [58]. Studies have demonstrated that early restoration of lymph flow sustains vessel integrity and reduces inflammatory signaling, ultimately promoting long-term lymphatic remodeling and function preservation [59–61]. Our subgroup analysis confirms that immediate LVA is effective in minimizing risk of secondary lymphedema in both breast and dermatologic malignancies, supporting the hypothesis that earlier intervention leads to superior outcomes.

Additionally, LVA may counteract radiotherapy-induced lymphatic damage, as 78.92% of patients in the LVA cohort had received adjuvant radiotherapy; yet, this cohort still exhibited significantly lower lymphedema rates compared to controls whom also had a high frequency of adjuvant radiotherapy use. This suggests that LVA provides a protective effect even in patients with additional risk factors, reinforcing its role as a key adjunct to oncologic surgery.

4.2 | Impact of Lymphovenous Anastomosis on Quality of Life and Patient-Reported Outcomes

Secondary lymphedema significantly reduces health-related quality of life, leading to chronic limb swelling, physical

discomfort, restricted mobility, and psychological distress [62–64]. While none of the studies included in the meta-analysis directly reported on quality of life measures, it has been shown in the literature how microsurgical treatments improve quality of life for those with breast cancer-related lymphedema [65–67]. Our study adds to the growing body of evidence demonstrating that patients who undergo immediate LVA report 26.53% risk reduction in symptoms associated with lymphedema due to its prevention.

Additionally, our analysis contributes to the research around the economic burden of secondary lymphedema, as lifelong management strategies—such as manual lymphatic drainage, compression therapy, and physical therapy—incur significant costs and impose long-term limitations on patients [68–70]. By substantially lowering the incidence of lymphedema, immediate LVA reduces dependency on conservative management, translating to lower long-term healthcare costs and improved patient autonomy.

4.3 | Lymphovenous Anastomosis in Sentinel Lymph Node Biopsy and Axillary Dissection

Within breast cancer treatment, sentinel lymph node biopsy (SLNB) and axillary lymph node dissection (ALND) cause direct trauma to the lymphatic system, with ALND carrying a particularly high risk of lymphedema due to extensive nodal clearance [71, 72]. Despite its less invasive nature, some studies have highlighted that SLNB can still result in subclinical lymphatic dysfunction, which may progress to symptomatic lymphedema over time [73]. Amongst the included studies in this review, all LVAs were conducted after ALND or other forms of lymphadenectomy, not after SLNB alone or with mastectomy. Additionally, all ALNDs and lymphadenectomies in this study were done during the same procedure. While we are unable to highlight its benefits amongst those patients that received SLNB, our study highlights the importance of integrating LVA in procedures that dissect lymph nodes. LVA can be helpful particularly in treating patients with additional risk factors which are known to increase risk of lymphedema such as high nodal burden cancer, obesity, or adjuvant radiation therapy [74–77]. Immediate LVA at the time of ALND offers a practical solution by rerouting lymphatic fluid into the venous circulation, preventing stagnation and inflammatory changes that lead to chronic lymphedema. Given our findings of a 27.81% risk reduction in breast cancer patients, LVA should be strongly considered as a standard adjunct for all patients undergoing ALND within their breast cancer treatment.

4.4 | Immediate Lymphovenous Anastomosis in Different Malignancies

The risk reduction associated with immediate LVA in preventing secondary lymphedema appears to vary by oncological malignancy, highlighting potential differences in pathophysiology, surgical burden, and lymphatic compromise across malignancies. The differences in risk reduction may be attributable to distinct tumor biology, variations in lymphatic disruption, and surgical techniques used for different malignancies. For example, breast cancer surgeries often involve axillary lymphadenectomy, where LVA may provide more consistent lymphatic drainage restoration, whereas dermatologic malignancies can require inguinal or cervical lymphadenectomy, which may introduce greater variability in lymphatic reconstruction efficacy. These findings reinforce the importance of considering malignancy-specific factors when evaluating LVA's role in lymphedema prevention.

4.5 | Study Quality, Limitations, and Future Directions

Despite the strength of our meta-analysis, several limitations must be acknowledged. Most included studies were retrospective cohort studies, thereby introducing selection bias and limiting the ability to establish causal relationships. Additionally, only a small number of randomized controlled trials have assessed prophylactic LVA, emphasizing the need for prospective, multi-institutional trials to further validate these findings. Heterogeneity in surgical technique, patient selection, and follow-up duration also presents a challenge. Future studies should focus on standardizing anastomotic techniques, vein caliber selection, and postoperative monitoring to optimize LVA outcomes. Furthermore, multiple year long-term follow-up data is limited, highlighting the need for extended studies assessing late-onset lymphedema development. Additionally, quality of life assessments should be utilized to assess decrease in morbidity associated with immediate LVA. Despite these limitations, this study differs from previous systematic reviews and meta-analyses in several keyways. First, it includes the largest sample size to date, incorporating a broader and more comprehensive data set that enhances statistical power and generalizability. Additionally, this study integrates more recent studies, reflecting advancements in surgical techniques, patient selection, and postoperative management. Secondly, we stratify the results based on malignancy type, specifically analyzing outcomes by both breast and dermatologic malignancies. Prior reviews have primarily focused on breast, limiting their ability to assess potential differences in efficacy across various other oncologic populations.

5 | Conclusion

This systematic review and meta-analysis provide compelling evidence that immediate LVA significantly reduces secondary lymphedema risk across oncological indications, with the most pronounced benefit observed in breast cancer patients. While some view LVA as only an experimental technique, this study highlights the potential of LVA to be the standard of care when lymphadenectomy occurs in oncological reconstruction. This study shows LVA as an effective intervention that significantly reduces lymphedema risk. Despite inherent study limitations, the findings strongly support the clinical utility of LVA as a preventative strategy. Future research should prioritize randomized trials and standardized surgical techniques to refine patient selection and optimize long-term outcomes.

Ethics Statement

Study is nonhuman subjects research and didn't require IRB approval.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The study was registered on PROPSERO and data is accessible at https://www.crd.york.ac.uk/PROSPERO/ (Record: CRD42025642808). Any additional details regarding the data analysis is available upon request from the authors.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

NICE National Institute for Health and Care Excellence

NICE guidance

Lymphovenous anastomosis during axillary or inguinal node dissection for preventing secondary lymphoedema

Interventional procedures guidance
Published: 16 April 2024

www.nice.org.uk/guidance/ipg785

Your responsibility

This guidance represents the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, healthcare professionals are expected to take this guidance fully into account, and specifically any special arrangements relating to the introduction of new interventional procedures. The guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

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Commissioners and/or providers have a responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties. Providers should ensure that governance structures are in place to review, authorise and monitor the introduction of new devices and procedures.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

1 Recommendations

Breast cancer

1.1 Lymphovenous anastomosis during axillary dissection for preventing secondary lymphoedema in adults with breast cancer can be used in the NHS while more evidence is generated. It can only be used with special arrangements for clinical governance, consent, and audit or research.

1.2 Clinicians wanting to do lymphovenous anastomosis during axillary node dissection for preventing secondary lymphoedema in people with breast cancer should:

- Inform the clinical governance leads in their healthcare organisation.
- Ensure that people (and their families and carers as appropriate) understand the procedure's safety and efficacy, and any uncertainties about these.
- Take account of NICE's advice on shared decision making, including NICE's information for the public.
- Audit and review clinical outcomes of everyone having the procedure. The main efficacy and safety outcomes identified in this guidance can be entered into NICE's interventional procedure outcomes audit tool (for use at local discretion).
- Discuss the outcomes of the procedure during their annual appraisal to

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reflect, learn and improve.

1.3 Healthcare organisations should:

- Ensure systems are in place that support clinicians to collect and report data on outcomes and safety for everyone having this procedure.
- Regularly review data on outcomes and safety for this procedure.

1.4 Patient selection should be done by a multidisciplinary team experienced in managing the condition.

1.5 This procedure should only be done by a multidisciplinary team experienced in it, including a surgeon with specific training in microvascular surgery.

Other cancers

1.6 More research is needed on lymphovenous anastomosis during axillary or inguinal node dissection for preventing secondary lymphoedema for other cancers in adults.

1.7 This procedure should only be done as part of a formal research study, and a research ethics committee needs to have approved its use.

More research

1.8 More research is needed on:

- patient selection
- quality of life
- longer-term outcomes for lymphoedema incidence in different conditions
- limb volume
- safety outcomes (including survival and metastatic cancer).

Why the committee made these recommendations

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Evidence from clinical trials and observational studies suggests that the procedure reduces the risk of lymphoedema after axillary node dissection in people with breast cancer. It also suggests that there are no major safety concerns. While there are some limitations in the evidence, including a lack of quality-of-life data and long-term follow up, overall it is considered adequate. So, it can be used with special arrangements for breast cancer.

The evidence for the procedure's efficacy in other cancers (that is, lower limb cancers and malignant melanoma) is more limited. Also, there are some safety concerns about the risk of the cancer spreading after lymphatic vessels around the dissected lymph nodes have been rediverted to nearby veins. So, it should be used only in research for other cancers.

2 The condition, current treatments and procedure

The condition

2.1 Lymphoedema is the build-up of lymph fluid in a limb, causing swelling of that limb. It is a common complication after treatments for various cancers, and can be chronic and debilitating. The condition can severely damage the skin, and cause aching in or difficulty moving the affected limb. There can also be recurrent skin infections, needing frequent antibiotic use and sometimes hospitalisation.

Current treatments

2.2 There are no curative treatments but there are various treatments to help control the symptoms of lymphoedema. They aim to reduce swelling and infection while improving lymphatic flow in the body, and include:

- decongestive lymphatic therapy, which comprises compression garments, manual lymphatic draining, skin care, exercise and massage done with specialist help or alone by the person with lymphoedema
- the 2 surgical techniques, liposuction and lymphovenous anastomosis.

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The procedure

2.3 This version of lymphovenous anastomosis is done during axillary or inguinal node dissection to reduce the risk of lymphoedema developing after surgery. This procedure, also known as LYMPHA (lymphatic microsurgical preventive healing approach), involves creating a bypass from the transected lymphatics to nearby veins. Before the node dissection, a dye is injected to map the lymphatic circulation from the arm or thigh. During the node dissection, the surgical team inserts the cut lymphatic vessels into a small branch of the axillary or saphenous veins with the aim of restoring normal lymph flow.

2.4 The standard LYMPHA technique is done by surgeons with microvascular experience, using an operating microscope and, typically, 9-0 to 12-0 sutures.

2.5 There is also a simplified technique known as S-LYMPHA, which can be done by surgeons without microsurgical training, without an operating microscope and using 7-0 sutures.

3 Committee considerations

The evidence

3.1 NICE did a rapid review of the published literature on the efficacy and safety of this procedure. This comprised a comprehensive literature search and detailed review of the evidence from 12 sources, which was discussed by the committee. The evidence included 4 systematic reviews, 1 randomised controlled trial, 1 prospective study and 6 retrospective cohort studies. It is presented in the summary of key evidence section in the interventional procedures overview. Other relevant literature is in the appendix of the overview.

3.2 The professional expert and the committee considered the key efficacy outcomes to be: a reduction in secondary lymphoedema and technical success of lymphovenous anastomosis.

3.3 The professional expert and the committee considered the key safety outcomes

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to be: pain, bleeding, infection, overall survival and disease-free survival.

3.4 Patient commentary was sought but none was received.

Committee comments

3.5 Current treatments for lymphoedema, such as manual lymphatic drainage and compression garments, are often uncomfortable, time-consuming and need to be lifelong. This procedure has the potential to improve a person's quality of life and could have other benefits such as reduced hospitalisation.

3.6 There has been limited uptake of the lymphatic microsurgical preventive healing approach (LYMPHA) in the UK. The clinical expert explained that this is mainly because it needs to be done with specialist equipment by microsurgery-trained surgeons. There is a simplified version of the procedure (S-LYMPHA) that can be done by the operating breast surgeon (without microsurgical training) and does not need specialist equipment. But most of the evidence is for LYMPHA and not S-LYMPHA.

3.7 The clinical expert explained that lymphatic reconstruction may potentially increase the risk of metastatic disease if the procedure is done for lower limb (non-central) cancers such as malignant melanomas, and that more safety evidence is needed.

3.8 The clinical expert advised that studies with 5-year follow up are needed to better establish the safety and efficacy of the procedure.

3.9 Patient consent should include that additional operating time is needed for this procedure, and that it is still possible that lymphoedema may develop.

ISBN: 978-1-4731-5887-0

Endorsing organisation

This guidance has been endorsed by Healthcare Improvement Scotland.

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Section 7.0

Previously Discussed Items

Septoplasty for Breathing Issues Alone May 2026

Plain Language Summary:

A surgery to straighten the divider inside the nose (nasal septum) may help with breathing problems.

Medical studies show that the surgery helps only for more severe disease based on patient symptom scales. HERC staff propose two options for discussion: one would add coverage for nasal surgery for severe disease and the other would not.

Changes after public comment period:

One public comment was received on this topic from an OHP provider. The commentor supported coverage and provided CPT codes and guideline wording regarding rhinoplasty that should be covered if septoplasty alone is not sufficient. These CPT codes and substantially similar guideline wording would be covered/included if the option that would including adding coverage for septoplasty for breathing issues is approved. Therefore, no changes were made to the staff recommendation based on this comment.

Staff Analysis Summary:

Significant proposed changes or discussion items:

Staff propose discussing two options.

1) Do not add coverage for septoplasty for breathing issues alone.
2) Add coverage for severe cases when other treatments have not been effective.

Coverage Question:

Should recent coverage decisions regarding septoplasty be reconsidered particularly for patients with significant nasal breathing issues?

Question source:

Mendy Maccabee, MD ENT in Hood River and Anthem medical director

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Background:

Reconstructive septoplasty is the surgical correction of defects and deformities of the nasal septum (partition between the nostrils) by altering, splinting or removing obstructive tissue while maintaining or improving the physiological function of the nose. Cosmetic rhinoplasty and/or septoplasty are performed solely to enhance appearance. However, Dr. Maccabee says that rhinoplasty or rhinoseptoplasty is sometimes needed in order to perform septoplasty.

Septoplasty can also be performed for a variety of medical indications. Septoplasty is currently not covered on the Prioritized List for breathing issues alone. Septoplasty is covered for patients with chronic sinusitis so that surgeons can access the sinuses in order to treat the sinusitis. Dr. Maccabee is requesting reconsideration of lack of coverage of septoplasty or rhinoseptoplasty for inability to breathe through the nose.

Rhinoplasty and septoplasty were discussed as part of the BUP ENT review, with final decisions made at the June 2025 VBBS/HERC meeting. Septoplasty was again discussed at the March 2026 VBBS/HERC meetings. In March, members requested that the two septoplasty issues, breathing alone and CPAP tolerance, be separated and the discussion from the EBGS/HERC discussion of septoplasty from the BUP review be summarized.

The Sino-Nasal Outcome Test (SNOT-22) and Nasal Obstruction and Septoplasty Effectiveness scale (NOSE) are standard symptom measurement instruments for breathing issues.

Previous HSC/HERC reviews:

HERC staff recommendations for the June 2025 EBGS/HERC meeting was to include coverage of septoplasty for inability to breathe through the nose. Committee members disagreed and requested that the section of the guideline referring to this indication (currently on an uncovered line) be deleted. From the June 2025 EBGS minutes:

> Septoplasty and rhinoplasty: members were concerned with adding coverage for nasal obstruction as this condition is more of an irritation rather than a medical problem, and removed the section about nasal obstruction from the

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> guideline…A procedure code for nasal valve repair was recommended for the Not Medically Necessary file

The June EBGS discussion did not include any evidence review of septoplasty for breathing issues.

At the March 2026 VBBS and HERC meetings, RCT data on breathing outcomes after septoplasty compared to optimal medical management was reviewed. Expert guidelines were also reviewed.

Current Prioritized List/Coverage status:

ICD-10-CM J34.2 (Deviated nasal septum) is on line 562 DEVIATED NASAL SEPTUM, ACQUIRED DEFORMITY OF NOSE, OTHER DISEASES OF UPPER RESPIRATORY TRACT

CPT *30520 (Septoplasty or submucous resection, with or without cartilage scoring, contouring or replacement with graft) is on lines

> 42 CLEFT PALATE WITH AIRWAY OBSTRUCTION
> 119 CHOANAL ATRESIA
> 244 LIFE-THREATENING EPISTAXIS
> 285 CANCER OF ORAL CAVITY, PHARYNX, NOSE AND LARYNX
> 309 GENDER AFFIRMING TREATMENT
> 464 CHRONIC SINUSITIS
> 495 NASAL POLYPS, OTHER DISORDERS OF NASAL CAVITY AND SINUSES
> 512 BENIGN NEOPLASM OF NASAL CAVITIES, MIDDLE EAR AND ACCESSORY SINUSES
> 562 DEVIATED NASAL SEPTUM, ACQUIRED DEFORMITY OF NOSE, OTHER DISEASES OF UPPER RESPIRATORY TRACT
> 599 ANOMALIES OF RELATIONSHIP OF JAW TO CRANIAL BASE, MAJOR ANOMALIES OF JAW SIZE, OTHER SPECIFIED AND UNSPECIFIED DENTOFACIAL ANOMALIES
> 625 TMJ DISORDERS

CPT *30620 (Septal or other intranasal dermatoplasty (does not include obtaining graft)) is on lines 42, 244, 464, 495, and 562

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CPT *30420 (Rhinoplasty, primary; including major septal repair) is on lines 309, 464, 495, and 562

Beginning 1/1/2027 with the BUP Prioritized List, CPT *30420 will be in the code group RHINOPLASTY AND SEPTOPLASTY AND CHRONIC SINUSITIS SURGERY. ICD-10-CM J34.2 will also be in code group RHINOPLASTY AND SEPTOPLASTY AND CHRONIC SINUSITIS SURGERY. CPT *30520 and 30620 will be placed only on currently covered lines with BUP.

Current Prioritized List guideline:

GUIDELINE NOTE 118, SEPTOPLASTY

Lines 42,119,201,244,285,309,464,495,512,562

Septoplasty is included on Line 309 for gender affirming treatment.

Septoplasty is included on Lines 42, 119, 201, 244, 285, 464, 495, 512 and 562 when

A) The septoplasty is done to address symptomatic septal deviation or deformity which
   1) Fails to respond to a minimum 6-week trial of conservative management (e.g. nasal corticosteroids, decongestants, antibiotics); AND
   2) Results in persistent or recurrent epistaxis, OR documented recurrent sinusitis felt to be due to a deviated septum and the patient meets criteria for sinus surgery in Guideline Note 35, SINUS SURGERY; OR
B) Septoplasty is performed in association with cleft lip or cleft palate repair or repair of other congenital craniofacial anomalies; OR
C) Septoplasty is performed as part of a surgery for a neoplasm or facial trauma involving the nose.

Septoplasty for other nasal obstruction not meeting the criteria above is included only on Line 562.

Septoplasty is not included on these lines for treatment of obstructive sleep apnea and is not included on Line 201 SLEEP APNEA, NARCOLEPSY, INSOMNIA, HYPERSOMNIA, AND REM BEHAVIORAL DISORDER.

BUP guideline

COVERAGE GUIDELINE ~~NOTE~~ 118, SEPTOPLASTY

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Code Groups ~~Lines~~ 42,119,201,244,285,309~~,463,499,518,570~~, 499 10XXX RHINOPLASTY AND SEPTOPLASTY AND CHRONIC SINUSITIS SURGERY

Septoplasty is medically necessary ~~included on Line 309~~ for gender affirming treatment.

Septoplasty is medically necessary ~~included on Lines 42, 119, 201, 244, 285, 463, 499, 518 and 570~~ when

A) The septoplasty is done to address symptomatic septal deviation or deformity which
   1) Fails to respond to a minimum 6-week trial of conservative management (e.g. nasal corticosteroids, decongestants, antibiotics); AND
   2) Results in one or more of the following:
      a) Persistent or recurrent epistaxis, OR
      b) Documented recurrent sinusitis felt to be due to a deviated septum and the patient meets criteria for sinus surgery in Coverage Guideline ~~Note~~ 35, SINUS SURGERY~~; OR~~
      c) ~~Nasal obstruction with documented absence of other causes of obstruction likely to be responsible for the symptoms (for example, nasal polyps, tumor, etc.) [note: this indication is included only on Line 570; OR~~
B) Septoplasty is performed in association with cleft lip or cleft palate repair or repair of other congenital craniofacial anomalies; OR
C) Septoplasty is performed as part of a surgery for a neoplasm or facial trauma involving the nose.

Septoplasty is not ~~covered~~ medically necessary for treatment of obstructive sleep apnea and is not included in code grouping ~~on Line~~ 201 SLEEP APNEA, NARCOLEPSY, INSOMNIA AND REM BEHAVIORAL DISORDER.

Date of last review: June 2025

GUIDELINE NOTE 216, RHINOPLASTY

Lines 42,119,201,244,285,309,464,495,512

Rhinoplasty is included on Line 309 for gender affirming treatment.

Rhinoplasty is included on Lines 42 and 119 when

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A) It is performed to correct a nasal deformity secondary to congenital cleft lip and/or palate or other severe congenital craniofacial anomaly.

B) Rhinoplasty is included on Lines 227, 285, 495, 512 and 562 when it is performed as part of reconstruction after accidental or surgical trauma or disease (for example, Wegener's granulomatosis, nasal malignancy, abscess, septal infection with saddle deformity) AND

1) There is prolonged, persistent obstructed nasal breathing unresponsive to a six-week trial of conservative management (e.g. nasal corticosteroids, decongestants, antibiotics); AND
2) Airway obstruction will not respond to septoplasty and turbinectomy alone; AND
3) Photographs demonstrate an external nasal deformity; AND
4) There is significant obstruction of one or both nares, documented by nasal endoscopy, computed tomography (CT) scan or other appropriate imaging modality.

C) Rhinoplasty is included on Line 464 when there is nasal airway obstruction causing chronic rhinosinusitis when all of the following are met:

1) The criteria for sinus surgery are met in Guideline Note 35, SINUS SURGERY; AND
2) Airway obstruction will not respond to septoplasty and turbinectomy alone; AND
3) Photographs demonstrate an external nasal deformity; AND
4) There is significant obstruction of one or both nares, documented by nasal endoscopy, computed tomography (CT) scan or other appropriate imaging modality

Care for acute nasal fractures (up to 14 days from the injury) is included on Line 227. Sequalae of nasal fractures, including nasal deformities, are included on Line 562.

Evidence:

Effectiveness of septoplasty for breathing issues alone

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1) **Carrie 2023**: Clinical effectiveness of septoplasty versus medical management for nasal airways obstruction: multicentre, open label, randomised controlled trial
    a. NAIROS trial, funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme in the UK
    b. N=307 adults with symptoms of nasal obstruction associated with septal deviation and at least moderate symptoms of nasal obstruction (score >30 out of 100 on the Nasal Obstruction and Symptom Evaluation (NOSE) scale). The NOSE scale is an patient survey that can help measure how a patient's breathing symptoms are affecting your quality of life.
        i. N=152 in surgical group at 6 months post-op (4 did not receive surgery). Some of these patients also received inferior nasal turbinate reduction, which is covered on the Prioritized List for the same conditions as septoplasty.
        ii. N=155 in the medical management group (5 received septoplasty)
            1. Participants randomized to receive medical management were supplied with six months' supply of isotonic nasal saline spray (Sterimar; Sofibel, Paris, France) to be used twice daily, and mometasone furoate nasal steroid spray to be used twice daily after the saline spray and then 100 µg twice daily for six weeks, then reduced to 100 µg once daily or 50 µg twice daily for the remainder of the six months.
            2. Participants could cross-over to septoplasty at 6 months
    c. **Six month outcomes:** Patient reported symptoms improved in both groups. In those participants randomized to receive septoplasty in the ITT population (n=152), mean SNOT-22 scores were 44.5 (95% confidence interval 41.1 to 47.8) at baseline and 19.9 (17.0 to 22.7) at six months. The corresponding scores for those participants randomized to receive medical management in the ITT population (n=155) were 44.1 (40.8 to 47.4) and 39.5 (36.1 to 42.9). Participants randomized to the septoplasty group (n=188) reported on average a greater improvement of 20.0 units over those randomized to the medical management group (n=190) (95% confidence interval improvement 16.4 to 23.7). Patients with moderate NOSE scores (less than 50) did not have a clinically-significant improvement in SNOT scores, but those with higher NOSE scores (severe, or extreme) did.

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i. Minimally clinically important change in SNOT score=9 points
ii. Note: SNOT is a subjective test of self reported physical and emotional symptoms and sleep, which is different from the NOSE scale used for patient inclusion criteria.

d. **12-month outcomes (crossover was allowed; 5 of 155 crossed over and received septoplasty):** The mean SNOT-22 score in the septoplasty group was 21.2 (95% confidence interval 17.7 to 24.6) at 12 months, whereas the corresponding values in the medical management group were 30.4 (26.6 to 34.3). Participants randomized to the septoplasty group (n=119) reported on average 10.1 units greater improvement in symptoms at 12 months compared with those randomized to the medical management group (n=125), as measured by SNOT-22 (95% confidence interval improvement 5.6 to 14.5, P<0.001). The study did not report whether effect size was different for patients with more severe symptoms at 12 months.
    i. MCID SNOT-22 score is 9 points
        1. Quality of life and symptom measures are both components of SNOT-22

e. Serious adverse events
    i. N=14 (out of 188) in the septoplasty group
    ii. N=9 (out of 190) in the medical management group
    iii. seven readmissions with bleeding (4% of 174 participants who underwent septoplasty), 20 infections requiring antibiotics (12%), 19 reported events of altered sense of smell (11%), 18 events of upper teeth numbness (11%), 17 reported changes in the appearance of the nose (10%), 7 clinician observed adhesions (4%), and 6 clinician observed septal perforations (3%). No participants required repeat surgery

f. Authors conclusions: Septoplasty is a superior treatment for nasal obstruction associated with septal deviation compared with a defined regimen of nasal steroid and saline sprays. Baseline NOSE scores can estimate the likely improvement in symptoms and guide decision making for patients and clinicians. The authors recommend that adults presenting with nasal obstruction associated with a deviated nasal septum should be offered septoplasty

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g. HERC staff note: clinically meaningful improvement in subjective SNOT-22 score only found for patients with initial NOSE scores in the severe range or higher (>50)

2) **Srinivasan 2021**: Comparison of the Efficacy of Septoplasty with Nonsurgical Management in Improving Nasal Obstruction in Patients with Deviated Nasal Septum – A Randomized Clinical Trial
   a. No reported funding source
   b. N=140 patients randomized, 117 with 6 month follow up data
      i. N=60 septoplasty group with 6 month follow up
         1. Baseline SNOT-22 score 19.5 (12-24.5), indicating mild to moderate disase
      ii. N=57 medical management (fluticasone, nasal decongestant, other medications) with 6 month follow up
         1. Baseline SNOT-22 score 15 (10-22), indicating mild to moderate disease
   c. At 6 month follow up
      i. VAS score surgical group 2.9 (1) vs non-surgical group 5.26 (2.3), P=0.001
      ii. SNOT-22 score surgical group 10 (8-16) vs non-surgical group 12 (8-20), P=0.002
         1. MCID SNOT-22 score is 8.9 points
   d. Authors' conclusions: Surgical correction of DNS by septoplasty improves nasal obstruction better than nonsurgical management at 6 months postsurgery. Note: the difference was not clinically significant in this cohort of patients, who had mild to moderate SNOT scores before surgery.

3) **Van Egmond 2019** Septoplasty with or without concurrent turbinate surgery versus non-surgical management for nasal obstruction in adults with a deviated septum: a pragmatic, randomized controlled trial
   a. Funded by the Netherlands Organisation for Health Research and Development
   b. N=197 adults with symptoms of nasal obstruction associated with septal deviation
      i. N=97 in surgical group

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1. Mean SNOT-22 score 64.1 (SD 15.0) (These scores were inverted on a 100-point scale and represent moderate disease, equivalent scoring to the studies above would be 35.9 (SD 15.0) or moderate disease for the mean group, with the standard deviation including mild disease))

ii. N=100 in the control group (watchful waiting or medical management)

1. Non-surgical management did not involve a prespecified treatment regime. Medications could be used
2. 30 patients actually had septoplasty
3. Mean SNOT-22 score 62.1 (SD 16.4) (These scores were inverted on a 100-point scale and represent moderate disease, equivalent scoring to the studies above would be 37.9 (SD 16.4) or moderate disease in the mean group with the standard deviation including mild to severe disease)

c. At our primary timepoint of 12 months, the mean Glasgow Health Status Inventory (GHSI) score of patients assigned to septoplasty was 72.2 (SD 12.2) and to non-surgical management was 63.9 (SD 14.5; mean difference 8.3 [95% CI 4.5–12.1]). The Glasgow Health Status Inventory is a broader measure of quality of life than the NOSE or SNOT score. It is patient reported and includes measures of general health, social health and physical health related to conditions treated by ENTs. Higher scores indicate better perceived health status and the score ranges from 0 to 100. This study inverted the GHSI score, making 100 no symptoms and 0 severe symptoms.

i. MCID for the GHSI is 35-44 points, making these changes not clinically significant

d. At 12 months, the NOSE scale for the septoplasty group was 67.5 (SD 24.5) and the non-surgical group was 49.6 (SD 23.6). The surgical group score was reduced 36.2, which is clinically significant. The non-surgical group score was reduced by 15.2 points, which is not clinically significant. . (

i. Note: scales are inverted from standard reporting

e. At 12 months, the SNOT-22 score for the septoplasty group was 76.8 (SD 17.1) and the non-surgical group was 67.0 (SD 19.5). The surgical group

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score was reduced 12.7, which is clinically significant. The non-surgical group score was increased by 4.9 points

i. Note: scales are inverted from standard reporting

f. Postoperative complications occurred in 23 (18%) patients who were assigned to septoplasty or had crossed-over to surgery. The most frequent complications were hemorrhage and infection (table 3); these complications occurred directly after surgery and were mild, meaning that patients either did not require treatment or could be treated at the outpatient clinic with nasal packing or local or oral antibiotics. Septal perforation occurred in two patients and septal abscess in one patient, who was hospitalized to receive intravenous antibiotics; consequently, the septal abscess was classified as a serious adverse event. No other serious adverse events related to the treatments under study occurred during the trial. No adverse events related to nasal medication were reported. Revision surgery because of persisting complaints was required in one patient

g. Authors conclusions: Septoplasty is more effective than non-surgical management for nasal obstruction in adults with a deviated septum and severe patient-reported breathing quality of life. This effect was sustained up to 24 months of follow-up

Submitted literature:

1) Alkholaiwi 2023: small retrospective cohort study (N=42) of qualify of life impacts of septoplasty
2) Hismi 2020: prospective cohort study of quality of life impacts of septoplasty
3) Han 2015: included in expert guidelines section below
4) Shedden 2005: phone survey of impact of nasal congestion on quality of life in patients with allergic rhinitis
5) Premara BCBS 2025 coverage policy for septoplasty: included in other payer policies section below

Expert guidelines:

1) **Han 2015** Clinical Consensus Statement: Septoplasty with or without Inferior Turbinate Reduction

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a. Limited to adults (age 18 and older)
b. Septoplasty can be used in the primary management of obstructive sleep apnea for patients with deviated septum
c. Septoplasty can be effective in reducing primary snoring in patients with a deviated septum
d. Septoplasty can reduce facial pain caused by intranasal contact points
e. Septoplasty may benefit anosmia or hyposmia, but the effect is unpredictable
f. A trial of medical therapy .4 weeks' duration is unnecessary to assess surgical candidacy for septoplasty
g. Septoplasty can improve continuous positive air pressure tolerance for patients with sleep apnea and a deviated septum
h. Septoplasty may be useful in managing epistaxis
i. Septoplasty can improve quality of life for patients with septal deviation.
j. Septoplasty can improve outcomes of sinus surgery when the septum is contacting the middle turbinate and obstructing the drainage of the ostiomeatal complex

2) American Academy of Otolaryngology-Head and Neck Surgery 2012 Clinical Indicators: Septoplasty
   a. Available at https://www.entnet.org/resource/clinical-indicators-septoplasty/
      i. Accessed January 15, 2026
   b. History (one or more required)
      i. Nasal airway obstruction (unilateral or bilateral) causing any of the following: mouth breathing, snoring, nasal congestion, sleep apnea, unresponsive to medical management.
      ii. Frequent nosebleeds, unresponsive to medical management, and for which deviation is a causative factor.
      iii. Atypical facial pain of nasal origin. (Positive response to topical anesthetic, where deformed septum contacts a turbinate or lateral wall, supports, but may not prove, septal causation or contribution.)
      iv. Asymptomatic deformity that prevents surgical access to other intranasal or paranasal areas, e.g., sinuses, turbinates.

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Other payer policies:

1) Premara BCBS 2025
    a. Rhinoplasty may be considered medically necessary for nasal obstruction when the following criteria are met:
        i. Clinical findings of collapsed internal nasal valve at rest or collapsed external nasal valve (lateral walls) with inspiration (nasal vestibular stenosis) OR
        ii. To correct a nasal deformity secondary to trauma that is causing a significant functional impairment (e.g., nasal bone fracture causing nasal airway obstruction) AND
        iii. Individual has symptoms of nasal obstruction (difficulty breathing or chronic rhinosinusitis [inflammation/swelling of the nasal passages and/or sinus cavities]) affecting quality of life AND
        iv. Infection, allergy, rhinitis, and polyps have been ruled out as the primary cause of nasal obstruction as evidenced by:
            1. Obstructive symptoms persist despite conservative management for 8 weeks or greater with one of the following:
                a. Decongestants or antihistamines
                b. Nasal lavage
                c. Oral or intranasal steroids
                d. A course of antibiotics for rhinosinusitis
                e. Allergy assessment and treatment
2) Aetna 2025
    a. Aetna considers septoplasty medically necessary when *any* of the following clinical criteria is met:
        i. Asymptomatic septal deformity that prevents access to other intranasal areas when such access is required to perform medical necessary surgical procedures (e.g., ethmoidectomy); *or*
        ii. Documented recurrent sinusitis felt to be due to a deviated septum not relieved by appropriate medical and antibiotic therapy; *or*
        iii. Recurrent epistaxis (nose-bleeds) related to a septal deformity; *or*

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iv. Septal deviation causing continuous nasal airway obstruction resulting in nasal breathing difficulty not responding to 4 or more weeks of appropriate medical therapy; *or*
v. When done in association with cleft palate repair.

3) NHS 2026
   a. Coverage criteria based on the NAIROS trial (Carrie 2024)
   b. Septoplasty covered for patients with
      i. severe symptoms on the NOSE (score 55 or higher) or SNOT-22 (score greater than 50) AND
      ii. Failure of trial of appropriate medical and conservative measures (intranasal corticosteroids and nasal irrigation for 3 months, avoidance of exacerbating factors, no use of nasal decongestants that cause rhinitis medicamentosa, and treatment of allergic or drug induced rhinitis if appropriate) AND
      iii. The severe nasal symptoms are associated with septal or nasal wall deformities or a clinical diagnosis of chronic sinusitis

Expert input:

Dr. Peggy Kelley, pediatric ENT

Indications for septoplasty for breathing are covered by commercial insurances. If a person has no response to medical therapy and is still unable to breathe through their nose secondary to a physical blockage of a deviated septum, a septoplasty is indicated. In fact, sometimes a septoplasty is needed to be able to get medical therapy to the turbinates. Nasal breathing is preferred over mouth breathing for more than cosmesis. The nose is set up to be a filter for our airway as well as to humidify and warm the air before reaching the lungs. These functions are only partially met with mouth breathing. Constant mouth breathing will decrease dental health as the teeth need to be bathed in saliva to breaks down the peridontal bacteria.

Dr. Sara Yang, OHSU adult ENT

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A septoplasty is not a cosmetic procedure. It does not alter the outward appearance of the nose. Its function is to address an anatomical obstruction that physically obstructs nasal air flow.

Topical medical therapy or nasal saline rinses impact the mucosal layer. It is wonderful for addressing nasal congestion but not nasal obstruction. There is no evidence or published papers that topical therapy would improve a deviated septum (anatomical issue).

Therefore, when a physical exam reveals an anatomical obstruction that is impacting nasal breathing (resulting in detriments to sleep, exercise, or daily functions) or obstructs the placement of topical medication for chronic nasal or sinus conditions, I believe that a septoplasty should be covered by insurance. One corrective surgery may overall reduce the healthcare utilization burden by addressing the root cause of the issue.

HERC staff summary:

The majority of the literature on the impact of septoplasty on quality of life in patients with breathing difficulties consists of retrospective and prospective cohort studies. Three RCTs were identified by HERC staff that compared septoplasty to medical management/watchful waiting and reported on quality of life measures. An RCT of 307 adults found clinically meaningful improvement in the SNOT and SNOT-22 scores, which are subjective quality of life rating scales, in patients undergoing septoplasty, but not in patients with medical management at 6 months and 1 year. Of note, this clinically meaningful impact was only found in patients with severe disease at baseline. Similarly, an RCT of 117 adults did not find a clinically meaningful difference between surgical and medical groups in the SNOT-22 scores at 6 months in patients with mild to moderate disease. The third RCT of 197 adults with mild to moderate disease did not find a clinically significant improvement in quality of life with the Glasgow Health Status Inventory at 12 months between surgical and medical management but did find clinically significant improvement in the NOSE and SNOT-22 scores with surgery; of note, there was considerable cross-over of the medical group to surgery in this study which would tend to make the differences between groups smaller than expected. All three studies reported

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significant adverse surgical events, including bleeding, abscess, need for repeat surgery, or readmission.

HERC staff conclude from this literature review that for patients with mild to moderate disease, there is mixed evidence that septoplasty is superior to medical management. However, in patients with more severe disease, septoplasty resulted in a clinically significant improvement in breathing symptoms compared to medical management. Serious complications from the surgery have been reported. The improvements seen with surgery are in patient reported outcomes.

Expert groups and Oregon experts recommend septoplasty for breathing issues. Private and public payers are covering septoplasty for this indication. The NHS is covering septoplasty for severe disease after a trial of medical management.

HERC staff propose two options for discussion. One is to make no change as the clinically significant impact of septoplasty is measured by a subjective score. The second is to adopt coverage for severe disease based on the Carrie 2023 study with wording added to the guideline based on NHS coverage policy.

HERC staff recommendation:

Consider the following options:

Option 1

Make no change in non-coverage of septoplasty for breathing issues alone

Option 2

A) Add ICD-10-CM J34.2 (Deviated nasal septum) to line 464 CHRONIC SINUSITIS and keep on line 562 DEVIATED NASAL SEPTUM, ACQUIRED DEFORMITY OF NOSE, OTHER DISEASES OF UPPER RESPIRATORY TRACT
B) Modify Guideline Note 118 as shown below [Note: additional changes to GN118 proposed in a separate issue summary]
C) Modify Guideline Note 216 as shown below

GUIDELINE NOTE 118, SEPTOPLASTY

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Lines 42,119,201,244,285,309,464,495,512,562

Septoplasty is included on Line 309 for gender affirming treatment.

Septoplasty is included on Lines 42, 119, 201, 244, 285, 464, 495, 512 and 562 when

D) The septoplasty is done to address symptomatic septal deviation or deformity which
   1) Fails to respond to a minimum 6-week trial of conservative management (e.g. nasal corticosteroids, decongestants, antibiotics); AND
   2) Results in persistent or recurrent epistaxis, OR documented recurrent sinusitis felt to be due to a deviated septum and the patient meets criteria for sinus surgery in Guideline Note 35, SINUS SURGERY; OR
   4) Nasal obstruction with documented absence of other causes of obstruction likely to be responsible for the symptoms (for example, nasal polyps, tumor, etc.) for patients with
      a. Severe symptoms on the NOSE (score 55 or higher) or SNOT-22 (score greater than 50) AND
      b. Failure of trial of appropriate medical and conservative measures (intranasal corticosteroids and nasal irrigation for 3 months, avoidance of exacerbating factors, no use of nasal decongestants that cause rhinitis medicamentosa, and treatment of allergic or drug induced rhinitis if appropriate) AND
      c. The severe nasal symptoms are associated with septal or nasal wall deformities or a clinical diagnosis of chronic sinusitis; OR

E) Septoplasty is performed in association with cleft lip or cleft palate repair or repair of other congenital craniofacial anomalies; OR

F) Septoplasty is performed as part of a surgery for a neoplasm or facial trauma involving the nose.

Septoplasty for other nasal obstruction not meeting the criteria above is included only on Line 562.

Septoplasty is not included on these lines for treatment of obstructive sleep apnea and is not included on Line 201 SLEEP APNEA, NARCOLEPSY, INSOMNIA, HYPERSOMNIA, AND REM BEHAVIORAL DISORDER.

GUIDELINE NOTE 216, RHINOPLASTY

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Lines 42,119,201,244,285,309,464,495,512

Rhinoplasty is included on Line 309 for gender affirming treatment.

Rhinoplasty is included on Lines 42 and 119 when

A) It is performed to correct a nasal deformity secondary to congenital cleft lip and/or palate or other severe congenital craniofacial anomaly.

B) Rhinoplasty is included on Lines 227, 285, 495, 512 and 562 when it is performed as part of reconstruction after accidental or surgical trauma or disease (for example, Wegener's granulomatosis, nasal malignancy, abscess, septal infection with saddle deformity) AND

1) There is prolonged, persistent obstructed nasal breathing unresponsive to a six-week trial of conservative management (e.g. nasal corticosteroids, decongestants, antibiotics); AND
2) Airway obstruction will not respond to septoplasty and turbinectomy alone; AND
3) Photographs demonstrate an external nasal deformity; AND
4) There is significant obstruction of one or both nares, documented by nasal endoscopy, computed tomography (CT) scan or other appropriate imaging modality.

C) Rhinoplasty is included on Line 464 when there is nasal airway obstruction causing chronic rhinosinusitis or nasal obstruction meeting Guideline Note 118 criteria when all of the following are met:

1) The criteria for sinus surgery are met in Guideline Note 35, SINUS SURGERY OR the criteria for septoplasty are met in Guideline Note 118 SEPTOPLASTY; AND
2) Airway obstruction will not respond to septoplasty and turbinectomy alone; AND
3) Photographs demonstrate an external nasal deformity; AND
4) There is significant obstruction of one or both nares, documented by nasal endoscopy, computed tomography (CT) scan or other appropriate imaging modality

Care for acute nasal fractures (up to 14 days from the injury) is included on Line 227.

Sequalae of nasal fractures, including nasal deformities, are included on Line 562.

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Public Comment Disposition: Septoplasty for Breathing Issues

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Discussion Table 1

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Commenters

Identification	Commenter
A	Mendy Maccabee (OHP provider) [Submitted April 14, 2026]

Public Comments

ID/#	Comment	Disposition
A	I, first wanted to take a moment to recognize OHP's commitment to patients and access and the first step of bringing nasal obstruction treatment to patients at OHP with the authorization of septoplasty. It may seem trivial but the impact of being able to breath through ones	Thank you for your comments. The staff coverage option (new since the March meeting) which would add coverage for septoplasty also includes adding coverage for

ID/#	Comment	Disposition
	nose when you have not been able to for years is really impactful for your members. I see patient after patient post operatively who say, "I can not believe you did not suggest surgery for me YEARS ago…." They are a grateful set of patients; thank you. I do want to take this opportunity to focus on the original ask and the standard approach for all the commercial payors; the problem being addressed is nasal airway obstruction. Septoplasty is an approach and is only appropriate for septal deviation in the mid portion of the septum (please see Dr. Brennan's submitted slide deck for anatomical reference and have it available for us to revisit at the upcoming meeting). For patients who have blockage along the bridge of the nose and/or columella (part of the nose you pinch between your thumb and forefinger right in the front of the nose) we can not access the deviation via septoplasty alone. More importantly, we can not put the nose structurally back together with long term integrity via the septoplasty approach in these cases. For deviations in this location we must use the rhinoplasty approach (cpt code 30420) or nasal valve reconstruction code (cpt code 30465) sometimes with cadaver, rib or ear cartilage donor tissue cpt codes. I realize that there is a social concept that "rhinoplasty" is a cosmetic procedure. It is. AND, it is as or more often a functional approach. The code and its utilization should not be unfairly deemed exclusively a cosmetic procedure. It simply is not. OHP is going to set its fee schedule for these codes and I assure you that the risk will be that most providers will not accept OHP patients for these functional and life impacting procedures because they are technically challenging cases and time consuming. Historically	rhinoplasty when septoplasty is not sufficient. For that option, CPT 30420 and 30465 would pair with deviated nasal septum if the guideline criteria are met. The wording you propose "rhinoplasty is allowable when septoplasty alone is inadequate to address the obstruction" are substantially similar to guideline wording already in place. The HERC does not set fee schedules for OHP.

ID/#	Comment	Disposition
	speaking OHP fee schedules have not covered practice costs. I do not think it is good practice to 'not' write a fair and accurate policy because of a bias against a code based on inaccurate cultural perception or because patients wont have access anyway due to low reimbursement. For bariatric surgery OHSU and most programs limit OHP patients and the wait list is long for your patients to access the procedure but when they do the impact is immense. I think that allowing access for nasal airway obstruction via septoplasty or rhinoplasty thru documented need is the right thing to do. Even if patient have long waits they will eventually still have access to impactful care and the policy will be fairly and accurately written to modern standards of care. The typical wording in nasal airway obstruction policies is that rhinoplasty is allowable when septoplasty alone is inadequate to address the obstruction. I have included Drs. Brennan, Schindler and Yang here who I am guessing will all agree that the policy should be one that allows access to these two approaches for adequate for access to the level of obstruction and rebuilding of the nasal structure. Respectfully, Mendy S. Maccabee MD FACS FAAOA ENT, Sinus & Allergy Care	

References Provided by Commenters

ID	References
A	None provided

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Clinical effectiveness of septoplasty versus medical management for nasal airways obstruction: multicentre, open label, randomised controlled trial

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Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2023;383:e075445 http://dx.doi.org/10.1136/bmj-2023-075445

Accepted: 13 September 2023

ABSTRACT

OBJECTIVE
To assess the clinical effectiveness of septoplasty.

DESIGN
Multicentre, randomised controlled trial.

SETTING
17 otolaryngology clinics in the UK's National Health Service.

PARTICIPANTS
378 adults (≥18 years, 67% men) newly referred with symptoms of nasal obstruction associated with septal deviation and at least moderate symptoms of nasal obstruction (score >30 on the Nasal Obstruction and Symptom Evaluation (NOSE) scale).

INTERVENTIONS
Participants were randomised 1:1 to receive either septoplasty (n=188) or defined medical management (n=190, nasal steroid and saline spray for six months), stratified by baseline symptom severity and sex.

MAIN OUTCOME MEASURES
The primary outcome measure was patient reported score on the Sino-Nasal Outcome Test-22 (SNOT-22) at six months, with 9 points defined as the minimal clinically important difference. Secondary outcomes included quality of life and objective nasal airflow measures.

RESULTS
Mean SNOT-22 scores at six months were 19.9 (95% confidence interval 17.0 to 22.7) in the septoplasty arm (n=152, intention-to-treat population) and 39.5 (36.1 to 42.9) in the medical management arm (n=155); an estimated 20.0 points lower (better) for participants randomised to receive septoplasty (95% confidence interval 16.4 to 23.6, P<0.001, adjusted for baseline continuous SNOT-22 score and the stratification variables sex and baseline NOSE severity categories). Greater improvement in SNOT-22 scores was predicted by higher baseline symptom severity scores. Quality of life outcomes and nasal airflow measures (including peak nasal inspiratory flow and absolute inhalational nasal partitioning ratio) improved more in participants in the septoplasty group. Readmission to hospital with bleeding after septoplasty occurred in seven participants (4% of 174 who had septoplasty), and a further 20 participants (12%) required antibiotics for infections.

CONCLUSIONS
Septoplasty is a more effective intervention than a defined medical management regimen with a nasal steroid and saline spray in adults with nasal obstruction associated with a deviated nasal septum.

TRIAL REGISTRATION
ISRCTN Registry ISRCTN16168569.

WHAT IS ALREADY KNOWN ON THIS TOPIC

In 2014, the UK National Institute for Health and Care Research commissioned a randomised controlled trial to address the lack of high quality evidence to support nasal septoplasty

A study in 2019 reported higher levels of general quality of life at 12 months in participants after septoplasty compared with those who received variable non-surgical management

In that study, score on the Sino-Nasal Outcome Test (SNOT-22) was a secondary outcome, with greater improvement observed in participants after septoplasty

WHAT THIS STUDY ADDS

Septoplasty is a clinically effective treatment for nasal obstruction associated with septal deviation compared with a defined regimen of nasal steroid and saline sprays

Participants who underwent septoplasty had greater improvement in nasal obstruction and quality of life, as measured using the SNOT-22 questionnaire

However, people with a deviated nasal septum and at least moderate nasal obstruction do tend to improve over time with medical treatment

Introduction

Septoplasty is a common operation to alleviate nasal obstruction associated with deviation of the nasal septum. It may be accompanied by reduction of the inferior turbinate to increase airflow through the nasal cavities. Surgery is typically predicated on clinical history and a visual assessment of the nasal septum. To date, no objective nasal airflow measures have proven definitively beneficial in the selection of patients. Despite the lack of an evidence base, in 2019/20 about 16 700 septoplasty procedures were performed in England[1] at an estimated cost of £15.9m ($19.9m; €18.5m) for the operations alone. More than 250 000 septoplasties are performed in the United States annually.[2]

Many UK clinical commissioning guidelines propose a trial of medical treatment before surgical referral.[3] Medical treatment usually entails intranasal steroid spray, although recommendations on dose and length

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of treatment are inconsistent. Some National Health Service commissioning bodies in England have placed septoplasty on a list of restricted treatments. Other healthcare providers will only routinely fund septoplasty for nasal obstruction that is causing documented medical problems, such as sleep or breathing disruption, and only after all non-surgical treatments have been tried.[4]

The Nasal Airways Obstruction Study (NAIROS) was designed to provide definitive evidence and recommendations for the clinical effectiveness of septoplasty, to inform guidance on which patients may benefit from this treatment, and to standardise treatment across the UK.

Methods

The Nasal Airways Obstruction Study was a multicentre, non-adaptive, open label randomised controlled trial conducted in 17 hospitals in the UK's NHS. The regional ethics committee approved the trial protocol.[5] Independent data monitoring and trials steering committees oversaw the trial.

Participants

Participants were adults (≥18 years) newly referred to otolaryngology clinics with symptoms of nasal obstruction associated with septal deviation and confirmed by endoscopic assessment. Participants were offered entry into the trial if their presenting Nasal Obstruction and Symptom Evaluation (NOSE)[6] score was ≥30 (out of a potential score of 100), with 30 defined as the cut-off to differentiate patients with nasal obstruction from those without.[7] We excluded participants with relevant systemic inflammatory diseases or previous septal surgery (see supplementary material for inclusion and exclusion criteria). All participants provided written informed consent.

Randomisation

The Newcastle Clinical Trials Unit Randomisation Service, an in-house bespoke internet based system, performed randomisation centrally using permuted random blocks of variable length. All allocations were generated by an automated process within the system. Participants were randomised 1:1 to receive either surgical intervention or medical management, stratified by sex and baseline severity of symptoms according to scores on the NOSE scale: 30-50 (moderate), 55-75 (severe), 80-100 (extreme).[7] Open label randomisation was administered centrally through the Newcastle University Clinical Trials Unit, using a secure web based system.

Interventions

Septoplasty—Participants randomised to septoplasty received surgery up to 12 weeks post-randomisation. The surgery was encouraged to take place within eight weeks of randomisation, with a further four weeks permissible for extenuating circumstances. Experienced surgeons not in training performed the surgery. Because septoplasty is a commonly performed procedure, data on individual surgeons was not collected, with the surgical team represented by the recruitment site within the analysis. As a pragmatic study, we permitted surgery for unilateral inferior turbinate reduction on the wider side at the discretion of the surgeon, reflecting the considerable variation in current UK surgical practice. Deviation of the septum often causes bilateral nasal obstruction as a result of the deviation blocking one side and the inferior turbinate becoming enlarged in the opposite nasal cavity. Surgical methods employed were the same as those used in standard surgical care at recruitment sites—the only stipulations being that the surgery had to be through a closed approach (that is, no external incisions), and no grafts were to be used. Surgeons were, however, allowed to adopt a variety of techniques to manipulate the nasal septum cartilage into place, and so overall results reflect the generality of current surgical practice. The only stipulation for the method used to perform the inferior turbinate reduction was that mucosal preserving techniques should be undertaken.

Medical management—Participants randomised to receive medical management were supplied with six months' supply of isotonic nasal saline spray (Sterimar; Sofibel, Paris, France) to be used twice daily, and mometasone furoate nasal steroid spray to be used twice daily after the saline spray and then 100 µg twice daily for six weeks, then reduced to 100 µg once daily or 50 µg twice daily for the remainder of the six months. Participants randomised to receive medical management were assured they would have the opportunity to discuss the option of septoplasty after the six month primary outcome time point.

Outcome measures

Primary outcome measure

The primary outcome measure was the score on the Sino-Nasal Outcome Test (SNOT-22) at six months (defined protocol time window −2 to 4 weeks for completion). SNOT-22 is a patient reported outcome measure that has been validated to assess symptoms related to chronic rhinosinusitis[8] but has been used to assess outcomes after septal surgery.[9] SNOT-22 comprises 22 items, each scored from zero to 5. The total score ranges from zero to 110, with higher scores indicating worse symptoms.

Secondary outcome measures

Four secondary patient reported outcome measures were assessed:

- SNOT-22 score at 12 months.
- SNOT-22 subscale (nose, sleep, ear/facial pain, psychological) score at baseline, six months, and 12 months.[8]
- Score on the NOSE scale at baseline, six months, and 12 months.[6] This scale comprises five items, each scored from zero to 4. The total score is multiplied by 5 to give an overall range from zero to 100, with higher scores indicating worse symptoms.

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- General quality of life, measured at baseline, six months, and 12 months using the physical component scores and mental component scores of the 36 item Short Form survey (SF-36), which assesses recall over the preceding week, with higher scores indicating better quality of life.[10] The scores are transformed into a range from zero to 100, with zero representing the worst possible health and 100 representing the best possible health.

Secondary clinical measures at baseline, six months, and 12 months were:

- The double ordinal airway subjective scale, which is a subjective comparator of right and left nasal patency,[11] with each nostril rated from 1 to 10, with higher scores indicating better airflow. The results are presented as the modulus of the absolute subjective double ordinal airway subjective scale=(left score−right score)/left score+right score)—that is, ignoring positive or negative results. Scores range from 0 to 1; scores closer to 0 indicating symmetrical nasal airways.
- Objective assessments of nasal patency after decongestant use, including peak nasal inspiratory flow, measured using a peak nasal inspiratory flow meter (GM Instruments, Kilwinning, UK).[12] Nasal partitioning ratio (using mean volumes from three maximal inhalation measurements, scored 0 to ±1, with 0 indicating symmetrical nasal airways and ±1 indicating complete left side (+1) and right side (−1) unilateral airflow), tidal volume, and maximal inhalation flow rate measured using a rhinospirometer (NV1 rhinospirometer; GM Instruments, Kilwinning, UK).
- An imbedded economic evaluation is to be reported separately in a future publication.

Statistical analysis

Analyses were performed according to a predetermined analysis plan.[13] Summary statistics of overall scores, including means with associated 95% confidence intervals, are presented. The primary intention-to-treat (ITT) analysis, whereby participants are retained in the arms to which they are randomised, was based on multivariable linear regression adjusted for baseline continuous SNOT-22 score and the stratification variables sex and baseline severity categories based on the NOSE scale (model 1). Goodness of fit for model 1 was assessed by a series of plots of residuals. We considered a two sided P<0.05 to be statistically significant.

The planned population defining analyses included an ITT analysis, a per protocol analysis, and a per treatment analysis.

ITT analysis—this analysis was limited to those participants who completed the primary outcome SNOT-22 within the specified window of six months (−2 to 4 weeks). This analysis was termed the compliant ITT analysis.

Per protocol analysis—this analysis was performed as per the ITT analysis, restricted to those participants randomised to, and undergoing, septoplasty within the specified 12 weeks after randomisation and who completed the primary outcome within the specified window, compared with those randomised to receive medical management who remained within that group and did not cross over to surgery.

Per treatment analysis—this analysis was performed as per the ITT analysis, comparing participants who underwent septoplasty, regardless of initial randomisation group, at any time during follow-up (but >10 weeks before the primary outcome measure at six months, to ensure postoperative inflammation had settled), and all those treated with medical management, both regardless of initial randomisation group, with participants who completed the primary outcome within the specified window.

We explored the impact of the recruitment site on the primary outcome analysis by inserting the centre as a random effect with the mixed effect model.

Table 1 | Baseline characteristics of recruited participants. Values are number (percentage) unless stated otherwise

Characteristics	Septoplasty (n=188)	Medical management (n=190)	Total (n=378)
Sex			
Male	126 (67)	127 (67)	253 (67)
Female	62 (33)	63 (33)	125 (33)
Age (years)			
Median (IQR)	38 (27.5, 51)	37 (28, 50)	38 (28, 50)
Mean (SD)	40.3 (14. 9)	39.4 (13.9)	39.8 (14.4)
Range	18-79	18-80	18-80
Ethnicity			
White	169 (90)	165 (87)	334 (88)
Asian (Indian/Pakistani/Bangladeshi ancestry)	13 (7)	14 (7)	27 (7)
Other ethnic origin	4 (2)	11 (6)	15 (4)
Missing	2 (1)	0 (0)	2 (<1)
Baseline NOSE score (continuous)			
Median (IQR)	70 (60, 82.5)	70 (60, 85)	70 (60, 85)
Mean (SD)	69.9 (17.4)	71.3 (17.3)	70.6 (17.4)
Range	30-100	30-100	30-100
Baseline NOSE categories			
Moderate	30 (16)	32 (17)	62 (16)
Severe	89 (47)	89 (47)	178 (47)
Extreme	69 (37)	69 (36)	138 (37)

IQR=interquartile range; NOSE Nasal Obstruction and Symptom Evaluation scale; SD=standard deviation.

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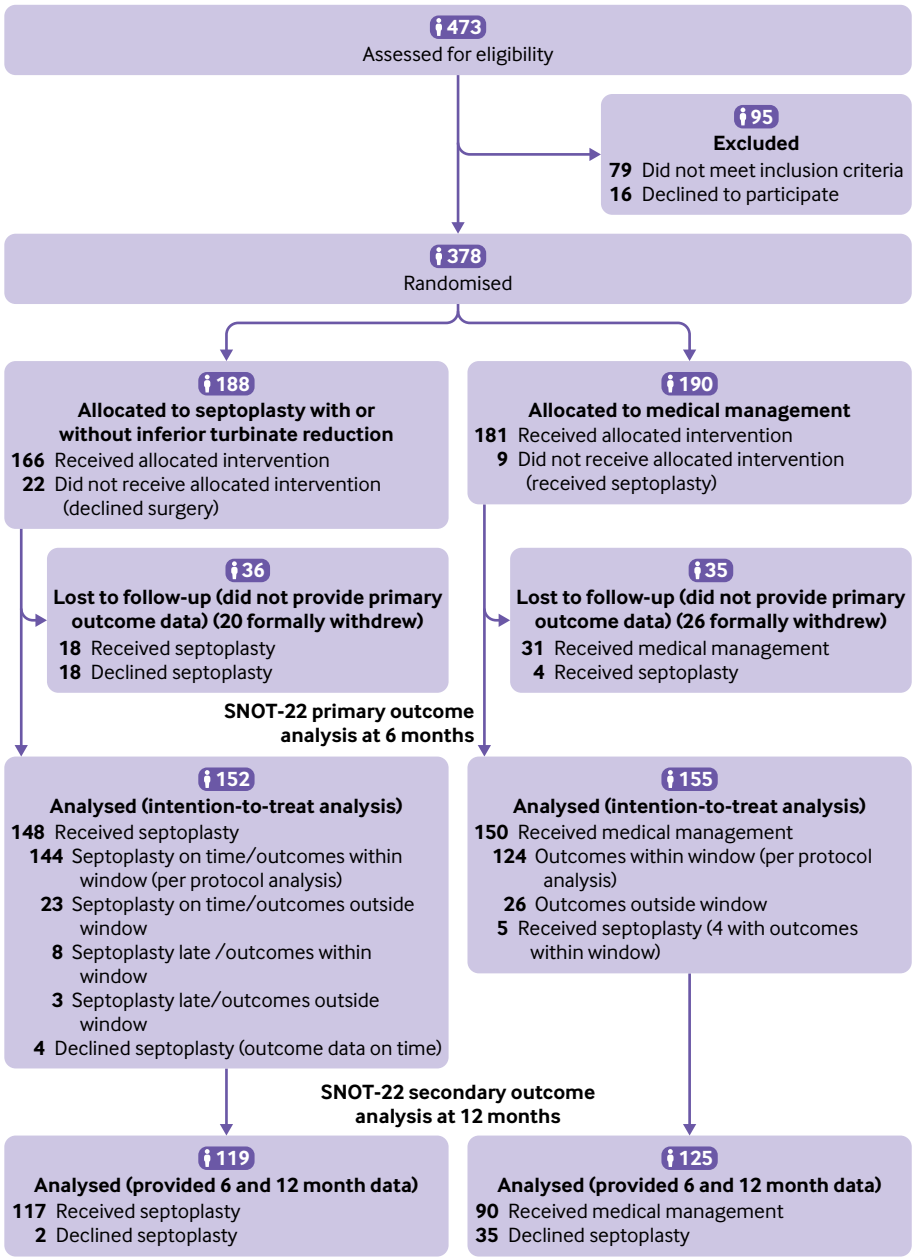

Fig 1 | Flow of participants through study

Analyses of the secondary outcome measures followed the same primary multiple linear regression modelling. Although inferior turbinate reduction was not a randomised intervention, its effect on the primary outcome was explored as a planned covariate in the linear regression model.

Further planned multivariable linear regression sensitivity of the ITT analyses considered adjustment for other important baseline factors in the regression model. To utilise the full information from the continuous measure, model 2 adjusted for continuous baseline score on the NOSE scale rather than the three categories used at baseline. Model 3 included age, ethnicity, recruitment site (as a random effect), smoking history, double ordinal airway subjective scale, endoscopy findings (location of deviation, severity of airway blockage, and enlargement of the inferior turbinate), and four nasal patency variables. These variables were initially regressed univariately against the primary outcome measure to screen for independent relatedness. Any variable with P>0.1 was included for consideration in further modelling based on forward selection. Non-linear continuous covariates were considered for fractional polynomial transformations, if appropriate.

The importance of baseline severity within the ITT population, as a continuous distribution of score on the NOSE scale at randomisation, was further explored graphically using a subpopulation treatment effect pattern plot (STEPP) analysis.[14] This analysis enabled the predicted point estimates of any treatment effect (with 95% confidence intervals)

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Table 2 | Patient reported SNOT-22 score at six months (primary outcome) adjusted for baseline SNOT-22 score and stratification variables sex and NOSE categories in 307 participants in intention-to-treat population

	Coefficients (95% CI)	P value
Septoplasty arm (reference category medical management)	−20.01 (−23.63 to −16.40)	<0.001
Baseline SNOT-22 score	0.50 (0.39 to 0.60)	<0.001
Male sex (reference category female sex)	−0.55 (−4.38 to 3.27)	0.78
NOSE severity (reference category moderate):		
Severe	1.98 (−3.85 to 7.81)	0.50
Extreme	5.81 (−1.00 to 12.62)	0.094
Constant	14.95 (8.48 to 21.43)	<0.001

NOSE=Nasal Obstruction and Symptom Evaluation scale; SNOT-22=Sino-Nasal Outcome Test-22.
Adjusted R^2=0.472. Probability $F_{5,301}$=55.69, P<0.001.

between the randomised groups to be displayed over the range of NOSE scale values (30-100), with the aim of further informing patient selection guidance and recommendations.

All data were analysed using STATA, version 16.

Missing data

SNOT-22 questionnaires with up to 20% of items missing were imputed with the average of the completed questions used for missing items. A sensitivity analysis using multiple imputation was also carried out that included all participants who provided consent and were randomised, including those with missing SNOT-22 scores at the primary endpoint. Baseline variables found to be predictive of missing data status were included in multiple imputation equations. To make the missing at random assumption as plausible as possible, the multiple imputation equation included baseline data on sex, NOSE scale categories, baseline SNOT-22 score, and predictors of missing data. Overall, 1000 multiple imputation datasets were created in STATA16 using chained equations. A conservative approach was adopted, and treatment group was included in the imputation model.

Sample size calculation

The sample of 378 participants was based on 90% power to detect a minimal clinically important difference of 9 points on SNOT-22,[8] assuming a conservative standard deviation of 24 points[15] and a type 1 error rate of 5%, and to allow for 20% drop-out.

Patient and public involvement

Patient and public involvement was integrated throughout the design and conduct of the trial. More than 20 patients were consulted about the primary outcome measure, with most favouring the items covered by SNOT-22 over NOSE scale questionnaire. Patients' views were integrated into the design to encourage any crossover to septoplasty to occur after six months. All patient facing documents were reviewed for acceptability.

Results

Between 26 January 2018 and 5 December 2019, 378 eligible participants (67% men) were randomised. Baseline personal characteristics were balanced across treatment groups (table 1).

The onset of the covid-19 pandemic resulted in the suspension of all face-to-face clinics from 30 March 2020, therefore remaining trial participants were invited to complete the primary outcome six month SNOT-22 measure (n=8, 2%) and the secondary outcome 12 month SNOT-22 measure (n=25, 7%) remotely. By then recruitment had been achieved and all trial interventions had been completed. Information on adverse events was collected remotely by telephone at the six month and 12 month follow-ups. Only 66 participants in the septoplasty group and 72 in the medical management group completed the 12 month objective flow measures.

Four SNOT-22 questionnaires had missing items at baseline—two in each treatment group (1%), five

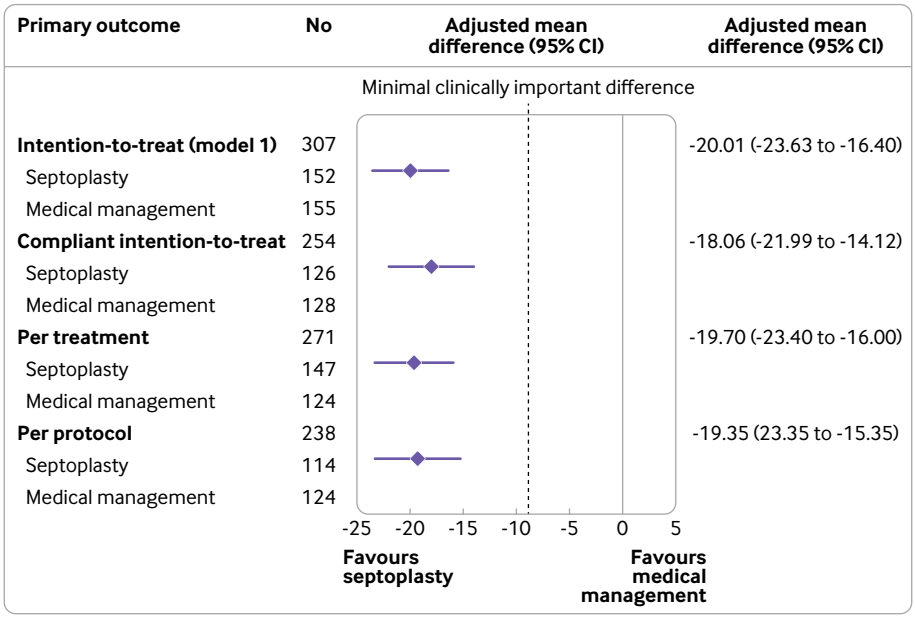

Fig 2 | Forest plot of primary analysis and sensitivity analysis for intention-to-treat population. CI=confidence interval

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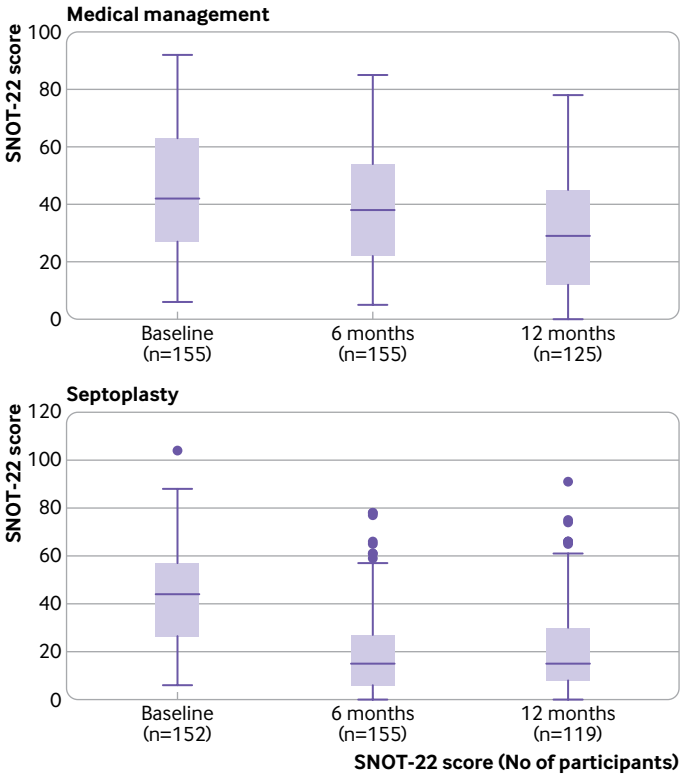

Fig 3 | Box plots showing summary statistics for SNOT-22 scores in intention-to-treat groups. Box represents middle 50% of data (lower quartile to upper quartile), horizontal line in box shows median (50th centile), whiskers show data that fall within 1.5× interquartile range, and points show data that fall outside these limits. SNOT-22=Sino-Nasal Outcome Test-22

at the primary six month endpoint (2%) and four at the final 12 month data collection point (1%). All of these were imputed as each had <20% missing. One participant had one item missing from the NOSE scale questionnaire (20%) at the six month follow-up. This was also imputed, using the mean of the other four responses.

Treatment received

Of the 378 participants randomised, 188 were assigned to receive septoplasty and 190 were assigned to receive medical management (fig 1). Overall, 307 participants (81%) were included in the ITT analysis of the primary outcome. In the ITT septoplasty group, four (3%) participants did not receive the surgical intervention; in the ITT medical management group, five (3%) participants received septoplasty. Consultant surgeons carried out 128 of 166 (77%) of the septoplasties for participants randomised to the septoplasty arm, who received the intervention. Associate specialists carried out 17 (10%) of the septoplasties, and other grades carried out 16 (10%). The records of five (3%) failed to record the grade of the most senior operative surgeon. In total, 112 out of 148 participants (76%) randomised to septoplasty and who received the intervention in the ITT analysis, underwent surgery within eight weeks after randomisation (see supplementary analysis figure S1). Twenty five (17%) underwent surgery within eight and 12 weeks after randomisation. One hundred and twenty two (64%) of the 190 participants randomised to medical management completed the drug adherence feedback, of whom 87 (71%) used nasal steroid spray >90% of the time, 101 (83%) used it >75%, and 17 (14%) had rarely used the drug.

Primary outcome analysis

Patient reported symptoms improved in both groups. In those participants randomised to receive septoplasty in the ITT population (n=152), mean SNOT-22 scores were 44.5 (95% confidence interval 41.1 to 47.8) at baseline and 19.9 (17.0 to 22.7) at six months. The corresponding scores for those participants randomised to receive medical management in the ITT population (n=155) were 44.1 (40.8 to 47.4) and 39.5 (36.1 to 42.9). Baseline SNOT-22 scores were approximately symmetrically distributed about the mean and were not transformed for the analysis (see supplementary material figures S2 and S3). In the primary ITT analysis, participants randomised to the septoplasty group reported on average 20.0 units greater improvement in symptoms compared with those randomised to the medical management group, as measured by SNOT-22 (95% confidence interval improvement 16.4 to 23.6, P<0.001; table 2). The lower limit of the 95% confidence interval is greater than the minimal clinically important difference of 9 points. With the presence of baseline SNOT-22 in the model (table 2), the stratification variables did not appear to have a major influence on the primary outcome. The primary outcome results were unchanged when further baseline variables were considered in the analysis, including the recruitment site when entered into model 2 as a random effect (see supplementary material tables S1 and S2 and figure S4).

The planned population defining analyses all showed similar results and supported the primary ITT analysis (fig 2). After multiple imputation to account for missing data (n=378), participants randomised to the septoplasty group (n=188) reported on average a greater improvement of 20.0 units over those randomised to the medical management group (n=190) (95% confidence interval improvement 16.4 to 23.7, P<0.001) supporting the primary ITT analysis

Secondary outcomes

The improvement in SNOT-22 scores in the septoplasty group remained at 12 months but was less noticeable compared with those in the medical management group (fig 3). The mean SNOT-22 score in the septoplasty group was 21.2 (95% confidence interval 17.7 to 24.6) at 12 months, whereas the corresponding values in the medical management group were 30.4 (26.6 to 34.3). Participants randomised to the septoplasty group (n=119) reported on average 10.1 units greater improvement in symptoms at 12 months compared with those randomised to the medical management group (n=125), as measured by SNOT-22 (95% confidence interval improvement 5.6 to 14.5, P<0.001).

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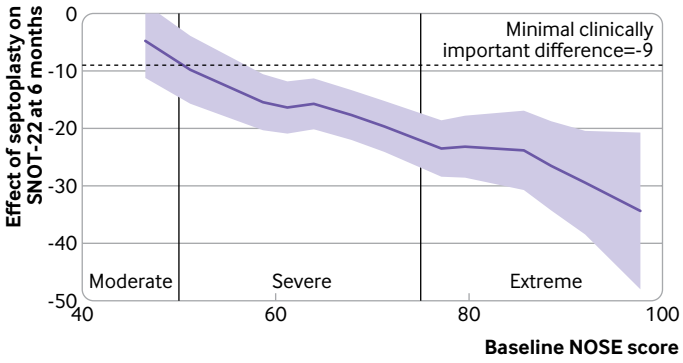

Fig 4 | Outcome data using subpopulation treatment effect pattern plot to assess individual changes in SNOT-22 scores from baseline to six months. Purple line shows average effect of being randomised to septoplasty for those with specific NOSE scores at baseline and shading represents 95% confidence intervals. Minimal clinically important difference is 9 points on SNOT-22. NOSE=Nasal Obstruction and Symptom Evaluation; SNOT-22=Sino-Nasal Outcome Test-22

Supplementary table S3 shows that the secondary outcomes measured at six months improved more in the septoplasty group than in the medical management group, including the objective flow measures. A noticeable improvement in SNOT-22 scores was observed between six and 12 months for 29 of the 37 participants randomised to receive medical management and who chose to undergo septoplasty after six months, restricted to those who provided 12 months' data. The SNOT-22 scores for these 37 participants had not improved between baseline and six months (see supplementary figure S5). The analysis between the groups in the 12 month objective assessments was affected by lack of face-to-face assessments during the covid-19 pandemic.

For the ITT population (n=307) mean scores on the SF-36 physical component summary and mental component summary at six months were 2.74 (95% confidence interval 1.23 to 4.25) and 4.39 (2.43 to 6.36) units higher, respectively (better health), in the septoplasty group than in the medical management group (adjusted for baseline severity and stratification variables, P<0.001; see supplementary tables S5-S8 for full details).

The STEPP analysis shows that for the 18 participants with moderate NOSE scores at baseline the average improvement in SNOT-22 score was around 5 units compared with medical management (fig 4). The 77 participants with scores around 60 had an average improvement of around 15 units compared with medical management, whereas the 57 participants with extreme scores at baseline improved by as much as 30 units compared with medical management. No major differences were noted in the STEPP analysis graphs between male and female participants. When included in the primary outcome multiple regression model, baseline NOSE scores scored on a continuous scale were positively related to the six month SNOT-22 scores (P=0.041, see supplementary table S1).

For the 148 participants who underwent septoplasty and had SNOT-22 scores at both baseline and six months, there was no difference in primary outcome scores between those chosen to receive inferior turbinate reduction and those chosen not to receive inferior turbinate reduction: 2.8 points difference (95% confidence interval −2.78 to 8.35 points difference; P=0.33).

No other clinically relevant factors showed a statistically significant association with the primary outcome of patient reported SNOT-22 score at six months (see supplementary tables S1 and S2). The primary outcome SNOT-22 scores were not altered appreciably by the reported adherence rates in participants treated with medical management (see supplementary figure S6).

Safety

Table 3 summarises the reported serious adverse events and adverse events. Specific complications related to septoplasty (including participants from both randomised groups who underwent septoplasty and including both serious adverse events and adverse events in table 3) were seven readmissions with bleeding (4% of 174 participants who underwent septoplasty), 20 infections requiring antibiotics (12%), 19 reported events of altered sense of smell (11%), 18 events of upper teeth numbness (11%), 17 reported changes in the appearance of the nose (10%), 7 clinician observed adhesions (4%), and 6 clinician observed septal perforations (3%). No participants required repeat surgery.

Discussion

Septoplasty results in significantly greater improvement in patient reported SNOT-22 scores at six months compared with a regimen of nasal steroid and saline sprays, and this improvement is sustained

Table 3 | Reported serious adverse events and adverse events among all participants

Adverse events	Septoplasty group (n=188)	Medical management group (n=190)	Total
Total reported serious adverse events	14	9	23
Anaesthetic complication	3	2	5
Infection	2	2	4
Postoperative bleeding	5	1	6
Vasovagal episode	2	0	2
Multi-pill overdose	0	3	3
Trauma unrelated to the trial	0	1	1
Overnight hospital admission after surgery	2	0	2
Total No of reported adverse events*	132	95	227
Deaths	0	0	0

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to 12 months. We therefore recommend that adults presenting with nasal obstruction associated with a deviated nasal septum, in the absence of coexistent nasal or sinus disease and with a baseline NOSE score >30, can reliably be offered surgery. The per protocol and per treatment analyses corroborated the ITT results, confirming the greater improvement in patient reported outcomes of those participants who received surgery compared with those treated medically.

The STEPP analysis provided evidence of the increasing improvement in SNOT-22 scores as baseline NOSE score severity increased. This effect was observed in both male and female participants. This analysis can enable clinicians to quantify expected improvements in outcomes of patients considering septoplasty, predicated on baseline NOSE score. The STEPP analysis, in parallel with an understanding of the potential risks associated with both medical treatment and surgery, substantially improved the quality of information available to the clinician and patient in the decision making process around septoplasty.

In 2014 when the National Institute for Health and Care Research commissioned this trial, no high level evidence existed for surgery compared with medical management for nasal obstruction associated with septal deviation. No specific guidance was available as to who should be referred for consideration of surgery, or the likely outcomes. The intervention was practice based, not evidence based. To our knowledge, in 2019 van Egmond et al reported the first randomised clinical trial assessing septoplasty.[16] Guidance on referrals has not been updated since its publication.[4] The study by van Egmond et al reached similar conclusions to that of the current study in a trial of 203 participants in the Netherlands randomised to receive either septoplasty or non-surgical management. Some important distinctions need to be mentioned between these two trials conducted in different healthcare systems: in the study by van Egmond et al, non-surgical management was not defined, whereas in the current study we specified a standardised medical management arm, which we considered offered the optimal medical treatment for any intranasal mucosal inflammation. The primary endpoint in the study by van Egmond et al was 12 months, and by that stage 30% of the non-surgical arm had crossed over to the surgical arm. The shorter time point of six months for our primary outcome aimed to minimise crossovers from the medical management arm while allowing sufficient healing time after surgery to give a true representation of any clinical difference between arms in an ITT analysis. In addition, we used a disease specific patient reported outcome measure rather than a general quality of life measure for the primary outcome.

We estimated a superiority for septoplasty of 20 points on SNOT-22 at six months compared with 9.7 points at 12 months in the study by van Egmond et al. Their data transformation and variable non-surgical arm treatments make direct comparison with the current study difficult. The two clinical trials report concordant results in showing that septoplasty is clinically effective. The current study substantially enhances understanding of the role of quantitative patient reported data in the selection of patients for surgery by showing that the degree of improvement in symptoms (as measured by SNOT-22) is closely related to baseline severity stratification (as measured by NOSE score). This improvement in SNOT-22 score remained across each of the four SNOT-22 subdomains— nose, sleep, ear/facial pain, psychological. The impact of septal surgery in improving SNOT-22 scores is also found in studies of snoring[17] and eustachian tube dysfunction.[18]

In the current study, although a greater and sustained improvement was observed in the surgical arm, we did note a potentially clinically important improvement in SNOT-22 scores in the medical management arm of 9.1 points between six and 12 months. In the ITT analysis, some of the improvement at 12 months in the medical management group may have been affected by 37 participants who were randomised to receive medical management undergoing septoplasty after six months. The primary outcome, SNOT-22 score at six months, did not improve from baseline in these 37 participants, suggesting that these participants undergoing septoplasty had an important impact on the medical management group.

The benefits of septoplasty were also seen in the secondary outcome measures, including clinical airflow assessment, patient reported outcome measures, and objective measurements of peak nasal inspiratory flow and rhinospirometry. Absolute subjective double ordinal airway subjective scale, the subjective comparator of the worse versus the better nostril airflow, revealed a substantial treatment related shift from predominantly unilateral nasal airflow to equal airflow through both nostrils, more noticeable in magnitude in the surgical arm than in the medical management arm at both six and 12 months. It may be a useful tool to audit surgical outcomes, or future trials of nasal airway surgery.

The results of the current study infer that turbinate surgery added no additional improvement to septoplasty alone. The decision to perform turbinate surgery was, however, pragmatic and left to the discretion of the operating surgeon. The results for inferior turbinate reduction may not be generalisable to other techniques or to bilateral reduction practices. The study by van Egmond et al similarly reported no additional benefit of turbinate surgery.[16] As in the current study, turbinate reduction was a surgeon led decision and not a randomised intervention. Neither clinical trial can draw firm conclusions on the impact of inferior turbinate reduction in combination with septoplasty. A recent single centre trial randomised participants undergoing septoplasty to inferior turbinate reduction or no inferior turbinate reduction.[19] This study reported a statistically significant and sustained additional benefit of inferior turbinate reduction, as measured using the NOSE score, implying that further multicentre clinical trials should be considered to define the

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impact of inferior turbinate reduction in combination with septoplasty.

Limitations of this study

The study has several limitations. At baseline, more than 80% of patients had NOSE scores in the severe or extreme category. This may reflect the population currently referred to secondary care. However, the conclusions for these two subgroups were strong. The benefits for those participants with moderate baseline symptoms was less clear, whereas those with moderate NOSE scores at baseline did not report an improvement that reached the minimal clinically important difference of 9 points on SNOT-22—only 18 participants were included in this subgroup of the STEPP analysis.

Nasal obstruction is a non-specific symptom with many underlying possible causes (chronic rhinosinusitis, allergic rhinitis, non-allergic rhinitis, nasal valve dysfunction). As a pragmatic trial, the current study did not seek to diagnose or treat these conditions before randomisation. Also, surgical interventions were performed by experienced surgeons. In NHS practice, septoplasty is often performed by junior trainee surgeons, albeit many are supervised by more senior colleagues. The evidence is limited for septoplasty outcomes and surgeon experience. However, previous studies have found no association between grade of surgeon and septoplasty outcomes when assessing the need for revision surgery[20] or the postoperative appearance of the septum.[21] Covid-19 had a considerable impact on the current trial. All forms of airway clinical assessment and objective measurements of nasal patency were suspended from March 2020 onwards. As a result of the smaller numbers of participants, this may have had an impact on the precision of the statistical results. All other patient reported outcome measures were collected remotely during the pandemic, ensuring that we could report the trial results reliably.

The current trial did not assess, and therefore cannot define, what should constitute an appropriate trial of medical management for patients and clinicians to consider before septal surgery is discussed. Participants in the medical management group reported an improvement in symptoms with mometasone nasal steroid and saline sprays. Participants with an element of underlying rhinitis contributing to the nasal obstruction in addition to the septal deviation may have responded to this treatment. Consensus opinion from the US recommends a course of medical management for four weeks before septoplasty is considered.[22]

Conclusions

Septoplasty is a superior treatment for nasal obstruction associated with septal deviation compared with a defined regimen of nasal steroid and saline sprays. Baseline NOSE scores can estimate the likely improvement in symptoms and guide decision making for patients and clinicians. The authors recommend that adults presenting with nasal obstruction associated with a deviated nasal septum should be offered septoplasty.

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We thank the clinical research staff across the UK at the following centres: Aneurin Bevan University Health Board; Bradford Teaching Hospitals NHS Foundation Trust; County Durham and Darlington NHS Foundation Trust; Guy's and St Thomas's NHS Foundation Trust; James Paget University Hospital NHS Foundation Trust; Leeds Teaching Hospitals NHS Trust; Liverpool University Hospitals NHS Foundation Trust; Newcastle Upon Tyne Hospitals NHS Foundation Trust; NHS Grampian; NHS Lanarkshire; NHS Tayside; North Cumbria Integrated Care NHS Foundation Trust; Plymouth Hospitals NHS Trust; Salisbury NHS Foundation Trust; Stockport NHS Foundation Trust; University Hospitals Birmingham NHS Foundation Trust; Wrightington, Wigan and Leigh Teaching Hospitals NHS Foundation Trust. The Newcastle Clinical Trials Unit staff, including previous team members: Trial Manager, Ann-Marie Hynes; Clinical Trial Administrators, Eva-Maria Holstein, Wendy Banks; Secretary, Ruby Smith-Whelan; Data Manager, Alaa Abouhajar; Senior Trial Managers, Lesley Hall, Jared Thornton, Sonya Carnell. Maria Allen and Ian Campbell for providing clinical trials pharmacy guidance and review on behalf the sponsor. Joan Mackintosh for qualitative data collection. The patient and public involvement advisors who provided helpful advice and guidance when reviewing the trial and patient facing documents. The members of the NAIROS Trial Steering Committee: Valerie Lund (chair), Natalie Rowland (independent statistician), Helen Mason (independent health economist), Russell Cathcart (independent clinician), Tim Woolford (independent clinician), Andrea Anderson and Irene Soulsby (independent lay members). The members of the NAIROS Data Monitoring Committee; Steff Lewis (chair), Stephen Gerry (independent statistician), and Gerald McGarry (independent clinician). Most importantly, we would like to thank every participant who took part in the NAIROS trial.

Contributors: All authors have contributed to writing, reviewing, and revising the manuscript. SC and JOH are joint first authors. SC is the corresponding author and NAIROS chief investigator.TF, DS, and DT performed the trial statistical analysis. TH and LT performed the trial health economic evaluation. NR and KL performed the qualitative research. KR, EC, and AS were the trial management team. NW managed the trial database. LR, JD, and CW performed the qualitative research that guided trial recruitment. AB and MD devised the nasal patency methodology and performed the related data analysis. DH and JW were co-applicants and contributed to the trial design and

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participant recruitment. YO contributed to the trial methodology design. JM acted as a co-applicant and primary care lead. QG, NK, SK, SL, SM, and PN were clinical co-applicants and contributed to participant recruitment. SC and JOH, as guarantors, accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. The corresponding authors attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding: The study was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme (reference 14/226/07). The NIHR commissioned the research trial with some stipulation on the trial design. Thereafter, the funders were independent of the running of the trial, analysis and interpretation, and the decision to publish the results.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: support from the National Institute for Health and Care Research and salaries part funded through host institutions (SC, JOH, TF, TH, NR, LR, AB, DDS, LT, KR, AJS, JD, MD, KL, CWilson, SK, JWilson, and MDT); no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The North East – Newcastle and North Tyneside 2 UK Health Research Authority Regional Ethics Committee (August 2017, study reference No 17/NE/0239).

Data sharing: The chief investigator and collaborators will act as custodians of the trial data and manage data sharing requests through ReShare, a UK online data repository recommended by the funder. Parties interested in data sharing will directly contact the chief investigator and collaborators and complete a project proforma and provide the rationale and the information required and comply with the regulation of responsibilities of users. If agreed to be appropriate, requested anonymised data will be made available. An access advisor who is independent of the trial team will periodically review access decisions.

The lead authors (SC and JOH) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Dissemination to participants and related patient and public communities: A lay summary of results will be available on the NAIROS website. Access to the Health Technology Assessment report will also be available through the trial website. Members of the patient and public involvement focus groups will review results and they will be involved in writing lay summaries of results for dissemination to relevant patient groups.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Supplementary information: Inclusion and exclusion criteria, figures S1-S6, and tables S1-S8

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Published online: 2021-08-23

Comparison of the Efficacy of Septoplasty with Nonsurgical Management in Improving Nasal Obstruction in Patients with Deviated Nasal Septum – A Randomized Clinical Trial

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Int Arch Otorhinolaryngol 2022;26(2):e226–e232.

Abstract

Introduction In the current era, the major indication for septoplasty is nasal obstruction due to deviated nasal septum (DNS). Even though septoplasty is a commonly performed surgery, its effectiveness in relieving nasal obstruction in DNS has not been proven.

Objective The present study involved the measurement of both objective (nasal patency) and subjective (quality of life measures) outcome measures for the evaluation of the efficacy of septoplasty as compared with medical management.

Methods Patients with DNS presenting with nasal obstruction were included and randomized into a septoplasty group or into a nonsurgical management group, with 70 patients in each group. The improvement in nasal obstruction was assessed subjectively by the visual analogue scale (VAS), and the sino-nasal outcome test-22 (SNOT-22) and the nasal obstruction symptom evaluation (NOSE) questionnaires and was measured objectively by assessment of nasal patency by peak nasal inspiratory flow (PNIF) at 0, 1, 3, and 6 months of treatment in both groups.

Results The average VAS, SNOT-22 and NOSE scores for the septoplasty versus the nonsurgical group before treatment were 6.28 versus 6.0, 19.5 versus 15, and 14 versus 12, respectively, and at 6 months post-treatment, the scores were 2.9 versus 5.26, 10 versus 12, and 8 versus 10 ($p = 0.001$), respectively. The average PNIF scores at 0 and 6 months were 60/50 l/min and 70/60 l/min, respectively, in the septoplasty group ($p = 0.001$); the scores at 0 and 6 months in the nonsurgical management group were 60/60 l/min and 70/70 l/min, respectively ($p = 0.001$).

Conclusion Surgical correction of DNS by septoplasty improves nasal obstruction better than nonsurgical management at 6 months postsurgery.

Keywords
- visual analogue scale
- PNIF
- SNOT-22
- NOSE score
- intranasal corticosteroids
- topical decongestants

received January 2, 2021
accepted March 5, 2021
published online August 23, 2021

DOI https://doi.org/10.1055/s-0041-1730993.
ISSN 1809-9777.

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Introduction

Deviated nasal septum (DNS) is a widespread clinical condition that affects up to 80% of the population, as shown in various studies.[1] It is characterized by displacement of the nasal septum, which normally divides the nasal cavity into right and left nasal passages. Although it is asymptomatic in the majority of patients, the most common and troublesome symptom of DNS is nasal obstruction.

Surgical correction of DNS by septoplasty is one of the most common otorhinolaryngology surgeries in adults.[2] In the current era, the major indication for septoplasty is nasal obstruction and other associated symptoms of DNS. Although septoplasty is a commonly performed surgery, its effectiveness in relieving nasal obstruction in adults with DNS has not been proven and remains indecisive. Scientific evidence from the literature on the benefits of septoplasty are not well-described.[3]

Many studies have revealed that septoplasty improves health-related quality of life significantly in the postoperative period.[4] The risk of bias is high, since all available evidence in the literature are based on studies that are only observational in nature, and randomized clinical trials are lacking. The beneficial effects could also be explained by additional factors like the course of the disease or additional interventions such as turbinate reduction or conchoplasty performed in these patients. The biases mentioned above make the advocated benefits of septoplasty questionable and possibly exaggerated.

The present study involves the measurement of both objective (nasal patency) and subjective (quality of life measures) outcome measures for the evaluation of the efficacy of septoplasty, and it is compared with medical management for ameliorating nasal obstruction in patients with DNS. The lack of evidence of the effectiveness of septoplasty explains the need for the present randomized clinical trial.

The aim of the present study was to assess and compare the efficacy of septoplasty with nonsurgical management in improving nasal obstruction in patients with DNS by both subjective and objective measures. The subjective assessment was done by the visual analogue scale (VAS), the nasal obstruction symptom evaluation (NOSE) scale and the sinonasal outcome test-22 (SNOT-22) scores, and the objective assessment was done by peak nasal inspiratory flow (PNIF).[5]

Materials and Methods

Study Design

The present study was a randomized clinical trial conducted during the period from February 2017 to December 2018. Informed consent was taken from all the patients who participated in the study. Approval from the Institute Research Council and Ethics Committee (JIP/IEC/2016/1061) was obtained. All provisions of the Declaration of Helsinki were followed. Patients > 18 years old with nasal obstruction due to DNS were included. Patients with prior septal surgeries, septoplasty done for indications other than DNS, and those with a strong preference to surgery were excluded from the study. With a 5% level of significance and 90% power, the sample size was calculated to be 70 in each group for an expected dropout rate of 20%.

Once the diagnosis of DNS was made based on the history of nasal obstruction, clinically by anterior rhinoscopy, and confirmed by diagnostic nasal endoscopy, the patients were randomized into either the septoplasty or the nonsurgical management group by the opaque envelope method.

Nasal patency was assessed at the time of enrollment into the study and at intervals of 1, 3, and 6 months after treatment, subjectively by VAS, SNOT-22, and NOSE score, and objectively by PNIF measurement in both groups.

The VAS scale ranges from 0 to 10; with 0 signifying the least severe and 10 the most severe nasal obstruction. In SNOT-22, problems are rated over the past 2 weeks, and each symptom is rated based on its severity. In the NOSE scale, 5 symptoms are considered, and severity is graded from 0 to 4, with 0 being 'not a problem' and 4 being 'severe problem'. The answers were added and multiplied by 5 to base the scale out of a possible score of 100 points for analysis.

Peak nasal inspiratory flow measures inspiratory flow through the nasal passage. The patients were asked to exhale fully, hold the flow meter horizontally, were ensured that the facemask formed an airtight seal around the nose and inhaled forcibly through the nose. The procedure was done in one nostril at a time by blocking the other. The peak nasal inspiratory maneuver should be a short, sharp, inspiratory action of a duration of ~ 1 second (►**Fig. 1**). The peak nasal inspiratory test was repeated three times, and the highest result was taken into account. The mask was disinfected between patients to avoid cross-infection.

The patients of the septoplasty group were put under sedation, and the procedure was performed under local anesthesia using aseptic precautions. A hemi-transfixion incision was made on the caudal end of the septum and extending from the floor of the vestibule to the dorsum of the columella. Following the incision, mucoperichondrial flaps were elevated from the quadrilateral cartilage until the bony

Fig. 1 Patient performing peak nasal inspiratory flow (PNIF) assessment using a PNIF meter.

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Table 1 Comparison of parameters from baseline to 6 months in the septoplasty group

S. No.	Parameter	Septoplasty group				*p-value**
		0 month	1 month	3 months	6 months	
1.	VAS score Mean (SD)	6.28 (1.4)	4.42 (1.6)	3.38 (1.2)	2.9 (1)	0.001
2.	SNOT-22 Median (IQ range)	19.5 (12–24.5)	16 (10–20)	12 (10–18.7)	10 (8–16)	0.001
3.	NOSE Median (IQ range)	70 (50–80)	50 (50–60)	50 (40–58.8)	40 (30–50)	0.001
4.	PNIF R Median (IQ range) L/min	60 (40–70)	60 (50–75)	60 (52.5–80)	70 (60–80)	0.001
5.	PNIF L Median (IQ range) L/min	50 (40–70)	60 (50–70)	60 (50–80)	60 (50–80)	0.001

Abbreviations: S. No., Serial number; IQ range, Interquartile range; NOSE, nasal obstruction symptom evaluation; PNIF L, peak nasal inspiratory flow on the left side; PNIF R, peak nasal inspiratory flow on the right side; SD, Standard Deviation; SNOT-22, Sino-nasal outcome test 22; VAS, visual analogue scale.
*Friedman test – nonparametric repeated measures.

cartilaginous junction using a Freer elevator, and an anterior and inferior tunnel were created connecting them. The cartilaginous incision was made anteriorly, and flap elevation and exposure was performed on the contralateral side. The inferior strip of cartilage was removed along the maxillary crest, and at least 1 cm of the caudal end of the septum was preserved to maintain support of the nasal tip.

Deviated portions of septum were removed, preserving nondeviated parts and a dorsal and a caudal strut to maintain support of the dorsum. Bilateral nasal cavities were packed with merocel or with an antibiotic-antiseptic coated pack to achieve hemostasis. The patients were kept reclined on a couch with 30° of head end elevation to reduce venous congestion in the septum and reduce bleeding. The pack was removed within 48 hours, and the patients were discharged on a weeklong course of antibiotics and analgesics.

The nonsurgical management group underwent subjective as well as objective assessments of nasal patency as soon as the diagnosis was established and were started on nonsurgical measures like topical nasal decongestants (1% ephedrine drops) for 1 week during each follow-up visit and topical nasal corticosteroid sprays (50 mcg of fluticasone nasal spray – 1 spray in each nostril administered twice daily up to a total dose of 200 mcg/day for 6 months). Patients in both groups were followed up at 1, 3, and 6 months from initiation of the the treatment with the same assessment repeated each time.

Results

The baseline characteristics, including the symptom scores and PNIF values, were comparable between the septoplasty and the nonsurgical management groups in our study. On studying the various parameters from baseline to 6 months in the septoplasty group, there was a significant improvement in symptom scores as well as in PNIF values ($p < 0.001$) (►**Table 1**). The improvement in symptom scores and in PNIF values was also significant in the nonsurgical management group over 6 months (►**Table 2**).

On comparing the septoplasty and the nonsurgical management groups for improvement in subjective and objective measures from baseline to 1 month, there was a statistically significant difference in NOSE scores ($p = 0.01$) and in PNIF left side scores ($p = 0.018$). There was no significant difference in VAS scores ($p = 0.679$), SNOT-22 scores ($p = 0.389$), and PNIF right side values ($p = 0.059$) (►**Table 3**). On comparing the improvement in symptom scores from baseline to 3 months in both groups, there was a significantly higher improvement in the septoplasty group when compared with the nonsurgical management group. The *p-value* for VAS, SNOT-22 and NOSE scores were 0.001, 0.021, and 0.035, respectively. There was also a significantly higher improvement in the septoplasty group in the objective assessment as measured by PNIF values from both the right ($p = 0.003$) and left side ($p = 0.001$) (►**Table 4**). At 6 months, there was a statistically significant difference in improvement in all the symptom scores and in PNIF values between the groups (►**Table 5**).

Discussion

A total of 140 patients were recruited in the present study. The patients were randomized into a septoplasty group ($n = 70$) and a nonsurgical management group ($n = 70$). The efficacy of each arm with respect to treatment was assessed at different timepoints, namely, baseline (0 month) and at the 1-, 3-, and 6-month post-treatment follow-up.

Out of the 140 patients with nasal obstruction due to DNS, 73 (52%) were males and 67 (48%) were females. In our study, the ratio between males and females affected by DNS was 1.1:1, which is similar to the findings seen in the study by Sriprakash.[6] In the studies by Moorthy et al. and by Sam et al., the ratio between males and females affected by DNS was 2:1.[7,8] Sam et al. mentioned the increased occurrence of

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Table 2 Comparison of parameters from baseline to 6 months in the nonsurgical management group

S. No.	Parameter	Nonsurgical management group				*p-value**
		0 month	1 month	3 months	6 months	
1.	VAS score Mean (SD)	6.0 (1.5)	4.37 (1.6)	4.33 (1.6)	5.26 (2.3)	0.001
2.	SNOT-22 Median (IQ range)	15 (10–22)	12 (10–20)	12 (10–20)	12 (8–20)	0.001
3.	NOSE Median (IQ range)	60 (50–80)	50 (40–70)	50 (25–62.5)	50 (30–70)	0.001
4.	PNIF R Median (IQ range) L/min	60 (50–80)	60 (50–80)	60 (55–85)	70 (60–90)	0.001
5.	PNIF L Median (IQ range) L/min	60 (40–72.5)	60 (50–85)	70 (50–90)	70 (50–90)	0.001

Abbreviations: S. No., Serial number; IQ range, Interquartile range; NOSE, nasal obstruction symptom evaluation; PNIF L, peak nasal inspiratory flow on the left side; PNIF R, peak nasal inspiratory flow on the right side; SD, Standard Deviation; SNOT-22, Sino-nasal outcome test 22; VAS, visual analogue scale.
*Friedman test – nonparametric repeated measures.

Table 3 Comparison of efficacy of treatment groups at 1 month

S.No.	Parameter	Septoplasty group		Nonsurgical management group		*p-value**
		0 month	1 month	0 month	1 month	
1.	VAS score Mean (SD)	6.28 (1.4)	4.42 (1.6)	6.0 (1.5)	4.37 (1.6)	0.679
2.	SNOT-22 Median (IQ range)	19.5 (12–24.5)	16 (10–20)	15 (10–22)	12 (10–20)	0.389
3.	NOSE Median (IQ range)	70 (50–80)	50 (50–60)	60 (50–80)	50 (40–70)	0.010
4.	PNIF R Median (IQ range)	60 (40–70)	60 (50–75)	60 (50–80)	60 (50–80)	0.059
5.	PNIF L Median (IQ range)	50 (40–70)	60 (50–70)	60 (40–72.5)	60 (50–85)	0.018

Abbreviations: S. No., Serial number; IQ range, Interquartile range; NOSE, nasal obstruction symptom evaluation; PNIF L, peak nasal inspiratory flow on the left side; PNIF R, peak nasal inspiratory flow on the right side; SD, Standard Deviation; SNOT-22, Sino-nasal outcome test 22; VAS, visual analogue scale.
*Mann-Whitney test.

trauma among males as one of the reasons for the male preponderance in DNS with trauma being a common etiology for DNS.[8]

The ratio of DNS on the right side to DNS on the left side in our study was 1:1. In the study by Moorthy et al., DNS was more common on the left side (1.47:1).[7] A preponderance of left-sided DNS was also observed in a large Korean series by Min et al. In their study, 56% of the patients had DNS on the left side and 39% had DNS on the right. The remaining 5% had S-shaped deformity.[9]

The laterality of DNS could be affected by fetal positions *in utero*. A right-sided DNS occurs in the left occipitoanterior position, and vice-versa. In the study by Mogarnad et al., right-sided deviations were more common, with a right side to left side ratio of 1.3:1.[10] Serifoglu et al. also found a predominance of right-sided nasal septal deviations in their study, with 107 patients presenting with DNS to the right side and 96 patients presenting with DNS to the left.[11] This shows that there is no definite pattern in the laterality of DNS, since its cause is multifactorial.

The age range of patients with DNS in our study was between 18 and 55 years old. The average age of all the patients included in our study was 31 years old. In the study by Sam et al., the average age of the patients with DNS was 34.7 years old, and in the study by Ozkul et al., the average age was 32.31 years old, which were in line with our

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Table 4 Comparison of efficacy of treatment groups at 3 months

S.No.	Parameter	Septoplasty group		Nonsurgical management group		*p-value**
		0 month	3 months	0 month	3 months	
1.	VAS score Mean (SD)	6.28 (1.4)	3.38 (1.2)	6.0 (1.5)	4.33 (1.6)	0.001
2.	SNOT-22 Median (IQ range)	19.5 (12–24.5)	12 (10–18.7)	15 (10–22)	12 (10–20)	0.021
3.	NOSE Median (IQ range)	70 (50–80)	50 (40–58.8)	60 (50–80)	50 (25–62.5)	0.035
4.	PNIF R Median (IQ range) L/min	60 (40–70)	60 (52.5–80)	60 (50–80)	60 (55–85)	0.003
5.	PNIF L Median (IQ range) L/min	50 (40–70)	60 (50–80)	60 (40–72.5)	70 (50–90)	0.001

Abbreviations: S. No., Serial number; IQ range, Interquartile range; NOSE, nasal obstruction symptom evaluation; PNIF L, peak nasal inspiratory flow on the left side; PNIF R, peak nasal inspiratory flow on the right side; SD, Standard Deviation; SNOT-22, Sino-nasal outcome test 22; VAS, visual analogue scale.
*Mann-Whitney test.

Table 5 Comparison of efficacy of treatment groups at 6 months

S.No.	Parameter	Septoplasty group		Nonsurgical management group		*p-value**
		0 month	6 months	0 month	6 months	
1.	VAS score Mean (SD)	6.28 (1.4)	2.9 (1)	6.0 (1.5)	5.26 (2.3)	0.001
2.	SNOT-22 Median (IQ range)	19.5 (12–24.5)	10 (8–16)	15 (10–22)	12 (8–20)	0.002
3.	NOSE Median (IQ range)	70 (50–80)	40 (30–50)	60 (50–80)	50 (30–70)	0.006
4.	PNIF R Median (IQ range) L/min	60 (40–70)	70 (60–80)	60 (50–80)	70 (60–90)	0.001
5.	PNIF L Median (IQ range) L/min	50 (40–70)	60 (50–80)	60 (40–72.5)	70 (50–90)	0.001

Abbreviations: S. No., Serial number; IQ range, Interquartile range; NOSE, nasal obstruction symptom evaluation; PNIF L, peak nasal inspiratory flow on the left side; PNIF R, peak nasal inspiratory flow on the right side; SD, Standard Deviation; SNOT-22, Sino-nasal outcome test 22; VAS, visual analogue scale.
*Mann-Whitney test.

study.[8,12] Possibly, the reason for this can be that patients with DNS usually present in their 3rd decade of life with symptoms of nasal obstruction.

At the end of 6 months, 10 patients were lost to follow-up in the septoplasty group, and 13 were lost to follow-up in the nonsurgical management group. The sample size of 70 patients in each group in our study was calculated with an anticipated dropout rate of 20%. The number of patients who completed the 6 months of follow-up required for the present study was sufficient for analysis.

In the study by Stewart et al., the follow-up rate after septoplasty was of 81% after 3 months and of 65% after 6 months.[13] The follow-up rates were better in our study. Patients who underwent surgical intervention were more inclined to comply with the follow-up for the treatment than the patients in the nonsurgical management group.

The baseline characteristics such as age, gender as well as the questionnaire scores and PNIF values were comparable between the two groups in our study.

Although there was a difference in the baseline SNOT-22 scores between the septoplasty and nonsurgical management groups (19.5 versus 15), this difference was not statistically significant ($p = 0.095$). The mean baseline SNOT-22 score in a study by Hytönen et al. was 21.52.[14] The mean SNOT-22 score in our study on 140 patients was 18.5. The mean scores before the treatment was initiated were similar in both studies.

The normal PNIF value in healthy individuals without DNS is between 130 and 140 L/min.[12,15,16] In our study, the median preoperative PNIF was 60/50 L/min, and the median postoperative score at 6 months was 70/60 L/min. This could possibly be due to blocking of one nostril and measuring PNIF on the other side leading to decreased inspiratory effort.

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In the septoplasty group, in the comparison of parameters from baseline to 6 months, there was a significant improvement in the VAS, SNOT-22, NOSE and PNIF scores over a period of 6 months ($p = 0.001$).

The nonsurgical management group also showed a significant improvement in parameters from baseline over a period of 6 months ($p = 0.001$).

Comparing the scores of both groups from baseline to 1 month, there was no significant difference in their efficacy ($p > 0.05$). This can be explained by the fact that most patients in the septoplasty group had postoperative edema and crusting in the nasal mucosa as a result of the surgical intervention.[17] This can be managed by daily regular saline nasal irrigation at home and diagnostic nasal endoscopy with suction clearance in their postoperative visit at the hospital. Nasal decongestants can be added to reduce postoperative edema. Nasal decongestants improve sinus ventilation and drainage due to their vasoconstrictor property, causing shrinkage of the turbinates and, therefore, relieving the obstruction of the osteomeatal complex.[18]

However, comparing the improvement in scores between both groups from baseline to 3 as well as 6 months, there was a significant difference in symptom scores as well as in PNIF values, with septoplasty showing better efficacy in alleviating nasal obstruction than nonsurgical management as measured by their p-value ($p < 0.05$).

In the study by Stewart et al., the mean NOSE scores improved from 67.5 to 26.6 from baseline to 6 months among patients who underwent surgery for DNS.[13] The median NOSE scores in the septoplasty group in our study were 70 at baseline and 40 at 6 months.

Our results are similar to those of a study by Ozkul et al., in which the mean preoperative and postoperative PNIF values were 102 L/min and 139 L/min, respectively, which showed an objective significant improvement in nasal obstruction by the septoplasty technique.[12]

A meta-analysis involving only 3 prospective controlled trials was performed by Singh et al., in which the authors demonstrated a reduction in the resistance of nasal airway following septoplasty ($p = 0.018$).[19]

Moore et al., in a systematic review, concluded that septoplasty improved nasal patency as reflected by objective measurements and, thus, has beneficial effects on the patients undergoing septal surgery.[20]

Hsu et al., in their retrospective cohort study, followed-up patients for 1 year before and after septoplasty with VAS, NOSE score and active anterior rhinomanometry. The patients showed a significant symptom improvement over the period of 1 year.[21]

Teixeira et al. evaluated the usefulness of PNIF in patients with nasal obstruction for objective assessment and found a positive correlation of PNIF with VAS scores.[22] Our study is the only prospective study to assess the improvement with treatment in DNS patients by all three subjective assessment scores (VAS, SNOT-22 and NOSE). An added strength to our study is the usage of an objective measurement tool in the form of PNIF values.

Our study was a well-planned prospective randomized clinical trial performed with a good sample size of 70 patients in each group. All patients in the surgical treatment group in our study underwent only septoplasty as the surgical technique. Most studies that evaluated subjective and objective parameters on DNS patients with nasal obstruction were observational or retrospective in nature or involved different types of surgical procedures and were performed with much smaller sample sizes.[23–25]

In septoplasty, DNS is straightened, causing a widening of the nasal passages. This results in improved ventilation and inspiratory effort in patients with nasal obstruction. It also improves mucociliary clearance and, therefore, improves nasal breathing.[26,27] It also alleviates other associated symptoms of DNS such as headache, epistaxis, snoring, and sleep disturbances, therefore improving quality of life.[14] This was evident from the improvement in subjective assessment scores in our study.

Limitations of the Study

The severity of nasal obstruction based on degrees of septal deviation was not measured. The evaluation of long-term complications in both treatment groups was not studied in detail. The cost-efficacy of the treatment groups was not studied in the present study. Septoplasty surgeries were not performed by the same surgeon in our study. The types of septal deviation and their specific treatment outcomes were not studied.

Conclusion

Septoplasty is more efficacious than medical management in the long run in alleviating nasal blockade in DNS patients. Nonsurgical management is effective in a short-term basis (when used for a period of 1 month) and fails to show significant improvement thereafter. Hence, it can be considered in patients while awaiting surgery. Patients with mild to moderate DNS can be considered for a trial of nonsurgical management and, if it fails to show improvement beyond 1 month, they should be submitted to septoplasty.

Note
The present paper was presented at the 14th Asia Oceana ORL-HNS Congress and AOICON 2019, held at Hyderabad, India, from 9 to 13 January 2019.

Source of Funding
None to declare.

Conflict of Interests
The authors have no conflict of interests to declare.

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Septoplasty with or without concurrent turbinate surgery versus non-surgical management for nasal obstruction in adults with a deviated septum: a pragmatic, randomised controlled trial

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Lancet 2019; 394: 314–21

Published Online June 18, 2019 http://dx.doi.org/10.1016/S0140-6736(19)30354-X

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Summary

Background Septoplasty (surgical correction of the deviated nasal septum) is the most frequently performed ear, nose, and throat operation in adults, but no randomised controlled trials or non-randomised comparative studies on the effectiveness of septoplasty have been published. Consequently, health-care providers, health insurance companies, and policy makers are concerned about the effectiveness of the procedure. We aimed to assess the effectiveness of septoplasty for nasal obstruction in adults with a deviated septum.

Methods We did this open, multicentre, pragmatic, randomised controlled trial in 16 secondary and two tertiary referral hospitals in the Netherlands. Adults (aged ≥18 years) with nasal obstruction, a deviated septum, and an indication to have septoplasty done were randomly allocated (1:1) to receive either septoplasty with or without concurrent turbinate surgery or non-surgical management. Patients were stratified by sex, age (<35 years or ≥35 years), and deviation severity (mild, moderate, or severe). The primary outcome was health-related quality of life, measured with the validated Glasgow Health Status Inventory at 12 months. Analyses were done on an intention-to-treat basis. The trial is registered with the Netherlands Trial Register, number NTR3868.

Findings Between Sept 2, 2013, and Dec 12, 2016, we randomly assigned 203 participants to receive either septoplasty with or without concurrent turbinate surgery (n=102) or non-surgical management (n=101). 189 participants were analysed at 12 months. At 12 months, mean score on the Glasgow Health Status Inventory of patients assigned to septoplasty was 72·2 (SD 12·2) and for those assigned to non-surgical management was 63·9 (SD 14·5, mean difference 8·3 [95% CI 4·5–12·1], favouring septoplasty). Septal abscess occurred in one surgical patient and septal perforation in two surgical patients. No side-effects of nasal medication were reported.

Interpretation Septoplasty is more effective than non-surgical management for nasal obstruction in adults with a deviated septum. This effect was sustained up to 24 months of follow-up.

Funding The Netherlands Organisation for Health Research and Development (ZonMw).

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Introduction

Septoplasty (surgical correction of the deviated nasal septum) is the most frequently performed ear, nose, and throat (ENT) operation in adults, but its effectiveness is uncertain.[1] In 2010, the professional membership body representing British ENT surgeons (ENT UK) noted that some hospital administrations were suggesting to abolish or severely restrict septoplasty because of doubts about its benefits.[2] The Dutch ear, nose, and throat society and the British National Institute for Health Research prioritised research on this topic, considering it an important knowledge gap in otorhinolaryngology.[3] Still, the American Academy of Otorhinolaryngology had to rely on consensus to substantiate its 2015 paper on septal surgery, as evidence was found poor.[4]

To date, no randomised controlled trials (RCTs) or non-randomised comparative studies on the effectiveness of septoplasty have been published.[5] Existing literature is methodologically flawed and inconclusive, which has led to a vigorous debate as to whether patients benefit from straightening the deviated septum, and if so, which patients benefit most.[6,7] Evidence-based guidelines are absent and annual performance rates differ remarkably between countries: the number of septoplasties per 10 000 inhabitants varies from 3·9 in England, 6·6 in the Netherlands, 8·7 in the USA, to 12·2 in Germany (Dutch Hospital Data, personal communication).[8–10]

The current era of value-based health care is characterised by an increasing demand for evidence that interventions provide outcomes valued by patients and society. The lack of evidence for septoplasty's effectiveness prompted several National Health Service (NHS) Clinical Commissioning Groups in England to add septal surgery to their list of restricted treatments and procedures. To overcome the evidence gap, this pragmatic RCT aimed to

Research in context

Evidence before this study

We systematically searched PubMed, the Cochrane Library (both from inception), and Ovid Embase (from Jan 1, 1974) up to Oct 10, 2017, for randomised controlled trials or non-randomised studies comparing septal surgery with non-surgical management for nasal obstruction in adults with a deviated septum. Keywords (MeSH and Emtree) and free text terms were included in the search query, which combined synonyms for nasal obstruction, nasal septal deviation, septoplasty, and various subjective as well as objective outcome measures, such as the Glasgow Health Status Inventory, Glasgow Benefit Inventory, SinoNasal Outcome Test, Nasal Obstruction Symptom Evaluation, EuroQol 5 Dimensions, Short Form 36, RhinoSinusitis Outcome Measure, and Rhinomanometry. No language or date restrictions were applied. Nonetheless, the systematic literature search yielded no results. The evidence base for septal surgery consists solely of observational studies, comparing preoperative and postoperative measurements of quality of life or nasal patency. These studies have a high risk of bias, as the reported effects could also be explained by other factors (such as natural course), leaving whether patients benefit from septoplasty uncertain.

Added value of this study

Because of the methodologically flawed and inconclusive literature, there are no evidence-based guidelines on septal surgery and annual performance rates differ remarkably between countries. Doubts about septoplasty's benefits have prompted several professional associations of ear, nose, and throat surgeons and the British National Institute for Health Research to call for further research. In response to their call, this is the first randomised controlled trial on the effectiveness of septal surgery.

Implications of all the available evidence

Given the evidence gap and the uncertainty surrounding the surgery's benefits, septoplasty was added to the restricted treatments and procedures list of several National Health Service Clinical Commissioning Groups in England, an example that might be followed by policy makers and insurance carriers across the globe. The results of this trial, showing that septoplasty is more effective than non-surgical management (medication or watchful waiting), are pivotal in reaching better informed decisions and developing evidence-based guidelines on the treatment of nasal obstruction in adults with a deviated septum.

assess the effectiveness of septoplasty compared with non-surgical management for nasal obstruction in adults with a deviated septum, in terms of subjective (health-related quality of life) and objective (nasal patency) outcome measures.

Methods

Study design and participants

We did an open, multicentre, pragmatic, randomised controlled trial in 16 secondary referral hospitals and two tertiary referral hospitals in the Netherlands. The trial protocol has been published previously and was approved by the accredited medical ethics committee of Radboud University Medical Center.[6] Adults (aged 18 years or older) with nasal obstruction, a deviated septum, and an indication to have septoplasty done, were eligible for trial participation.

Nasal septal deviation is commonly accompanied by (compensatory) turbinate hypertrophy, which can involve the mucosa as well as the conchal bone and might not regress spontaneously after septoplasty.[11] Accordingly, septal surgery often includes the lateralisation of turbinates or partial submucosal turbinectomy to prevent postoperative complaints of nasal obstruction due to this compensatory turbinate enlargement.[12,13] As the trial was pragmatic, concurrent turbinate surgery was allowed. The indication for septoplasty (with or without concurrent turbinate surgery) had to be based on an internal examination of the nose, consisting of anterior rhinoscopy and nasal endoscopy, which showed that the septal deviation was obstructing the nasal airway, leading to impaired nasal breathing. This assessment reflected regular practice and was also in line with the pragmatic nature of the trial.

Nasal obstruction had to be the main indication for septoplasty. Patients were excluded if the indication was primarily based on concurrent complaints, such as impairment of normal sinus drainage, sleep disorders, or headaches. We also excluded patients with enlarged turbinates but without a deviated septum, patients with a history of nasal septal surgery, patients with untreated allergic rhinitis or allergic rhinitis unresponsive to medical treatment, patients selected for septoplasty because of septal perforation, patients in whom septoplasty was to be done as part of a cosmetic rhinoplasty procedure, and patients with a cleft lip or palate.

Eligible patients visiting the outpatient clinic were approached for trial participation by their ENT surgeon. When patients gave informed consent to share their personal information, the ENT surgeon forwarded the clinical history, results of physical examination, and contact details to our research team. We contacted patients by telephone, informed them about the trial, and checked inclusion and exclusion criteria. Eligible patients who were willing to participate were invited for a baseline visit, during which written informed consent for trial participation was obtained. At baseline, demographic and disease-specific data were collected, and subjective and objective outcome measures were administered. Afterwards, patients were randomly assigned to a treatment group.

For the **protocol** see https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-015-1031-4

Randomisation and masking

An independent data manager generated a randomisation sequence (using block sizes of 6), with stratification according to sex, age (<35 years or ≥35 years), and severity of the deviation (mild, moderate, or severe). The deviation was classified by the ENT surgeon as mild if it obstructed less than half of the nasal passage; moderate if it obstructed half or more than half of the nasal passage; and severe if the deviation was in contact with the lateral nasal wall. The study physician accessed the trial randomisation website to obtain the treatment assignment. The assignment was concealed and could not be predicted in advance of or during enrolment. Assignments were balanced in a 1:1 ratio for the two treatment groups, septoplasty and non-surgical management. No masking was applied.

Procedures

Patients assigned to septoplasty had surgery within 6–8 weeks after the baseline visit. Septoplasty was done with or without concurrent turbinate surgery (unilateral or bilateral), as considered appropriate by the ENT surgeon. A detailed and standardised operation report was kept for each trial participant. Given the pragmatic nature of the trial, ENT surgeons were encouraged to operate according to their regular practice, and patients could use any kind of medication in addition to their surgical treatment.

Patients assigned to non-surgical management underwent watchful waiting or medical treatment. As the trial was pragmatic, we aimed to assess the effectiveness of septoplasty and non-surgical management in daily practice, instead of assessing their effectiveness under specific conditions dictated by the study. Consequently, non-surgical management did not involve a prespecified treatment regime; the decision between watchful waiting and medical treatment (usually local corticosteroids) was made on an individual patient basis. Also, similar to surgical patients, those assigned to non-surgical management could use additional medication if needed (such as normal saline nasal spray or drops, xylometazoline nasal spray or drops, paracetamol, or ibuprofen). If persistent complaints prompted patients assigned to non-surgical management to undergo septoplasty within the 24 months of trial follow-up, they were classified as cross-over and monitored as planned. At 3, 6, 12, and 24 months, follow-up visits were scheduled, during which subjective and objective outcomes were measured.

See Online for appendix

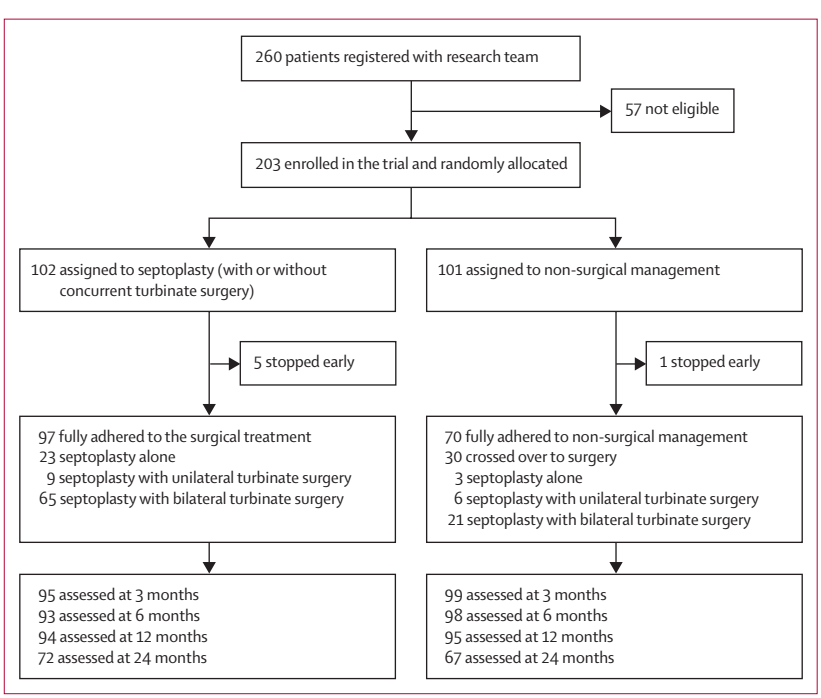

Figure 1: **Trial profile**

Outcomes

For all outcome measures, our timepoint of primary interest was 12 months. The primary outcome was health-related quality of life, measured using the patient-reported Glasgow Health Status Inventory (GHSI).[14,15] Secondary outcomes were objective assessments of nasal patency with peak nasal inspiratory flow (PNIF) and 4-phase rhinomanometry (4PR); health-related quality of life measured using the Nasal Obstruction Symptom Evaluation (NOSE) scale, sino-nasal outcome test-22 (SNOT-22), the three-level EuroQol, five dimensions (EQ-5D-3L), and Glasgow Benefit Inventory (GBI); and complications and serious adverse events. The study physician visited each of the participating centres to assess all outcomes. An overview of our subjective and objective measurement instruments is provided in the appendix (p 3). The instruments used for PNIF were produced by Clement Clarke International (Essex, UK) and for 4PR by RhinoLab GmbH (Freiburg im Breisgau, Germany). Objective measurements were done before and after application of 0·1% xylometazoline spray to examine the effect of mucosal decongestion on nasal patency.

The GHSI, PNIF, 4PR, NOSE scale, and GBI have all been validated for use in adults with nasal obstruction and a deviated septum.[16–18] The SNOT-22 has been validated for patients with chronic rhinosinusitis but is also used in patients with nasal obstruction because of its broad coverage of nasal complaints.[19]

Statistical analysis

The main comparison in our trial was septoplasty with or without concurrent turbinate surgery versus non-surgical management. The sample size calculation was based on a clinically relevant improvement on the GHSI of 10 (SD 15). Assuming a health-related quality of life of 70 in the non-surgical group and assuming an α of 0·05 and a power of 0·90, each treatment group had to include at least 48 patients. To allow for objective assessments of nasal patency and subgroup analyses, we decided to include 100 adults in each treatment group.

Effects of septoplasty on health-related quality of life and nasal patency were calculated as mean differences with 95% CIs. All analyses were done on an intention-to-treat basis (additional per-protocol analyses given in the appendix p 7). Analyses were stratified by sex, age (<35 years or ≥35 years), deviation severity (mild, moderate, or severe), deviation cause (congenital or traumatic), and type of surgery (septoplasty alone or septoplasty with concurrent turbinate surgery). If stratified analyses indicated potential modification of the effect of septoplasty, subgroups were analysed further using multiple regression. Considering the type of variables for which data were missing and the nature of the trial, missing data were assumed to be missing at random and were multiply imputed using chained equations. Baseline variables and study outcomes were used as predictors in the imputation model (appendix p 5). Analyses were done with SPSS (version 22) and R (version 3.5.1). Data collection was overseen by independent data managers and an independent monitor. The trial is registered with the Netherlands Trial Register, number NTR3868.

Role of the funding source

The funder of the trial had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the trial. MR and NvH had final responsibility for the decision to submit the report for publication.

Results

Between Sept 2, 2013, and Dec 12, 2016, clinical and contact information from 260 potential participants were shared with our research team by the participants' ENT surgeons. We enrolled 203 eligible patients; 57 patients either did not fulfil the eligibility criteria or were not willing to participate, mostly because of the time investment or strong treatment preferences. All 203 patients were randomly allocated: 102 were assigned to septoplasty and 101 to non-surgical management. 23 patients assigned to surgery received septoplasty alone; nine received septoplasty with unilateral turbinate surgery; and 65 received septoplasty with bilateral turbinate surgery (figure 1). The most frequently done type of turbinate surgery was lateralisation (116/230 [50%]), followed by partial turbinectomy (52 [23%]), turbinate coblation (22 [10%]), and turbinate cautery (16 [7%]); the remaining 24 (10%) were classified as other. Analyses at our primary timepoint of 12 months were done in 94 patients (92%) assigned to septoplasty and 95 patients (94%) assigned to non-surgical management.

Baseline characteristics of the trial participants are shown in table 1. There were slightly more men than there were women. The mean age was 38 years (SD 15) and the median duration of nasal obstruction before trial entry was 7 years (IQR 3–15). Most patients (n=125 [62%]) had

	Septoplasty with or without concurrent turbinate surgery (n=102)	Non-surgical management (n=101)
Age (years)		
Mean (SD)	39 (14)	37 (15)
Range	18–67	18–70
Sex		
Male	73 (72%)	66 (65%)
Female	29 (28%)	35 (35%)
Body-mass index		
Mean (SD)	25·0 (4·5)	25·6 (3·8)
Range	16·7–39·9	17·5–38·7
Duration of nasal obstruction (years)		
Median (IQR)	6 (2–12)	8 (4–15)
Nasal obstruction bilateral	64 (63%)	61 (60%)
Previous treatment for nasal obstruction	81 (79%)	87 (86%)
Local corticosteroids	73 (72%)	73 (72%)
Nasal decongestants	39 (38%)	42 (42%)
Turbinate surgery	2 (2%)	3 (3%)
History of nasal trauma	42 (41%)	42 (42%)
Smoking status		
Current smoker	26 (25%)	34 (34%)
History of smoking	34 (33%)	30 (30%)
Cocaine use	7 (7%)	11 (11%)
Snoring*	50 (49%)	44 (44%)
Allergic rhinitis*	32 (31%)	30 (30%)
Asthma*	24 (24%)	18 (18%)
Turbinate hypertrophy	46 (45%)	47 (47%)
Unilateral	29 (28%)	24 (24%)
Bilateral	16 (16%)	18 (18%)
Septal deviation bilateral	25 (25%)	23 (23%)
Septal deviation severity†		
Mild	32 (31%)	27 (27%)
Moderate	66 (65%)	67 (66%)
Severe	37 (36%)	32 (32%)
Primary outcome		
GHSI (mean [SD])	61·2 (12·2)	62·0 (13·3)
Secondary outcomes‡		
PNIF (mean [SD])§	91·6 (39·0)	87·1 (40·5)
4PR right side (mean [SD])§	1·32 (0·48)	1·19 (0·46)
4PR left side (mean [SD])§	1·30 (0·63)	1·24 (0·54)
NOSE scale (mean [SD])	32·8 (18·1)	34·4 (19·3)
SNOT-22 (mean [SD])	64·1 (15·0)	62·1 (16·4)
EQ-5D-3L utility score (mean [SD])	0·83 (0·19)	0·82 (0·19)
EQ-5D-3L VAS (mean [SD])	72·1 (16·1)	74·1 (17·0)

Data are n/N (%), unless otherwise specified. GHSI=Glasgow Health Status Inventory. PNIF=peak nasal inspiratory flow. 4PR=4-phase rhinomanometry. NOSE=Nasal Obstruction Symptom Evaluation. SNOT-22=sino-nasal outcome test-22. EQ-5D-3L=three-level EuroQol, five dimensions. VAS=visual analogue scale. *Self-reported; no diagnostics were done as part of the trial. †The deviation was classified by the ear, nose, and throat surgeon as mild if it obstructed less than half of the nasal passage; moderate if it obstructed half or more than half of the nasal passage; and severe if the deviation was in contact with the lateral nasal wall. ‡The Glasgow Benefit Inventory is only applicable to postoperative patients and was not administered at baseline. §Presented values are before decongestion of nasal mucosa.

Table 1: **Baseline characteristics**

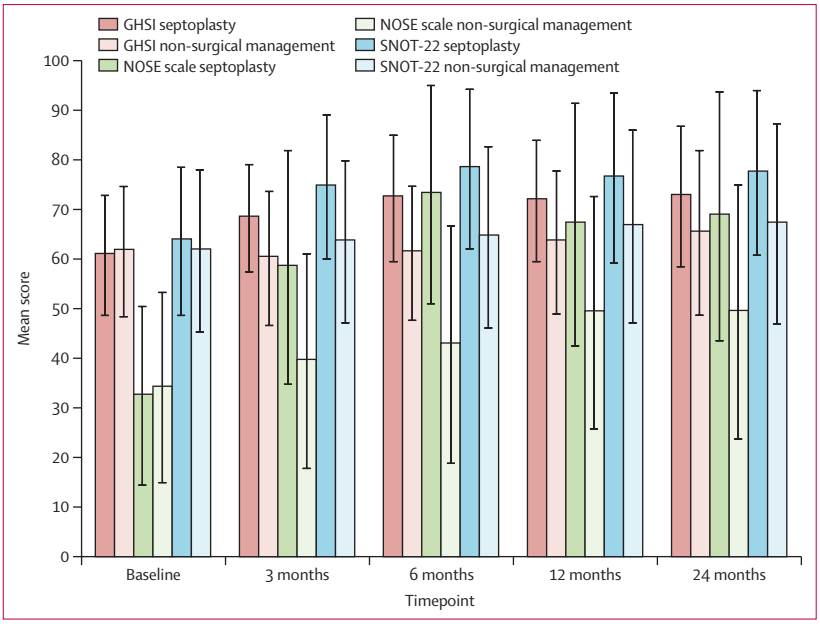

Figure 2: **Mean scores on the GHSI, NOSE scale, and SNOT-22**
GHSI=Glasgow Health Status Inventory. NOSE=Nasal Obstruction Symptom Evaluation. SNOT-22=sino-nasal outcome test-22.

	Septoplasty with or without concurrent turbinate surgery (n=94)	Non-surgical management (n=95)	Septoplasty with or without concurrent turbinate surgery *vs* non-surgical management (n=189)
Primary outcome			
GHSI	72·2 (12·2)	63·9 (14·5)	8·3 (4·5 to 12·1)
Objective secondary outcomes			
PNIF before decongestion	124·3 (45·7)	95·0 (37·6)	29·3 (16·9 to 41·8)
PNIF after decongestion	133·0 (50·8)	109·7 (48·2)	23·3 (8·6 to 38·0)
4PR right, before decongestion	1·07 (0·39)	1·25 (0·58)	−0·18 (−0·37 to 0·01)
4PR left, before decongestion	1·04 (0·51)	1·20 (0·54)	−0·16 (−0·36 to 0·05)
4PR right, after decongestion	1·03 (0·42)	1·23 (0·57)	−0·20 (−0·40 to −0·01)
4PR left, after decongestion	1·04 (0·47)	1·11 (0·46)	−0·07 (−0·25 to 0·11)
Subjective secondary outcomes			
NOSE scale	67·5 (24·5)	49·6 (23·6)	17·8 (11·0 to 24·7)
SNOT-22	76·8 (17·1)	67·0 (19·5)	9·7 (4·5 to 15·0)
EQ-5D-3L utility score	0·89 (0·15)	0·87 (0·13)	0·02 (−0·02 to 0·08)
EQ-5D-3L VAS	74·0 (16·4)	74·9 (17·6)	−1·0 (−5·8 to 3·9)
GBI	10·6 (13·8)	NA	NA

Data are mean (SD) or mean difference (95% CI). GHSI=Glasgow Health Status Inventory. PNIF=peak nasal inspiratory flow. 4PR=4-phase rhinomanometry. NOSE=Nasal Obstruction Symptom Evaluation. SNOT-22=sino-nasal outcome test-22. EQ-5D-3L=three-level EuroQol, five dimensions. VAS=visual analogue scale. GBI=Glasgow Benefit Inventory. NA=not applicable.

Table 2: **Subjective and objective outcomes at 12 months**

bilateral complaints. The septal deviation was bilateral in 48 (24%) patients. Turbinate hypertrophy was present in 93 (46%) patients, mostly unilaterally (n=53 [26%]).

At our primary timepoint of 12 months, the mean GHSI score of patients assigned to septoplasty was 72·2 (SD 12·2) and to non-surgical management was 63·9 (SD 14·5; mean difference 8·3 [95% CI 4·5–12·1]). At 3, 6, and 24 months, patients in the septoplasty group had higher GHSI scores than did patients in the non-surgical management group (appendix p 4). The largest difference between the two groups was found at 6 months, with scores of 72·8 (SD 12·8) in the septoplasty arm and 61·7 (SD 13·5) in the non-surgical management arm (mean difference 11·1, 95% CI 7·4–14·9 [figure 2; appendix p 4]).

At 12 months, nasal airflow before mucosal decongestion was 124·3 L/min (SD 45·7) in patients in the septoplasty group and 95·0 L/min (SD 37·6) in patients in the non-surgical management group (table 2). After mucosal decongestion, nasal airflow was 133·0 L/min (SD 50·08) in surgical patients and 109·7 L/min (SD 48·2) in non-surgical patients (table 2). The mean difference between the two groups in nasal resistance varied between –0·07 Pa/cm³/s (95% CI –0·25 to 0·11) and –0·20 Pa/cm³/s (–0·40 to –0·01) , indicating surgical benefit; although overall 4PR differences were rather small and less consistent than were the results from PNIF (table 2; appendix p 4; figure 3).

The disease-specific NOSE scale and SNOT-22 showed consistently large effects in favour of septoplasty (table 2). The EQ-5D-3L did not show significant differences between the two groups in generic health-related quality of life. However, the GBI score (available only in surgical patients because of the nature of the questionnaire) showed positive scores on each timepoint of outcome assessment, indicating that surgical patients felt that they benefited from their treatment (table 2; appendix p 4).

Subjective and objective benefits of septoplasty persisted over the full 24 months of follow-up. An overview of all trial outcomes at all timepoints is provided in the appendix (p 4).

Postoperative complications occurred in 23 (18%) patients who were assigned to septoplasty or had crossed-over to surgery (table 3). The most frequent complications were haemorrhage and infection (table 3); these complications occurred directly after surgery and were mild, meaning that patients either did not require treatment or could be treated at the outpatient clinic with nasal packing or local or oral antibiotics. Septal perforation occurred in two patients and septal abscess in one patient, who was hospitalised to receive intravenous antibiotics; consequently, the septal abscess was classified as a serious adverse event. No other serious adverse events related to the treatments under study occurred during the trial. No adverse events related to nasal medication were reported. Revision surgery because of persisting complaints was required in one patient (table 3).

Analyses of imputed data did not alter our findings (appendix p 5). Stratified analyses by sex, age, deviation severity, deviation cause, and type of surgery did not show potential modification of the effect of septoplasty

(appendix p 6). Additional per-protocol analyses did not alter our findings (appendix p 7).

Discussion

In this pragmatic RCT, we found that septoplasty is more effective than non-surgical management in adults with nasal obstruction and a deviated septum. Patients assigned to septoplasty scored significantly higher than did patients assigned to non-surgical management on disease-specific quality of life, measured with the GHSI, NOSE scale, and SNOT-22; and on nasal airflow, measured with PNIF. The difference between the two groups was largest at 6 months, but beneficial effects of surgery persisted over the full 24 months of follow-up.

So far, evidence for the effectiveness of septoplasty was based on observational studies, comparing preoperative and postoperative measurements of quality of life or nasal patency.[20–24] These studies had a high risk of bias, as the reported effects could also be explained by other factors (such as natural course).

The main strength of our trial is that this is the first RCT to answer the call for further research, which has been voiced from clinical practice. Some of our findings deserve further discussion. Masking of participants was impossible, as medical ethics committees in the Netherlands consider it unethical to do sham surgery in the control group. However, the effect of septoplasty was assessed using not only subjective, but also objective outcomes, which showed similar results.

Also, about 30% of patients assigned to the non-surgical management group crossed over to septoplasty over the full 24 months of follow-up. This crossover is part of the pragmatic nature of the trial, directed at assessing the effect of septoplasty in daily practice. Even with a crossover rate of 30%, analyses on an intention-to-treat basis showed that septal surgery was better than non-surgical management.

Generic health-related quality of life measured with EQ-5D-3L and nasal patency measured with 4PR did not show effects as clear as the other outcomes. This finding is probably due to the measurement properties of the instruments rather than the intervention, given the overall consistency of our findings. The EQ-5D-3L is valuable to assess utility, but has insufficient sensitivity and ceiling effects.[25] Also, 4PR has poor responsiveness, as shown by a clinimetrics study done after the trial had begun but before the trial's data collection was finished.[16] Despite the instruments' unfavourable clinimetric properties, EQ-5D-3L and 4PR results were pre-registered outcomes; accordingly, we reported the results. We selected multiple instruments for subjective and objective outcome assessments in our trial on the basis of the specific characteristics of each instrument. The GHSI was chosen as a primary outcome because it includes generic and disease-specific quality of life items, as opposed to the NOSE scale. Including generic quality-of-life questions facilitates a transdisciplinary view and enables the comparison of septoplasty with other interventions.

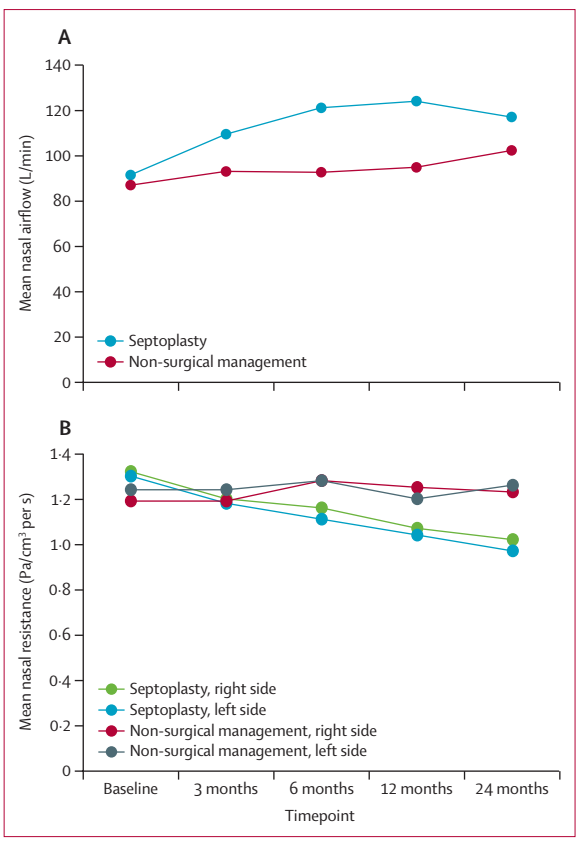

Figure 3: **Nasal airflow and nasal resistance**
(A) Mean nasal airflow in L/min as measured by peak nasal inspiratory flow (before decongestion) and (B) mean nasal resistance in Pa/cm³/s as measured by 4-phase rhinomanometry (before decongestion).

	Septoplasty with or without concurrent turbinate surgery (n=97)	Non-surgical management (n=100)*	All patients (n=197)†
Postoperative complications			
Haemorrhage	6/97 (6%)	2/30 (7%)	8/127 (6%)
Infection	7/97 (7%)	2/30 (7%)	9/127 (7%)
Septal abscess	1/97 (1%)	0	1/127 (1%)
Septal perforation	2/97 (2%)	0	2/127 (2%)
Other‡	2/97 (2%)	1/30 (3%)	3/127 (2%)
Revision septoplasty	1/97 (1%)	0	1/127 (1%)
Medication-related adverse events	0	0	0
Non-trial-related adverse events	35/97 (36%)	38/100 (38%)	73/197 (37%)
Trial-related serious adverse events§	1/97 (1%)	0	1/197 (1%)
Non-trial-related serious adverse events§	1/97 (1%)	4/100 (4%)	5/197 (3%)

Data are n/N (%). *30 patients crossed over. †127 patients had surgery. ‡Other complications were severe postoperative pain and severe postoperative swelling, not classified as septal haematoma. §Serious adverse events were untoward medical occurrences that made hospital admission necessary. No fatal or life-threatening serious adverse events occurred. All serious adverse events were reported to the accredited medical ethics committee and the funder.

Table 3: **Complications and adverse and serious adverse events**

The rate of mild postoperative complications in our trial was somewhat high.[26] This finding might be induced by the long-term follow-up and intensified monitoring of trial patients compared with regular care, in which underreporting could occur.

Most patients receiving surgical treatment had septoplasty with concurrent turbinate surgery, even though turbinate hypertrophy was detected in less than half of the patients at baseline. The most frequent type of turbinate surgery was lateralisation, which ENT surgeons might consider a pragmatic and minor procedure complementary to septal surgery that is often required to prevent postoperative complaints of nasal obstruction due to the turbinate enlargement that accompanies the septal deviation. As with the other subgroups, stratified analyses comparing septoplasty alone with septoplasty with concurrent turbinate surgery did not show clinically relevant differences (appendix p 6).

Furthermore, recruiting a sample that is representative of the whole target population can be a challenge with RCTs.[27] However, we believe that the results of this multicentre, pragmatic trial are applicable to all patients with nasal obstruction and a deviated septum, as seen in daily practice. We compared baseline characteristics of trial participants with 52 patients indicated for septoplasty in three hospitals that did not participate in our multicentre trial and found no relevant differences, especially not in previous treatment or severity of the deviation (appendix p 8). In both samples, about three-quarters of patients had already received medical treatment with local corticosteroids before trial entry, and in about a third of patients the septal deviation was classified as severe.

The clinical implications of this RCT are far-reaching. Despite the globally acknowledged evidence gap, septoplasty is one of the most common procedures within the field of otorhinolaryngology, affecting numerous patients each year. Over the past decades, uncertainty surrounding its effectiveness has put an increasing strain on septal surgery, as shown by the addition of septoplasty to the restricted treatments and procedures list of several NHS Clinical Commissioning Groups in England. Our trial, however, shows that many patients, despite medical treatment, continue to live with nasal obstruction for years before being referred to the ENT surgeon. In these patients, septoplasty offered considerable subjective and objective benefits compared with non-surgical management, which were sustained up to 24 months of follow-up. This information provides a basis for the development of evidence-based guidelines on the treatment of nasal obstruction in adults with a deviated septum.

Contributors

MMR and NvH conceived the trial and initiated the design. MMHTvE, CTMH, MMR, and NvH did the trial. MMHTvE, GH, MMR, and NvH analysed the data. All authors had full access to all the data in the trial. All authors drafted this manuscript and approved the final version. MMR and NvH had final responsibility for the decision to submit the report for publication.

Declaration of interests

MMHTvE, MMR, CTMH, and NvH report a grant from ZonMw (the Netherlands Organisation for Health Research and Development) to do the study. GH declares no competing interests.

Data sharing

Deidentified participant data will be made available to researchers whose proposed use of the data has been approved by the principal investigators (MMR and NvH), with a signed data access agreement and only for purposes specified in the approved research proposal. Requests for data must be sent to niels.vanheerbeek@radboudumc.nl. The trial protocol is available online.

Acknowledgments

We thank the patients who participated in the trial; the ear, nose, and throat (ENT) surgeons who contributed to the enrolment of trial participants (a full list of contributing surgeons is available in the appendix p 10); the independent data managers for creating the trial randomisation website and overseeing data collection; Tim Govers for data monitoring; medical students Charlotte Michels, Sanne Leuwerink, and Beau de Korte for administrative and practical support; Anne Schilder for advice regarding the design of the trial and feedback on the draft manuscript; and the Dutch ENT society for supporting the trial's initiation and conduct. The trial was funded by the Netherlands Organisation for Health Research and Development (ZonMw), project number 837002001.

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I.D.:_____ **SINO-NASAL OUTCOME TEST (SNOT-22)** DATE:_____

Below you will find a list of symptoms and social/emotional consequences of your rhinosinusitis. We would like to know more about these problems and would appreciate your answering the following questions to the best of your ability. There are no right or wrong answers, and only you can provide us with this information. Please rate your problems as they have been over the past two weeks. Thank you for your participation. Do not hesitate to ask for assistance if necessary.

1. Considering how severe the problem is when you experience it and how often it happens, please rate each item below on how "bad" it is by circling the number that corresponds with how you feel using this scale: →	No Problem	Very Mild Problem	Mild or slight Problem	Moderate Problem	Severe Problem	Problem as bad as it can be		5 Most Important Items
1. Need to blow nose	**0**	**1**	**2**	**3**	**4**	**5**		○
2. Nasal Blockage	**0**	**1**	**2**	**3**	**4**	**5**		○
3. Sneezing	**0**	**1**	**2**	**3**	**4**	**5**		○
4. Runny nose	**0**	**1**	**2**	**3**	**4**	**5**		○
5. Cough	**0**	**1**	**2**	**3**	**4**	**5**		○
6. Post-nasal discharge	**0**	**1**	**2**	**3**	**4**	**5**		○
7. Thick nasal discharge	**0**	**1**	**2**	**3**	**4**	**5**		○
8. Ear fullness	**0**	**1**	**2**	**3**	**4**	**5**		○
9. Dizziness	**0**	**1**	**2**	**3**	**4**	**5**		○
10. Ear pain	**0**	**1**	**2**	**3**	**4**	**5**		○
11. Facial pain/pressure	**0**	**1**	**2**	**3**	**4**	**5**		○
12. Decreased Sense of Smell/Taste	**0**	**1**	**2**	**3**	**4**	**5**		○
13. Difficulty falling asleep	**0**	**1**	**2**	**3**	**4**	**5**		○
14. Wake up at night	**0**	**1**	**2**	**3**	**4**	**5**		○
15. Lack of a good night's sleep	**0**	**1**	**2**	**3**	**4**	**5**		○
16. Wake up tired	**0**	**1**	**2**	**3**	**4**	**5**		○
17. Fatigue	**0**	**1**	**2**	**3**	**4**	**5**		○
18. Reduced productivity	**0**	**1**	**2**	**3**	**4**	**5**		○
19. Reduced concentration	**0**	**1**	**2**	**3**	**4**	**5**		○
20. Frustrated/restless/irritable	**0**	**1**	**2**	**3**	**4**	**5**		○
21. Sad	**0**	**1**	**2**	**3**	**4**	**5**		○
22. Embarrassed	**0**	**1**	**2**	**3**	**4**	**5**		○

2. Please mark the most important items affecting your health (maximum of 5 items)_____ ↑

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SNOT-22 Developed from modification of SNOT-20 by National Comparative Audit of Surgery for Nasal Polyposis and Rhinosinusitis Royal College of Surgeons of England.

Nasal Obstruction and Septoplasty Effectiveness Scale

Physician AAO-HNS#:_____**Patient ID:** _____ **Today's date:** __ __/__ __/__ __ __ __

➔ **To the Patient:** Please help us to better understand the impact of nasal obstruction on your quality of life by **completing following survey**. Thank You!

Over the past *ONE* month, how much of a problem were the following conditions for you?

Please circle the most correct response

	Not a Problem	*Very Mild Problem*	*Moderate problem*	*Fairly Bad Problem*	*Severe problem*
1. Nasal congestion or stuffiness	0	1	2	3	4
2. Nasal blockage or obstruction	0	1	2	3	4
3. Trouble breathing through my nose	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Unable to get enough air through my nose during exercise or exertion	0	1	2	3	4

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Nasal Obstruction and Septoplasty Effectiveness Scale

NOSE SCALE ADMINISTRATION

1. Have patient complete the questionnaire as indicated by circling the response closest to describing their current symptoms.

2. Sum the answers the patient circles and multiply by 20 to base the scale out of a possible score of 100 for analysis.

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Septoplasty for CPAP Tolerance May 2026

Plain Language Summary:

A surgery to straighten the divider inside the nose (nasal septum) may help people who use a breathing machine to help with sleep apnea, called a Continuous Positive Airway Pressure (CPAP) device.

Staff did not find strong evidence the surgery helps using CPAP and do not recommend adding coverage for this reason alone.

This issue summary has been changed from the March 19, 2026 meeting materials

Staff Analysis Summary:

Significant proposed changes or discussion items:

1) HERC staff recommend not adding coverage for septoplasty to allow CPAP use for sleep apnea

Changes after public comment period:

One public comment was received on the general topic of septoplasty. This comment was addressed in the companion issue on septoplasty for breathing issues.

Coverage Question:

Should the septoplasty be covered when nasal obstruction makes CPAP use ineffective for treatment of OSA?

Question source:

1) OHA Hearings Division

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Background:

OHA Hearings Division is requesting clarity regarding whether septoplasty is meant to be considered when a patient has obstructive sleep apnea and cannot tolerate their CPAP. Currently, the septoplasty guideline states that surgery is not covered for OSA, but it is unclear if this is only as a primary surgery for OSA treatment or as treatment for any OSA related indication.

Previous HSC/HERC reviews:

This issue was discussed at the March 2026 VBBS/HERC meetings. Members commented that expert guidelines on CPAP did not mention nasal surgery. HERC staff were directed to look at expert guidelines and break this portion of the septoplasty discussion into a separate issue summary. Members agreed with the staff analysis that nasal surgery was not indicated as a primary treatment of sleep apnea.

Current Prioritized List/Coverage status:

ICD-10-CM J34.2 (Deviated nasal septum) is on line 562 DEVIATED NASAL SEPTUM, ACQUIRED DEFORMITY OF NOSE, OTHER DISEASES OF UPPER RESPIRATORY TRACT

CPT *30520 (Septoplasty or submucous resection, with or without cartilage scoring, contouring or replacement with graft) is on lines

42 CLEFT PALATE WITH AIRWAY OBSTRUCTION
119 CHOANAL ATRESIA
244 LIFE-THREATENING EPISTAXIS
285 CANCER OF ORAL CAVITY, PHARYNX, NOSE AND LARYNX
309 GENDER AFFIRMING TREATMENT
464 CHRONIC SINUSITIS
495 NASAL POLYPS, OTHER DISORDERS OF NASAL CAVITY AND SINUSES
512 BENIGN NEOPLASM OF NASAL CAVITIES, MIDDLE EAR AND ACCESSORY SINUSES
562 DEVIATED NASAL SEPTUM, ACQUIRED DEFORMITY OF NOSE, OTHER DISEASES OF UPPER RESPIRATORY TRACT

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Septoplasty for CPAP tolerance

599 ANOMALIES OF RELATIONSHIP OF JAW TO CRANIAL BASE, MAJOR ANOMALIES OF JAW SIZE, OTHER SPECIFIED AND UNSPECIFIED DENTOFACIAL ANOMALIES
625 TMJ DISORDERS

CPT *30620 (Septal or other intranasal dermatoplasty (does not include obtaining graft)) is on lines 42, 244, 464, 495, and 562

CPT *30420 (Rhinoplasty, primary; including major septal repair) is on lines 309, 464, 495, and 562

Beginning 1/1/2027 with the BUP Prioritized List, CPT *30420 will be in the code group RHINOPLASTY AND SEPTOPLASTY AND CHRONIC SINUSITIS SURGERY. ICD-10-CM J34.2 will also be in code group RHINOPLASTY AND SEPTOPLASTY AND CHRONIC SINUSITIS SURGERY. CPT *30520 and 30620 will be placed only on currently covered lines with BUP.

Current Prioritized List guidelines:

GUIDELINE NOTE 118, SEPTOPLASTY

Lines 42,119,201,244,285,309,464,495,512,562

Septoplasty is included on Line 309 for gender affirming treatment.

Septoplasty is included on Lines 42, 119, 201, 244, 285, 464, 495, 512 and 562 when

A) The septoplasty is done to address symptomatic septal deviation or deformity which
   1) Fails to respond to a minimum 6-week trial of conservative management (e.g. nasal corticosteroids, decongestants, antibiotics); AND
   2) Results in persistent or recurrent epistaxis, OR documented recurrent sinusitis felt to be due to a deviated septum and the patient meets criteria for sinus surgery in Guideline Note 35, SINUS SURGERY; OR
B) Septoplasty is performed in association with cleft lip or cleft palate repair or repair of other congenital craniofacial anomalies; OR
C) Septoplasty is performed as part of a surgery for a neoplasm or facial trauma involving the nose.

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Septoplasty for CPAP tolerance

Septoplasty for other nasal obstruction not meeting the criteria above is included only on Line 562.

Septoplasty is not included on these lines for treatment of obstructive sleep apnea and is not included on Line 201 SLEEP APNEA, NARCOLEPSY, INSOMNIA, HYPERSOMNIA, AND REM BEHAVIORAL DISORDER.

GUIDELINE NOTE 27, TREATMENT OF SLEEP APNEA

Line 201

For adults over the age of 18 years:

A) CPAP is covered initially when all of the following conditions are met:
   1) 12 week 'trial' period to determine benefit. This period is covered if apnea-hypopnea index (AHI) calculated using the CMS definition of hypopnic episode of at least 4% oxygen desaturation or respiratory disturbance index (RDI) is greater than or equal to 15 events per hour; or if between 5 and 14 events with additional symptoms including one or more of the following:
      a) excessive daytime sleepiness defined as either an Epworth Sleepiness Scale score >10 or daytime sleepiness interfering with ADLs that is not attributable to another modifiable sedating condition (e.g. narcotic dependence), or
      b) documented hypertension, or
      c) ischemic heart disease, or
      d) history of stroke
   2) Additionally:
      a) Providers must provide education to patients and caregivers prior to use of CPAP machine to ensure proper use; and
      b) Positive diagnosis through polysomnogram (PSG) or Home Sleep Test (HST).

B) CPAP coverage subsequent to the initial 12 weeks is based on documented patient tolerance, compliance, and clinical benefit. Compliance (adherence to therapy) is

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defined as use of CPAP for at least four hours per night on 70% of the nights during a consecutive 30-day period.

C) Mandibular advancement devices (oral appliances) are covered for those for whom CPAP fails or is contraindicated.

D) Surgery for sleep apnea in adults is not included on this line (due to lack of evidence of efficacy). Surgical codes are included on this line only for children who meet criteria below

E) Hypoglossal nerve stimulation for treatment of obstructive sleep apnea is not included on this line due to insufficient evidence of effectiveness and evidence of harm.

For children age of 18 years or younger:

A) Adenotonsillectomy is an appropriate first line treatment for children with OSA. Adenoidectomy without tonsillectomy is only covered when a child with OSA has previously had a tonsillectomy, when tonsillectomy is contraindicated, or when tonsillar hypertrophy is not present. More complex surgical treatments are only included on this line for children with craniofacial anomalies.

B) Intranasal corticosteroids are an option for children with mild OSA in whom adenotonsillectomy is contraindicated or for mild postoperative OSA.

C) CPAP is covered for a 3-month trial for children through age 18 who have

1) undergone surgery or are not candidates for surgery, AND

2) have documented residual sleep apnea symptoms (sleep disruption and/or significant desaturations) with residual daytime symptoms (daytime sleepiness or behavior problems)

D) CPAP will be covered for children through age 18 on an ongoing basis if:

1) There is documentation of improvement in sleep disruption and daytime sleepiness and behavior problems with CPAP use, AND

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2) Annual re-evaluation for CPAP demonstrates ongoing clinical benefit and compliance with use, defined as use of CPAP
for at least four hours per night on 70% of the nights in a consecutive 30-day period

The development of this guideline note was informed by a HERC coverage guidance. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx

BUP guidelines

COVERAGE GUIDELINE ~~NOTE~~ 118, SEPTOPLASTY

Code Groups ~~Lines~~ 42,119,201,244,285,309~~,463,499,518,570~~, 499 10XXX RHINOPLASTY AND SEPTOPLASTY AND CHRONIC SINUSITIS SURGERY

Septoplasty is medically necessary ~~included on Line 309~~ for gender affirming treatment.

Septoplasty is medically necessary ~~included on Lines 42, 119, 201, 244, 285, 463, 499, 518 and 570~~ when

A) The septoplasty is done to address symptomatic septal deviation or deformity which
   1) Fails to respond to a minimum 6-week trial of conservative management (e.g. nasal corticosteroids, decongestants, antibiotics); AND
   2) Results in one or more of the following:
      a) Persistent or recurrent epistaxis, OR
      b) Documented recurrent sinusitis felt to be due to a deviated septum and the patient meets criteria for sinus surgery in Coverage Guideline ~~Note~~ 35, SINUS SURGERY~~; OR~~
      c) ~~Nasal obstruction with documented absence of other causes of obstruction likely to be responsible for the symptoms (for example, nasal polyps, tumor, etc.) [note: this indication is included only on Line 570; OR~~
B) Septoplasty is performed in association with cleft lip or cleft palate repair or repair of other congenital craniofacial anomalies; OR

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C) Septoplasty is performed as part of a surgery for a neoplasm or facial trauma involving the nose.

Septoplasty is not ~~covered~~ medically necessary for treatment of obstructive sleep apnea and is not included in code grouping ~~on Line~~ 201 SLEEP APNEA, NARCOLEPSY, INSOMNIA AND REM BEHAVIORAL DISORDER.

Date of last review: June 2025

Evidence:

Effectiveness of septoplasty for CPAP utilization

1) **Camacho 2015** The Effect of Nasal Surgery on Continuous Positive Airway Pressure Device Use and Therapeutic Treatment Pressures: A Systematic Review and Meta-Analysis
    a. N=18 articles (279 patients)
        i. N=17 retrospective or prospective case series
        ii. N=1 RCT (22 patients)
    b. N=11 studies (153 patients) that evaluated CPAP acceptance, compliance, tolerance, adherence, or use before and after nasal surgery
        i. N=3 studies (N=40 patients) used objective data from the CPAP device
        ii. N=3 studies (N=49 patients) used subjective reports of use from patients
        iii. N=6 studies (N=81 patients) did not report data source
    c. The percentage of patients regularly using CPAP prior to nasal surgery was 38.7% (36 of 93 patients) and the percentage of patients who were adherent (synonymous with compliant), accepting, or tolerating CPAP after nasal surgery was 90.2% (92 of 102 patients). A subgroup analysis demonstrated that 89.1% (57 of 64 patients) who were not using CPAP prior to nasal surgery subsequently accepted, adhered to, or tolerated CPAP after nasal surgery
    d. Authors conclusions: Isolated nasal surgery in patients with OSA with nasal obstruction reduces therapeutic CPAP device pressures, and the currently

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published literature's objective and subjective data consistently suggest that it also increases CPAP use in select patients

e. HERC staff notes: authors acknowledge possibility of publication bias; lack of reporting of actual surgeries in several studies meaning that additional surgeries could have been done (nasal polyp removal, functional rhinoplasty, etc.) that would affect CPAP tolerance; the authors discuss that patients who were motivated enough to seek surgery were likely more motivated to re-attempt CPAP therapy.

Submitted literature:

None received to date

Expert guidelines:

1) **American Academy of Sleep Medicine 2019** Treatment of Adult Obstructive Sleep Apnea with Positive Airway Pressure: An American Academy of Sleep Medicine Clinical Practice Guideline
    a. Recommendation 8: We suggest that behavioral and/ or troubleshooting interventions be given during the initial period of PAP therapy in adults with OSA. (CONDITIONAL)
        i. Troubleshooting interventions: Interventions focused on close patient communication to identify PAP-related problems and to initiate potential solutions during the initial period of PAP therapy
    b. Appropriate mask selection will benefit patients by reducing side effects such as air leak and discomfort, which may then potentially improve adherence and subsequently patient outcomes
    c. The use of humidification could also potentially reduce side effects from PAP therapy
    d. Nasal surgery is not mentioned in this guideline
2) American Academy of Otolaryngology-Head and Neck surgery 2017 Position Statement: Nasal Surgery and OSAS
    a. Available at https://www.entnet.org/resource/position-statement-nasal-surgery-and-osas/

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b. Nasal surgery can facilitate the treatment of OSA by improving compliance with CPAP (Continuous Positive Airway Pressure). There is significant correlation between nasal resistance or obstruction and CPAP non-acceptance where for each 0.1 Pa/cm3/s increase in resistance the odds ratio of non-acceptance increases 1.48-fold (Sugiura 2007). Nasal surgery lowers nasal resistance. Nakata & coworkers (Nakata et al 2008) showed that using septoplasty and inferior turbinate reduction for CPAP non-adherent patients demonstrated that there was a reduction in nasal resistance from 0.57 to 0.16 Pa/cm3/s, and postoperatively all patients became CPAP adherent. Nasal surgery may lower CPAP pressures by 2-3cm H2O (Friedman 2000; Zonato 2006). Nasal surgery (septoplasty and turbinoplasty) led to increased CPAP use and decreased CPAP pressure (Poirrier et al, 2014).

Other payer policies:

1) Anthem BCBS 2025
    a. Does not cover septoplasty for OSA/CAP tolerance
        i. Septoplasty has also been proposed for septal deviation when there is intolerance to continuous positive airway pressure (CPAP) for obstructive sleep apnea. Current literature is limited to small group sizes with short-term follow-up for CPAP compliance
        ii. Note: does cover septoplasty for “distressing symptoms of nasal obstruction when other treatable causes of obstruction are either not documented, documented as absent or documented as unlikely to be responsible for symptoms”
2) Aetna 2025
    a. Does not list CPAP compliance or OSA among covered indications for septoplasty.
3) EmblemHealth 2026
    a. Obstructive sleep apnea. (to aid in ability to utilize CPAP and help upper airway obstruction) (Note: for those members with allergic rhinitis who also have OSA, documentation of conservative management failure in the presence of allergic rhinitis [i.e., allergic precautions, antihistamines,

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topical nasal steroids and plus/minus desensitization injections] should be submitted)

4) United Healthcare 2026
    a. Does not list CPAP compliance or OSA among covered indications for nasal procedures

Expert input:

Dr. Peggy Kelley, pediatric ENT and Dr. Sara Yang, OHSU adult ENT.

Drs. Kelley and Yang recommended coverage of deviated nasal septum when causing or contributing to obstructive sleep apnea (OSA).

HERC staff summary:

Limited evidence has been published regarding the impact of septoplasty on CPAP utilization. The majority of the literature consists of case series or small cohorts as well as one very small RCT. The study authors point out a number of issues with the literature and conclude that the data is suggestive but that more definitive studies should be done. The AASM does not mention nasal surgery in their guideline for OSA treatment; instead, they discuss education and mask fitting to improve CPAP tolerance. The AAO-HNS do recommend nasal surgery for both primary treatment of OSA and for CPAP tolerance. The majority of private payers do not cover septoplasty for the indication of CPAP tolerance; however, these payers generally cover septoplasty for breathing issues which may result in some coverage for CPAP tolerance through that pathway. HERC staff received feedback from CCO medical directors that they felt that the evidence supporting nasal surgery for CPAP tolerance was very weak and that the current guideline should continue to indicate that nasal surgery is not covered for OSA-related indication. Based on re-review of the systematic review on this topic as well as specific coverage policy reviews, HERC staff no longer recommend coverage of septoplasty for CPAP tolerance/compliance.

HERC staff recommend making clarifying changes to Guideline Note 118 as shown below

HERC staff recommendation:

A) Modify GN 118 as shown below

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Septoplasty for CPAP tolerance

1) Specifically state that septoplasty is not medically necessary to improve CPAP adherence. This is consistent with CCO medical director feedback on the limitations of the literature in this area

GUIDELINE NOTE 118, SEPTOPLASTY

Lines 42,119,201,244,285,309,464,495,512,562

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Septoplasty is included on Lines 42, 119, 201, 244, 285, 464, 495, 512 and 562 when

A) The septoplasty is done to address symptomatic septal deviation or deformity which

1) Fails to respond to a minimum 6-week trial of conservative management (e.g. nasal corticosteroids, decongestants, antibiotics); AND

2) Results in persistent or recurrent epistaxis, OR documented recurrent sinusitis felt to be due to a deviated septum and the patient meets criteria for sinus surgery in Guideline Note 35, SINUS SURGERY; OR

B) Septoplasty is performed in association with cleft lip or cleft palate repair or repair of other congenital craniofacial anomalies; OR

C) Septoplasty is performed as part of a surgery for a neoplasm or facial trauma involving the nose.

Septoplasty for other nasal obstruction not meeting the criteria above is included only on Line 562. Sept

Septoplasty is not included on these lines for treatment of obstructive sleep apnea or for improving ability to use CPAP. ~~and is not included on Line 201 SLEEP APNEA, NARCOLEPSY, INSOMNIA, HYPERSOMNIA, AND REM BEHAVIORAL DISORDER~~

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pii: sp-00003-14 http://dx.doi.org/10.5665/sleep.4414

The Effect of Nasal Surgery on Continuous Positive Airway Pressure Device Use and Therapeutic Treatment Pressures: A Systematic Review and Meta-Analysis

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Background: The relationship between nasal surgery and its effect on continuous positive airway pressure (CPAP) device therapeutic treatment pressures and CPAP device use has not been previously systematically examined.

Study Objectives: To conduct a systematic review and meta-analysis evaluating the effect of isolated nasal surgery on therapeutic CPAP device pressures and use in adults with obstructive sleep apnea.

Methods: MEDLINE, Scopus, Web of Science, and The Cochrane Library were searched through July 15, 2014. The MOOSE consensus statement and PRISMA statement were followed.

Results: Eighteen studies (279 patients) reported CPAP data after isolated nasal surgery. Seven studies (82 patients) reported preoperative and postoperative mean therapeutic CPAP device pressures and standard deviations, which reduced from 11.6 ± 2.2 to 9.5 ± 2.0 centimeters of water pressure (cwp) after nasal surgery. Pooled random effects analysis demonstrated a statistically significant pressure reduction, with a mean difference of −2.66 cwp (95% confidence intervals, −3.65 to −1.67); $P < 0.00001$. Eleven studies (153 patients) described subjective, self-reported data for CPAP use; and a subgroup analysis demonstrated that 89.1% (57 of 64 patients) who were not using CPAP prior to nasal surgery subsequently accepted, adhered to, or tolerated it after nasal surgery. Objective, device meter-based hours of use increased in 33 patients from 3.0 ± 3.1 to 5.5 ± 2.0 h in the short term (< 6 mo of follow-up).

Conclusion: Isolated nasal surgery in patients with obstructive sleep apnea and nasal obstruction reduces therapeutic CPAP device pressures and the currently published literature's objective and subjective data consistently suggest that it also increases CPAP use in select patients.

Keywords: continuous positive airway pressure, nasal surgery, obstructive sleep apnea, sleep apnea syndromes

Citation: Camacho M, Riaz M, Capasso R, Ruoff CM, Guilleminault C, Kushida CA, Certal V. The effect of nasal surgery on continuous positive airway pressure device use and therapeutic treatment pressures: a systematic review and meta-analysis. *SLEEP* 2015;38(2):279–286.

INTRODUCTION

Nasal continuous positive airway pressure (CPAP) was introduced by Sullivan et al.[1] in 1981 as treatment for obstructive sleep apnea (OSA) and treatment has been shown to have a mortality benefit.[2] Although CPAP is highly efficacious, the non-adherence rate (< 4 h of nightly use 70% of nights) is between 46–83%.[3] CPAP side effects include insomnia, claustrophobia, nocturnal awakenings, irritation of the upper airway, sneezing, nasal dryness, rhinitis, rhinorrhea, laryngitis, and epistaxis.[4–7] Nasal obstruction is a common complaint among CPAP users, with an estimated prevalence of 25–45%.[4,7,8] Decreased cross-sectional area and reduced volume of the nasal airway is associated with patients being less compliant with CPAP therapy.[9] Increased nasal resistance has also been associated with decreased CPAP therapy adherence.[10] Studies demonstrate that isolated nasal surgery in patients with nasal obstruction reduces therapeutic CPAP pressures and/or improves CPAP acceptance, compliance, tolerance, adherence, or use.[5,10–26] The objective of this study is to conduct a systematic review of the literature and perform a meta-analysis to evaluate the effect of isolated nasal surgery on therapeutic CPAP device pressures and CPAP use in adults with OSA.

Submitted for publication January, 2014
Submitted in final revised form August, 2014
Accepted for publication August, 2014

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METHODS

Search Strategy

A search of four databases (MEDLINE, Scopus, Web of Science, and The Cochrane Library) was performed from inception through September 1, 2013, with an update through July 15, 2014. Keywords, MeSH terms, and phrases searched included combinations of: "continuous positive airway pressure," "nasal obstruction," "nasal surgery," "nose surgery," "rhinoplasty," "septoplasty," "septorhinoplasty," "septoturbinoplasty," "sleep apnea," "sleep apnea syndromes," "surgery," "turbinate reduction," "turbinectomy," and "turbinoplasty". An example of a search on MEDLINE is: ((("Continuous Positive Airway Pressure"[MeSH]) OR ("Sleep Apnea, Obstructive"[MeSH])) AND (("Nasal Obstruction/surgery*"[MeSH]) OR ("Nasal Septum/surgery*"[MeSH]) OR "nasal surgery" OR ("Nasal Surgical Procedures*"[MeSH]) OR "nose surgery" OR "rhinoplasty" OR ("Rhinoplasty/methods*"[MeSH]) OR "septoplasty" OR "septorhinoplasty" OR "septoturbinoplasty" OR "turbinate reduction" OR ("Turbinates/surgery"[MeSH]) OR "turbinectomy" OR "turbinoplasty")).

The titles and abstracts for each of the results were reviewed for relevance. The full text versions of relevant articles were

Downloaded from https://academic.oup.com/sleep/article/38/2/279/2416975 by State of Oregon Law Library user on 16 January 2026

obtained for complete evaluation. The references of the obtained articles were also reviewed and any relevant studies in the reference lists were also obtained and included if they met criteria. As an additional step, each time a relevant article was encountered during the review of titles and abstracts, the "related citations/articles" and "cited by" features of the four databases and Google Scholar were searched to identify any additional potentially relevant articles.

Study Selection

Inclusion criteria for the studies consisted of adult patients with OSA who were treated with CPAP and underwent isolated nasal surgery. Additionally, the included studies needed to report quantitative outcomes data comparing prenasal and postnasal surgery therapeutic CPAP pressures and/or prenasal and postnasal surgery CPAP acceptance, compliance, tolerance, adherence, or use after nasal surgery, without regard to follow-up length. All languages and study designs were included. Exclusion criteria consisted of studies reporting qualitative data only and studies on children. If a study reported individual patient data for nasal surgeries and non-nasal surgeries, then the nasal surgery data were abstracted and included in this review.

Data Abstractions and Study Quality Assessment

Two authors (VC and MC) performed a literature search and screened titles and abstracts, and retrieved articles for further review. Data collected included the ages, body mass indices (BMI), therapeutic CPAP device pressures, and CPAP use data. After the data were collected, the National Institute for Health and Clinical Excellence (NICE) quality assessment tool, consisting of eight items for each study, was used to evaluate the quality of each of the included studies. Data were placed into an Excel 2013 spreadsheet. Authors of studies in which there were insufficient data reported (e.g., study means, standard deviations [SD], etc.) to include in the meta-analysis were contacted via email or phone, in an attempt to obtain these additional data. The corresponding authors were contacted for the following studies: Bican et al.,[19] Friedman et al.,[16] Nakata et al.,[10] Park et al.,[26] Pniak et al.,[24] Poirier et al.,[11] and Powell et al.[25] The raw data were no longer available for studies by Friedman et al. or Powell et al. Means and SD for CPAP pressures and use were provided by Rotenberg (Poirier et al. study). There was no reply from corresponding authors for Park et al., Bican et al., Nakata et al., and Pniak et al.

Statistical Analysis

The statistical analysis was performed with the Statistical Package for Social Sciences software (SPSS) version 20.0 and the Cochrane Collaboration's Review Manager (REVMAN) Software version 5.2. The prenasal and postnasal surgery means, mean differences (after - before), standard deviations, and 95% confidence intervals (CI) were calculated. If a study provided individual patient data, but did not report a P value, then the data were manually entered into SPSS in order to calculate the means, SD, and mean differences. The null hypothesis before initiating the study was that there is no difference between prenasal and postnasal surgery data. When combining data, a two-tailed, paired *t* test was performed and $P < 0.05$ was considered statistically significant. The REVMAN random effects model for pooling effects was applied if heterogeneity of treatment effects was present and a fixed-effects model was used if no heterogeneity was present. Forest plots were graphically inspected and heterogeneity was assessed with the I^2 statistic (low: 25%, moderate: 50% and high: 75%)[27] and the Cochran Q statistic (it is generally suggested to use a heterogeneity significance level of $P \leq 0.10$).[28] Additionally, a sensitivity analysis was performed by removing each study from the meta-analysis to investigate the effect the individual studies on the summarized effect and heterogeneity. Visual inspections of the funnel plots were performed to assess for publication bias. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement[29] and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) consensus statement[30] were adhered to as much as possible.

RESULTS

The search identified a total of 792 articles after removal of duplicates. After the preliminary review of the titles and abstracts, a total of 29 studies were agreed to as being relevant and the full text was downloaded for further evaluation. Review of the articles' reference lists identified an additional 7 articles, which were also obtained. Of these 36 articles, a total of 18 were excluded for the following reasons: no quantitative CPAP data prenasal and postnasal surgery were presented in the article,[31,32] non-nasal surgeries were performed (i.e. uvulopalatopharyngoplasties, pillar implants or multilevel surgeries)[33–41] or no nasal surgery was performed.[4,7,9,42–45] Zonato et al.[13] reported individual data for nasal surgeries and multilevel surgeries; therefore, the data for nasal surgeries could be separated and included as part of the review. A total of 18 articles were included in this study, with a total of 279 patients identified within those articles, who underwent isolated nasal surgery and had quantitative data available.[5,10–25] Figure 1 demonstrates the flow diagram for the article selection. The mean patient age was 52.5 ± 8.7 y and the mean BMI was 29.5 ± 4.0 kg/m^2.

Methodological Quality of the Included Studies

The studies included in this review were all either retrospective or prospective case series (Level 4 evidence), except for one study by Powell et al.[25] that was a randomized, double-blind, placebo-controlled clinical trial (RCT), which is Level 1 evidence. The NICE quality assessment tool demonstrated that the included studies satisfied between three to six of the eight items, with most satisfying more than four items (presented in Table S1, supplemental material). The main limitations in general are that none of the studies were multicenter, patients were not recruited consecutively, and there was only one randomized controlled trial and the remaining studies were case series.

CPAP Results

Therapeutic CPAP Pressures

A total of 10 studies (135 patients) described therapeutic CPAP device pressures as an outcome after isolated nasal surgery.[5,10–16,20,21,24] Two studies reported the mean difference (MD) of the therapeutic pressures (Balcerzak et al.[20] reported a MD of

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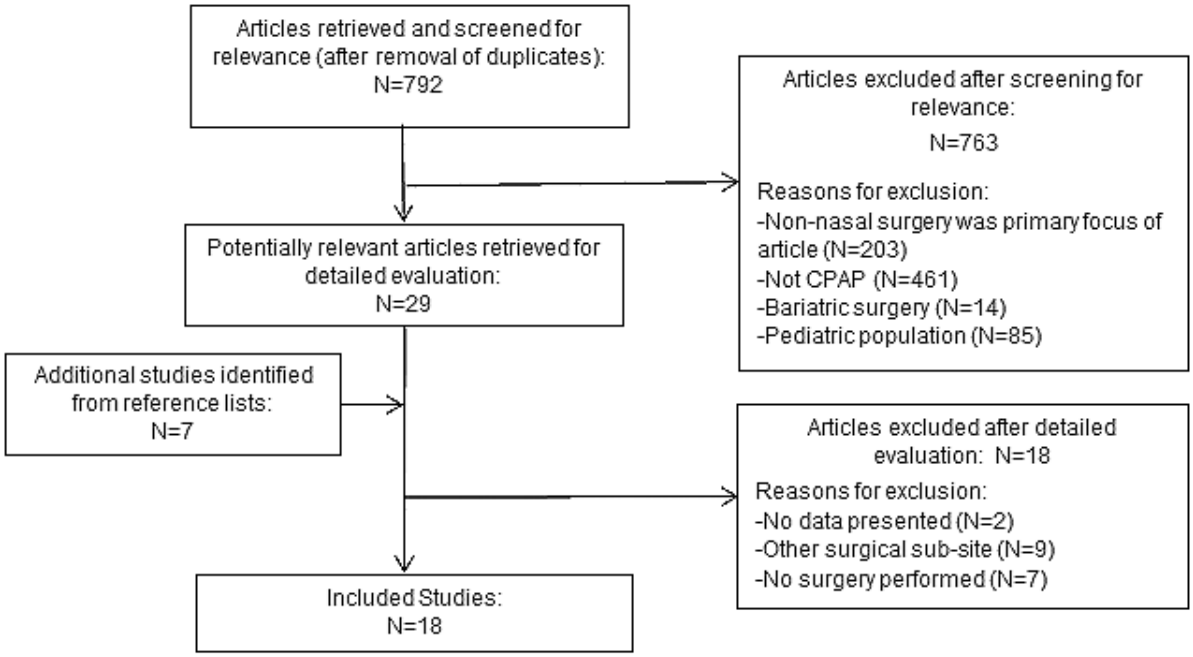

Figure 1—Literature search and study selection. CPAP, continuous positive airway pressure; N, number of studies.

−2.7 cwp and Ripberger and Pirsig[21] reported a MD of −5 cwp), but lacked the SD, therefore, were excluded from meta-analysis. Friedman et al.[16] reported the therapeutic CPAP means prenasal and postnasal surgery, but did not report the SD; therefore, the study was excluded from pooled meta-analysis calculations.[16] The remaining 7 studies (82 patients) reported both preoperative and postoperative therapeutic CPAP device pressures and SD, which were provided in the article or were obtained by contacting the authors of the original studies.[5,10–15]

With regard to determination of the therapeutic CPAP device pressures, Park et al.,[6] Poirier et al.,[11] and Mayer-Brix et al.[5] reported the therapeutic pressures based on the patients' CPAP devices, whereas in the remaining 5 studies in the meta-analysis reported therapeutic pressures based upon the in-laboratory polysomnography titrations.[5,10–15] Hypopnea scoring criteria for the studies included ≥ 10 sec for the hypopnea duration, in combination with: ≥ 3% oxygen desaturation with a 50% decrease in thermistor for Sufioglu et al.,[12] ≥ 3% oxygen desaturation or arousal associated with a hypopnea for Nakata et al.,[10] > 4% oxygen desaturation for Nowak et al.,[14] ≥ 4% oxygen desaturation with a ≥ 50% decreased effort to breathe for Katsantonis et al.,[46] whereas the remaining studies did not specify which hypopnea scoring criteria was used.[5,11,13,15,26]

The combined data for the 7 studies demonstrated a prenasal and postnasal surgery therapeutic CPAP device pressure that reduced from a mean ± SD of 11.6 ± 2.2 to 9.5 ± 2.0 centimeters of water pressure (cwp), with results shown in Table 1. The pooled random effects analysis (Figure 2) demonstrated a statistically significant reduction in the mean pressures, with a MD of −2.66 cwp (95% CI, −3.65 to −1.67; overall effect: Z score = 5.27 (P < 0.00001)). The I^2 (82%) and Cochran Q statistic (P < 0.00001) suggest significant heterogeneity across included studies, and therefore justified the need for a random-effects model. A sensitivity analysis showed that removing the Sufioglu et al.[12] study resulted in a low level of heterogeneity (I^2 = 27% and Cochran Q statistic = 0.23) but did not significantly affect the summarized effect size (MD: −3.00 cwp; 95% CI: −3.56 to −2.43, Z score = 10.39, and P < 0.00001). The study by Sufioglu et al.[12] states that a postoperative CPAP titration was not performed in five patients who were cured of OSA (apnea-hypopnea index [AHI] < 5/h).[12] Visual inspection of the funnel plot also demonstrated that the study by Sufioglu et al.[12] was slightly outlying when compared to the remaining studies.

A subgroup analysis was performed for studies that specifically stated in the article that nasal mask interfaces were used (studies did not specify nasal pillows versus nasal triangle masks), which resulted in the exclusion of studies by Sufioglu et al.[12] and Nakata et al.[10,12] When pooling the data from the remaining five studies (49 patients), the nasal CPAP pressures decreased from 11.3 ± 2.0 to 8.8 ± 1.9 cwp.[5,11,13–15] There was no heterogeneity across these studies, demonstrated by an I^2 of 0% and Cochran Q statistic of P = 0.54. The fixed effects analysis for this subgroup demonstrated a statistically significant decrease in the mean pressure with MD of −2.81 cwp (95% CI, −3.22 to −2.40; overall effect: Z score = 13.46, P < 0.00001 [see Figure 3]).

Individual patient therapeutic CPAP pressure data were reported for 20 patients, overall 85% (17 patients) decreased, 5% (one patient) remained the same, and 10% (two patients) increased their therapeutic CPAP pressures.[5,13,15]

Type of Nasal Surgery Performed and the Effect on Therapeutic CPAP Pressures

Data analyses were performed for the specific nasal surgery subsites: (1) septoplasty, (2) turbinoplasty, (3) septoplasty with turbinoplasty, and (4) unspecified; there were four

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Table 1—Patient demographics and pre and postnasal surgery therapeutic mean CPAP pressure data.

Study authors, year	N	Mean age (years)	BMI (kg/m²)	Nasal surgery sub-site	Mean CPAP cwp prenasal surgery	Mean CPAP cwp postnasal surgery	P value
Poirier et al., 2013	18	52	31.8	ST	11.9 ± 0.9	9.2 ± 0.7	0.062
Sufioglu et al., 2012	28	53 ± 9.6	30.3 ± 4.1	E, R, S, T, ST	11.2 ± 1.2	10.4 ± 1.4	0.062
Zonato et al., 2006	13	49 ± 9	30 ± 4	ST, T	11.9 ± 2.7	10.1 ± 2.3	0.009 *
Nakata et al., 2005	5	54.2 ± 9.2	26 ± 2.8	ST, T	16.8 ± 1.2	12.0 ± 1.9	< 0.045 *
Nowak et al., 2003	10	55.8 ± 3.6	27.4 ± 0.7	S, ST, T	10.0 ± 0.6	7.1 ± 1.2	< 0.05 *
Dorn et al., 2001	5	50.4 ± 9.1	31.9 ± 5.1	E, R, S, ST	11.8 ± 3.9	8.5 ± 1.6	0.055
Friedman et al., 2000	22	–	35.7	ST	9.3	6.7	< 0.01 *
Mayer-Brix et al., 1989	3	–	–	ST	9.7 ± 0.6	6.0 ± 1.0	0.032 *
Total **	104	52.5 ± 8.7	29.5 ± 4.0		11.6 ± 2.2	9.5 ± 2.0	< 0.00001 *

cwp, centimeters of water pressure; E, endoscopic sinus surgery; N, number of patients; R, septorhinoplasty; S, septoplasty; ST, septoturbinoplasty; T, turbinoplasty. * Statistically significant P value based on either the reported study value or a paired samples t-test and the calculated 2-tailed significance for the paired difference. ** Total calculations are based on studies providing both the means and standard deviations.

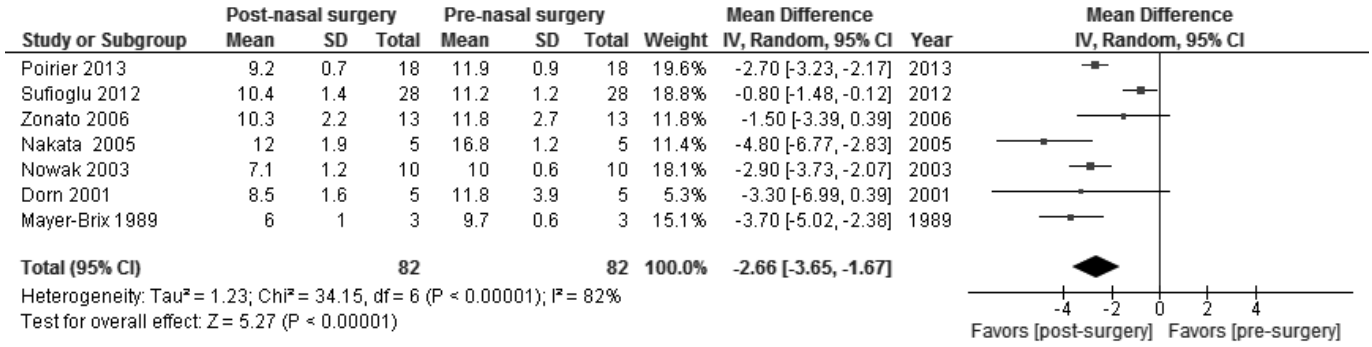

Figure 2—Prenasal and postnasal surgery random effects analysis. There was a statistically significant decrease in therapeutic continuous positive airway pressure device pressures with a mean difference of −2.66 cwp (95% confidence interval [CI], −3.65 to −1.67; P < 0.00001). SD, standard deviation.

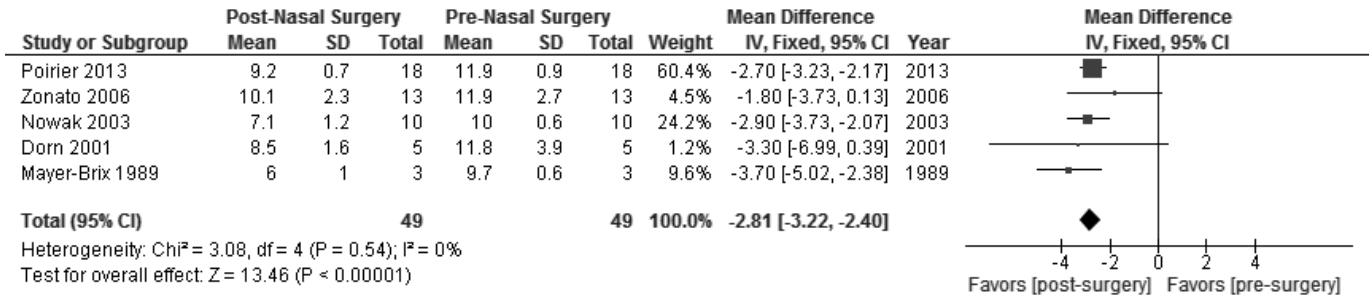

Figure 3—Subgroup analysis for studies in which continuous positive airway pressure (CPAP) was delivered by a nasal mask interface, prenasal and postnasal surgery. The fixed-effects analysis demonstrated a statistically significant decrease in therapeutic CPAP device pressures with a mean difference of −2.81 cwp (95% confidence interval [CI], −3.22 to −2.40; P < 0.00001). SD, standard deviation.

studies[10,12,14,15] during which multiple procedures such as septoplasties, turbinoplasties, rhinoplasties, and sinus surgeries, were performed but did not list individual patient data. Therefore the data are presented in the category of "unspecified." Overall, 2 studies reported individual patient data and the specific subsite,[5,13] and Poirier et al.[11] performed the same procedure in all patients, and therefore could be included in individual subsite data analyses. Outcomes for the combined nasal surgery subsites are presented in Table 2. The largest MD was observed in the septoplasty with turbinoplasty group (25 patients), demonstrating a MD of −2.60 cwp (95% CI −3.33, −1.87); overall effect: Z score = 5.52, P < 0.00001. The MD for the remaining nasal surgery sub-sites included: (1) unspecified (48 patients), −1.90 cwp (95% CI −2.80, −1.00); overall effect: Z score = 2.99, P = 0.0001; (2) turbinoplasty (8 patients), −2.2 cwp; paired *t* test P = 0.048; and (3) septoplasty (one patient), −2.0 cwp.

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Table 2—Pre and postnasal surgery therapeutic mean CPAP pressure data stratified by nasal surgical sub-sites.

Nasal surgery performed	Study authors (number of patients in individual studies)	N	Mean CPAP pressure prenasal surgery (cwp)	Mean CPAP pressure postnasal surgery (cwp)	Mean difference	P value
Septoplasty	Zonato et al.	1	10.0	8.0	−2.0 cwp	–
Turbinoplasty	Zonato et al.	8	12.4 ± 3.3	10.2 ± 2.5	−2.2 ± 2.6 cwp	0.048*
Septoplasty with turbinoplasty	Poirier et al. (N = 18) Zonato et al. (N = 4) Mayer-Brix et al. (N = 3)	25	11.6 ± 1.1	9.0 ± 1.5	−2.60 cwp (CI −1.87, −3.33)	< 0.00001*
Unspecified**	Sufioglu et al. (N = 28) Nakata et al. (N = 5) Nowak et al. (N = 10) Dorn et al. (N = 5)	48	11.6 ± 2.4	9.7 ± 2.1	−1.90 cwp (CI −1.00, −2.80)	0.0001*

cwp, centimeters of water pressure; N, number of patients. *Statistically significant P value. Only three studies provided individual patient data that allow sub-site analyses. **The 4 nasal surgery studies that did not report individual patient data, however, the articles reported that septoplasties, turbinoplasties, rhinoplasties and/or sinus surgeries were performed.

CPAP Use After Nasal Surgery

Eleven studies (153 patients) evaluated CPAP acceptance, compliance, tolerance, adherence, or use before and after nasal surgery.[10,11,17–19,21–25] Three studies (n = 40) reported objective data from the CPAP devices themselves,[11,25,26] three studies (n = 49) reported subjective, patient self-reported use,[19,21,25] and six studies (n = 81) did not specify whether objective or subjective data was collected (Note: Powell et al. reported both objective and subjective data for all patients).[10,17,18,22–24]

The percentage of patients regularly using CPAP prior to nasal surgery was 38.7% (36 of 93 patients) and the percentage of patients who were adherent (synonymous with compliant), accepting, or tolerating CPAP after nasal surgery was 90.2% (92 of 102 patients). A subgroup analysis demonstrated that 89.1% (57 of 64 patients) who were not using CPAP prior to nasal surgery subsequently accepted, adhered to, or tolerated CPAP after nasal surgery. There were differences in the inclusion criteria between studies (i.e., six studies included patients not tolerating CPAP prior to nasal surgery,[10,11,18,22,24,26] two studies included patients already using CPAP, but with nasal obstruction present,[17,25] and three studies did not specify[19,21,23]). The CPAP device downloaded data for prenasal surgery hours of CPAP use mean and SD were 3.0 ± 3.1 h and postnasal surgery were 5.5 ± 2.0 h. The calculated treatment effect of nasal surgery based on Powell et al.'s RCT (difference between the treatment group and placebo controls) at 1 mo was 32 min (95% CI −21, 84), P = 0.22.[25] Table 3 summarizes prenasal and postnasal surgery objective and subjective CPAP use data.

DISCUSSION

There are five main findings in this study. First, there is a statistically significant relationship between nasal surgery and therapeutic CPAP pressures. Poiseuille's Law has demonstrated that resistance to airflow is directly proportional to the length and is inversely proportional to the fourth-power of the radius.[47] Therefore, a 10% increase in the cross-sectional area of the nasal airway can result in an increase of 21% of nasal airflow.[25] Thus, decreasing the size of the inferior turbinates or decreasing other sources of nasal obstruction (deviated septums, septal spurs, polyps, etc.) can provide a reduction in the nasal airway resistance, and therefore may lead to a decreased therapeutic CPAP pressure. In this meta-analysis, the pooled data for 82 patients demonstrates a MD of −2.66 cwp with a range of −0.8 to −4.8 cwp. The sensitivity analysis identified the study by Sufioglu et al.[12] as the source of heterogeneity, which is possibly caused by not performing a postoperative CPAP titration in five patients who were cured of OSA (AHI < 5/h), therefore the prenasal and postnasal CPAP device pressure MD is potentially smaller (0.8 cwp) than it would have been had those cured patients undergone a postoperative CPAP titration. The remaining studies' MD decreased by at least 1.5 cwp. Additionally, the visual inspection of the funnel plot for therapeutic CPAP device pressures demonstrated that the study by Sufioglu et al.[12] was slightly outlying when compared to the remaining studies. One difference in this study compared to the others is that this study reported the use of thermistors whereas the other studies did not specify whether thermistors or nasal cannulas were used.[12] Despite this difference, a similar MD prenasal and postnasal surgery would be expected because the same technique was used within the same study group. Because of publication bias against negative studies, it is possible that additional studies demonstrating minimal or no difference in CPAP device pressures after nasal surgery never made it to publication and therefore the study by Sufioglu et al.[12] would not be an outlier in that situation.[28]

Second, regardless of the nasal surgery subsite, there is at least a MD of −1.9 cwp between preoperative and postoperative CPAP device pressures (as outlined in Table 2). The greatest difference was seen in patients undergoing a combined septoplasty with turbinoplasty (MD of −2.6 cwp). It must be pointed out that only the study by Zonato et al.[13] reported outcomes for isolated septoplasty (one patient) and isolated turbinoplasty (eight patients). Additionally, only three of seven studies reported both preoperative and postoperative means and SD and also had individual patient data or performed the same procedure in all patients, which allowed the subsite data to be combined (34 patients). A significant limitation in the ability to subanalyze the data for the remaining four studies (48 patients) was

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Table 3—Data regarding prenasal and postnasal surgery acceptance, adherence, tolerance, or use.

Study authors, Study year, Follow-up duration	# Pts	Prenasal Surgery: # Pts regularly using CPAP	Postnasal Surgery: # Pts adherent, accepting or tolerating CPAP	Prenasal Surgery: Objective hours of use	Postnasal Surgery: Objective hours of use	Postnasal Surgery: Subjective hours of use	Postnasal Surgery: Subjective hours of use	Additional information
Park et al.* 2014, 2 mo	7	0/7	7/7	0.0	≥ 4	–	–	RCS. Pressures reduced in 6 out of 7 patients.
Poirier et al.* 2013, 6 mo	16	0/16	16/16	0.5 ± 0.73	5.0 ± 2.37	–	–	PCS. 2 of 18 patients were cured.
Powell et al.*,** 2001, 1 mo	17	17/17	17/17	5.77 ± 2.08	5.97 ± 1.43	–	–	RCT. Treatment group used CPAP 32 min more at 1 mo compared to placebo controls.
Pniak et al.*** 2012, 3–6 mo	8	0/8	3/8	–	–	–	–	RCS. Improved subjective nasal patency.
Bican et al.** 2010, 2.5–6.5 mo	20	12/20	20/20	–	–	–	–	RCS. Tolerating CPAP device was easier. Mean postop pressure: 8.5 cwp.
Nakata et al.*** 2005	12	0/12	12/12	–	–	–	–	RCS: Nasal resistance decreased from 0.57 ± 0.31 to 0.16 ± 0.03 Pa/cm³/sec (P value < 0.01).
Esteller et al.*** 2004, > 12 mo	9	–	8/9	–	–	–	–	PCS. Tolerance was easier, and adherence increased (5 hours a day, 5 nights a week).
Biermann et al.*** 2001, 36 mo	39	–	–	–	–	–	6.7 ± 1.4	RCC. Treatment group used CPAP 48 min more at 3 years compared to control group.
Hollandt et al.*** 1997, 21 mo	6	0/6	2/6	–	–	0.0	5.85 ± 2.90	PCS. Two patients accepted PAP therapy after nasal surgery.
Ripberger et al.** 1994, 18 mo	12	–	–	–	–	–	–	PCS. Pressure decreased by an average of 5 cwp and the CPAP acceptance increased.
Series et al.*** 1992, 3 mo	7	0/7	7/7	–	–	–	–	RCS. 7 pts intolerant to CPAP due to discomfort, became tolerant after nasal surgery.
Total	153	36/93 (38.7%)	92/102 (90.2%)	3.0 ± 3.1	5.5 ± 2.0	–	–	57/64 pts (89.1%) not using CPAP subsequently accepted, adhered to or tolerated it after surgery.

Poirier et al.'s results exclude two patients who were cured of OSA. * Objective CPAP device data reported. ** Subjective, patient-reported data. *** Study did not specify if objective or subjective use data was reported. #, number; cwp, cm of water pressure; mo, months; PCS, prospective case series; Pts, patients; RCC, retrospective case-control; RCS, retrospective case series; RCT, randomized-controlled trial.

that multiple procedures were listed in these studies, without individual patient data. Therefore, it is possible that other procedures such as endoscopic sinus surgery for nasal polyposis or a functional rhinoplasty combined with septoplasty and turbinoplasty could be as effective or more effective in reducing CPAP device pressures; however, without stratified data, these conclusions cannot be made. Given that the currently published literature reporting outcomes for individual patient data is limited, we recommend that future researchers report outcomes for individual patients stratify the data for isolated subsites (i.e. septoplasty, turbinoplasty, etc.).

Third, overall CPAP use increased after nasal surgery and was demonstrated by 11 studies (153 patients). It should be noted that the patients in these studies were motivated enough to reattempt CPAP therapy. Two issues exist: first, only three studies specified that objective device data was used, whereas the remaining eight studies either reported subjective outcomes or did not specify. Second, one of the challenges in combining the "use" data is that studies refer to "use" by different terminology, such as: acceptance, compliance, adherence, tolerance, and use. We reviewed each of the study descriptions of "use" in order to organize the results into appropriate categories. The hours of use in each study reporting it varied significantly because of the differences in the inclusion criteria between studies, which ranged from including patients not tolerating CPAP prior to nasal surgery,[10,11,18,22,24] to including patients already using CPAP, but with complaints of nasal obstruction significant enough to warrant surgery.[17,25] Despite the differences in the inclusion criteria, there was an increase in objective and subjective CPAP use after surgery and there was a progressive increase in hours of use as the

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duration of follow-up from nasal surgery increased. There can be significant nasal crusting and edema after nasal surgery, and the healing phase may last 2–6 w. Therefore, studies reporting on pressure reduction and hours of use, should follow patients for 3–6 mo after surgery to ensure the healing is complete and the edema has resolved, because this can affect the results of CPAP use and therapeutic CPAP device pressures.

Fourth, in order to facilitate future research, we would like to recommend standardized terminology. Regarding the term "use", studies have demonstrated that self-reported CPAP usage overestimates the actual usage by approximately 1 h when compared to the CPAP device download data[8,48–50]; therefore, we recommend reporting the device download data as "use". The terms "adherence" and "compliance" have been used interchangeably,[3,50] and have been previously defined as "using CPAP for ≥ 4 h per night.[3,48,51]" When reporting the percentage of nights that patients are adherent, 70% is often used as a cutoff "regularly using" CPAP therapy.[48,51] The term "tolerance", as related to CPAP and nasal surgery, has been defined by the use of a visual analog scale (10 cm) with anchors 0 cm = "unable to tolerate or use" and 10 cm = "easily tolerated and use all 7 nights per week."[25] The term "acceptance", if used, should be defined by the authors reporting it to avoid ambiguity.

Fifth, there is a need for additional high-quality studies to allow for additional data analyses and to increase the power to draw more definitive conclusions. Most of the studies in this review were retrospective case series, with only five prospective case series and one randomized controlled trial. The study by Powell et al.,[25] which was very well planned, can serve as an example for future randomized, double-blind, placebo-controlled clinical trials. Two limitations with the study by Powell et al. were that only 22 patients were included, and the follow-up was short (1 mo, which is within the window of healing). When planning a study on nasal surgery and CPAP, important data to collect includes: the total number of nights of CPAP use versus nonuse, the percentage of nights with CPAP use versus nonuse, the percentage of nights with usage ≥ 4 h per night versus < 4 h per night, the average usage on nights CPAP was used and the average usage on all nights.[52] Additional important information to report includes: the 95th percentile leak, Epworth Sleepiness Scale questionnaire data,[53] the effect of treatment on quality of life, inferior turbinate sizes before and after surgery,[54] and information on nasal obstruction, which can be assessed with the Nasal Obstruction Symptom Evaluation (NOSE) scale questionnaire.[55]

CONCLUSION

Isolated nasal surgery in patients with OSA with nasal obstruction reduces therapeutic CPAP device pressures, and the currently published literature's objective and subjective data consistently suggest that it also increases CPAP use in select patients.

ACKNOWLEDGMENTS

The authors thank Dr. Makoto Kawai for translating the Japanese article by Dr. Sato et al. into English.

DISCLOSURE STATEMENT

This was not an industry supported study. Dr Kushida has received research support from Aerial BioPharma, Pacific Medico Co., Ltd., Resmed, Apnex Medical, Impax Laboratories, Inc., and Cephalon; has consulting relationships with Apnex, Seven Dreamers Laboratories, Noven Pharmaceuticals, UCB, Philips-Respironics, and Zephyr; and has received royalties from Philips Respironics. The other authors have indicated no financial conflicts of interest. The work was performed at Stanford Hospital and Clinics, Stanford, CA. The views herein are the private views of the authors and do not reflect the official views of the Department of the Army or the Department of Defense.

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Table S1—National Institute for Health and Clinical Excellence Study Quality Assessment of cases series studies.

	General Characteristics					Quality assessment of included studies *							
Author, Year, Study type	**Study site**	**N**	**Follow-up (months)**	**BMI (kg/m²)**	**Data**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Park, 2014, RCS	South Korea	7	2	21	BMI, comp, NB, nCPAP autotitr press	No	Yes	Yes	Yes	No	No	Yes	No
Poirier, 2013, PCS	Canada	18	6	32	BMI, comp, NB, nCPAP autotitr press, NOSE	No	Yes	Yes	Yes	Yes	No	Yes	Yes
Pniak, 2012, RCS	Czech Republic	28	3–6	29	comp, ESS, NB, nCPAP	No	Yes	Yes	Yes	No	No	Yes	No
Sufioglu, 2012, PCS	Turkey	28	3	30	BMI, CPAP PSG titr press, ESS, VAS	No	Yes	Yes	Yes	Yes	No	Yes	Yes
Bican, 2010, RCS	Turkey	20	2.5–6.5	31	BMI, CPAP PSG titr press, ESS	No	Yes	No	Yes	No	No	Yes	Yes
Baclerzak, 2007, RCS	Poland	19	3–4	–	BMI, ESS, NB, nCPAP autotir press	No	Yes	No	Yes	No	No	Yes	No
Zonato, 2006, RCS	Brazil	17	–	30	BMI, nCPAP PSG titr press	No	Yes	No	Yes	No	No	Yes	Yes
Nakata, 2005, RCS	Japan	5	–	27	BMI, CPAP PSG titr press, ESS	No	Yes	No	Yes	No	No	Yes	Yes
Esteller 2004, PCS	Spain	9	> 12	30	BMI, comp, NB	No	Yes	Yes	Yes	Yes	No	Yes	No
Nowak, 2003, RCS	France	10	–	27	BMI, comp, nCPAP PSG titr press	No	Yes	Yes	Yes	No	No	Yes	No
Dorn, 2001, RCS	Germany	5	1.5	32	BMI, ESS, nCPAP PSG titr press	No	Yes	No	Yes	No	No	Yes	No
Biermann, 2001, RCC	Germany	39	36	33	BMI, ESS, comp, nCPAP PSG titr press	No	Yes	Yes	Yes	Yes	No	No	Yes
Powell, 2001, RCT	USA	17	1	29	BMI, comp, ESS, NB, nCPAP, VAS	No	Yes	Yes	Yes	Yes	No	Yes	Yes
Friedman, 2000, PCS	USA	22	1.5	36	BMI, nCPAP PSG titr press	No	Yes	Yes	Yes	Yes	No	Yes	Yes
Hollandt, 1997, PCS	Germany	6	21	31	BMI, comp, NB, nCPAP PSG titr press	No	Yes	No	Yes	Yes	No	Yes	Yes
Ripberger, 1994, PCS	Germany	12	18	–	comp, nCPAP PSG titr press	No	Yes	Yes	No	Yes	No	Yes	Yes
Series, 1992, RCS	Canada	7	3	–	comp, nCPAP, NR	No	Yes	No	Yes	No	No	Yes	No
Mayer-Brix, 1989, RCS	Germany	3	–	–	comp, NB, nCPAP autotitr press, NR	No	Yes	No	Yes	No	No	Yes	No

–, not reported; AD, adherence; BMI, body mass index; comp, compliance; CPAP, continuous positive airway pressure; CPAP autotitr press, CPAP device autotitration pressure; mo., months; nCPAP, nasal CPAP; N, number of patients with isolated nasal surgery, NA, not applicable; NB, nasal breathing; NOSE, NOSE questionnaire; NR, nasal resistance; PCS, prospective case series; press, pressures; PSG, polysomnography; titr, titration; RCC, retrospective case-control; RCS, retrospective case series; RCT, randomized controlled trial; VAS, visual analog scale; yrs, years. * Quality assessment questions 1-8: 1) Case series collected in more than one center? 2) Is the hypothesis/aim/objective of the study clearly described? 3) Are the inclusion and exclusion criteria clearly reported? 4) Is there a clear definition of the outcomes reported? 5) Were data collected prospectively? 6) Is there an explicit statement that patients were recruited consecutively? 7) Are the main findings of the study clearly described? 8) Are outcomes stratified?

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pii: jc-18-00759 https://dx.doi.org/10.5664/jcsm.7640

JCSM
Journal of Clinical Sleep Medicine

SPECIAL ARTICLES

Treatment of Adult Obstructive Sleep Apnea with Positive Airway Pressure: An American Academy of Sleep Medicine Clinical Practice Guideline

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Introduction: This guideline establishes clinical practice recommendations for positive airway pressure (PAP) treatment of obstructive sleep apnea (OSA) in adults and is intended for use in conjunction with other American Academy of Sleep Medicine (AASM) guidelines in the evaluation and treatment of sleep-disordered breathing in adults.

Methods: The AASM commissioned a task force of experts in sleep medicine. A systematic review was conducted to identify studies, and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process was used to assess the evidence. The task force developed recommendations and assigned strengths based on the quality of evidence, the balance of clinically significant benefits and harms, patient values and preferences, and resource use. In addition, the task force adopted recommendations from prior guidelines as "good practice statements" that establish the basis for appropriate and effective treatment of OSA. The AASM Board of Directors approved the final recommendations.

Good Practice Statements: The following good practice statements are based on expert consensus, and their implementation is necessary for appropriate and effective management of patients with OSA treated with positive airway pressure:

1. Treatment of OSA with PAP therapy should be based on a diagnosis of OSA established using objective sleep apnea testing.
2. Adequate follow-up, including troubleshooting and monitoring of objective efficacy and usage data to ensure adequate treatment and adherence, should occur following PAP therapy initiation and during treatment of OSA.

Recommendations: The following recommendations are intended as a guide for clinicians using PAP to treat OSA in adults. A STRONG (ie, "We recommend…") recommendation is one that clinicians should follow under most circumstances. A CONDITIONAL recommendation (ie, "We suggest…") reflects a lower degree of certainty regarding the outcome and appropriateness of the patient-care strategy for all patients. The ultimate judgment regarding any specific care must be made by the treating clinician and the patient, taking into consideration the individual circumstances of the patient, available treatment options, and resources.

1. We recommend that clinicians use PAP, compared to no therapy, to treat OSA in adults with excessive sleepiness. (STRONG)
2. We suggest that clinicians use PAP, compared to no therapy, to treat OSA in adults with impaired sleep-related quality of life. (CONDITIONAL)
3. We suggest that clinicians use PAP, compared to no therapy, to treat OSA in adults with comorbid hypertension. (CONDITIONAL)
4. We recommend that PAP therapy be initiated using either APAP at home or in-laboratory PAP titration in adults with OSA and no significant comorbidities. (STRONG)
5. We recommend that clinicians use either CPAP or APAP for ongoing treatment of OSA in adults. (STRONG)
6. We suggest that clinicians use CPAP or APAP over BPAP in the routine treatment of OSA in adults. (CONDITIONAL)
7. We recommend that educational interventions be given with initiation of PAP therapy in adults with OSA. (STRONG)
8. We suggest that behavioral and/or troubleshooting interventions be given during the initial period of PAP therapy in adults with OSA. (CONDITIONAL)
9. We suggest that clinicians use telemonitoring-guided interventions during the initial period of PAP therapy in adults with OSA. (CONDITIONAL)

Keywords: obstructive sleep apnea, OSA, positive airway pressure, PAP

Citation: Patil SP, Ayappa IA, Caples SM, Kimoff RJ, Patel SR, Harrod CG. Treatment of adult obstructive sleep apnea with positive airway pressure: an American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med.* 2019;15(2):335–343.

INTRODUCTION

Since the publication of the previous American Academy of Sleep Medicine (AASM) positive airway pressure (PAP) practice parameters,[1–3] the scientific literature has continued to expand regarding the effects of PAP on clinical outcomes in adults with obstructive sleep apnea (OSA). In addition, research on improving PAP adherence and advancements in device technology have continued to evolve. Given these advancements, updating the prior practice parameters was considered timely.

The AASM commissioned a task force (TF) of content experts to update and consolidate previous AASM PAP practice parameters and reviews relevant to the treatment of adult OSA with PAP modalities.[1,3,4] This guideline does not address the initiation and management of PAP in patients with obesity hypoventilation syndrome, sleep-related hypoventilation, or those with concurrent forms of obstructive and central sleep apnea. The efficacy of continuous PAP (CPAP), auto-adjusting PAP (APAP), bilevel PAP (BPAP), and other advanced PAP modalities for central sleep apnea and hypoventilation are addressed in other active AASM guidelines.[5,6] Furthermore, several prior

recommendations on the management of OSA with PAP were not readdressed in the present guideline. Nevertheless, the TF adopted and modified two prior statements as good practice statements, as they were considered essential to providing high quality care to patients with OSA who are treated with PAP.

This guideline, in conjunction with the accompanying systematic review,[7] provides a comprehensive update of the available evidence and a synthesis of clinical practice recommendations.

METHODS

The AASM commissioned a TF of both board-certified sleep medicine specialists and experts with proficiency in the use of PAP in adults with OSA to develop this guideline. The TF was required to disclose all potential conflicts of interest (COI) per the AASM's COI policy prior to being appointed to the TF, and throughout the research and writing of this paper. In accordance with the AASM's conflicts of interest policy, TF members with a Level 1 conflict were not allowed to participate. TF members with a Level 2 conflict were required to recuse themselves from any related discussion or writing responsibilities. All relevant conflicts of interest are listed in the disclosure statement.

The TF conducted a systematic review of the scientific literature to answer 11 PICO (Patient, Population or Problem, Intervention, Comparison, and Outcomes) questions regarding the initiation of PAP therapy in patients with OSA that focus on patient-oriented, clinically relevant outcomes (see systematic review, Table 1).[7] The purpose of the review was to determine the effectiveness of PAP, alternative PAP modes (ie, APAP, BPAP), and concurrent strategies designed to improve outcomes by enhancing acceptance and use of PAP for OSA treatment (eg, patient education and telemonitoring). The TF did not compare PAP against other treatment options (eg, oral appliance therapy, surgical therapy). Assessment of the evidence was performed according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process.[8] The TF assessed the following four components to determine the direction and strength of a recommendation: quality of evidence, balance of beneficial and harmful effects, patient values and preferences, and resource use. Details of these assessments can be found in the accompanying systematic review.[7] Taking these major factors into consideration, each recommendation statement was assigned a strength (STRONG or CONDITIONAL). Additional information is provided in the form of remarks immediately following the recommendation statements, when deemed necessary by the TF. Remarks are based on the evidence evaluated during the systematic review and are intended to provide context for the recommendations to guide clinicians in the implementation of the recommendations in daily practice.

As this guideline focuses on the indications for PAP therapy for OSA in adults, rather than the use of specific components or accessories of the PAP device, recommendations for three of the PICO questions were not included. A summary of the systematic review and meta-analyses of the evidence for these PICO questions can be found in the additional considerations section, as these factors are still important for clinicians to consider in the context of their individual patient's circumstances, when initiating PAP therapy.

The AASM expects this guideline to have an impact on professional behavior, patient outcomes and, possibly, health care costs. This clinical practice guideline reflects the state of knowledge at the time of publication and will be reviewed and updated as new information becomes available.

GOOD PRACTICE STATEMENTS

The following are good practice statements, the implementation of which is necessary for appropriate and effective management of patients with OSA who are treated with PAP.

Treatment of OSA with PAP therapy should be based on a diagnosis of OSA established using objective testing.[9]

This good practice statement applies specifically to a new diagnosis of OSA, which should be established by either a home sleep apnea test or in-laboratory sleep testing prior to initiation of treatment for OSA. Patients with a previously established diagnosis of OSA who are currently on PAP therapy and have good symptom control should continue PAP therapy, even when prior testing results are not readily available.

Adequate follow-up, including troubleshooting and monitoring of objective efficacy and usage data to ensure adequate treatment and adherence, should occur following PAP therapy initiation and during treatment of OSA.

OSA is a chronic disease that rarely resolves except with substantial weight loss or successful corrective surgery. As with other chronic diseases, periodic follow-up by a qualified clinician (eg, physician or advanced practice provider) is necessary to confirm adequate treatment, assess symptom resolution, and promote continued adherence to treatment. Initial treatment of OSA requires close monitoring and early identification of difficulties with PAP use, as adherence over the first few days to weeks has been shown to predict long-term adherence.[10,11] Objective monitoring of PAP therapy should be performed to complement patient reporting of difficulties with PAP use, as patients often overestimate their use of PAP treatment.[12]

The timing of adequate follow-up after treatment is initiated will vary depending on patient circumstances. However, patients should be followed in the initial weeks to months after PAP initiation to promote adherence and assess response to treatment. Subsequently, yearly evaluation by a trained health care provider is reasonable, although longer periods of follow-up may be appropriate for selected patients who are highly adherent to PAP therapy, have sustained resolution of OSA-related symptoms, and have no concerns regarding their PAP therapy. In contrast, patients with persistent or recurrent sleep-related complaints or persistent difficulties with PAP use should receive more frequent follow-up to address their issues. Routine sleep testing to re-evaluate OSA status in patients

Table 1—Implications of STRONG and CONDITIONAL recommendations for users of AASM clinical practice guidelines.

User	STRONG Recommendations "We recommend…"	CONDITIONAL Recommendations "We suggest…"
Clinicians	Almost all patients should receive the recommended course of action. Adherence to this recommendation could be used as a quality criterion or performance indicator.	Most patients should receive the recommended course of action; however, different choices may be appropriate for different patients. The clinician must help each patient determine if the suggested course of action is clinically appropriate and consistent with his or her values and preferences.
Patients	Almost all patients should receive the recommended course of action, although a small proportion of patients may not.	Most patients should receive the suggested course of action, though some may not. Different choices may be appropriate for different patients. The patient should work with their clinician to determine if the suggested course of action is clinically appropriate and consistent with his or her values and preferences.
Insurance Providers	The recommended course of action can be adopted as policy for most situations. Adherence to the recommended course of action could be used as a quality criterion or performance indicator.	The ultimate judgment regarding the suitability of the suggested course of action must be made by the clinician and patient together, based on what is best for the patient. This decision-making flexibility should be accounted for when establishing policies.

AASM = American Academy of Sleep Medicine.

on PAP therapy with good symptom control and no change in clinical status (eg, significant weight loss or upper airway surgery) is considered low value care.

CLINICAL PRACTICE RECOMMENDATIONS

The following clinical practice recommendations are based on a companion systematic review, which evaluated the evidence using the GRADE methodology and should be read concurrently with this clinical practice guideline.[7] The recommendations in this guideline define principles of practice that should meet the needs of most patients in most situations. A STRONG recommendation is one that clinicians should follow for almost all patients (ie, something that might qualify as a quality measure). A CONDITIONAL recommendation reflects a lower degree of certainty in the appropriateness of the patient-care strategy for *all* patients. It requires that the clinician use clinical knowledge and experience, while strongly considering the individual patient's values and preferences to determine the best course of action. The ultimate judgment regarding any specific care must be made by the treating clinician and the patient, taking into consideration the individual circumstances of the patient, available treatment options, and resources.

The implications of the strength of recommendations for clinicians, patients, and policymakers are summarized in **Table 1.** Remarks are provided to guide clinicians in the implementation of these recommendations. A flowchart for the implementation of the recommendations is presented in **Figure 1**.

PAP Therapy

Recommendation 1: We recommend that clinicians use positive airway pressure, compared to no therapy, to treat OSA in adults with excessive sleepiness. (STRONG)

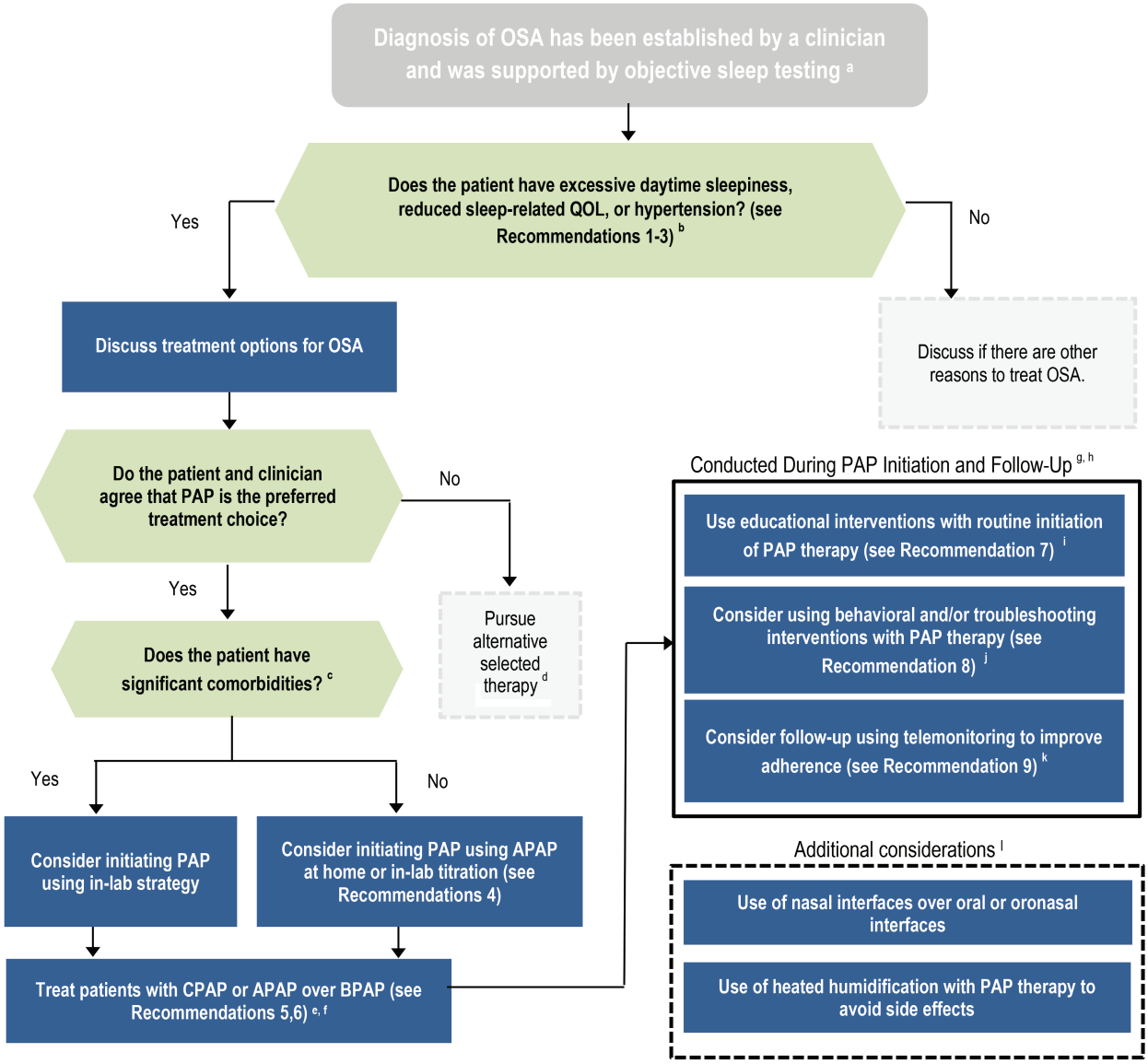
The TF assessed whether PAP should be offered to adult patients with OSA, based on improvements in the critical outcome of sleepiness, compared to no therapy. The TF identified 38 randomized controlled trials (RCTs) that assessed the efficacy of PAP to reduce excessive sleepiness. Meta-analyses demonstrated a clinically significant improvement in sleepiness with the use of PAP to treat adults with OSA as compared with no treatment. The overall quality of evidence, based on the critical outcome of sleepiness, was high. While a benefit of PAP use includes a reduction in daytime sleepiness, the potential harms include side effects such as nasal dryness or irritation, dry mouth, sore throat, and sinus infection as well as loss of intimacy,[4,9] all of which can be mitigated with appropriate interventions or are reversible with discontinuation of PAP. The potential burdens to the patient may include the costs of treatment and inconvenience such as maintaining the equipment and attending follow-up visits with the sleep clinician. The TF concluded that in adult patients with OSA and excessive sleepiness, the benefits of PAP therapy compared to no PAP therapy likely outweigh the potential harms and burdens, and that the majority of well-informed patients would choose the intervention over no treatment.

Recommendation 2: We suggest that clinicians use positive airway pressure, compared to no therapy, to treat OSA in adults with impaired sleep-related quality of life. (CONDITIONAL)

Remarks: Sleep-related quality of life (QOL) in adult patients with OSA may be adversely affected by OSA-related symptoms. Examples of such symptoms include: snoring, sleep-related choking, insomnia, disruption of bedpartner's sleep, morning headaches, nocturia, impairments in productivity or social functioning, and daytime fatigue.

The TF assessed whether PAP compared to no therapy should be offered to adult patients with OSA to improve the critical outcome of sleep-related QOL. OSA-related symptoms that can reduce sleep-related QOL include, but are not limited to; snoring, nocturnal choking, insomnia, disruption of their partner's sleep, morning headaches, nocturia, impairments in productivity or social functioning, and daytime fatigue. The TF identified 19 RCTs that assessed the efficacy of PAP to

Figure 1—Flow chart for implementation of clinical practice guideline.



a = Kapur et al., 2017.[9] b = symptoms that can impair sleep-related QOL include but are not limited to snoring, sleep-related choking, insomnia, disruption of bedpartner's sleep, morning headaches, nocturia, impairments in productivity or social functioning, and daytime fatigue. c = comorbidities may include: congestive heart failure, chronic opiate use, significant lung disease such as chronic obstructive pulmonary disease, neuromuscular disease, history of uvulopalatopharyngoplasty, those with known sleep-related oxygen requirements or expected to have nocturnal arterial oxyhemoglobin desaturation due to conditions other than OSA including hypoventilation syndromes and central sleep apnea syndromes. d = alternative therapies may include, but are not limited to, weight loss, positional therapy, oral appliance therapy or surgical interventions. e = BPAP is defined as a respiratory assist device that delivers inspiratory and expiratory positive airway pressure. f = BPAP devices may need to be used for patients with therapeutic pressure requirements greater than can be provided with CPAP or APAP; the decision to use BPAP should be based on the clinician's clinical judgement and needs of the individual patient. g = PAP therapy should be performed in conjunction with adequate follow-up to ensure adequate treatment and adherence. h = recommendations included within these boxes should be considered concurrently. i = educational interventions include those focused primarily on providing information about what OSA is, downstream consequences of untreated OSA, what PAP therapy is, how to use it, and the potential benefits of PAP therapy. j = behavioral interventions include those focused on behavior change related to use of PAP therapy using strategies such as cognitive behavioral therapy or motivational enhancement. Troubleshooting interventions include those focused on close patient communication to identify PAP-related problems and to initiate potential solutions. k = telemonitoring interventions include those that remotely monitor data obtained from a PAP device to identify PAP-related problems and to initiate potential solutions. l = when implementing the above recommendations, providers should consider additional strategies that will maximize the individual patient's comfort and adherence. APAP = auto-adjusting positive airway pressure, BPAP = bilevel positive airway pressure, CPAP = continuous positive airway pressure, OSA = obstructive sleep apnea, PAP = positive airway pressure, QOL = quality of life.

improve sleep-related QOL. Meta-analyses of sleep-related QOL, as assessed by the Calgary Sleep Apnea QOL Index (SAQLI) and the Functional Outcomes of Sleep Questionnaire (FOSQ), demonstrated a clinically significant improvement. However, meta-analyses of global QOL, as assessed by the SF-36 component scores, demonstrated no clinically significant

improvement. The overall quality of evidence, based on the critical outcome of sleep-related QOL, was moderate due to imprecision. The benefits and potential harms of PAP for patients with impaired sleep-related QOL are the same as for patients with sleepiness.[4,9] The TF concluded that in adult patients with OSA and impaired sleep-related QOL, the benefits of PAP therapy compared to no PAP therapy likely outweigh the potential harms and burdens, and that the majority of well-informed patients would choose the intervention over no treatment.

Recommendation 3: We suggest that clinicians use positive airway pressure, compared to no therapy, to treat OSA in adults with comorbid hypertension. (CONDITIONAL)

The TF assessed whether PAP should be offered to adult patients with hypertension and OSA, compared to no therapy to reduce the critical outcome of blood pressure (BP). The TF identified 5 RCTs that reported on the efficacy of PAP therapy on BP in this patient population. Meta-analyses demonstrated clinically significant BP reductions in nocturnal, daytime, and 24-hour systolic and diastolic BP when all patients in the studies were considered, with the largest effects seen for nocturnal measurements. When stratified by resistant hypertensive, hypertensive, and normotensive status, BP reduction was clinically significant in the meta-analyses for the group with hypertension and most BP measures in the group with resistant hypertension. The overall quality of evidence, based on the critical outcome of mean arterial BP, was moderate due to imprecision. The TF notes that the majority of studies evaluating the impact of PAP on BP recruited patients with predominantly moderate to severe OSA. (Note: studies did not systematically report BP based on OSA severity, which limited the ability to make recommendations specific to OSA severity.) The benefits and potential harms of PAP for patients with comorbid hypertension are the same as for patients with excessive sleepiness.[4,9] The TF recognized that patients experiencing symptoms of OSA (eg, excessive sleepiness) may be more accepting of PAP therapy, with the possibility of secondary benefits related to blood pressure reduction. Non-sleepy patients with OSA, however, may have a more nuanced view of whether to pursue treatment of OSA, particularly given the efficacy of standard antihypertensive treatments. The TF recognized that some non-sleepy patients will place a high value on any intervention that potentially reduces blood pressure, including PAP therapy. Nevertheless, the TF concluded that in adult patients with OSA and comorbid hypertension, the benefits of PAP therapy compared to no PAP therapy likely outweigh the potential harms and burdens, and that the majority of well-informed patients would choose the intervention over no treatment.

There is insufficient and inconclusive evidence to either recommend or withhold PAP to treat non-sleepy adults with OSA as a means to reduce cardiovascular events or mortality.

The TF assessed whether PAP compared to no therapy should be offered to adult patients with OSA to improve the critical outcomes of cardiovascular (CV) event and mortality risk. The TF identified 17 studies (11 observational studies and 6 RCTs) that assessed the impact of PAP therapy on cardiovascular events, and 13 studies (9 observational studies and 4 RCTs) that assessed the impact of PAP therapy on all-cause mortality. Meta-analyses of observational studies suggested a reduction in CV events and mortality with PAP therapy. In contrast, meta-analyses of randomized controlled trials demonstrated no clinically significant improvements in CV events or mortality. The quality of evidence for incident CV events and mortality ranged from very low to moderate due to study type and imprecision. Thus, the TF judged that the meta-analyses demonstrated insufficient and inconclusive findings regarding the impact of PAP therapy on incident CV events and mortality. Therefore, no recommendation is made regarding the use of PAP based on reduced incident CV events and mortality.

Some patients may, however; place a high value on any intervention that potentially reduces CV risk even when they are non-sleepy. In this situation, the patient and clinician should have a balanced discussion about the current state of the evidence about CV risk reduction with PAP therapy for OSA and the potential harms of PAP therapy when there are no other indications to treat the patient's OSA. Conversely, the uncertainty of any CV benefit, may lead some non-sleepy patients with OSA to decline treatment of their OSA. In these patients, conservative management of OSA, with monitoring for development of OSA symptoms over time, may be appropriate.

Initiation of PAP Therapy

Recommendation 4: We recommend positive airway pressure therapy be initiated using either APAP at home or in-laboratory PAP titration in adults with OSA and no significant comorbidities. (STRONG)

Remarks: When APAP is initiated in the home setting, therapy is maintained over the long-term by either using a fixed, continuous pressure setting determined from PAP monitoring data or continuing in the auto-adjusting mode. In-laboratory titration refers to both full-night and split-night titration. The choice of PAP initiation in the home or lab should be based on access, cost-effectiveness, patient preference, sleep clinician judgement, and other factors.

This recommendation is based on studies that excluded patients with the following comorbidities or conditions: congestive heart failure, chronic opiate use, significant lung disease such as chronic obstructive pulmonary disease, neuromuscular disease, history of uvulopalatopharyngoplasty, sleep-related oxygen requirements, or expectation for nocturnal arterial oxyhemoglobin desaturation due to conditions other than OSA, including hypoventilation syndromes and central sleep apnea syndromes.

This recommendation is based on the clinical trials reviewed, in which mask fittings and education on PAP use at a sleep center and/or close follow-up by trained staff during the treatment period were provided to the home APAP group. In some studies, daytime acclimatization to PAP was included.

The TF examined whether initiation of PAP using APAP at home (ie, without an in-laboratory titration) versus in-laboratory titration improved the critical outcomes of adherence, sleepiness, and QOL. The TF did not specifically assess patient outcomes with split-night titration testing as this was recently assessed by an AASM clinical practice guideline on diagnostic sleep testing and was deemed to be a reasonable approach under certain circumstances.[9] The guideline assumes that a diagnosis of OSA has already been established. The TF identified 10 RCTs that compared initiation of PAP using home APAP versus an in-laboratory PAP titration. Meta-analyses demonstrated no clinically significant differences in adherence, sleepiness, or QOL between APAP at home and in-laboratory PAP titration. The overall quality of evidence for this recommendation was high.

Potential benefits of using APAP in the home setting include lower cost, reduced time away from home, faster initiation of treatment, and greater access to care, whereas the potential harms may include inadequate patient education and the inability to identify and rectify problems related to mask fit, leak, or other PAP-related issues on the night of APAP use. The potential benefits of an in-laboratory PAP titration include providing education by a trained sleep technologist, real-time visual identification of efficacy of therapy, and the ability to provide immediate interventions to make PAP treatment more comfortable for the patient, whereas the potential harms include the need for an overnight stay away from home at the testing facility with the associated costs and patient time and the potential delay in initiation of therapy.

The TF concluded that the majority of well-informed adult patients with OSA and without significant comorbidities would prefer initiation of PAP using the most rapid, convenient and cost-effective strategy. This recommendation assumes that adequate education on PAP use and mask fittings with or without daytime acclimatization by trained staff are available. Furthermore, when APAP is implemented, the clinician is strongly encouraged to monitor the clinical response and PAP usage and therapy data within the first few weeks to make necessary PAP adjustments when indicated. Independent of payor restrictions, home APAP will be more rapid and convenient for most patients and has been shown to be more cost-effective.[13–15] Nevertheless, final determination of which strategy is ideal for an individual patient should be based on patient preferences and abilities, the sleep clinician's judgment, anticipated or known previous difficulty with PAP treatment, and availability of resources and cost of each strategy in a particular region.

PAP Modalities

Recommendation 5: We recommend that clinicians use either APAP or CPAP for ongoing treatment of OSA in adults. (STRONG)

Remarks: This recommendation is based on studies that mostly excluded patients with the following comorbidities or conditions: congestive heart failure, chronic opiate use, significant lung disease such as chronic obstructive pulmonary disease, neuromuscular disease, history of uvulopalatopharyngoplasty, sleep-related oxygen requirements or expectation of nocturnal arterial oxyhemoglobin desaturation due to conditions other than OSA, including hypoventilation syndromes and central sleep apnea syndromes.

The TF examined whether APAP versus CPAP improved the critical outcomes of adherence, sleepiness, and QOL. The TF identified 26 RCTs that investigated the effects of ongoing treatment with APAP compared with fixed CPAP. Meta-analyses demonstrated no clinically significant differences between APAP versus CPAP in adherence, self-reported and objective sleepiness, or QOL. The overall quality of evidence for this recommendation was moderate due to imprecision.

The TF judged that the benefits and harms of APAP and CPAP are similar, and the balance of effects does not favor either intervention. The main potential benefit of APAP to patients is the ability to automatically adjust pressure requirements over time in response to acute and chronic changes (eg, alcohol consumption, body position, or weight changes). No substantial differences in harms were identified for APAP versus CPAP use. Although meta-analyses demonstrated a lack of clinically significant differences in treatment adherence and outcomes, and patient preference varied between studies, the TF determined that individual patient tolerance of PAP, adherence, and symptom response may differ for one form of PAP or the other.

The TF concluded that either APAP or CPAP should be used for ongoing treatment of adult OSA, with the choice of therapy being tailored to patient tolerance and symptom response.

Recommendation 6: We suggest that clinicians use CPAP or APAP over BPAP in the routine treatment of OSA in adults. (CONDITIONAL)

Remarks: This recommendation is based on BPAP defined as a respiratory assist device that delivers inspiratory and expiratory positive airway pressure. This recommendation applies to all BPAP devices including flexible, modified, and auto-adjusting BPAP.

BPAP devices may need to be used for patients with higher therapeutic pressure requirements than can be provided by CPAP or APAP devices. The decision to use BPAP should be based on the clinician's judgement and needs of the individual patient. Furthermore, this recommendation is for the initial treatment of OSA and does not address management of patients who have previously failed CPAP or APAP. In addition, treatment of other forms of sleep-related breathing disorders associated with hypercapnia, which may require the use of BPAP, are covered in other AASM guidelines.[5,16]

To improve PAP adherence, BPAP has been used as an alternative to CPAP, in part due to issues of patient intolerance of high CPAP settings.[17] The TF examined whether BPAP versus CPAP improves the critical outcomes of adherence, sleepiness, and QOL (Note: while no direct evidence was available for the comparison of APAP to BPAP, the TF considers APAP to be equivalent to CPAP for the implementation of this recommendation. See recommendation 5 and **Figure 1**. The TF identified 5 RCTs that compared the use of BPAP to CPAP. Meta-analyses demonstrated no clinically significant differences in adherence,

self-reported sleepiness, and residual OSA with BPAP compared to CPAP. Studies reporting on sleep-related QOL and sleep quality also demonstrated no clinically significant differences. The overall quality of evidence for this recommendation was very low due to publication bias from industry funding and imprecision associated with small sample size.

The main potential benefit of BPAP over CPAP or APAP is improved comfort by lowering the pressure during exhalation, which may then increase adherence. The potential harms of BPAP over CPAP or APAP are a sub-optimally low expiratory pressure level that fails to prevent the occurrence of obstructive breathing events and the higher cost of BPAP. Furthermore, the historically perceived benefits of BPAP are less likely to be relevant since modified pressure profile technology, which also lowers expiratory pressures, has been integrated into modern PAP devices. The TF judged that although the benefits of treatment with BPAP versus CPAP or APAP are similar, the low quality of evidence and potential harms or burdens did not favor the regular use of BPAP for the routine treatment of OSA. Therefore, the TF concluded that the majority of well-informed adult patients with OSA would prefer initiation of treatment with CPAP or APAP over BPAP. However, there is a small subset of patients that require PAP treatment with pressures higher than 20 cm H_2O, which CPAP units are not typically capable of delivering. In these situations, BPAP devices may be needed for optimal treatment and can be utilized during an initial or subsequent in-laboratory PAP titration study. In addition, for specific patients who are unable to tolerate CPAP or APAP due to high pressure requirements and despite the use of modified pressure profiles, a trial of BPAP may be offered either during the initial in-laboratory titration or following a period of demonstrated non-acceptance.

Educational and Behavioral Interventions With PAP

Recommendation 7: We recommend that educational interventions be given prior to initiation of PAP therapy in adults with OSA. (STRONG)

Recommendation 8: We suggest that behavioral and/or troubleshooting interventions be given during the initial period of PAP therapy in adults with OSA. (CONDITIONAL)

Remarks: These recommendations are based on interventions defined as follows:

Educational interventions: Interventions focused primarily on providing information prior to initiation of PAP about what OSA is, its downstream consequences, what PAP therapy is, and the potential benefits of PAP therapy.

Behavioral interventions: Interventions focused on behavior change prior to and during the initiation and subsequent use of PAP therapy using strategies such as cognitive behavioral therapy or motivational enhancement.

Troubleshooting interventions: Interventions focused on close patient communication to identify PAP-related problems and to initiate potential solutions during the initial period of PAP therapy.

The intervention period may include interactions prior to, during and after PAP titration and follow-up.

The TF examined whether an educational, behavioral, or troubleshooting intervention versus no intervention prior to or during PAP treatment improves the critical outcome of adherence. QOL was initially considered a critical outcome; however, none of the accepted studies reported on this outcome. The TF identified 18 RCTs that evaluated the use of some combination of an educational, behavioral, or troubleshooting intervention as an adjunct to initiation of PAP therapy compared to PAP therapy with usual care. Meta-analyses demonstrated a clinically significant improvement in PAP adherence with all three types of interventions. The overall quality of evidence was moderate due to imprecision.

The potential harms of each of these interventions are minimal. The potential burdens to the patient are negligible for educational interventions but include the time required to receive the intervention and the cost of the additional care for the more intensive behavioral and troubleshooting interventions.

The TF judged that the benefits of educational interventions outweigh potential harms and burdens, while the benefits of behavioral and troubleshooting interventions likely outweigh the potential harms and burdens in most patients. As such, the TF concluded that the vast majority of well-informed adult patients with OSA would prefer that an educational intervention be provided with initiation of PAP therapy over initiation of PAP without education. In addition, the TF concluded that the majority of well-informed adult patients with OSA would likely prefer that a behavioral and/or troubleshooting intervention be given during the initial period of PAP therapy over no such intervention.

Monitoring During Treatment

Recommendation 9: We suggest that clinicians use telemonitoring-guided interventions during the initial period of PAP therapy in adults with OSA. (CONDITIONAL)

Remarks: This recommendation is based on interventions defined as follows: Telemonitoring includes the remote monitoring of PAP parameters such as PAP use, residual OSA severity, unintentional mask leaks, and PAP settings during treatment initiation and follow-up.

The TF examined whether behavioral, educational and troubleshooting interventions guided by remote monitoring of PAP therapy versus no remote monitoring improved the critical outcomes of adherence, sleepiness, and side effects. QOL was initially considered a critical outcome; however, none of the accepted studies reported on this outcome. The TF identified 5 RCTs that evaluated the use of remote monitoring of PAP variables to trigger early interventions versus no such system as an adjunct to PAP therapy. Meta-analyses demonstrated a clinically significant improvement in adherence, but not in sleepiness, with use of telemonitoring. PAP-associated side effect severity scores tended to be lower with a telemonitoring-guided intervention; however, these differences were not clinically

significant. The overall quality of evidence was moderate due to imprecision. The potential harms of remote monitoring interventions are small, primarily related to potential loss of privacy. How tele-monitoring guided interventions are implemented could lead to substantial increases in costs to healthcare systems, or conversely, may reduce costs if reductions in healthcare utilization substantially offset the investment in tele-monitoring systems. Nevertheless, the TF determined that the benefits of telemonitoring-guided adherence interventions likely outweigh the potential harms and burdens in most patients. Based on clinical experience, the TF concluded that the improvement in adherence would be valued by most patients. The TF concluded that the majority of well-informed adult patients with OSA would prefer enrollment in such a system compared to treatment without such an intervention.

ADDITIONAL CONSIDERATIONS

The AASM supports patient-centered care in which an individual patient's specific health needs and desired health outcomes are the driving force behind all health care decisions. When implementing the recommendations in this guideline, clinicians should consider strategies that will maximize the individual patient's comfort and adherence. The TF performed a systematic review of several interventions that aim to improve comfort and adherence including modified pressure profile, mask interfaces, and humidification. These are summarized below. A detailed evidence review can be found in the accompanying systematic review.[7]

Modified Pressure Profile PAP

Many PAP devices have now integrated modified pressure profiles, which lower the treatment pressure used during expiration. The potential benefit of using modified pressure profile PAP is increased patient comfort, while the potential harms of modified pressure profile PAP are similar to standard PAP. The TF identified 7 RCTs that investigated the use of modified pressure profile PAP to improve clinical outcomes and reduce side effects. Meta-analyses demonstrated no clinically significant differences in adherence, sleepiness, and QOL with modified pressure profile PAP versus standard PAP. Insufficient, standardized data were available to perform a meta-analysis on side effects; however, the reported data demonstrated no clinically significant differences. The data suggest that there are no systematic benefits to the routine initiation of treatment with modified pressure profile PAP, compared to standard PAP for OSA, despite perceived minimal potential harms and burdens. However, modified pressure profile PAP may have value in some patients in other contexts (eg, poorly adherent patients or patients with difficulty tolerating CPAP during in-laboratory titration studies) that have not yet been well studied.

Mask Selection

Appropriate mask selection will benefit patients by reducing side effects such as air leak and discomfort, which may then potentially improve adherence and subsequently patient outcomes. The TF identified 11 studies (3 observational studies and 8 RCTs) that evaluated the effects of different PAP interfaces on reducing the apnea-hypopnea index (AHI); improving adherence, sleepiness and QOL; and reducing side effects. Meta-analyses demonstrated a clinically significant improvement in adherence with nasal PAP versus oronasal interfaces, but there was no clinically significant difference in adherence between nasal or intra-nasal interfaces. With regards to self-reported sleepiness, meta-analyses demonstrated no clinically significant differences between interfaces. Studies reporting on QOL demonstrated no clinically significant differences between intra-nasal versus nasal interfaces. Finally, the studies analyzed indicated that there were fewer side effects with nasal compared with oronasal and oral interfaces. These data suggest that, for the routine initiation of PAP therapy in adults with OSA, clinicians should generally use nasal or intranasal mask interfaces over oronasal or oral interfaces. However, individual patient factors or preferences vary; therefore, the mask interface that minimizes side effects and optimizes efficacy and adherence should be used.

Humidified PAP

The use of humidification could also potentially reduce side effects from PAP therapy. The TF identified 9 RCTs that evaluated the use of PAP with humidification versus PAP without humidification to improve adherence, sleepiness, QOL, or PAP-related side effects. Meta-analyses demonstrated a clinically significant reduction in several side effects associated with the use of PAP, including dry mouth/throat, nasal discharge, nasal congestion, dry nose, bleeding nose, sinus pain or headache, sore throat, hoarse voice, and reduced smell. However, meta-analyses demonstrated no clinically significant improvement in PAP adherence, sleepiness, or QOL with the use of humidification compared with no humidification. The possibility of humidification causing "rain out" (ie, condensation of water into the PAP circuit, face, and nose or mouth of the patient) may deter its use. While the use of humidification may increase the ongoing costs (eg, purchasing distilled water, heated hoses) and maintenance requirements, these data suggest clinicians should generally use heated humidification with PAP devices to reduce side effects that may occur while treating adults with OSA.

SUMMARY

This clinical practice guideline provides recommendations for the use of PAP, approaches to the initiation of PAP treatment, and interventions to promote PAP adherence in adults with OSA. The recommendations are the result of the task force interpretation of evidence collected for the systematic review and application to the clinical care of adults with OSA. Four recommendations are strongly suggested and include: (1) using PAP to treat excessive sleepiness, (2) initiating PAP therapy with either APAP at home or an in-laboratory CPAP titration, (3) continuing PAP therapy for OSA with either CPAP or APAP, and (4) using educational interventions to initiate PAP therapy in adults with OSA. All other recommendations were conditional and include using PAP to treat impaired sleep-related QOL or

concomitant hypertension; implementing CPAP or APAP over BPAP in the routine treatment of OSA; and utilizing behavioral, troubleshooting, and telemonitoring interventions during the initial period of PAP therapy. The TF determined that a recommendation could not be made for the use or withholding of PAP therapy to treat non-sleepy patients to reduce incident cardiovascular disease. When implementing the recommendations, providers should consider additional strategies that will maximize the individual patient's comfort and adherence such as nasal/intranasal over oronasal mask interface and heated humidification, as discussed in the additional considerations section. Readers are strongly encouraged to read the companion systematic review[7] for a more detailed presentation and evaluation of the evidence. This clinical practice guideline reflects the state of knowledge at the time of publication and will be reviewed and updated as new information becomes available.

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ACKNOWLEDGMENTS

The task force thanks Dr. Romola Bucks (University of Western Australia) and Dr. Gerry Taylor (Case Western Reserve University) for lending their expertise in determining how neurocognitive outcomes should be addressed in this guideline.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication December 18, 2018
Submitted in final revised form January 14, 2019
Accepted for publication January 14, 2019
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DISCLOSURE STATEMENT

Dr. Indu Ayappa disclosed that she receives royalties from patents held on some PAP devices. Dr. Ayappa's potential conflict was managed by requesting that she refrain from participation on any discussions pertaining to devices for which she may hold a patent. She was also asked to refrain from voting on recommendations pertaining to those devices. Dr. Sanjay Patel disclosed that he receives compensation from Bayer Pharmaceuticals to assess the impact of OSA and its treatment on pulmonary hypertension and other cardiovascular outcomes. He was asked to refrain from participation on any discussion pertaining to the use of PAP to treat hypertension. He was also asked to refrain from voting on recommendations pertaining to the use of PAP to treat hypertension. Mr. Harrod is employed by the American Academy of Sleep Medicine. No other task force members had any relevant conflicts of interest to disclose.

Tympanostomy Tube Coverage for Adults 2026 Re-Review

Plain Language Summary

Tympanostomy tubes are tiny tubes placed in the eardrum to help air and fluid move more freely in the middle ear, among other conditions. It's not clear when these tubes are covered for adults.

Staff recommend updating the ear tube guideline to explain when these are covered for adults.

This issue summary has not changed since the March 19 meeting materials

Staff Analysis Summary:

Significant proposed changes or discussion items:

1. The guideline about when ear tubes are inserted should be modified to clarify when these tubes are covered for adults.

Tympanostomy Tube Coverage for Adults 2026 Re-Review

Coverage Question: Should limited coverage be re-established for tympanostomy tubes in adults?

Question source: Mendy Maccabee, ENT in Hood River and Anthem medical director

Background:

Pressure equalization tubes (PE tubes, also known as tympanostomy tubes) are tiny tubes inserted into the eardrum to treat middle ear conditions, mainly middle ear infections (acute otitis media) and fluid collections (serous otitis media). The procedure to insert PE tubes is known as tympanostomy.

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During the 2025 ENT BUP review, the two guidelines for tympanostomy tubes in acute otitis media and in chronic otitis media were combined. The acute otitis media guideline did not have any age restrictions for PE tube placement. The chronic otitis media guideline restricted PE tubes to patients "with specific higher risk conditions (including craniofacial anomalies, Down's syndrome, and cleft palate, or documented speech and language delay)" and "children up to and including age 7." The combined guideline does not have age mentioned in the acute otitis media section, and includes a restriction that PE tubes are only covered for children up to age 21 for chronic otitis media with a clause "note: tympanostomy tubes are not medically necessary for adults due to lack of impact on language acquisition." This BUP guideline was adopted early (January 1, 2026) as it was felt to be an improvement on the two previous guidelines.

From Dr. Maccabee:

> I also...must strenuously object to the cut off for tympanovstomy tubes at age 21. That makes no medical sense. There would be no data support for this. While the ICD10 code for requesting a tube for an adult would be different (OME, COME, SOME, ETD) it is a critical procedure for prevention of hearing loss, cholesteatoma and the need for much more invasive reparative interventions.....There are no adults jumping up and down for unnecessary tubes, no provider would request this for any reason other than necessary prevention of long term sequelae...

Previous HSC/HERC reviews:

This topic was discussed at the June and August 2025 VBBS and HERC meetings as part of the BUP review. "Members requested that the proposed new guideline be modified to include all children up to the age of 21 to correspond to EPSDT coverage. Wording should also be included in the guideline to indicate that coverage for adults is not included due to lack of issues with language acquisition. Members requested that HERC staff work on a proposal to have the guideline changes effective 10/1/2025."

Current Prioritized List/Coverage status:

PT tubes, tympanostomy and adenoidectomy are currently on lines:

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169 ACUTE MASTOIDITIS
308 HEARING LOSS - AGE 5 OR UNDER
372 CHOLESTEATOMA; INFECTIONS OF THE PINNA
386 ACUTE OTITIS MEDIA
444 HEARING LOSS - OVER AGE OF FIVE
472 CHRONIC OTITIS MEDIA

GUIDELINE NOTE 29, TYMPANOSTOMY TUBES

Lines 386,422,444,472

Tympanostomy tubes (CPT *69433, 69436) are only included on these lines as treatment for:

A) Patients with recurrent acute otitis media (three or more well-documented and separate episodes of acute otitis media in six months or four or more well-documented and separate episodes in the past 12 months with at least one episode in the past six months) in patients who have unilateral or bilateral middle ear effusion at the time of assessment for tube candidacy, OR
B) Chronic otitis media with a documented effusion for 3 months or longer in children under age 21 who are at high risk (note: tympanostomy tubes are not medically necessary for adults due to lack of impact on language acquisition):
    1) Children at high risk are defined as having one of the following:
        a) Permanent hearing loss of 25dB or greater independent of otitis media with effusion; OR
        b) Craniofacial anomalies; OR
        c) Syndromes that include cognitive, speech, or language delays; OR
        d) Blindness or uncorrectable visual impairment; OR
        e) Cleft palate; OR
        f) Developmental delay; OR
        g) Intellectual disability; OR
        h) Learning disorder; OR
        i) Attention-deficit/hyperactivity disorder; OR
        j) Speech and language delay

Formal audiometry is medically necessary for children with chronic otitis media with effusion present for 3 months or longer. Children with language delay, learning problems,

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or significant hearing loss should have hearing testing upon diagnosis. Children with chronic otitis media with effusion who are not at risk for language delay (such as those with hearing loss <25dB in the better hearing ear) or developmental delay should be reexamined at 3- to 6-month intervals until the effusion is no longer present, significant hearing loss is identified, or structural abnormalities of the eardrum or middle ear are suspected.

Adenoidectomy is included on these lines at the time of tympanostomy tube insertion for children under age 4 with symptoms directly related to the adenoids (for example, ear infection associated with rhinorrhea and/or upper respiratory infection) OR in children aged 4 years or older.

Removal of retained tympanostomy tubes requiring anesthesia (CPT code *69424) or as an office visit, is included on Line 422 as a complication, pairing with ICD-10-CM H74.8.

The development of this guideline note was informed by a HERC coverage guidance. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx

Evidence:

1) **AHRQ 2013**: Otitis Media With Effusion: Comparative Effectiveness of Treatments
    a. only limited research is available on treatment effectiveness in adults; we could identify only one study about treatments for adults

Submitted literature:

None received to date

Expert guidelines:

1) The American Academy of Otolaryngology-Head and Neck Surgery (AAO-HSN) only has clinical practice guidelines for children, not adults, regarding tympanostomy tube placement

Other payer policies:

1) Aetna 2025: Aetna considers myringotomy and tympanostomy tube (also known as ventilation tube and grommet) insertion medically necessary for *any* of the following indications:
    a. Autophony due to patulous eustachian tube; *or*

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b. Barotitis media control; *or*
c. Children with cleft palate and history of otitis media with effusion and persistent hearing loss; *or*
d. Cholesteatoma; *or*
e. Chronic retraction of tympanic membrane or pars flaccida; *or*
f. Complications of otitis media such as meningitis, facial nerve paralysis, coalescent mastoiditis, or brain abscess; *or*
g. Otitis media with effusion after 3 months or longer and bilateral hearing impairment (defined as 20 dB hearing threshold level or worse in both ears) (tympanostomy tube); *or*
h. Recurrent episodes of acute otitis media (more than 3 episodes in 6 months or more than 4 episodes in 12 months) (tympanostomy tube); *or*
i. Severe otalgia in acute otitis media (myringotomy); *or*
j. To obtain a culture (diagnostic tympanocentesis/myringotomy) of the middle ear fluid prior to beginning or changing antimicrobial therapy (this may be necessary in situations such as otitis media that has failed to respond to appropriate antimicrobial therapy, or for otitis media in individuals or neonates who are immunocompromised)

2) Anthem BCBS 2025: The use of combined myringotomy and tympanostomy tube insertion is considered **medically necessary** for individuals who meet any of the following criteria:

a. Children or adults with recurrent acute otitis media (AOM) (more than 3 episodes in 6 months or more than 4 episodes in 12 months) with or without otitis media with effusion (OME) who have middle ear effusion at the time of assessment for tube candidacy; **or**
b. Children with unilateral or bilateral OME for greater than or equal to 3 months with hearing loss greater than 20 dB in one or both ears; **or**
c. Children with recurrent AOM or OME of any duration when the child is at risk for speech, language, or learning delay or disorder from OM based on baseline sensory, physical, cognitive, or behavioral factors
d. Children or adults with structural damage to the tympanic membrane (TM) or middle ear, such as cholesteatoma, chronic retraction of tympanic membrane or pars flaccida; **or**

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e. Children or adults with barotitis (barotrauma); **or**
f. Children or adults with autophony due to patulous eustachian tube; **or**
g. Children or adults with middle ear dysfunction due to head and neck radiation or skull base surgery; **or**
h. Children or adults with a severe complication of acute otitis media including, but not limited to: meningitis, intracranial abscess, mastoiditis, or facial nerve paralysis; **or**
i. Adults with OME greater than 3 months and continued symptoms of aural pressure or hearing loss; **or**
j. Children or adults with persistent AOM despite at least 2 different courses of recommended empiric antibiotic therapy.

Expert input:

See Dr. Maccabee's comments in the background section

HERC staff summary:

PE tubes in adults with otitis media and effusion has been poorly studied. However, there are other rare indications for PE tubes in adults. Additionally, HERC has never intended to restrict PE tubes for acute otitis media to children and the current (2026) guideline does not appear to have that restriction. Based on expert input and private payer policies, HERC staff recommend modifying the tympanostomy tube guideline to clarify that adult PE tubes are not covered for chronic otitis media (consistent with HERC intent for 10+ years) but are covered for recurrent acute otitis media.

HERC staff recommendations:

1) Modify GN29 as shown below

GUIDELINE NOTE 29, TYMPANOSTOMY TUBES

Lines 386,422,444,472

Tympanostomy tubes (CPT *69433, 69436) are only included on these lines as treatment for:

A) ~~Patients~~ Adults and children with recurrent acute otitis media (three or more well-documented and separate episodes of acute otitis media in six months or four or

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more well-documented and separate episodes in the past 12 months with at least one episode in the past six months) in patients who have unilateral or bilateral middle ear effusion at the time of assessment for tube candidacy, OR

B) Chronic otitis media with a documented effusion for 3 months or longer in children under age 21 who are at high risk (note: tympanostomy tubes are not medically necessary for adults for chronic otitis media due to lack of impact on language acquisition):
   1) Children at high risk are defined as having one of the following:
      a) Permanent hearing loss of 25dB or greater independent of otitis media with effusion; OR
      b) Craniofacial anomalies; OR
      c) Syndromes that include cognitive, speech, or language delays; OR
      d) Blindness or uncorrectable visual impairment; OR
      e) Cleft palate; OR
      f) Developmental delay; OR
      g) Intellectual disability; OR
      h) Learning disorder; OR
      i) Attention-deficit/hyperactivity disorder; OR
      j) Speech and language delay

Formal audiometry is medically necessary for children with chronic otitis media with effusion present for 3 months or longer. Children with language delay, learning problems, or significant hearing loss should have hearing testing upon diagnosis. Children with chronic otitis media with effusion who are not at risk for language delay (such as those with hearing loss <25dB in the better hearing ear) or developmental delay should be reexamined at 3- to 6-month intervals until the effusion is no longer present, significant hearing loss is identified, or structural abnormalities of the eardrum or middle ear are suspected. Adenoidectomy is included on these lines at the time of tympanostomy tube insertion for children under age 4 with symptoms directly related to the adenoids (for example, ear

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infection associated with rhinorrhea and/or upper respiratory infection) OR in children aged 4 years or older.

Removal of retained tympanostomy tubes requiring anesthesia (CPT code *69424) or as an office visit, is included on Line 422 as a complication, pairing with ICD-10-CM H74.8.

The development of this guideline note was informed by a HERC coverage guidance. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx

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Comparative Effectiveness Review
Number 101

Effective Health Care Program

Otitis Media With Effusion: Comparative Effectiveness of Treatments

Executive Summary

Background

Definition of Otitis Media With Effusion

Otitis media with effusion (OME) is defined as a collection of fluid in the middle ear without signs or symptoms of acute ear infection.[1] OME has several potential causes. The leading causes include viral upper respiratory infection, acute otitis media (AOM), and chronic dysfunction of the eustachian tube.[2,3] However, other potential explanations include ciliary dysfunction, proliferation of fluid-producing goblet cells, allergy and residual bacterial antigens, and biofilm.[4] More recent research suggests that mucoglycoproteins cause the hearing loss and much of the fluid presence that is the hallmark of OME.[5,6] The presence of fluid in the middle ear decreases tympanic membrane and middle ear function, leading to decreased hearing, a "fullness" sensation in the ear, and occasionally pain from the pressure changes.

Prevalence of Otitis Media With Effusion

OME occurs commonly during childhood, with as many as 90 percent of children (80% of individual ears) having at least one episode of OME by age 10.[7] OME disproportionately affects some subpopulations of children. Those with cleft palate, Down syndrome, and other craniofacial anomalies are at high risk for anatomic causes of OME and

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at **www.effectivehealthcare.ahrq.gov/reports/final.cfm**.

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Effective Health Care

compromised function of the eustachian tube.[8] Individuals of American Indian, Alaskan, and Asian backgrounds are believed to be at greater risk,[9] as are children with adenoid hyperplasia. In addition, children with sensorineural hearing loss will likely be more affected by the secondary conductive hearing loss that occurs with OME.

Although rare, OME also occurs in adults. This usually happens after patients develop a severe upper respiratory infection such as sinusitis, severe allergies, or rapid change in air pressure after an airplane flight or a scuba dive. The incidence of prolonged OME in adults is not known, but it is much less common than in children.[10]

Many episodes of OME resolve spontaneously within 3 months, but 30 to 40 percent of children have recurrent episodes, and 5 to 10 percent of cases last more than 1 year.[1,11,12]

Despite the high prevalence of OME, its long-term impact on child developmental outcomes such as speech, language, intelligence, and hearing remains unclear.[7] The near universality of this condition in children and the high expenditures for treating OME (about $4 billion per year in the United States) make this an important topic for a comparative effectiveness review.

Diagnosis of Otitis Media With Effusion

Diagnostically, the core feature of OME is middle ear effusion (MEE), that is, fluid behind the eardrum in the middle ear. Tympanocentesis, which is the removal of fluid from behind the eardrum by using a needle to puncture the tympanic membrane, remains the gold standard for diagnosing MEE and OME. However, because tympanocentesis is an invasive procedure, it is rarely used for diagnosis. Tympanocentesis is not the same as myringotomy, in which the tympanic membrane is punctured to relieve pressure. A variety of supplemental examination techniques assist with identification. The most studied additional diagnostic method is pneumatic otoscopy, which is considered an accurate way to diagnose MEE by trained examiners.[7] To use this procedure, clinicians blow air through an otoscope, causing movement of the tympanic membrane that they can compare with normal movement of the membrane. Tympanometry is a supplemental diagnostic tool that indirectly measures middle ear pressure and tympanic membrane mobility. A "flat" tympanogram (Type B tympanogram) is consistent with OME. Additionally, children with OME often have a corresponding conductive hearing loss on pure-tone audiometry that measures 25 decibels (dB) or 10 dB above the IW hearing level of children with normal hearing.

Natural History and Treatment

Despite recent practice guidelines and systematic reviews,[8,13-20] the comparative benefits and harms of treatments and treatment strategies for OME are uncertain. The uncertainty stems from a lack of consensus regarding clinical and long-term functional outcomes of OME. Specifically, the authors of the most recent systematic review of the natural history of OME[8] found mixed evidence regarding the impact of OME in early childhood on later developmental outcomes. Although they concluded that children with early OME were at greater risk for temporary conductive hearing loss, they were unable to draw strong conclusions about the effect of early OME on later speech and language development. This lack of strong conclusions means it is not clear whether OME needs to be treated. Second, difficulty predicting the course of recurrence for individual patients, especially those with comorbid conditions, makes clinical decisions difficult. During topic refinement, the RTI-UNC Evidence-based Practice Center (RTI-UNC EPC) considered each of the known treatments in terms of uncertainty within the published literature (including gaps in the evidence), importance to clinicians, outcomes important to patients, and relevance to the U.S. population. Treatments examined in this review are indicated under Key Question 1.

Scope and Key Questions

The RTI-UNC EPC was charged with conducting this review because of the continuing uncertainty about efficacy, effectiveness, and particularly comparative effectiveness, as well as harms, for the included therapies. Providing more up-to-date and comprehensive comparative information will help many stakeholder groups make decisions about when and how to treat patients with this condition. This comparative review includes all interventions currently in use for treating OME—surgical, pharmacological, and nonpharmacological; we excluded antihistamines and decongestants, which have been extensively reviewed previously and demonstrated to have no benefit in this population. Antibiotics are the subject of a recent Cochrane review, and in cooperation with our Technical Expert Panel (TEP), we decided to not duplicate their work. We did not include this review as evidence because it was published in September 2012 after the deadline for including new reports in our

review.[21] For the most part, the treatments examined in the review are limited to those therapies that clinical guidelines recommended for managing OME.[20] However, we included several additional comparisons because more recent literature was available. Most notably, we included the findings of a recently published trial that examined adenoidectomy as an initial treatment with concurrent tympanostomy tubes (TT) placement in comparison with TT alone or watchful waiting because of the prominence of this large, carefully designed trial.[22]

The intent of our review was to cover the entire range of individuals who have OME; in particular, we sought evidence specific to populations who have not been examined in past reviews such as adults and children with comorbid conditions such as Down syndrome, cleft palate, or existing hearing loss. We did not limit the timeframe for outcomes, nor did we exclude any settings.

The EPC addressed five Key Questions (KQs) in this comparative effectiveness review.

KQ 1. What is the comparative effectiveness of the following treatment options (active treatments and watchful waiting) in affecting clinical outcomes or health care utilization in patients with OME? Treatment options include: tympanostomy tubes, myringotomy, oral or topical nasal steroids, autoinflation, complementary and alternative medical procedures, watchful waiting, and variations in surgical technique or procedures.

KQ 2. What is the comparative effectiveness of the different treatment options listed in KQ 1 (active treatments, watchful waiting, and variations in surgical procedures) in improving functional and health-related quality of life outcomes in patients with OME?

KQ 3. What are the harms or tolerability among the different treatment options?

KQ 4. What are the comparative benefits and harms of treatment options in subgroups of patients with OME?

KQ 5. Is the comparative effectiveness of treatment options related to factors affecting health care delivery or the receipt of pneumococcal vaccine inoculation?

We developed an analytic framework (Figure A) to guide our analysis. The populations of interest are in the box to the far left in the figure; the interventions appear in the middle; and the two sets of outcomes (for KQ 1 and KQ 2 on benefits, and also KQ 4 on important subgroups) appear on the far right. KQ 3 concerns harm (various types of adverse events). Finally, KQ 5 relates to a set of health care delivery or clinical factors (pneumococcal vaccination) that may influence choices of treatments or their clinical and quality-of-life outcomes.

Methods

Literature Search Strategy

Search Strategy

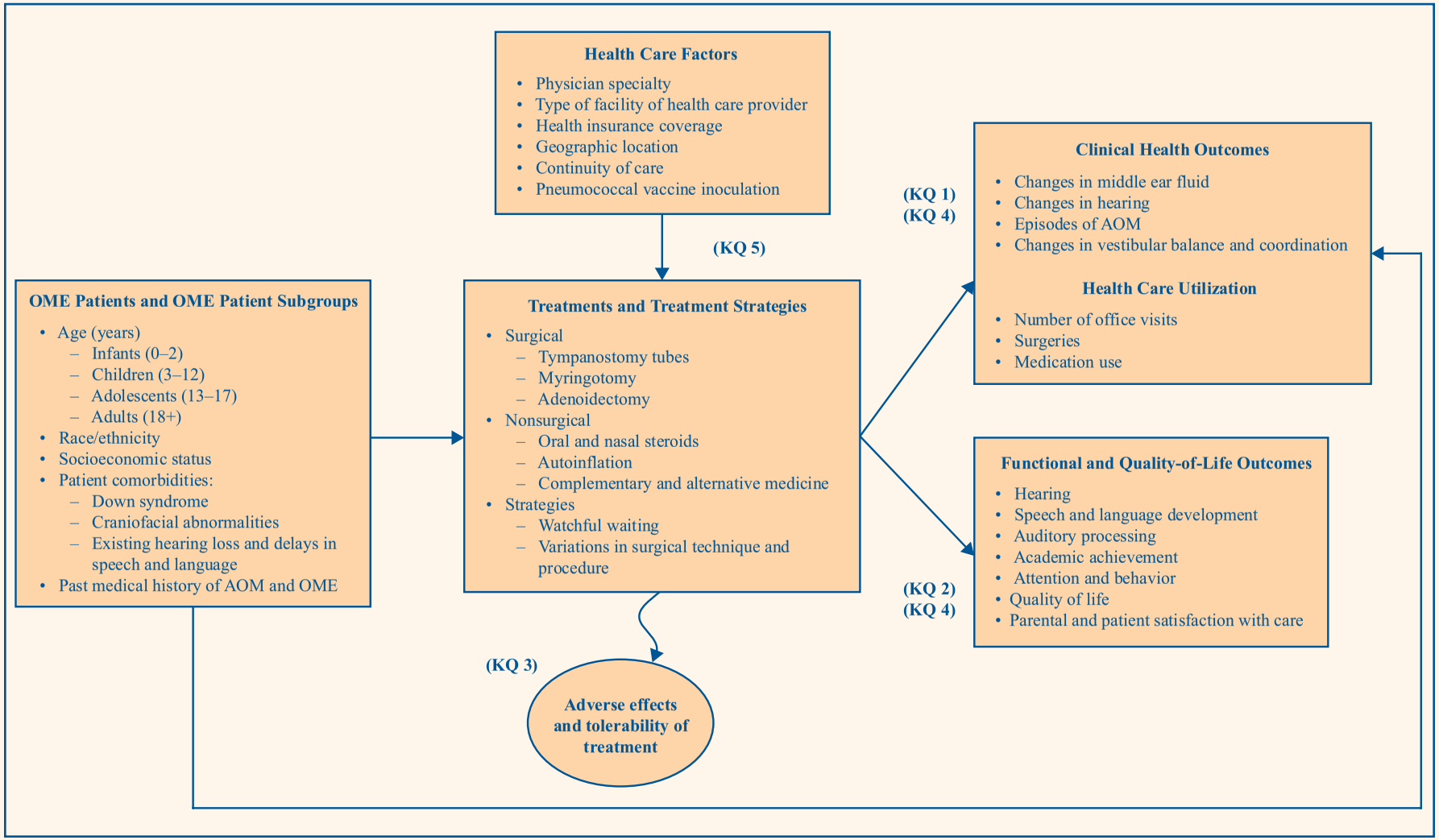
Five recently published systematic reviews on comparisons of interest (two on TT, one on adenoidectomy, one on steroids, and one on autoinflation)[13,15-18] were identified during the topic refinement stage of the review. An update of the steroid review[23] was added during peer review. As discussed in our review protocol, The Cochrane Collaboration conducted four of the reviews, and the Swedish Council of Technology in Health Care commissioned the fifth. The reviews covered the following treatment options for OME: TT, adenoidectomy, steroids, and autoinflation.

To avoid duplicating the work of these teams, we used these reviews as a starting point. We included evidence from these systematic reviews plus additional evidence that these reviews did not consider. The additional evidence included: additional outcomes data from studies that were included in the recent reviews but were not the focus of those reviews, observational studies done at any time, newer studies published since the last search dates in those reviews, and studies focusing on populations excluded from the reviews, such as adults with OME or children with Down syndrome or cleft palate, who may be differently affected by OME.

We searched MEDLINE® (via PubMed), Embase,® The Cochrane Library, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL®) to identify studies not included in the systematic reviews. An experienced research librarian used a predefined list of search terms and medical subject headings (MeSH). We reviewed our search strategy with our TEP and incorporated their input into our search strategy. We limited the electronic searches to English-language materials. We completed the initial search on 1/8/2012, and we completed an update during peer review on 8/13/2012.

We searched unpublished and grey literature relevant to the review topic. Methods for identifying grey literature included a review of trial registries. In addition, AHRQ requested Scientific Information Packets (SIPs) from the developers and distributors of the interventions identified

Figure A. Analytic framework for comparisons of interventions for otitis media with effusion



AOM = acute otitis media; KQ = Key Question; OME = otitis media with effusion

in the literature review. We included unpublished studies that met all inclusion criteria and contained enough information on their research methods to permit us to make a standard risk-of-bias assessment of individual studies. Finally, we manually searched reference lists of reviews, including trials and background articles, to look for relevant citations that our searches might have missed and that addressed our KQs. We imported all citations into an electronic database (EndNote® X4).

Inclusion and Exclusion Criteria

We developed inclusion and exclusion criteria with respect to the PICOTS (i.e., populations, interventions, comparators, outcomes, timeframes, and settings) framework. The review included only English-language studies of individuals with OME. We included five systematic reviews that had been determined a priori to fit our PICOTS criteria and the relevant studies included in those reviews; we also retained eligible studies that the earlier reviews had not used, and these included randomized controlled trials (RCTs), nonrandomized controlled trials, and cohort studies. We imposed no other restrictions so that we could consider studies with individuals of any age, racial or ethnic background, or coexisting condition.

The treatments of interest were TT, myringotomy, adenoidectomy, oral or intranasal steroids, autoinflation of the eustachian tube, complementary and alternative medicine (CAM) procedures, watchful waiting, and variations in surgical technique or procedures. With two exceptions, included studies had to compare at least two of these treatments. We considered inactive controls in comparison with steroid treatment and usual care in comparison with autoinflation, based on the Cochrane review inclusion criteria. Based on discussions with our TEP, because the effectiveness of CAM treatments was unknown and there were concerns about the quality of nonrandomized studies, we limited studies of CAM to RCTs.

We specified a broad range of outcomes (see Figure A). We included clinical outcomes such as changes in middle ear fluid, episodes of AOM, and hearing thresholds; use of health care; functional and quality-of-life outcomes such as speech and language development, behavior, and parental satisfaction with care; and harms.

We were interested primarily in treatment outcomes of 3 months or longer, but we included outcomes of less than 3 months. We focused on end-of-intervention results when they were the only endpoint data available, such as in the autoinflation treatment studies.

We did not exclude studies based on geography or the setting of the service provision.

Study Selection

A total of six trained members of the team reviewed article abstracts and full-text articles. First, two members of the team independently reviewed each abstract using the inclusion/exclusion criteria. One reviewer was always a senior member of the review team. If both reviewers agreed that the study did not meet eligibility criteria, we excluded it; otherwise, we included the abstract for full article review. Two members of the team independently reviewed each full-text article. One reviewer was always a senior member of the review team. If both reviewers agreed that a study did not meet eligibility criteria, we excluded it. Each reviewer recorded the primary reason for exclusion. If the reviewers disagreed about whether an article should be excluded or about the primary reason for exclusion, they resolved conflicts by discussion and consensus or by consulting a third member of the team. We screened unpublished studies identified through a grey literature search and review of SIPs using the same title/abstract and full-text review processes.

Data Abstraction

We developed a template for evidence tables for data synthesis using the PICOTS framework. For the five systematic reviews and additional studies that met our inclusion criteria, we abstracted relevant information into these evidence tables: characteristics of study populations, interventions, comparators, settings, study designs, methods, and results. We directly reviewed individual studies included in the systematic reviews to capture additional outcomes data that were not the focus of the earlier reviews and to determine the availability of subgroup analyses not included in the reviews.

Six trained members of the team participated in the data abstraction. One of the reviewers initially abstracted the relevant data from each included article using Microsoft Excel® software and a second more senior member of the team reviewed each data abstraction against the original article for completeness and accuracy.

Risk-of-Bias Assessment

The risk-of-bias assessment was conducted using two tools, one appropriate for trials based on the Cochrane

risk-of-bias tool[24] and modified by our EPC to be used to evaluate observational studies (including instructions to reviewers that some questions concerning trial study design would be considered not applicable) and AMSTAR (assessment of multiple systematic reviews),[25] appropriate for systematic reviews. We did not reevaluate the risk of bias of the studies included in the previous systematic reviews,[13,15-18,23] but the original review study authors had determined these studies to be of low or medium risk of bias.

Two independent reviewers rated the risk of bias for each study. Disagreements between the two reviewers were resolved by discussion and consensus or by consulting a third member of the team. Results of this assessment were summarized in a rating of low, medium, or high risk of bias. High risk-of-bias studies were those that had at least one major issue that had the potential to cause significant bias and might invalidate the results.

Data Synthesis

Across all included studies, the populations, interventions, and outcome measures in the additional data were heterogeneous and did not lend themselves to a pooled analysis beyond what was currently available in the meta-analyses from the five earlier systematic reviews. Because we determined that additional quantitative analyses were not necessary or appropriate, we did all analyses qualitatively. Evidence used in the synthesis included the results from the earlier meta-analyses, additional data from individual studies contained in those systematic reviews, and data from the articles added from our own searches.

Strength of the Body of Evidence

We graded the strength of evidence based on the guidance established for the Agency for Healthcare Research and Quality Effective Health Care Program EPCs conducting comparative effectiveness reviews, as detailed in the paper by Owens and colleagues.[26] The EPC approach incorporates four key domains: risk of bias, consistency, directness, and precision of the evidence. The overall grade for strength of evidence is based on the scores for the four domains and reflects the strength of the body of evidence to answer the KQs on the comparative effectiveness, efficacy, and harms of the treatments and treatment strategies covered in this review.

A grade of high strength of evidence indicates that we have high confidence that the evidence reflects the true effect. Moderate strength of evidence implies that we have moderate confidence that the evidence reflects the true effect. Low strength or evidence suggests that we have low confidence that the evidence reflects the true effect. Insufficient strength of evidence signifies either that evidence is completely unavailable or that it does not permit estimation of an effect. Typically, evidence from just one study was considered insufficient to permit confidence in the estimation of an effect. Exceptions were single study bodies of evidence consisting of a relatively larger, low risk of bias trial, particularly if it showed a large magnitude of effect.

Two reviewers assessed each domain independently and assigned an overall grade for each treatment comparison for each key outcome listed in the framework. They resolved any conflicts through consensus discussion. If they did not reach consensus, the team brought in a third party to settle the conflict.

Applicability

We assessed the applicability of individual studies as well as the body of evidence. For individual studies, we examined factors that may limit applicability based on the PICOTS structure such as population characteristics, intervention characteristics, and comparators. We abstracted key characteristics of applicability into the evidence tables. During data synthesis, we assessed the applicability of the body of evidence using the abstracted characteristics. KQ 4 includes a detailed analysis of intervention effectiveness in population subgroups.

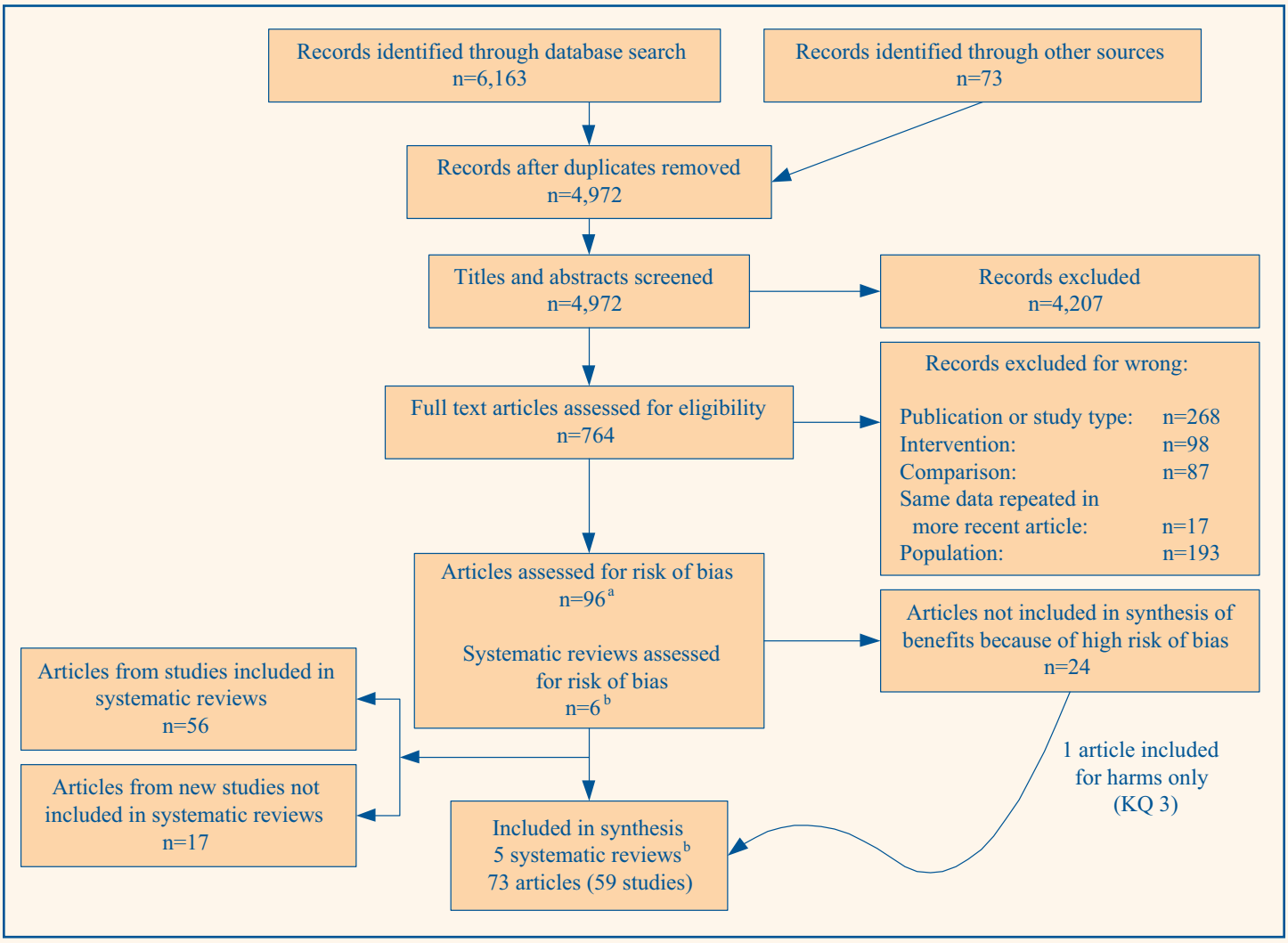
Results

This section is organized by KQ and then grouped by intervention comparison. The summaries of evidence findings are presented in Tables A–D by KQ. The full report contains summary tables. Appendix C contains evidence tables for included studies, and Appendix F has the strength of evidence grades for the main outcomes of each KQ. Except where otherwise noted, across KQs, the studies we included were limited to otherwise healthy children.

Literature Searches

We identified a total of 4,967 unduplicated citations and determined that 764 met criteria for full-text review (Figure B). We excluded 668 full-text articles based on our inclusion criteria and before risk-of-bias assessment. There were a total of 73 full-text articles, detailing 59 studies and five systematic reviews. Of the 59 studies, 42 studies were included in one of the five systematic reviews, and we included 17 additional studies. Of the 59 studies included in this review, 49 were RCTs (33 by person, 12 by ear, and 4 by person and ear), 6 were nonrandomized control trials

Figure B. Disposition of articles on otitis media with effusion



[a]We accepted the risk of bias assessment conducted by the review authors for the studies included in one of the 5 earlier systematic reviews (56 articles). We conducted our own risk of bias assessment for 17 new articles not included in one of those reviews.
[b]One of the 5 included systematic reviews was updated during our peer review period. We reviewed both the original report and the update.

(1 by person and 5 by ear), and 4 were cohort studies. Of the 17 articles not included in one of the five systematic reviews, we assessed 15 as medium risk of bias, 1 as low risk of bias and 1 as high risk of bias. Of the five included systematic reviews, four were limited to RCTs. We assessed four systematic reviews as low risk of bias and one as medium risk of bias.

We recorded the reason that each excluded full-text publication failed to satisfy the eligibility criteria and compiled a comprehensive list of such studies (Appendix B of the full report).

We did not include 23 high-risk-of-bias studies in our analyses (Appendix C of the full report). Virtually all lacked information on any baseline patient characteristics; of particular concern, unknown differences between groups based on age or time with OME could invalidate outcomes. Other serious concerns were a lack of control for selective concurrent treatment and lack of control for confounders in cohort studies.

Key Question 1. Comparative Effectiveness: Clinical Outcomes or Health Care Utilization

All but four of the 59 studies included in this review examined clinical outcomes. Thirty one studies and 12 meta-analyses examined signs and symptoms of OME. Thirty studies and six meta-analyses examined hearing as an outcome. Only three studies examined subsequent AOM as an outcome. No studies reported use of health services or balance outcomes. A description of the treatment comparisons and comparative effectiveness follows.

Tympanostomy Tube Comparisons

Six individually located studies[27-32] and eight studies[33-40] from one systematic review[13] addressed comparisons of TT. These studies compared different types of tubes (e.g., design, materials, size), approaches to insertion, or topical prophylaxis therapies. All comparisons were made between ears of the same individual.

Ten[27-31,33-37] of the 14 studies provided evidence for KQ 1; the other four provided evidence only for harms. Of these 10 studies, 7 were RCTs. Length of tube retention was higher in the longer term TT. Other TT comparisons and endpoints differed across studies. Because of sparse data, the diversity of comparisons, and inconsistent findings, the evidence is insufficient for comparisons of other design features or for hearing outcomes.

Tympanostomy Tubes Versus Watchful Waiting/Myringotomy

Two individual studies[41,42] and two systematic reviews[13,15] addressed comparisons between RCTs of TTs with either myringotomy or watchful waiting. The Browning et al.[15] systematic review reviewed 10 studies;[43-52] 7 were in comparison with watchful waiting or delayed treatment,[43-45,48,50-52] 2 were in comparison with myringotomy in the control ear,[46,49] and 1[47] included both myringotomy and watchful waiting arms. The Hellstrom et al.[13] systematic review included six of the studies that were in the Browning review; in addition, data on hearing outcomes from Gates et al. (1989)[53] were reported only in the Hellstrom review. We included as a companion study the Medical Research Council Trial of Alternative Regimens in Glue Ear Treatment (MRC TARGET)[22] that was a recently published version of the preliminary data included in the Browning review.[44] We also present additional reports of later followup of the cohorts of Maw and colleagues (1999),[43] Rovers and colleagues (2000),[45] and Paradise and colleagues (2001).[48]

TT placement decreased time with middle ear effusion by 32 percent compared with watchful waiting or delayed treatment (high strength of evidence) and up to 42 percent in comparison with myringotomy (moderate strength of evidence) at 1 year after surgery. Compared with watchful waiting or myringotomy (data combined), there was a 13 percent reduction through 2 years after surgery (moderate strength of evidence). Evidence was insufficient for longer followup. TT improved hearing through 9 months after surgery compared with watchful waiting (3–6 months: 8.8 dB; 6–9 months: 4.2 dB) (high strength of evidence); TT improved hearing by 10 dB at 4 to 6 months after surgery in comparison with watchful waiting or myringotomy (data combined) (high strength of evidence). Thereafter the differences in hearing became attenuated and were not significant at either 7 to 12 months compared with watchful waiting or myringotomy (low strength of evidence) or 12 to 18 months after surgery compared with watchful waiting (low strength of evidence). Evidence was insufficient for longer time periods and for other clinical outcomes or health utilization.

Tympanostomy Tubes Plus Adenoidectomy Versus Myringotomy Plus Adenoidectomy or Adenoidectomy Alone

Seven individually located studies[54-60] and four studies[53,61-63] reported in the Hellstrom review examined outcomes in relation to TT plus adenoidectomy as compared with myringotomy plus adenoidectomy or adenoidectomy alone. We included another report[64] that was a followup study to the Bonding and Tos report (1985)[61] included in the Hellstrom review. Four of the studies compared TT in one ear with an ear that received no surgery, in children who all had had adenoidectomies. Three studies (four articles)[59,61,63,64] compared ear outcomes between ears with TT and ears with myringotomy, among children who all had had adenoidectomies. The other four studies[53,57,58,60] compared TT with myringotomy among children who all had had adenoidectomies.

Two small studies found that TT conferred no additional benefit to adenoidectomy alone for reducing the recurrence of OME (insufficient strength of evidence); three studies comparing TT and adenoidectomy with myringotomy and adenoidectomy produced mixed results (insufficient strength of evidence). Five of six studies failed to find a difference in hearing at various endpoints between TT and myringotomy among children who had also received adenoidectomies (low strength of evidence). We found mixed results for hearing when comparing TT with watchful waiting in children who also received adenoidectomies (insufficient strength of evidence).

Myringotomy Comparisons

Only one RCT compared two different procedures for myringotomy on both middle ear and hearing outcomes.[65] The two procedures were radio frequency myringotomy with mitomycin C, a topical chemotherapeutic agent and radio frequency myringotomy alone. A majority of individuals in each arm received adenoidectomy (73% and 67%, respectively). There was insufficient evidence for concluding superiority of either myringotomy procedure for OME signs and symptoms or hearing outcomes.

Myringotomy Plus Adenoidectomy Comparisons

One retrospective cohort study compared two different procedures for myringotomy.[66] The comparison was between laser myringotomy and cold knife myringotomy. In both groups all individuals received an adenoidectomy. The evidence is insufficient for determining superiority for either myringotomy approach for OME signs and symptoms. No study examined hearing or any other clinical outcome.

Adenoidectomy Versus Other Interventions

Eight RCTs provided all the evidence for adenoidectomy in comparison to TT, myringotomy, watchful waiting, or no surgery among patients with OME. Seven of the RCTs were included in the Cochrane review by van den Aadweg et al.[16,46,49-51,67-69] and the eighth was the newly published MRC TARGET trial.[22] The trials examined adenoidectomy with and without myringotomy versus nonsurgical treatment or myringotomy only; adenoidectomy with unilateral TT versus a unilateral TT only (comparison by ears); adenoidectomy with bilateral TT versus bilateral TT only; and adenoidectomy plus TT versus watchful waiting.

Adenoidectomy was superior to no treatment for resolution of OME at both 6 months (risk difference of 0.27 [95% CI, 0.13 to 0.42] measured through otoscopy and 0.22 [95% CI, 0.12 to 0.32] as measured through tympanometry; high strength of evidence) and 12 months postsurgery (risk difference of 0.29 [95% CI, 0.19 to 0.39] through tympanometry; high strength of evidence). Adenoidectomy was superior to no treatment for hearing in one study at 6 months but not at 12 months; in a second study, no differences were detected between adenoidectomy and no treatment (insufficient strength of evidence for mixed findings). One single study found that adenoidectomy and myringotomy were superior to myringotomy alone for reducing time with effusion ($p<0.001$).and improving hearing at 24 months (better ear standard mean difference of -0.66 [95% CI, -0.93 to -0.40]; low strength of evidence). Because results were mixed, the evidence was insufficient for determining the effectiveness of adenoidectomy when added to TT in relation to effusion or hearing (insufficient strength of evidence). Hearing outcomes were superior with adenoidectomy and TT compared with watchful waiting at 24 months (low strength of evidence). There was insufficient evidence to determine the effectiveness of adenoidectomy compared with other treatments for recurrence of AOM.

Oral or Topical Nasal Steroids

The included evidence consisted of one systematic review conducted by The Cochrane Collaboration,[18] that was updated while we were conducting our review,[23] that examined oral steroids and topical intranasal steroids. The update review includes the studies included in the earlier review, nine RCTs of oral steroids[70-78] and three RCTs of topical intranasal steroids,[79,80] and adds one recent RCT conducted by Williamson et al.[80,81] All studies were in comparison with placebo controls; some of the oral steroid studies included antibiotics in both arms. All studies examined signs and symptoms of OME and hearing.

Results of a meta-analysis[18] comparing oral steroids with controls did not show differences in middle ear effusion at 1–2 months post treatment (low strength of evidence); nor did a meta-analysis comparing oral steroids with control along with adjunct antibiotics (moderate strength of evidence). Due to limited data, evidence was insufficient for determining the effectiveness of oral steroids with and without antibiotics for OME signs and symptoms at followup beyond 3 or more months. Topical intranasal steroids did not show differences in cure rate at various followup points with antibiotics (insufficient strength of evidence) or without antibiotics (low strength of evidence). The evidence was insufficient for determining the effectiveness of oral steroids with and without antibiotics for hearing at any time point. The RCT by Williamson et al.[80,81] comparing intranasal steroids with controls did not find differences in OME cure rate or in hearing at one or more months post treatment (low strength of evidence). There was insufficient evidence for comparing either oral or topical intranasal steroids with controls for any other clinical outcomes.

Autoinflation

One Cochrane review conducted by Perera et al.[17] summarized evidence from six RCTs of any form of autoinflation, a technique designed to increase pressure in the oropharynx forcing open the eustachian tube though a nasal balloon or other process. The review included five studies with children[82-86] and one study with adults, 16–75 years of age.[87] All studies were in comparison with no autoinflation, and other treatments (e.g., antibiotics, analgesics) were permitted as long as they were given equally to both arms. Meta-analyses comparing autoinflation with controls found an improvement in OME at 1 month or less, post treatment (low strength of evidence). Evidence was insufficient for drawing

conclusions regarding improvements in OME at longer time periods or for other clinical outcomes, including hearing.

Key Question 2. Comparative Effectiveness: Functional Outcomes or Quality of Life

Only a subset of the treatment comparisons reported functional or quality of life outcomes. These include TT versus watchful waiting, TT plus adenoidectomy versus myringotomy plus adenoidectomy, and steroids versus control. In general, there were no differences between the treatments. The studies included to address KQ 2 are described under KQ 1.

Tympanostomy Tubes Versus Watchful Waiting/Myringotomy

Meta-analyses reported by Browning et al.[15] did not find any differences in language development at 6 and 9 months post treatment between TT and watchful waiting (moderate strength of evidence for no differences). With one exception, studies examining children during preschool and elementary school years failed to find a difference in language skills. In the one exception where a difference favoring TT was reported, the investigators used a teacher rating of children's language; this difference disappeared at 8 years of age when they used a direct assessment of language (low strength of evidence for no difference). We did not find differences between TT and watchful waiting in any RCTs reporting cognitive development, academic achievement or quality of life at any time point (all low strength of evidence for no difference). Studies reported mixed findings for behavior outcomes at less than 1 year (insufficient strength of evidence); three studies reporting behavior at more than 1 year reported no difference (low strength of evidence). No studies comparing TT with myringotomy reported on functional or quality of life outcomes (insufficient strength of evidence).

Tympanostomy Tubes Plus Adenoidectomy Versus Myringotomy Plus Adenoidectomy

One study comparing TTs plus adenoidectomy with myringotomy plus adenoidectomy reported quality of life outcomes.[60] The two groups did not differ at any time point (insufficient strength of evidence). Strength of evidence was insufficient for all speech/language, cognitive, and behavioral outcomes because there were no studies including these outcomes.

Oral or Topical Nasal Steroids

Two studies comparing steroids to control (three reports)[79-81] examined functional outcomes. In one small study, patients receiving intranasal steroids plus oral antibiotics did not differ in parents' assessment of their children's symptoms from patients receiving placebo plus antibiotics (insufficient strength of evidence); nor did patients receiving intranasal steroids differ from controls in parent reported hearing outcomes (low strength of evidence). No studies comparing topical or oral steroids to control examined any other functional outcomes (insufficient strength of evidence).

Key Question 3. Harms or Tolerability

Six of the treatment comparisons included in the review reported on harms. These included comparisons between different types of TT, TT versus watchful waiting/myringotomy, TT plus adenoidectomy versus myringotomy plus adenoidectomy/adenoidectomy alone, steroids, and autoinflation. Only a limited range of harms was included for any comparison. Few significant differences in harms were reported.

Tympanostomy Tube Comparisons

We reviewed nine studies that reported on otorrhea.[27-32,37-39] Otorrhea rates differed by TT type, with placement of longer term TT related to a higher probability of otorrhea (low strength of evidence). For other harms such as perforation, cholesteatoma, occlusion, tympanosclerosis, and the presence of granulation tissue, the evidence was too limited to determine a direction of effect (insufficient strength of evidence).

Tympanostomy Tubes Versus Watchful Waiting/Myringotomy

We reviewed nine studies that compared side effects for TT with side effects for watchful waiting or myringotomy.[57,64,88-94] Otorrhea and tympanosclerosis occurred more frequently in ears that had TT than watchful waiting or myringotomy (low strength of evidence). Evidence was insufficient for other harms due to either conflicting results or data reported in only a single study.

Tympanostomy Tubes Plus Adenoidectomy Versus Myringotomy Plus Adenoidectomy/Adenoidectomy Alone

We reviewed nine studies that examined harms.[33-35,48,53,95-98] These included repeat TTs, otorrhea, perforation, and tympanosclerosis or myringosclerosis. The risk of tympanosclerosis was higher with TT than myringotomy or no surgery in addition to adenoidectomy (moderate strength of evidence). Results for other harms were either mixed, were reported in single studies, or were lacking precision (insufficient strength of evidence).

Adenoidectomy

Only two studies (three articles)[22,46,53] reported harms. In both studies, there was one report of a postoperative hemorrhage following adenoidectomy (low strength of evidence). Evidence was insufficient for other harms.

Oral or Topical Nasal Steroids

Evidence for harms of steroids comes from the systematic review and its update.[28,29] A meta-analysis of two RCTs in the updated review[29] comparing oral steroids plus antibiotics with control plus antibiotics reported no difference in mild to moderate adverse events at 2 weeks to 6 months. A second RCT[31,99] found no significant differences in mild adverse harms such as stinging nose, nose bleed, dry throat, or cough between those receiving nasal steroids and those receiving placebo control (low strength of evidence). Evidence concerning serious harms was sparse for either nasal or oral steroids (insufficient strength of evidence).

Autoinflation

None of the studies that compared autoinflation to control[17] provided quantitative information on rates of serious or mild harms, only verbal statements indicating there were few harms noted (insufficient strength of evidence).

Key Question 4. Comparative Effectiveness of Interventions for Subgroups of Patients

One of the explicit goals of this review was to examine treatment options for subgroups of patients including individuals defined by age groups and subpopulations at greater risk for OME such as individuals of American Indian, Alaskan, and Asian backgrounds and individuals with cleft palate, Down syndrome, and other craniofacial anomalies. Our search found very few studies of any subgroups that met our inclusion criteria. Two treatment comparisons examined comparative effectiveness of interventions for subgroups of patients—TT plus adenoidectomy versus myringotomy plus adenoidectomy/adenoidectomy alone and autoinflation.

Tubes Plus Adenoidectomy Versus Myringotomy Plus Adenoidectomy or Adenoidectomy Alone

One study[60] included children with sleep apnea and OME. The study did not find differences in hearing thresholds between children who received TT plus adenoidectomy and children who received myringotomy plus adenoidectomy (insufficient strength of evidence). Quality of life scores were measured in only one study (insufficient strength of evidence).

Autoinflation

One study[87] included in the systematic review of autoinflation[17] included adults 16 to 75 years of age. The autoinflation group was significantly more likely to experience a complete recovery than those in the control group at the end of treatment and 50 days later (low strength of evidence).

Key Question 5. Comparative Effectiveness by Health Care Factors

No included studies or systematic reviews examined effectiveness of intervention comparisons by any health care factors.

Discussion

Key Findings and Strength of Evidence

Key Question 1. Comparative Effectiveness: Clinical Outcomes or Health Care Utilization

Table A summarizes the strength of evidence for comparative effectiveness of treatments on clinical outcomes. We are able to draw some conclusions regarding surgical treatments.

We examined several design, placement, and material features of TTs. Longer acting TT such as Goode T-tubes and Paparella tubes were retained longer than shorter acting Shah and Shepard TTs; No other TT features were associated with clinical outcomes.

Compared with watchful waiting, TT decreased the number of children with MEE at 1 year after surgery (high strength of evidence); compared with myringotomy, TT decreased time with effusion at 1-year followup (moderate strength of evidence). TTs continued to improve MEE at 2-year followup (moderate strength of evidence), but the effect washed out thereafter. TT also improved hearing relative to watchful waiting or myringotomy, but the effect was shorter in duration, not lasting beyond 9 months after treatment (high strength of evidence). We found only limited evidence for drawing conclusions about the relative benefits of TT for other clinical outcomes such as OME recurrence or episodes of AOM.

We examined the evidence for whether TT or myringotomy differentially improved clinical outcomes when they were added to adenoidectomy. Based on finding no differences in hearing at any time point in five studies, we concluded that hearing outcomes do not differ (low strength of evidence); evidence was insufficient for all other clinical outcomes. However, TT plus adenoidectomy

Table A. Strength of evidence for interventions to improve clinical outcomes			
Intervention and Comparator	**Number of Studies (Sample Sizes)**	**Outcome and Results**	**Strength of Evidence**
TT vs. watchful waiting, delayed treatment, or myringotomy	MA of 3 RCTs (N=574)	TT had less persistent middle ear effusion at 1 year compared with watchful waiting or delayed treatment: 32% less time (95% CI, 17% to 48%).	High for benefit
	2 studies (N=294)	TT had less time with effusion through 1 year compared with myringotomy.	Moderate for benefit
	MA of 3 RCTs (N=426)	TT had less persistent middle ear effusion at 2 years compared with watchful waiting or myringotomy: 13% less time (95% CI, 8% to 17%).	Moderate for benefit
	MA of 3 RCTs (N=523) + 1 RCT (N=248)	TT had better measured hearing for up to 9 months than watchful waiting. MA results: -4.20dB (95% CI, -4.00 to -2.39).	High for benefit
	MA of 3 RCTs (by ears) (N=230)	TT had better measured hearing for up to 6 months than watchful waiting or myringotomy: -10.08 (95% CI, -19.12 to -1.05).	High for benefit
	MA of 3 RCTs (by ears) (N=234)	No difference between TT and watchful waiting or myringotomy in measured hearing at 7-12 months: -5.18dB (95% CI, -10.43 to 0.07).	Low for no difference
	MA of 2 RCTs (N=328); MA of 2 RCTs (N=283)	No difference between TT and watchful waiting in measured hearing at 12 months: -0.41dB (95% CI, -2.37 to 1.54) and 18 months -0.02 dB (95% CI, -3.22 to 3.18).	Low for no difference
TT + adenoidectomy vs. myringotomy + adenoidectomy	6 studies: 3 RCTs by person (N=431); 2 RCTs (by ears) (N=338); 1 NRCT (by ears) (N=193)	No difference in measured hearing between groups at 6 and 12 months and at more than 3 years.	Low for no difference
Adenoidectomy vs. no treatment	MA of 2 RCTs (by ears) (N=153); MA of 3 RCTs (by ears) (N=297)	Adenoidectomy had better OME resolution than no treatment at 6 months. The risk difference was 0.27 (95% CI, 0.13 to 0.42) measured through otoscopy and 0.22 (95% CI, 0.12 to 0.32) measured through tympanometry.	High for benefit
	MA of 3 RCTs (by ears) (N=298)	Adenoidectomy had better OME resolution than no treatment at 12 months. The risk difference was 0.29 (95% CI, 0.19 to 0.39).	High for benefit
Adenoidectomy + myringotomy vs. myringotomy	1 RCT (N=237)	Adenoidectomy and myringotomy had less mean time with effusion than myringotomy alone at 24 months: -0.76 standard mean difference (95% CI, -1.02 to -0.49).	Low for benefit
	1 RCT (N=237)	Adenoidectomy and myringotomy had better hearing than with myringotomy alone at 24 months measured as standard mean difference time with hearing level ≥ 20: worse ear: -0.65 (95% CI, -0.91 to -0.39); better ear: -0.66 (95% CI, -0.93 to -0.40).	Low for benefit
TT + adenoidectomy vs. WW	1 study (n = 250)	TT plus adenoidectomy improved hearing at 3 to 24 months.	Low for benefit
Oral steroids vs. controls	MA of 3 RCTs (N=106);	No difference in persisting OME at 1-2 months (no antibiotics provided in either group): OR=0.55 (95% CI, 0.21 to 1.48).	Low for no difference

Table A. Strength of evidence for interventions to improve clinical outcomes (continued)			
Intervention and Comparator	**Number of Studies (Sample Sizes)**	**Outcome and Results**	**Strength of Evidence**
Oral steroids + antibiotics vs. controls + antibiotics	MA of 3 RCTs (N=243)	No difference in persisting OME at 1-2 months (antibiotics provided to both groups): OR=0.75 (95% CI, 0.45 to 1.27).	Moderate for no difference
Topical intranasal steroids vs. controls	1 RCT (N=217)	No difference in OME cure rates at 1, 3, and 9 months.	Low for no difference
	1 RCT (N=217)	No difference in hearing loss at 3 and 9 months.	Low for no difference
Autoinflation vs. controls	MA of 2 RCTs (N=185)	Improvement in OME at <1month: RR=3.84 (tympanometry change C2 to C1 or A) and RR=2.72 (tympanometry change B to C1 or A).	Low for benefit

CI = confidence intervals; dB = decibels; MA = meta-analysis; NRCT = non-randomized controlled trial; N = number; OME= otitis media with effusion; OR = odds ratio; RCT = randomized controlled trial; RR = risk ratio; TT = tympanostomy tubes; vs. = versus

improved hearing at 3 to 24 months compared with watchful waiting (low strength of evidence). Adenoidectomy is superior to no treatment for improving the likelihood of OME resolution at 6 and 12 months after surgery (high strength of evidence). Adenoidectomy plus myringotomy was superior to myringotomy alone at 2 years after surgery for improving OME resolution and hearing (low strength of evidence). Evidence was insufficient for other outcomes. Evidence was also insufficient for comparisons between different approaches to myringotomy with and without adenoidectomy because of the limited number of studies.

We have reached some conclusions for nonsurgical interventions. Oral steroids do not offer any improvements in OME at 1 to 2 months after treatment (low strength of evidence). Similarly, oral steroids with antibiotics do not provide improvements in OME at 1 to 2 months (moderate strength of evidence). A recent study (low risk of bias) provided additional evidence that OME and hearing outcomes were not improved through the use of topical intranasal steroids through 9 months after treatment. These findings support the current clinical practice guidelines that recommend against the use of oral and intranasal steroids in treating OME in children. Although autoinflation improved MEE at less than 1 month after treatment (low strength of evidence), evidence was insufficient for reaching conclusions for other outcomes, largely because outcomes across studies testing autoinflation were not measured at consistent lengths of followup or through consistent measures.

Key Question 2. Health-Related Quality of Life and Functional Outcomes

Table B summarizes the strength of evidence for health-related quality of life and functional outcomes. We found only limited evidence regarding these outcomes. Language comprehension and language expression outcomes at 6 to 9 months were not significantly better among children with OME who received TT than among those who were limited to watchful waiting or delayed treatment (moderate strength of evidence). Results for cognitive development, behavioral competence, and academic achievement were similar; outcomes from TT versus watchful waiting or delayed treatment at various followup times did not differ (low strength of evidence). Evidence was insufficient to reach conclusions related to differences in either behavioral outcomes or quality of life for this treatment comparison.

Quality of life outcomes were measured in one small study comparing TT and adenoidectomy versus myringotomy and adenoidectomy, but we considered the evidence to be insufficient to reach conclusions. Topical steroids do not improve parent-reported hearing difficulties of their children at up to 9 months (low strength of evidence). However, evidence was insufficient to reach conclusions about other quality of life outcomes for oral steroids.

Key Question 3. Harms Associated With Interventions To Treat Otitis Media With Effusion

Table C summarizes the OME interventions on which we had low, moderate, or high strength of evidence about

Table B. Health-related quality of life and functional status			
Intervention and Comparator	**Number of Studies (Sample Sizes)**	**Outcome and Results**	**Strength of Evidence**
TT vs. watchful waiting or delayed treatment	MA of 3 RCTs (N=394) and 2 RCTs (N=503)	No difference in language comprehension at 6 to 9 months post-intervention (mean difference, 0.09; 95% CI, -0.21 to 0.39) or at preschool and elementary school age.	Moderate for no difference
	MA of 3 RCTs (N=393) and 2 RCTs (N=503)	No difference in language expression at 6 to 9 months post-intervention (mean difference, 0.03; 95% CI, -0.41 to 0.49) or at preschool and elementary school age.	
	2 RCTs (N=503)	No difference in cognitive development at 9 months post-intervention or at preschool and elementary school age.	Low for no difference
	3 RCTs (N=710)	No difference in behavior at 1 year or more.	Low for no difference
	2 RCTs (N=503)	No difference in academic achievement at elementary school age.	Low for no difference
Intranasal steroids vs. controls	1 study (N=144)	No difference in parent-reported hearing difficulties at 3 and 9 months or in median days with hearing loss at 3 months.	Low for no difference

N = number; NR = not reported; SR = systematic review; TT = tympanostomy tubes; vs. = versus

Table C. Strength of evidence for harms of interventions			
Intervention and Comparator	**Number of Studies (Sample Sizes)**	**Outcome and Results**	**Strength of Evidence**
TT vs. TT	1 RCT (N=30 ears); 2 observational studies (N=779 ears)	Otorrhea occurred more frequently in ears with longer-term TT than in ears with shorter-term TT after 1 year or more.	Moderate for harms of longer-term TT
TT vs. watchful waiting or myringotomy	5 studies (N=1,129)	Tympanosclerosis occurred more frequently in ears that had TT, based on examinations after the TT had been extruded.	Moderate for harms of TT
	4 studies (N=960)	Otorrhea occurred more frequently in ears with TT.	Low for harms of TT
TT plus adenoidectomy vs. adenoidectomy alone or with myringotomy	3 studies (N=485)	Tympanosclerosis occurred more frequently in ears with TT than ears with only adenoidectomy or myringotomy.	Moderate for harms of TT
Adenoidectomy vs. other treatments	2 studies (N=739)	Although rare, adenoidectomy increased the risk of postsurgical hemorrhage.	Low for harms of adenoidectomy
Oral nasal steroids vs. control	5 studies (N=637)	No difference in mild adverse events such as vomiting and diarrhea.	Low for no difference
Topical nasal steroids vs. control	2 studies (N=215)	No difference in mild adverse events such as nasal stinging, dry throat, and cough.	Low for no difference

N = number; NR = not reported; SR = systematic review; TT = tympanostomy tubes; vs. = versus

safety and harms. In relation to TT, we considered concerns such as otorrhea, tympanosclerosis, cholesteatoma, or surgical complications. In relation to steroid treatment, we considered problems such as diarrhea and nasal stinging.

Otorrhea was more common among ears with TT than those without (low strength of evidence), especially for those TT designed to stay in longer. Tympanosclerosis was more common in children who had TT than those who were actively monitored or who had myringotomy (low strength of evidence). Likewise, tympanosclerosis was more common when TT were added to adenoidectomy than for adenoidectomy alone or with myringotomy (moderate strength of evidence). Additionally, the risk of post-surgical hemorrhage, although rare, was associated with adenoidectomy, not any other comparison treatments.

We concluded that mild adverse events are not significantly higher with topical nasal steroids than with placebo (low strength of evidence). However, evidence was insufficient to reach conclusions related to oral steroids and serious adverse events from oral or topical steroids. Evidence was also insufficient concerning the surgical risks from the insertion of TT or those from myringotomy procedures with adenoidectomy.

KQ 4. Outcomes for Important Patient Subgroups

Table D provides the limited evidence we found for patient subgroups. Although we attempted to examine treatment effectiveness or harms for key subgroups characterized by clinical variables (e.g., cleft palate, Down syndrome, or sensorineural hearing loss) or sociodemographic factors (such as age), we could not identify studies that covered most of our subgroups of interest.

One study examined children with sleep apnea and OME, and one examined adults with OME. Among children with sleep apnea, all of whom had adenoidectomy to treat that condition, the addition of TT or myringotomy did not differ significantly in terms of any measured outcomes (insufficient strength of evidence). The study of autoinflation in one systematic review[17] found differences in rates of recovery between those receiving autoinflation and those who were in the control group. Individuals in the autoinflation group were significantly more likely to experience a complete recovery than those in the control group at both the end of treatment ($p<0.001$) and at 50 days after treatment ($p<0.001$). Similarly, the ears of the participants receiving autoinflation had better recovery rates than control ears at both time points ($p<0.001$). Strength of evidence was low for benefit.

Key Question 5. Health Care Factors

No studies examined issues related to health insurance coverage, physician specialty, type of facility of the provider, geographic location of patients, presence or absence of continuity of care, or prior use of pneumococcal virus inoculation. Evidence is thus insufficient for all such factors.

Applicability

This review was intended to apply to individuals with OME of all ages. Findings about all interventions are likely to be applicable to otherwise healthy children other than infants. In some cases, study authors did not provide sufficient information on age of the target population (e.g., provided only the average age without providing the age range) or included a wide age range of children, rendering it difficult to ascertain applicability of the tested intervention to specific age groups. The evidence base is clearly limited for adults and for infant children, and it is virtually nonexistent for children with major coexisting or congenital conditions, such as those with cleft palate, Down syndrome, and sensorineural hearing loss, who may be disproportionately affected by OME.

We provided evidence on all the commonly used treatments for OME, including TT, myringotomy, adenoidectomy and watchful waiting; we also examined outcomes from use of steroids upon the advice of our TEP, even though they are not recommended in current U.S. guidelines. We also provided evidence for autoinflation, an alternative noninvasive treatment strategy. We note the limitation in the evidence that not all studies comparing TT to other surgical or non-surgical treatments provided information regarding the type of TT used, limiting

Table D. Strength of evidence for subgroups

Intervention and Comparator	Number of Studies (Sample Sizes)	Outcome and Results	Strength of Evidence
Autoinflation vs. control	1 RCT (N=396 ears)	Adults (16–75) with OME: differences between groups in composite measure of recovery (otoscopy, tympanometry, audiometry) at end of tx and 50 days after tx.	Low for benefit (one study)

OME = otitis media with effusion; tx = treatment; RCT = randomized control trial

conclusions that can be made at this level of specificity. We also sought to include CAM procedures, but no RCTs met our inclusion criteria.

We did not limit the outcomes of interest. However, the bulk of the literature concerned reductions in OME and measured hearing. Only a few studies included quality-of-life outcomes, and none included satisfaction with care. Included studies were limited to head-to-head comparisons that collected a variety of harms, but they were not uniformly collected in all studies. We recognize that other study designs may have expanded our identification of possible harms. We did not limit the time frame for followup but were most interested in outcomes 3 months or more following treatment. Studies were conducted in clinical settings. They generally included populations from the United States and Western Europe, but a few studies were conducted in other countries including Egypt, Iran, and Japan.

Research Gaps

Research gaps in treatments for OME exist in several areas. We recommend the following for improving the research base.

The first area is to expand research in subgroups that were targeted in this review but for whom no evidence could be amassed. These groups include infants and toddlers who are developmentally vulnerable for language acquisition and for whom a mild conductive hearing loss over a shorter period of time may be more detrimental than for older children. Children with craniofacial anomalies such as cleft palate and other developmental disorders including Down syndrome and sensorineural hearing loss have not been a part of most treatment studies. When we did find studies on children with comorbid conditions, we excluded them for reasons such as having no valid comparison group (e.g., case series with no comparator) or data combined with children with acute AOM. Additionally, only limited research is available on treatment effectiveness in adults; we could identify only one study about treatments for adults.

The second area is to examine treatments that have heretofore not been subjected to rigorous research methods. For instance, despite the interest in CAM treatments, the lack of carefully designed investigations of these treatments is clear. While insertion of TT remains a common procedure, we have little evidence regarding different types of TT or routines for insertion. An ongoing Swedish trial plans to enroll a large cohort of children in an RCT comparing different TT; results from this trial may be able to provide the needed evidence regarding which TT are more (or less) beneficial. Some researchers are designing treatments to counteract the otological effects of gastroesophageal reflux disease; further research of promising treatments is welcome.

Methods deficiencies constitute a third gap. Measures are not uniform; investigators do not report on reoccurrence of AOM and functional outcomes; time points for collecting outcomes differ; and baseline measures are not always provided. Pain or discomfort resulting from OME was not measured in any studies. Studies do not routinely document effect sizes and many researchers fail to report their statistical power calculations of the sample size needed to find an effect (the RCTs of Williamson et al., the MRC, and Paradise et al. being notable exceptions). Missing data are often not addressed, and even if attrition is acknowledged, statistical procedures are rarely used to correct for this problem. We encourage investigators to give far more attention to their methods in the service of greatly improving the literature base.

Conclusions

Overall, we found a small and uneven body of evidence across treatment comparisons and outcomes. Compared with watchful waiting or myringotomy, we found strong and consistent evidence that TT decreased effusion and improved hearing over a short period but did not affect longer-term speech, language, or other functional outcomes. However, we found weaker evidence that TT placement also increases the rate of side effects such as otorrhea and tympanosclerosis. Although adenoidectomy decreases the number of children with OME in the short term relative to watchful waiting, less is known about its long-term effects particularly with respect to functional outcomes. Steroids were not found to provide a benefit. Additional research and better methods are needed to develop a comprehensive evidence base to support decisionmaking among the various treatment options, particularly in subpopulations defined by age and coexisting conditions.

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Full Report

This executive summary is part of the following document: Berkman ND, Wallace IF, Steiner MJ, Harrison M, Greenblatt AM, Lohr KN, Kimple A, Yuen A. Otitis Media With Effusion: Comparative Effectiveness of Treatments. Comparative Effectiveness Review No. 101. (Prepared by the RTI-UNC Evidence-based Practice Center under Contract No. 290-2007-10056-I.) AHRQ Publication No. 13-EHC091-EF. Rockville, MD: Agency for Healthcare Research and Quality. May 2013. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

AHRQ Pub. No. 13-EHC091-1-EF
May 2013

Hydrophilic Urinary Catheters

Plain Language Summary:

Urinary catheters drain urine when the bladder cannot empty on its own because of nerve damage or other disease or injury. Some catheters have a hydrophilic coating that becomes slippery in water.

Staff do not recommend covering hydrophilic catheters. Studies don't show these catheters work any better than normal catheters but cost more.

Staff Analysis Summary:

Staff propose 2 options for discussion:

1. Do not cover hydrophilic intermittent urinary catheters
2. Limit cover of hydrophilic catheters to situations where they do not cost more than another type of catheter

Changes after public comment period:

Nine public comments were received on this topic, all of which were in favor of covering hydrophilic intermittent urinary catheters. One was from an Oregon provider and several were from Oregon residents. The other comments were from individuals from advocacy groups or Coloplast. Multiple articles were submitted, but all of these articles were either included in the current or previous issue summaries or were previously excluded.

Most commentors cited the reduced risk of UTI with hydrophilic catheters compared to standard catheters which resulted in lower health care costs. Several commentors noted increased patient satisfaction with hydrophilic catheters. There were comments about hydrophilic catheters being more convenient as they do not have a separate lubricant package; however, patient convenience is not a coverage criteria under OHP.

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Based on the submitted comments and the testimony heard at the March VBBS meeting, HERC staff have added an option to allow coverage of hydrophilic catheters if they are the least costly option and are medically necessary and appropriate for the patient.

Coverage Question: Should hydrophilic intermittent urinary catheters be covered?

Question source: HERC staff; OHA DME division

Background:

People who cannot empty their bladders due to neurologic diseases such as multiple sclerosis, neurologic injury such as spinal cord injury, or obstruction such as benign prostatic hypertrophy develop chronic urinary retention. This increases the risk of urinary tract infection, kidney disease and bladder damage. Patients with these conditions are generally treated with either permanent urinary drainage devices such as suprapubic catheters or with intermittent catheterization. There are many types of catheters used for intermittent catheterization, including plain plastic, silicone coated, Teflon coated or hydrophilic.

Hydrophilic catheters have a polymer coating that binds to the surface of the catheter. When the polymer coating is submersed in water, it absorbs and binds the water to the catheter. The catheter surface becomes smooth and slippery. This slippery surface remains intact upon insertion into the urethra and maintains lubrication through the length of the urethra. The hydrophilic coating is designed to reduce the friction as the catheter is inserted with the intention of reducing the risk of urethral damage. These types of catheters due not require additional lubricant. Because of their coating, hydrophilic catheters must be discarded after each use (i.e. are not reusable). They are marketed as causing a lower risk of urinary tract infections.

Effective for the dates of service on or after January 1, 2026, CMS has created 3 new HCPCS codes for hydrophilic catheters

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A4295: Intermittent urinary catheter; straight tip, hydrophilic coating, each (CMS OR NR-$2.58)
A4296: Intermittent urinary catheter; coude (curved) tip, hydrophilic coating, each (CMS OR NR-$9.15)
A4297: Intermittent urinary catheter; hydrophilic coating, with insertion supplies (CMS OR NR-$9.99)

Before the creation of the new HCPCS codes, hydrophilic catheters were coded with HCPCS codes:

A4351: Intermittent urinary catheter; straight tip, with or without coating (teflon, silicone, silicone elastomer, or hydrophilic, etc.), each ($1.98 on OHP fee schedule 12/2025)

- As of 1/1/2026: Intermittent urinary catheter; straight tip, with or without coating (teflon, silicone, or silicone elastomer, etc.), each (CMS OR NR-$2.87)

A4352: Intermittent urinary catheter; coude (curved) tip, with or without coating (teflon, silicone, silicone elastomeric, or hydrophilic, etc.), each ($7.01 on OHP fee schedule 12/2025)

- As of 1/1/2026: Intermittent urinary catheter; coude (curved) tip, with or without coating (teflon, silicone, or silicone elastomeric, etc.), each (CMS OR NR-$9.15)

A4353: Intermittent urinary catheter, with insertion supplies ($7.65 on OHP fee schedule 12/2025) (CMS OR NR-$9.99)

Hydrophilic catheters typically cost $2.50-9.00 per catheter compared to non-hydrophilic catheters that cost approximately $1-1.50 each. Of note, Medicare has indicated that initially, both hydrophilic and non-hydrophilic catheter codes will receive the same reimbursement (based on current reimbursement level); however, Medicare has indicated that the reimbursement level of hydrophilic catheters will be part of their next review cycle. These catheters are typically allowed up to 200 units a month, making even small cost differences significant.

OHA DME policy staff as well as Washington Medicaid staff are interested in an evidence review of the effectiveness of hydrophilic catheters.

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Previous HSC/HERC reviews:

This topic was discussed at the January 2026 VBBS and HERC meetings as a new HCPCS code review. The evidence review included a Ontario Health Assessment review, a CMS review, and a review by the Healthcare Infection Control Practices Advisory Committee of the CDC. The HERC staff summary was "Trusted evidence review sources (Ontario Health Technology Assessment) did not find evidence that hydrophilic urinary catheters reduced infection risk. The CDC concluded that "hydrophilic catheters might be preferable" as a weak recommendation. The CDC review noted that only 2 studies found significant change in UTI risk including one of bladder cancer patients; all other studies found no difference in risk. CMS has found sufficient support for hydrophilic catheters improving health outcomes and have moved to create specific HCPCS billing codes for these types of catheters."

Several members requested that HERC staff contact providers regarding use of these types of catheters. Specifically, Duty requested that HERC staff confer with the bladder cancer group at OHSU to see if that high risk group might need hydrophilic catheters. Hoffman requested that staff contact the OHSU spina bifida center regarding use in high risk children.

This topic was again discussed at the March 2026 VBBS/HERC meetings. Testimony was heard from a variety of industry and specialty society representatives who all recommended coverage. There was insufficient time for member discussion and this topic was tabled.

Current Prioritized List/Coverage status:

Urinary retention, neurogenic bladder, and similar diagnoses are on line 324 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION

Urinary catheters are generally considered DME and are normally on the Ancillary file (covered for covered diagnoses).

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Submitted literature:

1) **Ye 2021** Catheters for intermittent catheterization: a systematic review and network meta-analysis
    a. N=25 RCTs comparing at least 2 types of catheters (6 trials of children, 18 trials with adults)
        i. SNC: single-use non-coated catheter—a single-use uncoated catheter. After removing it from sterile packaging, the user needs to add some lubricant before insertion;
        ii. GSNC: gel-lubricated single-use non-coated catheter —a single-use uncoated catheter with pre-packaged lubricant, which is ready to use;
        iii. SHC: single-use hydrophilic-coated catheter —a single-use catheter with a hydrophilic polymer coating. The user needs to add sterile water for about 30 s to active the hydrophilic polymer coating; (iv)
        iv. CNC: clean reused non-coated catheter —a reusable uncoated catheter, which is usually washed with soapy water and air-dried after each use, but the user needs to add some lubricant before use each time;
        v. PSHC: pre-activated single-use hydrophilic-coated catheter —a single-use catheter with a hydrophilic polymer coating which has been activated, and is ready-to-use.
    b. N=16 trials reporting incidence of symptomatic UTI (916 patients)
        i. When SNC was used as the reference, only GSNC (OR 0.30, 95% CI 0.10–0.86) and PSHC (OR 0.41, 95% CI 0.19–0.83) were associated with a statistically significant lower incidence of symptomatic UTI
    c. N=8 trials reporting on hematuria
        i. No significant difference between catheter types
    d. N=9 trials reporting on patient satisfaction
        i. None of the catheters exhibited significant advantages compared with SNC
2) **Liao 2022** Effects of hydrophilic coated catheters on urethral trauma, microtrauma and adverse events with intermittent catheterization in patients with bladder dysfunction: a systematic review and meta-analysis

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a. N=5 studies reporting on urethral stricture
    i. Diagnosis was made by endoscopic or radiographic examination, not be patient symptoms or other patient specific outcome
b. The incidence of urethral stricture was 3.1% (6/194) in patients using hydrophilic catheters and 11.5% (23/200) in patients using non-hydrophilic catheters (RR=0.28; 95% CI 0.13–0.60)

Expert input:

The OHSU group that treats bladder cancer patients uses standard urinary catheters.

Drs. Casey Seideman and Christopher Austin from OHSU pediatric urology strongly feel that hydrophilic catheters remain an option for certain pediatric patients.

From Dr. Austin:

> We do have a lot of patients who use hydrophilic catheters currently, many of which are covered by OHP. We prescribe hydrophilic catheters to patients, especially girls who catheterize themselves to make the process quicker and simpler for them (If you think about having to catheterize yourself 5-6 times a day for the rest of your life- you would agree that making it quicker and more convenient is not a luxury). Catheter manufactures have made catheters smaller and more discrete, especially for females. Having to carry packets or large tubes of lubricant is an added barrier to getting kids to comply with treatment recommendations. We also have some patients with challenging anatomy or discomfort with catheterizing that is safer or more comfortable when they use hydrophilic catheters. None of this will be reflected in published evidence. I would urge that you consider some exceptions to cover them. I would be happy to have some of my faculty and staff work with your committee in drafting what the exceptions should be. It is a great burden on me and my partners to be constantly writing letters requesting exceptions and filling out prior authorization paperwork for our patients that we are dedicated to caring for. I fear that this change will cause a great deal of distress for our many patients that use these products and my staff who care for them.

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HERC staff summary:

HERC staff conclude that the available evidence does not find that hydrophilic catheters are superior to other types of catheters for any health outcome for any condition. Expert local groups are not routinely using these catheters for patients undergoing treatment for bladder cancer but pediatric urologists recommended coverage for children without providing literature or other evidence. HERC staff were directed to consider drafting an Ancillary guideline outlining specific groups that might benefit more from coverage; however, based on expert input and submitted comments, HERC staff have been unable to determine which group(s) would benefit more from these catheters and therefore staff are not proposing a guideline at this time. Coverage for specific patients can be evaluated through the exceptions process. Based on the likely future higher cost for these catheters, HERC staff continue to recommend placing the new HCPCS codes on Excluded Services Guideline E1. Alternatively, limited coverage could be considered by placing the new HCPCS codes on the Ancillary file with a new Ancillary guideline limiting coverage to the situation in which these catheters are not most costly than other options.

HERC staff recommendation:

1) Option 1:
    a. Add an entry to Excluded Services Guideline E1 regarding hydrophilic catheters as shown below

EXCLUDED SERVICES GUIDELINE E1, INTERVENTIONS WITH MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS FOR CERTAIN CONDITIONS

The following interventions result in marginal clinical benefit or have low cost-effectiveness and should be excluded from coverage:

Procedure Code	Intervention Description	Rationale	Last Review
A4295-A4297	Intermittent urinary catheter; hydrophilic coating	More costly than equally effective alternatives	March 2026

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Option 2:

1) Advise Medicaid to add HCPCS A4295-A4297(Intermittent urinary catheter; hydrophilic coating) to the Ancillary file

2) Add a new Ancillary services guidelines as shown below

ANCILLARY GUIDELINE AX: INTERMITTENT URINARY CATHETERS

Hydrophilic intermittent urinary catheters (HCPCS A4295-A4297) may be covered as an alternative to non-hydrophilic catheters (HCPCA A4291-A4293) if they are no more costly than non-hydrophilic catheters.

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Public Comment Disposition: [Hydrophilic Urinary Catheters]

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Discussion Table

IDs/#s	Summary of Issue	HERC Staff Response
A, B, C, D, E1, F, G, H	Hydrophilic catheters result in superior clinical outcomes, including reduced urinary tract infections (UTIs) and urethral trauma as compared with standard catheters.	The evidence reviewed to date, including articles submitted by commentors, does not show a statistically significant reduction in UTI risk with use of hydrophilic catheters compared to other types of catheters.
E2, I1	There should be continuity of care that allows coverage for hydrophilic catheters for those currently using them using the new HCPCS codes. Non continuation of coverage represents a	Prior to 2026, there was no way to differentiate types of intermittent catheters based on coding. The lack of distinct billing codes also resulted in no difference in cost between catheter types. The new HCPCS codes effective in 2026 allow for distinguishing the type of catheter used. It is anticipated that CMS will give the new codes for hydrophilic catheters a higher reimbursement rate than the

IDs/#s	Summary of Issue	HERC Staff Response
	substantial reduction in Medicaid benefits that is not allowed.	older codes for non-hydrophilic catheters. The HERC review found no differences in outcomes between hydrophilic and non-hydrophilic catheters. With the expected increase in cost for the hydrophilic catheters, these catheters are no longer the least costly alternative. OHP allows a limited coverage of a non-covered DME item until a patient can transition to a covered item.
I2	Hydrophilic catheters result in reduced costs from complications such as UTIs when compared with standard catheters.	The evidence reviewed to date, including articles submitted by commentors, does not show a statistically significant reduction in UTI risk with use of hydrophilic catheters compared to other types of catheters. The economic modeling studies used a reduction in UTI risk to model cost savings; if there is no reduction in UTI risk then these models are not accurate.
A, B, G	Patients find hydrophilic catheters to be more convenient or comfortable.	Services provided solely for the convenience of the member are not medically necessary under OHP.
I	Hydrophilic catheters could be offered by OHA at the same cost as other catheters.	Staff have created a separate option to cover hydrophilic catheters if they are the least costly option for the health plan. This option would maintain access to hydrophilic catheters if costs remain comparable to other catheters.

Commenters

Identification	Commenter
A	Ann Marie Alfrey, (Area Agency on Aging for Jackson and Josephine Counties) [Submitted April 6, 2026]
B	Ian Ruder, (listed no affiliation but cited employment from NewMobility.com and used a United Spinal Association email address) [Submitted April 13, 2026]
C	Jeanine Gleba obo Cheryl Ory, (United Ostomy Associations of America) [Submitted April 13, 2026]
D	Katie Ciancetta, (Oregon resident) [Submitted April 13, 2026]
E	Matt Castelluccio, (United Spinal Association) [Submitted April 16, 2026]
F	West Livaudais, (Executive Director of Oregon Spinal Cord Injury Connection) [Submitted April 13, 2026]
G	Kelsey Box, (submitted on Coloplast letterhead) [Submitted April 15, 2026]
H	Micki Kleven, (OHP provider) [Submitted April 16, 2026]
I	Laura Williard, (American Association for Homecare) [Submitted April 16, 2026]

Public Comments

ID/#	Comment	Disposition
A	Self-lubricated catheters are not the same as standard ones. Dropping Medicaid coverage for self-lubricated catheters will cause a definite and substantial reduction in quality of life and comfort for people with disabilities. The staff report does not adequately address the difference in these products. Self-lubricated catheters (often called hydrophilic or pre-lubricated catheters) are designed to make intermittent catheterization easier, safer, and more comfortable. Here are the main benefits:	Thank you for your comments. The HERC values patient input and experience. Unfortunately, patient or caregiver convenience cannot be taken into consideration for OHP coverage. There are self-lubricated catheters that are not hydrophilic. For example, there are catheters

ID/#	Comment	Disposition
	1. Greater Comfort The catheter is already coated or becomes slick when activated (often with water), reducing friction. This makes insertion and removal smoother and less painful compared to dry or manually lubricated catheters. 2. Reduced Risk of Injury Lower friction means less irritation to the urethra. Helps prevent micro-tears, which can otherwise lead to discomfort or complications over time. 3. Lower Risk of Urinary Tract Infections (UTIs) Many are designed for single use and come sterile. The smooth surface reduces the chance of bacteria sticking and entering the urinary tract. 4. Easier and More Convenient to Use No need to carry separate lubricant. Often come in ready-to-use packaging, making them more discreet and quicker to use—especially helpful when away from home. 5. More Consistent Performance Pre-lubrication ensures even coating every time, unlike manual lubrication which can be uneven. 6. Better for Frequent Use Particularly beneficial for people who need to catheterize multiple times a day, as they minimize cumulative irritation. When they're especially helpful: People with sensitive urethras Long-term catheter users Individuals with limited hand dexterity (simpler prep)	that are self-lubricated with silicon oil. These types of self-lubricating non-hydrophilic catheters will continue to be covered with the original HCPCS codes for OHP patients. Most types of intermittent urinary catheters are designed for single use and come in sterile packaging. Thank you for submitting literature for our review. • The first reference you provided was for an older 2006 Ontario Health Technology Assessment. The updated 2019 OHTA report was included in the January meeting materials. • Stensballe 2005 was an RCT included in Ye 2021 which was included in the March meeting materials. •Liao 2022 was included in the March meeting materials •the last reference did not include enough information to identify the article

ID/#	Comment	Disposition
B	I live in Portland, Oregon and have used a power wheelchair for the past 28 years after being paralyzed in a motor vehicle accident. I currently work full-time from home as the editor of New Mobility, the longest running magazine and website (newmobility.com) for active wheelchair users. Working in this position for the past 15 years has given me a unique perspective on the importance of having access to needed medical equipment and how being denied access to that equipment directly translates to often catastrophic health problems. You will receive plenty of eloquent emails and testimony about how hydrophilic catheters have been proven to reduce UTIs and the ER visits and hospitalizations that follow, so instead of repeating the same statistics, I want to share an experience that I hope will show why maintaining access to hydrophilic catheters is necessary. I recently had the chance to interview some of the designers of one of the leading hydrophilic catheters and ask them the very questions I imagine you are asking yourselves: are hydrophilic catheters worth the extra cost? Are hydrophilic catheters luxury or needed items? They showed me footage from inside multiple bladders as users tried regular catheters and hydrophilic catheters. On the video you could see the tiny droplets of blood created as the non-hydrophilic catheter went into the bladder to drain it. Even with ample lubrication, each user had some visible damage. Now imagine doing this to yourself 4-10 times a day. You are basically tearing yourself apart just to urinate. In addition to raising your chances of infection and other complications, you are inflicting great physical pain onto your body. I personally have no sensation, but many users do, and I've heard from countless friends that the cumulative discomfort can be unbearable. In the videos of the hydrophilic	Thank you for sharing perspective on this issue. We will share your comments with VbBS and HERC.

ID/#	Comment	Disposition
	catheters, the insertion was noticeably smoother thanks to the hydrophilic coating. I couldn't see any blood droplets. The bladder drained quickly and easily. My friends who rely on hydrophilic catheters say the process feels better and leads to better results in draining the bladder.*I came away convinced that not only are hydrophilic catheters needed, but they should become the standard for all catheter users. Instead of asking 'Is this worth the added cost?' or 'Is this needed?', we should be asking, 'Is it humane to not cover these?' Like I said before, ask yourself if you'd be willing to rip your urethral walls multiple times a day knowing there is a safer, healthier alternative? No one should have to endure this, and to deny Oregonians the option merely to save a few dollars is the modern day equivalent of advocating for bloodletting or using leeches despite the availability of all the superior and more proven options. I know you are faced with difficult spending decisions, but please — for the sake of all of us who depend on catheters, and the thousands of Oregonians who will in the future — do not cut coverage to hydrophilic catheters. Help us stay healthy, Ian Ruder *I do not use a hydrophilic catheter because I have an indwelling catheter and no major designer has released an indwelling hydrophilic catheter yet – in part because they fear insurance won't cover them. If one was available, I would switch instantly.	
C	Dear Oregon Medicaid Value-based Benefits Subcommittee:	Thank you for your comments. The HCPCS codes available before 2026 did not allow determination of the type of catheter being

ID/#	Comment	Disposition
	United Ostomy Associations of America, Inc. (UOAA) is a 501(c)(3) national nonprofit organization that supports, empowers, and advocates for people who have had or will have ostomy or continent diversion surgery. We have over 285 affiliated support groups across the United States with six (6) in the state of Oregon. There are between 725,000 to one million Americans living with an ostomy or continent diversion, and over 100,000 new life-saving ostomy surgeries occur in America yearly. As the voice and leading organization advocating for people living with an ostomy, we know first-hand how important access to ostomy and urological supplies are for this patient population. Many individuals in our community depend on both ostomy supplies and catheters to manage their health and daily bodily functions. On behalf of UOAA, our organization has serious concerns with Oregon Medicaid's proposal to remove coverage for hydrophilic intermittent catheters. Intermittent catheters (ICs) are covered by Medicare under the "prosthetic devices" benefit category which "replace all or part of an internal body organ". In 2024 the Centers for Medicare and Medicaid Services (CMS) made a decision to modify existing HCPCS codes and create three new codes (A4295, A4296 and A4297) to distinguish hydrophilic coating technology within the intermittent catheter product category. This decision recognizes the clinical benefits of hydrophilic coating technology and was also made to improve coding accuracy. These new codes went into effect in January 2026. Thirty-four state Medicaid plans have already implemented the new hydrophilic HCPCS codes, and all others are working on the finalization. UOAA has learned that Oregon Medicaid has decided that coverage is not medically necessary for A4295 A4296, and for A4297 and will not cover these	purchased. The new codes now allow identification of the hydrophilic catheters, which are not as cost-effective as non-hydrophilic catheters. OHP patients will continue to have access to medically necessary less expensive intermittent catheter supplies. The reviewed evidence did not find a significant reduction in infection, stricture or other outcomes with hydrophilic catheters. Staff have added an option for coverage of hydrophilic urinary catheters when they are equivalent in cost.

ID/#	Comment	Disposition
	products. Oregon Medicaid is the only state that is withdrawing coverage for hydrophilic intermittent catheters. We believe this must be a simple misunderstanding since prior to this coding update, Oregon Medicaid actually covered hydrophilic-coated catheters under HCPCS codes A4351, A4352, or A4353 (legacy codes- now used for non-hydrophilic catheter billing). It is critical that individuals who were using hydrophilic catheters previously continue to have access to their medically prescribed prosthetics as well as new patients going forward. Hydrophilic catheters are specifically designed to reduce friction during insertion and removal. The lubricated coating helps minimize trauma to the urethra, which lowers the risk of microtears, bleeding, and long-term urethral damage. Without access to these, individuals may be forced to use less advanced or reused catheters, increasing the likelihood of complications such as strictures or chronic irritation. For people who catheterize multiple times per day, even a small increase in infection risk can quickly escalate into recurrent UTIs, kidney infections, or even sepsis—conditions that are not only dangerous but also costly to treat. Our organization respectfully requests that HCPCS codes A4295, A4296, and A4297 be included in Oregon Medicaid coverage. Thank you for the opportunity to provide these comments and your consideration of our concerns to ensure access to these supplies.	
D	Dear Health Evidence Review Commission, Thank you for receiving my comments on Medicare's decision to no longer provide hydrophilic catheters. Seven years ago I survived a spinal cord injury. Many people who live with spinal cord injuries have	Thank you for your comments and sharing your personal experience. HERC is grateful for the input of those affected by issues under review. Your comments will be made available to members for review. The current review is

ID/#	Comment	Disposition
	neurogenic bladders, meaning the bladder cannot empty normally because the muscles controlling the bladder sphincter are paralyzed. Not emptying the bladder frequently using a catheter often results in bladder spasms and urinary tract infections (UTI). For the first four years of my injury I emptied my bladder using regular catheters and a separate packet of lubrication to ensure the catheter enters and exits the urethra without causing abrasians. The problem with using catheters that are not pre-lubricated, is that it opens the body to more bacteria and more frequent UTIs. It's incredibly difficult to handle separate packets of materials in a bathroom, and then insert the catheter into the bladder without introducing bacteria to a part of the body that is very sensitive to bacteria. During this four years of intermittent catheterization I lost count of how many UTIs I had and how often I needed to take antibiotics to clear the infection. It is quite common for people with SCIs to become antibiotic resistant because UTIs are so common. My urologist suggested I begin using hydrophilic catheters, which are pre-lubricated. This means only handling one package, and many of these catheters have a small device that the user can hold onto while inserting, so that virtually zero bacteria is introduced to the urinary tract. Since I switched to hydrophilic catheters, I have had zero UTIs. I went from having a UTI about every 2 months to never having a UTI again, purely because of the types of catheters I use. Since many people with SCIs become antibiotic resistant, it is quite common to be hospitalized with severe bladder infections. I am fortunate in that my infections were	focused only on Oregon Health Plan, Oregon's version of Medicaid, rather than Medicare (the federal program for older and disabled Americans). Thank you for the Ali 2024 reference. This study is a comparative cohort study. As RCT evidence is available, this was considered a lower quality of evidence based on the study design and therefore excluded from the coverage review. Thank you for your comments and sharing your personal experience. HERC is grateful for the input of those affected by issues under review. Your comments will be made available to members for review.

ID/#	Comment	Disposition
	never that severe. Because I no longer get UTIs, due to using hydrophilic catheters, I am able to maintain a part time job and run errands for my family. During my time of having frequent UTIs, I often did not leave the house at all, because UTIs often cause bladder spasms and heavy incontinence. For three years we had to wash my wheelchair cushion nearly daily, because even wearing Depends did not prevent urine from leaking everywhere. Living with a spinal cord injury is incredibly difficult, and hydrophilic catheters is one thing that makes life a little easier. My days of staying at home due to UTIs and incontinence left me incredibly depressed and almost unable to take care of myself, much less my family. If a urologist has prescribed hydrophilic catheters to a patient, it is due to the urologist's knowledge and experience with how to prevent infection. Please allow these doctors to help us remain healthy. Thank you, Katie Ciancetta Salem, Oregon	
E1	Dear Members of the Value-based Benefits Subcommittee, I am not a clinician, nor a policy maker, but as Interim CEO of the United Spinal Association I have the personal lived experience of over 20 years of catheterizations and that of the countless shared life experiences of	Thank you for your comments and sharing your personal experience. HERC is grateful for the input of those affected by issues under review. The reviewed evidence did not find a significant reduction in infection, stricture or other

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	our community members, many of whom are Oregon residents, to tell you: • Hydrophilic urological intermittent catheters absolutely can reduce urinary tract infections. • Hydrophilic urological intermittent catheters save healthcare costs. By taking away the coverage of hydrophilic catheters that people have depended upon for years, you are endangering lives. It took me twenty years to find a catheter that helps reduce UTIs. I struggled with many products until I found a closed hydrophilic-coated system that gave me safe independence with cathing. My journey is far, far from unique. Please gather more information before someone suffers a UTI that can lead not only to life threatening medical complications but can result in people dying. You simply must not to turn the clock back on individuals' health and innovation that provide significantly better healthcare outcomes. The cost savings achieved through preventive healthcare, saves precious dollars as well as lives.	outcomes with hydrophilic catheters. Your comments will be made available to members for review.
E2	As you will recall, the United Spinal Association previously commented on the critical need for coverage of hydrophilic catheters. To reiterate, the current access issue arises in the context of a CMS coding update that took effect on January 1, 2026. CMS established new HCPCS codes—A4295, A4296, and A4297—to clearly differentiate hydrophilic-coated intermittent catheters from non-hydrophilic products. These	Thank you for your comments. Under Oregon Administrative Rules (OAR 410-122-0080), OHP can only cover "...the least costly, medically appropriate item that meets the medical needs of the client." The HCPCS

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	codes were created to improve coding accuracy and reflect established clinical distinctions. They did not signal a change in clinical evidence, medical necessity, or standard of care. Prior to this coding update, Oregon Medicaid covered hydrophilic-coated catheters when they were billed under HCPCS codes A4351, A4352, or A4353. As a result, individuals who had been stable and successful using hydrophilic catheters are now set to lose access solely because the products they use are billed under new codes that are not yet covered. From the patient perspective, this represents an administrative disruption rather than a clinically justified change. United Spinal respectfully urges Oregon Medicaid to reassess its current policy and align coverage with the updated CMS HCPCS structure by adding A4295, A4296, and A4297 to the state Medicaid fee schedule with appropriate reimbursement. Implementation of the hydrophilic HCPCS codes at the same rate as the existing non-hydrophilic HCPCS codes (A4351, A4352 and A4353) will not add additional cost to the state of Oregon. Additionally, this will retain coverage for hydrophilic-coated intermittent catheters protect continuity of care, support clinician-directed treatment decisions, and help prevent avoidable medical complications for individuals living with spinal cord injury and disorder. Thank you for your attention to this issue and for your continued service to Oregon Medicaid beneficiaries. Again, we welcome the opportunity to provide additional information, clinical perspectives, or patient input to support this review.	codes available before 2026 did not allow determination of the type of catheter being purchased. The new codes now allow identification of the hydrophilic catheters, which are not as cost-effective as non-hydrophilic catheters. Staff have added an option for coverage of hydrophilic urinary catheters when they are equivalent in cost.

ID/#	Comment	Disposition
	Sincerely, M. J. Castelluccio Matt Castelluccio Interim CEO United Spinal Association	
F	April 16, 2026 Dear Members of the Oregon Health Authority and Oregon Medicaid Program, My name is West Livaudais and I live in Portland, OR. Thank you for the opportunity to share my experience and why coverage of hydrophilic intermittent catheters is important for patients like me. I live with spinal cord injury and have a neurogenic bladder, which means I must use intermittent catheters 5-6 times every day to empty my bladder. Catheterization is not optional for me—it is a necessary medical treatment that allows me to stay healthy and avoid serious complications like UTIs. I currently use hydrophilic catheters, which are designed with a coating that becomes slippery when activated with water. These catheters are different from non-hydrophilic catheters because coating prevents micro-abrasions on my urethra that standard catheters cause. These abrasions make me more susceptible to UTIs.	HERC appreciates you sharing your personal experience as it values input from those affected by issues under review. Your comments will be available to members.

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	Two years ago, I transitioned to hydrophilic catheters and immediately I stopped having UTIs every 60-90 days. It reduced my use of the ED. In the previous 5 years, I had used the ED 3 times and been hospitalized once for severe UTIs. They have reduced my need for antibiotics due to UTIs to almost zero. For patients like me, small differences in catheter design can make a big difference in health outcomes. With hydrophilic catheters, I have experienced: Fewer urinary tract infections Less irritation Fewer antibiotics due to UTIs Fewer ED and urgent care visits due to UTIs More consistent bladder management resulting in less incontinence When catheterization is more difficult or painful, patients may delay or avoid it, which can lead to serious complications such as infections, kidney damage, or hospital visits. This decision affects Medicaid beneficiaries directly and will affect whether we can access the products that work best for our medical needs. If hydrophilic catheters were not covered, it would mean a return to UTIs, antibiotics, ED visits - HIGHER COSTS for MEDICAID.	

ID/#	Comment	Disposition
	Ensuring coverage helps patients like me: Stay healthy Avoid infections and complications Remain independent Prevent more costly medical care in the future Hydrophilic catheters are not a convenience item—they are an important medical tool that helps people with bladder conditions manage their health safely and effectively. I respectfully ask Oregon Medicaid to continue to provide coverage for hydrophilic intermittent catheters so that patients like me can maintain our health, independence, and quality of life. Thank you for considering my experience and for the work you do to support patients in Oregon. Sincerely, West Livaudais, MPH Founder/Executive Director of Oregon Spinal Cord Injury Connection Portland, Oregon	
G	Dear Members of the Oregon Health Authority and Oregon Medicaid Program,	HERC appreciates you sharing your personal experience as it values input from those affected by issues under review. Your comments will be available to members.

ID/#	Comment	Disposition
	My name is Kelsey Box, and I live in Klamath Falls. Thank you for the opportunity to share my experience and why coverage of hydrophilic intermittent catheters is important for patients like me. I live with a spinal cord injury, which means I must use intermittent catheters 5-6 times every day to empty my bladder. Catheterization is not optional for me—it is a necessary medical treatment that allows me to stay healthy and avoid serious complications. I currently use hydrophilic catheters, which are coated to become slippery when activated by water. For me, these catheters: • They are easier and more comfortable to insert • Reduces friction or pain • I can catheterize independently, discreetly, and outside the home Using hydrophilic catheters allows me to, most importantly, live a healthy life and without more barriers than there already is. When I have had to use standard/non-hydrophilic catheters, my experience has been very different. For example: • Damage to the urethra. • More infections	

ID/#	Comment	Disposition
	• Hygiene is a challenge and very inconvenient when lubrication is required Compared with hydrophilic catheters, non-hydrophilic catheters make catheterization more painful, more difficult and harder to perform outside the home. For patients like me, small differences in catheter design can make a big difference in health outcomes. With hydrophilic catheters, I have experienced: • Fewer urinary tract infections. • Less irritation or trauma • More consistent catheterization and bladder management When catheterization is more difficult or painful, patients may delay or avoid it, which can lead to serious complications such as infections, kidney damage, or hospital visits. As a Medicaid beneficiary, coverage decisions directly affect whether I can access the products that work best for my medical needs. If hydrophilic catheters were not covered, it would mean financial burden, forced to switch to products that cause complications and loss of independence. Ensuring coverage helps patients like me: • Stay healthy • Avoid infections and complications	

ID/#	Comment	Disposition
	• Remain independent • Prevent more costly medical care in the future Hydrophilic catheters are not a convenience item—they are an important medical tool that helps people with bladder conditions manage their health safely and effectively. I respectfully ask Oregon Medicaid to continue to provide coverage for hydrophilic intermittent catheters so that patients like me can maintain our health, independence, and quality of life. Thank you for considering my experience and for the work you do to support patients in Oregon. Sincerely, Kelsey Box Klamath Falls, Oregon	
H	Dear Members of the Oregon Health Authority and Medicaid Program, My name is Micki Kleven and I am an Occupational Therapist working with individuals with spinal cord injuries in the state of Oregon. I am writing on behalf of my patients, as well as my partner who is a C4-C5 incomplete quadriplegic, and all of our dear friends who we have met through the spinal cord injury community regarding the proposal to no longer fund hydrophilic intermittent catheters. These individuals living with spinal cord injury live with a secondary condition called neurogenic bladder that requires the use of	Thank you for sharing your personal and professional perspectives on this issue. Thank you for submitting literature for our review. • de Ridder 2005 was an RCT included in Ye 2021 which was in the March meeting materials • Vapnek 2003 was an RCT included in Ye 2021 which was in the March meeting materials

ID/#	Comment	Disposition
	catheterization to empty the bladder. These catheters must be used each time they use the restroom in order to safely evacuate the bladder fully and prevent urinary tract infections, which often lead to hospitalizations and more life-threatening conditions such as autonomic dysreflexia or sepsis. Hydrophilic intermittent catheters have been shown to decrease the risk of UTIs in individuals with spinal cord injury as cited in this research article by Ridder, et al., this research article by Vapnek, et al., this research article by Cardenas, et al., and many more. Decreased rates of UTIs means less Oregon Medicaid money going to ER or Urgent Care visits, antibiotics, caregivers, and hospitalizations. It means fewer individuals with spinal cord injuries out of the workforce while they treat UTI symptoms, and fewer individuals with spinal cord injuries dying from preventable causes. So, while cutting funding for hydrophilic catheters may seem like a good plan to save Medicaid dollars, it is short-sighted, and would ultimately lead to an increase in overall Medicaid spending to remedy the detrimental long-term effects this decision would have on Oregon Medicaid beneficiaries. I have personally witnessed the damage that uncontrolled UTIs can cause, as I recently lost a dear friend in December to a stroke that was brought on by autonomic dysreflexia. This bout of autonomic dysreflexia was brought on by a kidney infection that began as a UTI and traveled to	• Cardenas 2011 was an RCT included in Ye 2021 which was in the March meeting materials Staff have added an option for coverage of hydrophilic urinary catheters when they are equivalent in cost.

ID/#	Comment	Disposition
	his kidneys, ultimately killing him. He would have celebrated his 40th birthday this summer. Lack of access to appropriate equipment is, quite literally, life threatening to individuals with a spinal cord injury. For this reason, I respectfully ask that you continue covering hydrophilic intermittent catheters for your beneficiaries. I do not want to lose any further patients, friends, or my partner to something as preventable as a UTI because of lack of access. Thank you for considering my professional expertise, as well as my personal experiences on this matter. Thank you for your support of Oregon Medicaid beneficiaries and the hard work that you do. Sincerely, Micki Kleven, OTD, OTR/L, ATP/SMS Assistant Professor of Occupational Therapy Academic Fieldwork Coordinator	
I1	Federal Continuity of Pricing Requirements Federal Medicare payment policy regulates establishment of payment amounts for new HCPCS codes to maintain access when HCPCS coding changes occur. Federal regulations require continuity of pricing when the Centers for Medicare and Medicaid Services (CMS) establishes a new HCPCS code for an item that was previously included in a different HCPCS code. Under these regulations, the new HCPCS	Thank you for your comments. Under Oregon Administrative Rules (OAR 410-122-0080), OHP can only cover "...the least costly, medically appropriate item that meets the medical needs of the client." The HCPCS codes available before 2026 did not allow determination of the type of catheter being purchased. The new codes now allow identification of the hydrophilic catheters,

ID/#	Comment	Disposition
	code's Medicare payment amount is established at the same payment rate as the previous HCPCS code.[1] This framework reflects a clear federal policy principle: coding changes must not result in disruption of beneficiary access to medically necessary items. Accordingly, new hydrophilic catheter HCPCS codes are established and the item was previously included in another HCPCS code with an established payment amount, Medicare rules require the payment amount for the new HCPCS code to be the same as when the item was included in a different HCPCS code. Oregon Medicaid should follow the same principle by establishing payment rates for the A4295, A4296 and A4297 at the same rates, respectively, as A4351, A4352, and A4353. Oregon Medicaid previously covered and paid for hydrophilic intermittent catheters when they were included in A4351, A4352 and A4353; it should now cover and pay for these same items under their new HCPCS codes, A4295, A4296 and A4297. CMS approved State Plan Amendment (SPA) #24-0020 the rates for durable medical equipment and supplies are based on 80% of the 2024 Medicare fee schedule unless the 2012 rate is higher, in which case the rate will be frozen. Unless Oregon Health Authority submits a new SPA, the rates would be frozen at the current established fee schedules. The following chart summarizes the HCPCS codes changes as of January 1, 2026, and identifies Medicare's continuity of payment regulations as applied to the new HCPCS codes that include hydrophilic intermittent catheters.	which are not as cost-effective as non-hydrophilic catheters. HERC does not create fee schedules for the Oregon Health Plan. Staff have added an additional option so that hydrophilic catheters could be covered if equivalent in cost.

ID/#	Comment			Disposition
	Prior to 1/1/26	**New and Revised HCPCS Codes (effective 1/1/26)**	**2026 Medicare Payment Amount**	
	A4351	A4351 – non-hydrophilic (Intermittent urinary catheter; straight tip, with or without coating (Teflon, silicone, or silicone elastomer, etc.) each)	$2.58	
		A4295 – hydrophilic – (Intermittent urinary catheter; straight tip, hydrophilic coating, each)	$2.58	
	A4352	A4352 – non-hydrophilic (Intermittent urinary catheter; coude (curved) tip, withot without coating (Teflon, silicone, or silicone elastomeric, etc.) each)	$9.15	
		A4296 – hydrophilic (Intermittent urinary catheter; coude (curved) tip, hydrophilic coating each)	$9.15	
	A4353	A4353 – non-hydrophilic (Intermittent urinary catheter, with insertion supplies)	$9.99	

ID/#	Comment	Disposition

	A4297 – hydrophilic (Intermittent urinary catheter; hydrophilic coating, with insertion supplies)	$9.99

Federal Medicaid Due Process Requirements

Federal Medicaid regulations establish clear protections when coverage for a currently provided item is reduced or terminated. Under 42 C.F.R. § 431.201, an "action" includes the termination, suspension, or reduction of Medicaid services.[3] Any policy change that results in a previously covered catheter becoming non-covered constitutes a termination of service. By eliminating coverage for hydrophilic intermittent catheters when that coverage was previously available to Medicaid recipients, Oregon Medicaid is clearly reducing available Medicaid services. In these instances, federal regulations require the state to comply with due process procedures to provide some protections to the affected populations.

Therefore, if Oregon Medicaid continues with its decision to eliminate coverage for hydrophilic intermittent catheters, it must comply with the following requirements:• Advance written notice (42 C.F.R. § 431.211)[4]• Adequate notice content, including reasons and legal authority (42 C.F.R. § 431.210)[5]• Opportunity for a fair hearing (42 C.F.R. § 431.214)[6]• Notice of hearing rights (42 C.F.R. § 431.206)[7]• Managed care adverse benefit determination requirements (42 C.F.R. § 438.404)[8]• Notice of changes in services (42 C.F.R. § 435.917)[9]CMS has consistently made

ID/#	Comment	Disposition
	clear that states and managed care entities may not avoid these requirements by reclassifying services as "non-covered" when beneficiaries are actively receiving them. Federal Benefit Sufficiency Requirements and Clinical Impact Federal standards further require that Medicaid services be sufficient in amount, duration, and scope to reasonably achieve their intended purpose (42 C.F.R. § 440.230).[10] Restricting access to hydrophilic intermittent catheters—particularly where clinically indicated—may fail to meet this requirement and can lead to increased infections, complications, and higher downstream costs to the Medicaid program.	
I2	Fiscal Impact and Program Cost Considerations Eliminating coverage for hydrophilic intermittent catheters is unlikely to produce cost savings for the Oregon Medicaid program—and may instead increase total expenditures. Hydrophilic catheters are designed with surface coating that binds water to create a smooth, lubricious layer, eliminating the need for separate lubricant during use. Individuals using non-hydrophilic catheters require ongoing lubricant supplies to safely perform catheterization. Based on available estimates, if all current users were transitioned to non-hydrophilic catheters, Oregon Medicaid would incur approximately $656,640[10] annually in additional lubricant costs alone. This estimate does not include the well-documented downstream costs associated with increased urinary tract infections (UTIs), urethral	Thank you for your comments. The reviewed evidence did not find a significant reduction in infection, stricture or other outcomes with hydrophilic catheters. The economic studies that found cost savings used models that relied on reduced infection risk.

ID/#	Comment	Disposition
	trauma, emergency department visits, and hospitalizations that are more likely when hydrophilic catheters are not available. These avoidable complications can significantly increase total cost of care for intermittent catheter users. Given the previous coding structure and that Oregon Medicaid is unlikely to have a current breakdown of hydrophilic versus non-hydrophilic catheter utilization, this uncertainty further underscores the risk of unintended financial consequences from eliminating coverage. At a minimum, the program would be shifting costs rather than reducing them—potentially increasing overall spending. Maintaining coverage and applying continuity of pricing by crosswalking payment rates from the prior HCPCS codes would preserve access to clinically appropriate products without introducing new costs to the system. This approach aligns with federal policy, supports beneficiary health outcomes, and avoids unnecessary increases in both supply and medical expenditures.	
I3	Request to the Committee In light of these considerations, AAHomecare respectfully requests that the VBBS Committee: 1. Add and recognize current hydrophilic intermittent catheter HCPCS codes as covered services;	Thank you for detailing your recommendations which will be available to the members for review.

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	2. Set payments for the new HCPCS codes that now include only hydrophilic intermittent catheters equal to those for the HCPCS codes that previously included hydrophilic intermittent catheters. 3. Ensure continuity of care for beneficiaries currently utilizing hydrophilic catheters; 4. Ensure compliance with federal notice and due process requirements; and 5. Engage stakeholders, including providers and patient advocates, to support implementation **Conclusion** Hydrophilic intermittent catheters are essential to maintaining patient health, independence, and dignity while reducing avoidable healthcare utilization. Federal law is clear that both coverage and payment policies must preserve continuity of care and protect beneficiary rights. AAHomecare stands ready to work collaboratively with the Oregon Health Authority and the HERC VBBS Committee to ensure that coverage policies are clinically appropriate, operationally feasible, and fully compliant with federal requirements. Thank you for your consideration. Sincerely,	

ID/#	Comment	Disposition
	Laura Williard Senior VP of Payer Relations **American Association for Homecare (AAHomecare)**	

References Provided by Commenters

ID	References
A	Medical Advisory Secretariat. Hydrophilic Catheters: An Evidence-Based Analysis. Stensballe et al. European Urology (RCT on friction, pain, trauma). Liao et al. Systematic Review & Meta-analysis (2022). Meta-analysis on UTI outcomes with hydrophilic catheters.
B	www.newmobility.com
C	No references submitted
D	https://pmc.ncbi.nlm.nih.gov/articles/PMC11167762/
E	Hydrophilic%20Coated%20ICs%20Coverage%20Request-%20United%20Spinal%20to%20Oregon%20Medicaid%204.17.26f.pdf(232.4KB)
F	No references submitted

ID	References
G	No references submitted
H	https://pubmed.ncbi.nlm.nih.gov/16137822/ https://pubmed.ncbi.nlm.nih.gov/12576829/ https://pubmed.ncbi.nlm.nih.gov/21570027/
I	**Footnotes** 1. 42 C.F.R. § 414.236 – Continuity of pricing for DMEPOS items and services. 2. 42 C.F.R. § 431.201 – Definitions (including "action"). 3. 42 C.F.R. § 431.211 – Advance notice requirements. 4. 42 C.F.R. § 431.210 – Content of notice. 5. 42 C.F.R. § 431.214 – Hearing rights. 6. 42 C.F.R. § 431.206 – Informing applicants and beneficiaries. 7. 42 C.F.R. § 438.404 – Managed care adverse benefit determinations. 8. 42 C.F.R. § 435.917 – Changes affecting services. 9. 42 C.F.R. § 440.230 – Sufficiency of amount, duration, and scope. 10. Calculation based on Oregon Medicaid and Managed Care populations obtained via Policy Reporter and standard utilization assumptions: (1) Estimated affected population: 1,340,925 × 0.17% = 2,280 patients; (2) Annual utilization: 200 catheters/month × 12 months = 2,400 per patient/year; (3) Total annual catheter use: 2,280 × 2,400 = 5,472,000 units; (4) Lubricant cost per unit: $0.12; (5) Total annual lubricant cost: 5,472,000 × $0.12 = $656,640. *Estimates are illustrative and do not include additional costs associated with increased complications such as urinary tract infections, emergency department visits, or hospitalizations*.

Spinal Cord (2021) 59:587–595
https://doi.org/10.1038/s41393-021-00620-w

REVIEW ARTICLE

Catheters for intermittent catheterization: a systematic review and network meta-analysis

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Received: 23 August 2020 / Revised: 13 February 2021 / Accepted: 25 February 2021 / Published online: 28 April 2021
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Abstract

Study design Systematic review and network meta-analysis.

Objectives Intermittent catheterization (IC) is considered the standard treatment for neuro-urological patients who are unable to empty their bladders. The present study aimed to conduct a systematic evaluation and network meta-analysis of all available types of intermittent catheters, and determine which one is best suited for clinical use.

Methods We searched MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) databases to identify relevant studies. Only randomized clinical trials (RCTs) were included. Five types of catheters were identified based on the included studies. A Bayesian network meta-analysis was then performed. The surface under the cumulative ranking (SUCRA) curve was used to determine the best catheter for each outcome.

Results A total of 25 RCTs, involving 1233 participants, were included. The pooled odds ratios of symptomatic UTI were lower for two ready-to-use single-use catheters (gel-lubricated non-coated catheter, OR: 0.30, 95% CI 0.095–0.86; pre-activated hydrophilic-coated catheter, OR: 0.41, 95% CI 0.19–0.83) as compared to single-use non-coated catheter. In terms of patient satisfaction, the SUCRA results showed that the pre-activated hydrophilic-coated catheter may the preferred option (SUCRA = 82.8%). However, there were no significant differences in all outcome measures between traditional single-use non-coated catheters and clean non-coated catheters.

Conclusion Ready-to-use single-use catheters are associated with lower rates of UTI compared to traditional catheters. Patients may be most satisfied with the pre-activated one. For traditional single-use non-coated catheters and clean non-coated catheters, there is still no convincing evidence as to which is better. Thus, more well-designed trials are needed.

Introduction

Intermittent catheterization (IC) is a procedure that involves using a urinary catheter to empty the bladder, which typically is done several times a day. IC is considered as a standard treatment for adults and children with incomplete bladder emptying due to neurological disorders [1]. However, with long-term IC usage, some life-threatening complications may occur. The most frequent complication is urinary tract infection (UTI) [2], which can result in bacteremia/sepsis. Urethral trauma, usually evaluated by haematuria, has also been reported and shown to affect the risk of UTI [3].

Since the first introduction of IC, the material, coating and design of the catheter have undergone continuous improvements to reduce the incidence of UTI, attenuate urinary tract injury and enhance patient satisfaction. IC was originally performed using sterile technique [4] (single-use catheter with sterile gloves and sterile containers). Lapides et al. [5] later proposed a clean reusable catheter, which is more cost-effective without increasing infection rates. Reused IC refers to the reuse of a catheter after washing with soap, boiling and/or soaking in disinfectants and air

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Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41393-021-00620-w.

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drying, instead of discarding it. Coated catheters are now available for IC, which are only single-use and designed to improve lubrication and reduce urethral injury. The most widely used one is hydrophilic-coated catheter, with a layer of hydrophilic polymers that absorb water and bind to the catheter surface [6]. The friction of hydrophilic-coated catheter is greatly lower than that of the traditional plastic lubricated catheter [7].

IC can be done by caregivers or by the patients themselves after discharge from the rehabilitation facility. Several new designs, with the concepts of "No touch" or "Ready to use", have been developed to facilitate the procedure, reducing the risk of infection during the procedure, and improving patient comfort. For non-coated catheters, there are some designs such as a closed, touchless, self-contained catheter system that can be used in a sterile collection bag [8], and the catheters are pre-lubricated without a need to add gel manually [9]. For hydrophilic-coated catheters, the first design required immersion in water for 30 s to activate it before use; the later design is packed in water (pre-activated) and ready for use [10].

Although four meta-analyses [11–14] have suggested the benefit of hydrophilic-coated catheters over non-hydrophilic ones, the variety of catheters can make data synthesis challenging. The confounding factors may include sterile or clean technique, single-use or re-use, pre-lubricated, pre-activated and other design features.

Another comparison, single-use versus re-use catheters, is still controversial. Two cost-effectiveness studies [11, 15] demonstrated the economic advantage of re-use catheters, and the results suggest that re-use catheters may be more acceptable for long-term use to individuals in developing countries. A Cochran systematic review [13] in 2014 concluded that single-use catheters have no clear advantages over re-use catheters, and this potential endorsement of re-use catheters may have a strong impact on healthcare providers' decision-making. However, this Cochran review was withdrawn [16], since an independent appraisal [17] had found significant problems with data extraction and analysis.

Therefore, we undertook a network meta-analysis of all available types of catheters to identify the one that is most suitable for IC. This kind of analysis can reduce the confounding effects in pair-wise meta-analysis due to the variety of catheters, as well as integrate both direct and indirect comparisons.

Methods

Search strategy

This systematic review is reported based on the Preferred Reporting Items for Systematic reviews and Meta-analyses Statement (PRISMA) [18]. The PRISMA checklist is shown in supplementary information. MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials databases were searched to identify relevant articles published up to June 2020. The following search terms were used: *IC, urethral catheterization, self-catheterization, clinical trials as the topic* and *random*. The detailed search strategy is presented in Supplementary Table S1. Relevant references from the 2014 Cochrane review were also identified. Screening of titles and abstracts, as well as full-text reading if necessary, were done by two authors independently. Disagreements were resolved by a third reviewer. The study protocol was registered at PROSPERO (No. CRD42018114852).

Selection criteria

The inclusion criteria were as follows: (i) randomized controlled trials or randomized cross-over trials; (ii) participants who used some form of IC; (iii) comparison of different types of intermittent catheters; and (iv) outcomes were symptomatic UTI, asymptomatic bacteriuria, haematuria and/or patient satisfaction. Observational studies, editorials, commentaries and review articles were excluded. Based on the experimental groups in the included studies, we defined five types of catheters of interest for analysis, as follows: (i) single-use non-coated catheter (SNC)—a single-use uncoated catheter. After removing it from sterile packaging, the user needs to add some lubricant before insertion; (ii) gel-lubricated single-use non-coated catheter (GSNC)—a single-use uncoated catheter with pre-packaged lubricant, which is ready to use; (iii) single-use hydrophilic-coated catheter (SHC)—a single-use catheter with a hydrophilic polymer coating. The user needs to add sterile water for about 30 s to active the hydrophilic polymer coating; (iv) clean reused non-coated catheter (CNC)—a reusable uncoated catheter, which is usually washed with soapy water and air-dried after each use, but the user needs to add some lubricant before use each time; and (v) pre-activated single-use hydrophilic-coated catheter (PSHC)—a single-use catheter with a hydrophilic polymer coating which has been activated, and is ready-to-use. Only studies with at least two of the above-mentioned catheter types were included.

Data extraction

Data extraction was performed by two authors independently. Disagreements were resolved by a third reviewer when necessary. The following information was extracted from each qualified article: author list, publication year, study population, study design, study location, subject age range, sample size, study duration, catheter types, the number of participants who dropped out, and clinical outcomes.

Outcome assessment

The outcomes were symptomatic UTI, asymptomatic bacteriuria, urinary injury measured by haematuria, and patient satisfaction. The definitions of these outcomes were as follows: (i) symptomatic UTI—a positive urine culture of ≥ 10^3 cfu/mL with at least 1 symptom compatible with UTI, including fever, cloudy/malodorous urine, suprapubic/flank pain, worsening incontinence, malaise and/or pain associated with catheterization [19, 20]. Since some trials had discrepant definitions of symptomatic UTI, we also considered the definitions used in the trials, in a sensitivity analysis; (ii) asymptomatic bacteriuria—the presence of at least 1 bacterial species (≥10^5 cfu/mL) in a single catheter urine specimen without any symptoms compatible with UTI; (iii) haematuria—the presence of red blood cells in the urine, urethral bleeding, or gross and microscopic haematuria; and (iv) patient satisfaction—the subjective general opinion or preferences. All trials reporting satisfaction included a binary item of overall satisfaction, and the non-binary items were disregarded.

Data quality assessment

Two authors independently evaluated the quality of the studies using the Cochrane Risk of Bias tool covering selection bias, performance bias, detection bias, attrition bias, reporting bias and other potential sources of bias. The studies were classified into three grades: "high", "unclear" and "low" risk of bias.

Statistical analysis

A network meta-analysis was performed to compare all five types of IC catheters using a Bayesian approach [21], producing four networks with one outcome each. All analyses were performed in R 3.4.4 [22] using the 'GeMtc' package. The intervention efficacy or clinical impact are presented as odds ratios (ORs) and 95% confidence intervals (CIs). The ranking probabilities and the surface under the cumulative ranking curves (SUCRA) [23] are utilized to evaluate the relative ranking of different types of catheters for each outcome. Study heterogeneity was evaluated using the Higgins–Thompson I^2 method [24]. To evaluate inconsistency among the included trials in the networks, the Z test [25] and node splitting model [26] were used to quantify the degree of difference between direct and indirect comparisons. The level of statistical significance was set at $P < 0.05$.

As the definitions of symptomatic UTI varied between various studies, we conducted a sensitivity analysis assessing only studies with clear, detailed definitions and those which only met the standard provided by the Infectious Diseases Society of America (IDSA) 2009 consensus statement [19] and the American Academy of Pediatrics (AAP) guidelines for UTI [20].

Results

The literature search identified 2914 records, and 40 studies were selected for a full review after excluding duplicate publications and screening title and abstract. After full-text screening, 25 studies [9, 10, 27–49] were included. The PRISMA flow diagram is shown in Fig. 1.

Characteristics of the included studies

Table 1 lists the main characteristics of the studies. Fourteen were randomized controlled trials, and 11 were randomized cross-over trials. Among the 1233 participants, most were diagnosed with neurogenic bladder, while a few had other causes of urinary retention, such as prostatic hyperplasia. Six trials [30, 33, 44, 46, 48, 49] focused on children, and one [47] included individuals with myelomeningocele and involved a small number of children. In two [30, 33] of these seven trials, the children did self-IC, while in the remaining five [44, 46–49] they did it either themselves or IC was done by a trained caregiver. The remaining 18 trials included only adult subjects. In these 18 trials, IC was performed by the patients themselves [9, 10, 28, 32, 35, 39, 40, 42, 43, 45], by caregivers [29, 31, 34, 37, 38], or by both [27, 36, 41]. Males made up 75.9% of the total study sample. There were 16 trials [9, 27, 29–33, 36, 38–41, 45, 47–49] assessing the

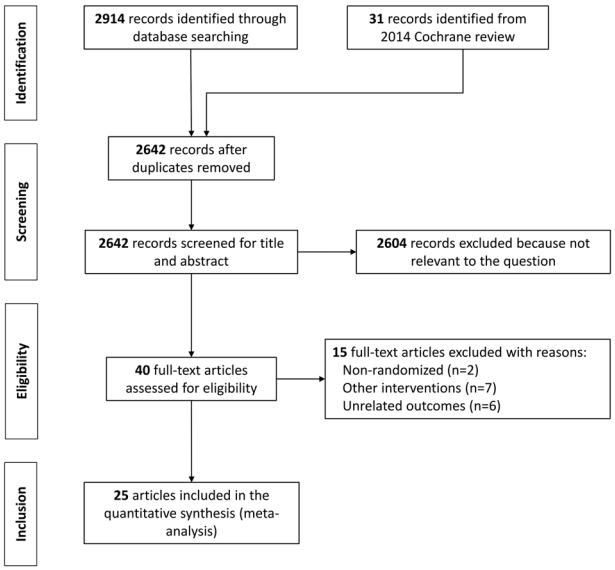

Fig. 1 PRISMA flow diagram. Flow diagram summarizing the phased study selection process.

Table 1 Characteristics of studies included in the meta-analysis.

Author	Year	Design	Country	Diagnostic group	Duration	Age*	Sample size	Dropouts (%)	Male%	Catheters
King [27]	1992	RCT	USA	NB (SCI)	28 d	30 ± 12	46	12 (21%)	87	SNC, CNC
Quigley [28]	1993	RCT	USA	NB (9 stroke; 11 SCI)	4 d	NA	20	10 (33%)	NA	SNC, GSNC
Duffy [29]	1995	RCT	USA	Varied	3 m	72 ± 11	80	2 (2%)	100	SNC, CNC
Sutherland [30]	1996	RCT	USA	NB	8 w	12 ± 4/12 ± 6	30	3 (9%)	100	SHC, CNC
Fingerhut [31]	1997	RCT	USA	NB (SCI)	3 m	38 ± 22	29	NA	55	GSNC, CNC
Pachler [32]	1999	RCoT	Denmark	BPH	3 w	71(50–87)	32	11 (26%)	100	SHC, CNC
Giannantoni [9]	2001	RCoT	Italy	NB (SCI)	7 w	38 ± 16	18	NA	89	SNC, GSNC
Schlager [33]	2001	RCoT	USA	NB (Myelomeningocele)	4 m	Children	10	0 (0%)	40	SNC, CNC
Pascoe [10]	2001	RCoT	UK	NB	1 w	Adults	25	2 (7%)	NA	SHC, PSHC
Vapnek [35]	2003	RCT	USA	NB	12 m	40 ± 13	62	13 (17%)	100	SHC, CNC
Day [34]	2003	RCT	Canada	NB	9 m	21–71	11	8 (42%)	73	SNC, GSNC
Stensballe [37]	2005	RoCT	Denmark	NB (SCI)	3 m	24(18–42)	40	9 (18%)	100	GSNC, SHC, PSHC
Ridder [36]	2005	RCT	Europe	NB (SCI)	12 m	38 ± 15	123	66 (35%)	100	SNC, PSHC
Moore [38]	2006	RCT	Canada	NB (SCI)	12 m	42 ± 15	36	0 (0%)	82	SNC, CNC
Cardenas [39]	2009	RCT	USA	NB (SCI)	12 m	42 ± 10	45	11 (20%)	64	SNC, SHC
Sarica [40]	2010	RCoT	Turkey	NB (SCI)	6w	37 ± 12	10	11 (52%)	100	SNC, GSNC, SHC
Cardenas [41]	2011	RCT	North America	NB (SCI)	6 m	37 ± 14	114	110 (49%)	81	SNC, PSHC
Chick [44]	2012	RCoT	Canada	NB (spina bifida)	12 m	13(3–20)	20	31 (61%)	50	SHC, CNC
Denys [42]	2012	RCoT	France	NB	30 d	46 (19–64)	97	9 (9%)	65	SHC, PSHC
Chartier-kastler [43]	2013	RCoT	Europe	NB	6 w	54 (23–88)	118	7 (6%)	87	SHC, PSHC
Leek [45]	2013	RCoT	Australia	Varied	8 w	60 (27–80)	22	3 (12%)	26	SNC, CNC
Kiddoo [46]	2015	RCoT	Canada	NB (spina bifida)	24 w	11 ± 6	45	21 (32%)	47	CNC, PSHC
Lucas [47]	2016	RCT	USA	NB (myelomeningocele)	12 m	1–42	47	3 (6%)	44	SNC, SHC
Defoor [48]	2017	RCT	USA	NB	12 m	13 (2–17)	78	23 (23%)	49	SNC, SHC
Madero-Morales [49]	2019	RCT	Mexico	NB (spina bifida)	8 w	13 ± 10	75	8 (10%)	39	SNC, CNC

Age*, presented as mean ± SD or mean (range).

RCT randomized controlled trial, *RCoT* randomized cross-over trial, *NA* not available, *NB* neurogenic bladder, *SCI* spinal cord injury, *BPH* benign prostatic hyperplasia, *SNC* single-use non-coated catheter, *GSNC* gel-lubricated single-use catheter, *SHC* single-use hydrophilic-coated catheter, *CNC* clean reused non-coated catheter, *PSHC* pre-activated single-use hydrophilic-coated catheter.

incidence of symptomatic UTI, and 10 [27, 28, 30, 32–35, 38, 45, 49] assessing the incidence of asymptomatic bacteriuria. For haematuria, 8 trials [9, 30, 32, 35–37, 40, 41] were included; while for patient satisfaction, 9 trials [10, 32, 36, 37, 40, 42–44, 46] were included. The specific data of each comparison arm is shown in Supplementary Table S2. Cochrane tool risk of bias details are listed in Supplementary Fig. S1, which reveals a moderate risk of bias across trials.

Symptomatic UTI

Sixteen trials which reported the incidence of symptomatic UTI, comparing SNC, GSNC, SHC, CNC and PSHC (916 total participants) were included. When SNC was used as the reference, only GSNC (OR 0.30, 95% CI 0.10–0.86) and PSHC (OR 0.41, 95% CI 0.19–0.83) were associated with a statistically significant lower incidence of symptomatic UTI (Fig. 2A). According to the SUCRA values

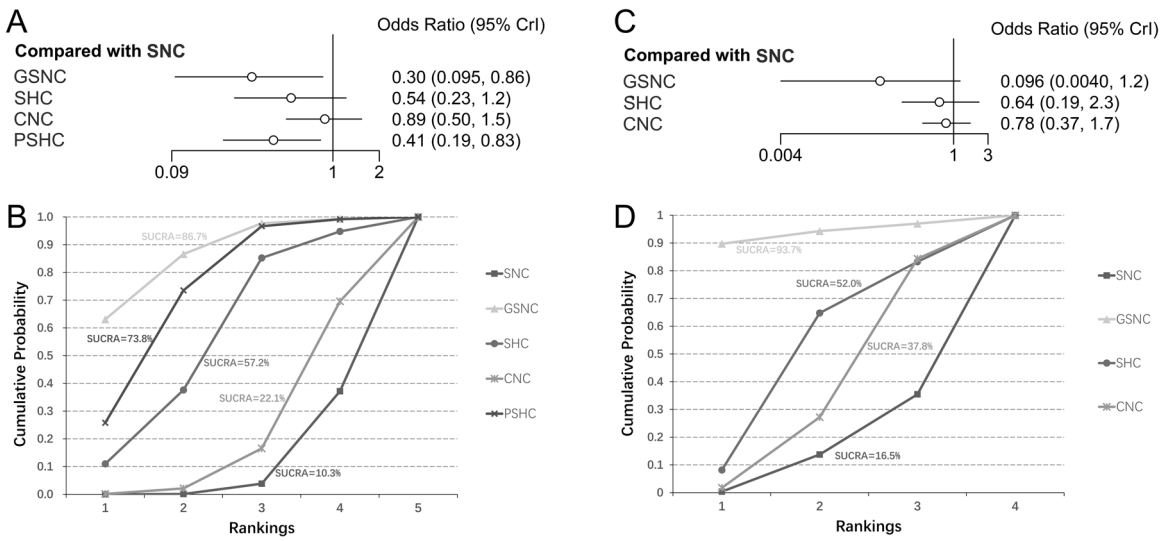

Fig. 2 Analysis of symptomatic UTI and asymptomatic bacteriuria. A Forest plot of symptomatic UTI, with single-use non-coated catheter as the comparator; **B** SUCRA plot of symptomatic UTI; **C** forest plot of asymptomatic bacteriuria, with single-use non-coated catheter as the comparator; **D** SUCRA plot of asymptomatic bacteriuria.

(Fig. 2B), GSNC (SUCRA = 86.7%) was the preferred option to decrease the risk of symptomatic UTI, followed by PSHC (SUCRA = 73.8%), SHC (SUCRA = 57.2%) and CNC (SUCRA = 22.1%). Assessment of heterogeneity (Supplementary Fig. S2) revealed $I^2 = 29.9\%$ for the comparison of GSNC versus SNC and $I^2 = 63.1\%$ for CNC versus GSNC; while the remaining comparisons showed no heterogeneity ($I^2 = 0\%$). Overall, we found no significant inconsistency ($Z = 3.99$, $p = 0.41$) in the analysis.

Sensitivity analysis of symptomatic UTI

The specific definition of symptomatic UTI described in each trial is given in Supplementary Table S3. We conducted a sensitivity analysis for symptomatic UTI assessing only studies with clear, detailed definitions and those that only met the standard of the IDSA 2009 consensus statement and AAP guidelines. Four trials [30, 36, 41, 47] were excluded, and PSHC was not included in this analysis due to the exclusion of two trials [36, 41]. The results of SUCRA-based analysis (Supplementary Fig. S3) showed a similar trend as in the initial analysis. Notably, the probability of GSNC being the preferred choice was 91.0% and that of SHC being the second preferred choice was 67.6%. The estimated risk for the comparison of GSNC versus SNC remained statistically significant (OR 0.29, 95% CI 0.09–0.86).

Asymptomatic bacteriuria

For asymptomatic bacteriuria, the network analysis comprised nine trials comparing SNC, GSNC, SHC and CNC (378 total participants). Base on the SUCRA results (Fig. 2D), GSNC (SUCRA = 93.7%) was the preferred choice to prevent asymptomatic bacteriuria, and SHC was likely (SUCRA = 52.0%) to be the second choice. No significant differences were observed for GSNC, SHC and CNC (OR 0.096, 95% CI 0.004–1.2; OR 0.64, 95% CI 0.19–2.3; and OR 0.78, 95% CI 0.37–1.7, respectively), when compared to SNC (Fig. 2C). In addition, there was no evidence of significant heterogeneity and no inconsistency between the studies (Supplementary Fig. S4).

Haematuria

Eight trials comparing SNC, GSNC, SHC, CNC and PSHC (643 total participants) with regards to haematuria or urethral bleeding were included. Although no significant difference in haematuria incidence was observed for the four catheters, the SUCRA results indicated that the hydrophilic-coated catheter may be the preferred option to decrease the risk of haematuria (OR: 0.19, 95% CI 0.01–1.5; SUCRA 87.7%; Fig. 3A, B). No significant inconsistency ($Z = 1.57$, $p = 0.67$) was observed between the studies. Assessment of heterogeneity gave $I^2 = 72.0\%$ for the comparison of PSHC with SNC and $I^2 = 57.3\%$ for PSHC versus GSNC; the remaining comparisons were not significant (Supplementary Fig. S5).

Patient satisfaction

Nine trials that reported patient satisfaction were included in the analysis (849 total participants). In six [10, 32, 37, 40, 42, 43] of these trials, the satisfaction was reported by the patients themselves; while in the other three

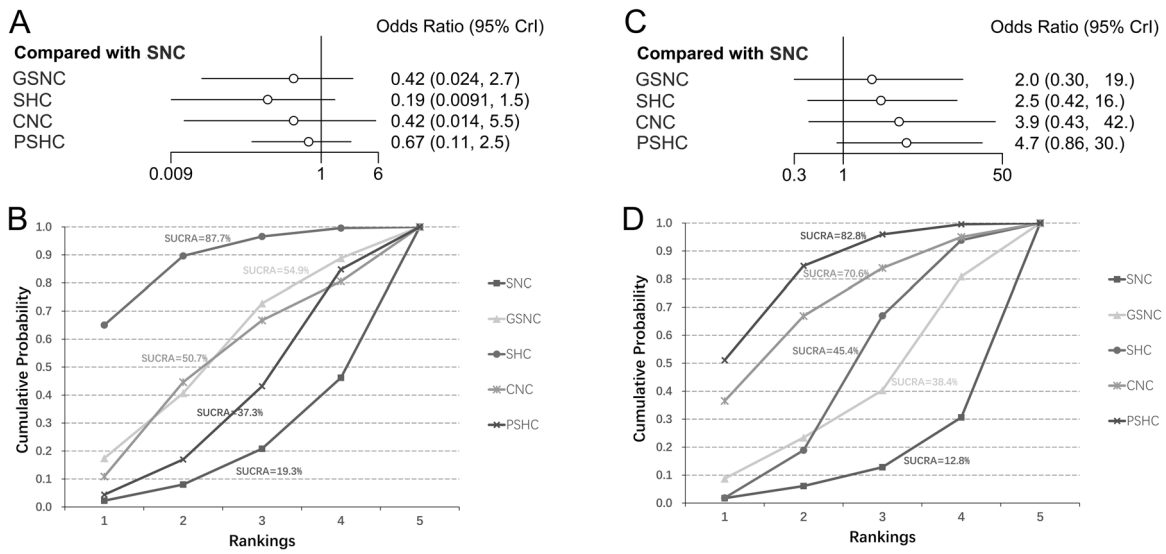

Fig. 3 Analysis of haematuria and patient satisfaction. A Forest plot of haematuria, with single-use non-coated catheter as the comparator; **B** SUCRA plot of haematuria; **C** forest plot of patient satisfaction, with single-use non-coated catheter as the comparator; **D** SUCRA plot of patient satisfaction.

[36, 44, 46], part of the evaluation was done by the patient and part by the care provider. SUCRA analysis indicated that in terms of overall patient satisfaction the catheters were ranked as follows: PSHC, CNC, SHC, GSNC and SNC (Fig. 3D). None of the catheters exhibited significant advantages compared with SNC (Fig. 3C). Assessment of heterogeneity (Supplementary Fig. S6) demonstrated no significant heterogeneity for the comparison of SHC versus SNC and GSNC; the remaining comparisons showed a slight but significant heterogeneity. There was no significant inconsistency ($Z = 3.46$, $p = 0.33$) observed between the studies.

Discussion

The types of catheters used in IC vary across the globe, including single-use or re-use, coated or uncoated, pre-lubricated, pre-activated and others. Previous pair-wise meta-analyses [12–14] have suggested the advantage of using hydrophilic-coated catheters for IC. However, these studies often clustered two different catheters (SNC and CNC) in the category of uncoated catheters when uncoated was compared to hydrophilic-coated catheters, and clustered two different hydrophilic-coated catheters (PSHC and SHC) in the same category. In the 2014 Cochrane review [13], when comparing single-use and re-use catheters, the hydrophilic-coated catheters, gel-lubricated catheters and traditional single-use catheters were classified in the same group (single-use), leading to possibly misleading conclusions. Therefore, the present study attempted to evaluate all available types of catheters as separate entities by performing a network meta-analysis. More importantly, the sample size (1233 total participants) of this meta-analysis and the number of included studies were greater than those of the previous meta-analyses [11–14]. It is hoped that the results will guide patients and healthcare providers when making treatment decisions.

Some findings are important based on pooled analyses and SUCRA results. First, GSNC and PSHC were associated with a significantly decreased risk of symptomatic UTI compared to SNC. The SUCRA results indicated the GSNC is the preferable option for UTI prevention. The results from asymptomatic bacteriuria gave a similar rank order, but did not reach statistical significance, probably because all patients on IC are at risk of asymptomatic bacteriuria. Asymptomatic bacteriuria has less clinical significance than UTI and requires no treatment. It was noteworthy that when subdividing the hydrophilic-coated catheters into PSHC and SHC, only PSHC shows a statistically significant reduction in UTI rate. These data can be explained by the fact that both GSNC and PSHC are ready-to-use and no-touch techniques, whereas the users need to add sterile water to the traditional hydrophilic-coated catheter (SHC) for about 30 s to active the hydrophilic coating, or manually add some lubricants and disinfectants to SNC before use. These operations may confer some risks. Goessaert et al. [50] reported that even in the hospital setting, nurses and nursing students might make more sterilization errors and spent more time performing the traditional method (sterile with a catheterization-set), than with the no-touch method. Moreover, as a non-hospital procedure, IC is widely performed by patients themselves in real-life circumstances. Many patients with spinal cord injury have decreased manual dexterity or are juveniles. The ready-to-use and no-touch technique that requires less

preparation and has less chance of making sterilization errors may be especially useful for those patients.

Previous studies have mentioned that the definitions of symptomatic UTI are not consistent across trials. Two previous meta-analyses [13, 14] used the definition taken from an outdated consensus statement [51], while the IDSA 2009 consensus statement [19] had already provided the latest definition of UTI. Considering the variation in the definitions, we conducted a sensitivity analysis focusing on trials with clear, detailed definitions, and those that approximately met the IDSA standard. The core definition of symptomatic UTI was significant bacteriuria plus the presence of symptoms or signs. The main differences between the two definitions are as follows: the National Institute on Disability and Rehabilitation Research (NIDRR) defined the significant bacteriuria of UTI as $\geq 10^2$ cfu/ml; while the IDSA standard defined the significant bacteriuria of UTI as $\geq 10^3$ cfu/ml. One trial [41] has applied the former definition, which may have led to a risk of overestimating the incidence of UTI. This study was excluded in the sensitivity analysis. The incidence of symptomatic UTI in this trial (82%) was higher than that in the remaining trials. Another three trials [30, 36, 47] were excluded due to the lack of a clear and precise description of the inclusion criteria and the definition of symptomatic UTI, especially the diagnostic standard of bacterial colonies in urine samples. Given the exclusion of the De Ridder [36] and Cardenas [41] studies, the PSHC arm was excluded from the sensitivity analysis. The sensitivity analysis revealed a similar rank order as the initial analysis, and the gel-lubricated catheter was still significantly superior to other catheters in terms of avoiding symptomatic UTI.

Regarding haematuria, the SUCRA results demonstrated the superiority of SHC compared to GSNC and other uncoated catheters. This may be attributed to the fact that hydrophilic catheters have a smooth and slippery surface with lower friction force and higher osmolality [7]. However, Stensballe et al. [37] measured the withdrawal friction and the incidence of haematuria for the hydrophilic catheter and the gel-lubricated catheter and reported that there is no direct relationship between friction force and haematuria, which may partially explain our insignificant results. Haematuria is an acute form of urethral trauma, and trauma to the urethral mucosa can lead to long-term complications such as urethral stricture, which was rarely reported in most trials. The reason may be that a great number of patients might only have mucosal irritation symptoms, which indicate a very slight urethral trauma that cannot be detected by laboratory tests.

Some subjective indicators should be paid more attention than objective ones, such as the overall patient satisfaction and other related parameters. Patient satisfaction or preference is affected by comfort, ease of handling, convenience, cost and insurance reimbursement. The SUCRA analysis revealed that with respect to patient satisfaction PSHC and CNC were the top two. The advantage of PSHC is that it has a slippery surface and is ready-to-use, which offer comfort and ease of operation at the same time. Traditional single-use hydrophilic catheters can make some individuals feel that 'lubricant [water in the packaging] would leave a mess on the bathroom floor', and make them prefer to use multi-use catheters [44]. The evaluation criteria of satisfaction varied greatly; however, we noted that all trials reporting satisfaction include a binary measure of overall satisfaction. The remaining non-binary items could not be used for network analysis at present. It is hoped that there will be a unified scale to measure IC satisfaction in the future, which is convenient for accurate evidence synthesis.

Another important issue nowadays is whether the SNC or the multi-use non-coated catheter is preferred. Our meta-analysis showed that if hydrophilic-coated and gel-lubricated catheters were left out of comparison, there were no significant differences for the four outcomes between the SNC and CNC. The 2014 Cochrane review [13] reached a similar conclusion and stated that no benefit was proven for single-use catheters compared to re-use catheters. However, such a statement strongly encourages healthcare insurers to carefully consider the cheaper re-use catheters, thus leading to great potential risks. There still is no general consensus whether the healthcare insurers should cover the cost of single-use catheters.

A cost-effectiveness analysis, which represents a key to interpret the clinical and financial trade-offs, was not included in the current meta-analysis. Two previous cost-effective studies [11, 15] obtained different conclusions based on two probabilistic Markov models with various groups and health states. Bermingham et al. [11] reported that clean re-use catheters were more cost-effective than single-use catheters, whereas Clark et al. [15] supported the use of SHCs, especially when long-term UTI complications were included in the analysis. However, these two studies were both performed based on the National Health Service drug tariff in the UK, and data from developing countries are still missing. More rigorous trials with cost-effectiveness analyses are needed for adequate decision-making, especially in developing countries.

This study has some limitations. First, the variety of definitions of clinical outcomes in the included studies might contribute to statistical heterogeneity. The above sensitivity analysis was an attempt to address this issue. Second, most studies had limitations of high dropout rate, which in turn resulted in a low quality of evidence. That is, the clinical outcomes of various IC options could be different for individuals who did not complete the study than for those who had completed the study, which may have resulted in an underestimate of UTI risks. Third, most studies had a short follow-up period, hence, some long-term complications such

as urethral stricture and renal failure were not observed and reported. Forth, due to the obvious differences in the operation of diverse catheters, the blinding method was not used in any of the included studies. Fifth, the cleaning technique is another variable that should be considered. Cleaning technique is the procedure of IC with or without a rigorous aseptic technique (sterile gloves, container and asepsis of genitals), and it can be performed with a single-use catheter or a reused catheter. Unfortunately, few trials have evaluated cleaning techniques, which may introduce confounding. Finally, most of the study subjects included were male, and seven trials [29, 30, 32, 35–37, 40] enroled only males, which could reduce the significance of the results in guiding IC use by female. Despite these limitations, the present network meta-analysis is the first to integrate all current literature and thus determine the most suitable type of catheter for IC.

Conclusion

Our network meta-analysis indicated that GSNC and PSHC reduce the risk of UTI. The ready-to-use and no-touch technique showed significant advantages compared to traditional techniques. For reasons such as ease of use and comfort, patients were most satisfied with PSHC. In terms of urethral injury measured by haematuria, the hydrophilic-coated catheter seemed to perform best. However, based on the present analysis and previous cost-effective studies, there is still no convincing evidence whether SNC or CNC is better. Further well-designed and high-quality RCTs with a strict definition of outcomes, adequate sample size, follow-up periods and cost-effectiveness analysis, are necessary to obtain more conclusive results.

Funding This study is supported by grants from 1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University (ZYGD18011, ZY2016104 and ZYJC18015).

Author contributions Study design: DHY and YTC; data collection: ZYJ and BHL; data analysis: DHY, XJ, and LYX; writing of this paper: DHY and YTC; revision of this paper: DHY, HL, and KJW.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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International Urology and Nephrology (2022) 54:1461–1470
https://doi.org/10.1007/s11255-022-03172-x

UROLOGY - REVIEW

Effects of hydrophilic coated catheters on urethral trauma, microtrauma and adverse events with intermittent catheterization in patients with bladder dysfunction: a systematic review and meta-analysis

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Received: 8 January 2022 / Accepted: 8 March 2022 / Published online: 21 April 2022
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Abstract

Background Hydrophilic coated catheters are recommended to reduce the side effects of intermittent catheterization (IC) in patients with bladder dysfunction. However, there is lack of Level one evidence to support the use of this intervention.

Search methods Several electronic databases were systematically searched to evaluate complication incidences for hydrophilic coated (HC) and non-hydrophilic catheters (NHC).

Results Twelve studies were eligible for inclusion in the review. The meta-analyses exploring microscopic hematuria frequencies (RR = 0.69; 95% CI 0.52–0.90) and urethral stricture frequencies (RR = 0.28; 95% CI 0.13–0.60) showed a lower risk ratio associated with HC in comparison to NHC, whereas gross hematuria was no statistically significant difference in two groups. Subgroup analyses of gross hematuria which was grouped according to "catheterization frequency", "single/multiple catheterization" and "self/other catheterization" were performed and the values of combined RR were also no statistically significant difference.

Conclusions Compared with non-hydrophilic catheters, the hydrophilic coated catheters have positive significance in reducing the incidence of urethral microtrauma and the urethral stricture. However, more studies are warranted for evaluating effects of hydrophilic coated catheters on the incidence of gross hematuria.

Keywords Hydrophilic catheters · Intermittent catheterization · Hematuria · Urethral stricture · Adverse events

Introduction

Causes of bladder dysfunction are neurogenic or non-neurogenic. Neurogenic bladder dysfunction is often secondary to spinal cord injury and central nervous system disease (multiple sclerosis or spina bifida), of which complications often manifest as urinary tract infections (UTI), urinary incontinence and upper urinary tract lesion [1]. Common non-neurogenic bladder dysfunction includes outlet obstruction, such as benign prostatic hyperplasia and postoperative urinary retention, which probably leads to vesicoureteral reflux. Bladder dysfunction hinders urine discharge, increases pressure in bladder, eventually causes urinary retention, which aggravates the risk of renal failure [2]. The treatment of bladder dysfunction is aimed at alleviating urinary incontinence, protecting the upper urinary tract, and improving bladder function as well as patients' quality of life.

Intermittent catheterization (IC) is a preferred treatment for patients with significant urination problems [3] which is used in 56% spinal cord injury patients for bladder management in the United States [4]. IC makes the bladder store a reasonable amount of urine at low pressure and empty it at appropriate intervals, which simulates physiological urinary function. Thereby, IC prevents overdistention and decreases pressure of bladder [5], improves blood circulation in bladder wall [6], reduces the incidence of urinary retention, and ultimately prevents deterioration of upper urinary tract [7].

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However, there are non-negligible side effects of IC, such as inducible urethral trauma, microtrauma, urethral stricture, bladder stone and false passages formation [8–10]. In recent years, several types of conduits are gradually available for IC to solve these disadvantages, including especially gel pre-lubricated polyvinyl chloride (external lubricant at most) and hydrophilic-coated catheter (polyvinylpyrrolidone coated at most) [10]. Compared with gel pre-lubricated polyvinyl chloride, HC is increasingly used to reduce intubation friction, urethral injury and urethral adhesion due to its special hydrophilic lubrication characteristics and non-sensitization [11].

Three previously published meta-analyses investigated the effects of HC and non-hydrophilic catheters (NHC) on urethral bleeding morbidity in IC patients [3, 12, 13], however, the results were contradictory. In addition, these studies provide few reliable evidence of urethral microtrauma and urethral stricture which are also important outcomes in the early and late stages of IC, respectively, except for gross hematuria. Consequently, the aim of our study is to evaluate whether HC improves the direct adverse effects compared with NHC, especially in urethral trauma, microtrauma, urethral stricture and rare adverse events.

Materials and methods

Inclusion/exclusion criteria

Population Studies considering adults (over 18 years old), adolescents (12–18 years old) and children (less than 12 years old) population with bladder dysfunction requiring IC.

Intervention Hydrophilic catheters—single-use.

Control Non-hydrophilic catheters—single-use or multiple-use.

Outcomes Gross hematuria, urethral microtrauma (microscopic hematuria), urethral stricture, false passages, bladder stone.

Study Randomized controlled trials, controlled before-and-after study, prospective cohort studies and cross-over trials.

Availability English; full text.

Data sources

We searched the following electronic databases to identify studies: Embase, PubMed, The Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, Medline, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), British Nursing Index and three Chinese databases (The CNKI, Wan Fang Database and the VIP). The database has been established until December 31, 2021 and the search has been carried out by combining subject words with free words. English search terms include: 1. hydrophilic urethral catheters, hydrophilic-Coated Catheters, hydrophilic coated catheter. 2. Self-lubricated urethral catheters, pre-lubricated catheter, ultra-slippery, aqueous lubrication, surface wettability and lubrication, lubricant, aqueous lubrication, hydrogel coatings hydrogels, aqueous. 3. Reducing friction. 4. Urethra trauma, urethral micro trauma, urinary tract trauma, urethral epithelial micro-trauma. 5. Long-term follow-up study, long-term follow-up, reduce treatment-related complications, adverse events, false passages, urethral stricture, bladder stone. At the same time, the references of the included literatures have been manually retrieved to supplement the relevant literatures.

Literature screening

Two evaluators read the obtained literature independently. After excluding the trials that clearly did not meet the inclusion criteria, the full text of the trials that might meet the inclusion criteria was read to determine whether they really met the inclusion criteria. After the cross-check, if there is a disagreement, a third party will assist in adjudication. Data extraction was performed using standardized forms of the Cochrane Collaboration. The extracted contents include: ① basic information of the included study, ② baseline characteristics included in the study, ③ specific details of the intervention including catheter material/catheter brand, the coating type and the lubrication mode, ④ key factors for the risk of bias include catheter size, self-catheterization or other-catheterization, single-use or multiple-use of catheterization, daily frequency of intubation, ⑤ Outcome indicators and outcome measures.

Bias risk assessment for included studies

Methodologic quality was independently assessed by 2 reviewers using Cochrane.

Statistical analysis

Risk Ratios (RRs) were used as a measure of the relationship between hydrophilic or non-hydrophilic catheters and outcome indicators. The 95% confidence interval (CI) for the dichotomous data was calculated. The pooled RRs were adopted the Mantel–Haenszel method. If there were no events in one or both arms, the Peto method was used. The percentage of variability of each study attributable to heterogeneity beyond chance was evaluated by the chi-square test ($P < 0.10$) and I^2 statistics. According to heterogeneity test, we adopted the random effects model ($I^2 > 50\%$, $P < 0.10$) or the fixed effects model. Then, the

probability of publication bias was evaluated with Egger's test and funnel plots. All statistical analyses were conducted with Stata15.0.

Results

Literature screening process and results

Figure 1 shows the selection process at each step and the reasons for excluded studies. Finally, 12 papers containing 850 participants met the inclusion criteria [14–25], including 9 randomized controlled trials [14, 15, 17, 19, 21–23, 25], 1 controlled before-and-after study [20], 1 prospective cohort studies [18], and 1 cross-over trials [16]. Table 1 illustrated patients' characteristics (age and gender), catheter materials and catheter size. Meta-regression was performed with the year of publication, male proportion and age as independent variables, and the results showed that the regression equation had no statistical significance ($p > 0.05$).

Risk bias assessment form for included studies

In these studies, blinding of participants and interveners were not possible, but even unblinded methods were considered unlikely to have an impact on objective evaluation indicators. Therefore, they were classified as low risk. Patient withdrawal (an average of 17.71%) was common in the literature [14–17, 19, 22–25], which was an unbalanced and potentially biased factors (Fig. 2).

The results of the study

Gross hematuria

Studies have used different terms such as urethral bleeding, hematuria and gross hematuria to describe the same condition. A total of eight trials reported the number of patients with gross hematuria [14–17, 19–22]. The incidence of gross hematuria was 17.9% (57/318) in patients using hydrophilic catheters and 21.0% (73/347) in patients using non-hydrophilic catheters (RR = 0.80; 95% CI 0.45–1.42) (Fig. 3). The risk of gross hematuria was not statistically significant between two groups. As "catheterization frequency", "single/multiple catheterization" and "self/other catheterization" are key indicators for gross hematuria incidence, we performed subgroup analysis for the three aspects. Figure 4 shows that there was still no statistically significant difference in the risk of gross hematuria incidence. In addition, the proportion of male was found that it did not affect the results of the final forest plot of gross hematuria by meta-regression (additional Fig. 3④). Moreover, there was also no evidence of heterogeneity ($p = 0.060$; $I^2 = 55.8\%$) or publication bias ($t = -1.94$, $P = 0.148$) (additional Fig. 3②). For the results of the sensitivity analysis, all the included studies were within the confidence interval except one study at the lower limit of the 95% CI (additional Fig. 3③). In brief, HC did not significantly improve the incidence of gross hematuria compared with NHC.

Microscopic hematuria

In this study, we considered microscopic hematuria as the following definition: the presence of red blood cells (RBC)

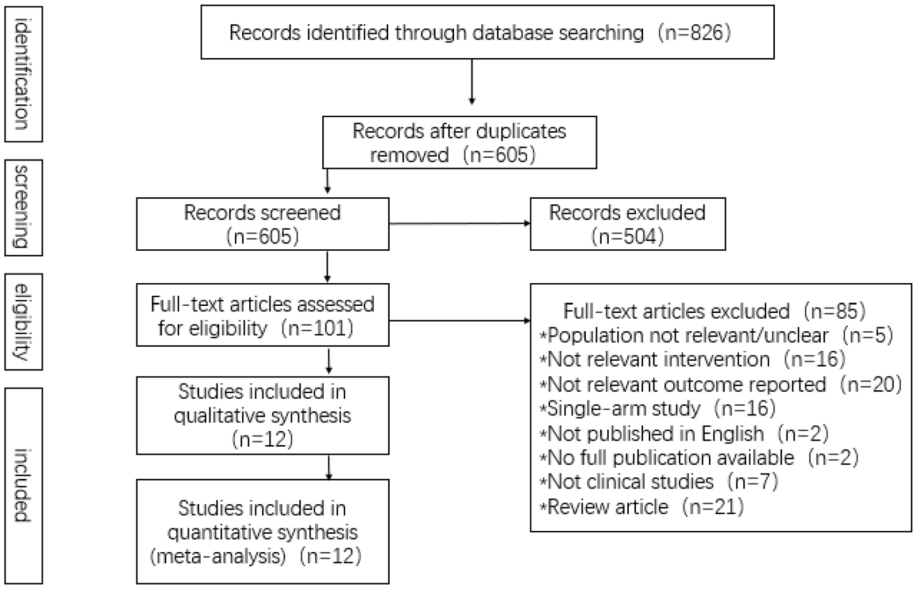

Fig. 1 PRISMA flow diagram—clinical search strategy

Table 1 Summary of extracted clinical data

Study	Location	Age	Gender [a]	Catheter material (brand), C/T[b]	Size
William DeFoor (2017) [14]	America	12.9/13.6	38/40	C: unknown T: unknown/ lofric (Wellspect Healthcare)	Unknown
De Ridder (2005) [15]	Spain, Belgium	37.5±14.6/ 36.7±14.6	M	C:PVC[c] (Conveen,Coloplast) T:PU[d]/Speedicath (Coloplast)	ch10,12,14
Pachler (1999) [16]	Denmark	71.3	M	C:PVC (Mentor santa barbara) T:PVC/lofric (Astra pharmaceuticals)	Unknown
Diana D. Cardenas (2011) [17]	America, Canada	35.1±13.2/ 37.2±14.4	100/39	C:PVC (Conen)T: PU/ Speedicath	Unknown
Tariq Burki (2019) [18]	Saudi Arabia	5	47/54	C:PE[e] T: unknown	Unknown
Ronald (1996)	America	11.7±3.8/ 12.1±5.7	M	C:PVC (Mentor) T:unknown/Lofric	11.5 ± 2.5/11.1 ± 2.1
Wyndaele (2000) [20]	Belgium	45±15	M	C:unknown T:unknown/Urocath-Gel1	12–14 French
Luca Cindolo (2003) [21]	Italy	62.3/67.4	80/20	C:PVC T:PVC/EasiCath (Coloplast, Denmark)	12-Charr
Sataa Sallami (2010) [22]	Tunisia	62/60.9	M	C:PVC T:unknown/LoFric (Astra Tech; Molndal, Sweden)	Unknown/Number 16 or 18
Jonathan et al. (2003) [23]	America	39.8±12.9/ 39.6±16	M	C:PVC T: unknown/Lofric	MOST are 14Fr, a few are 16Fr, 12Fr
Stensballe (2005) [24]	Denmark	24	M	C:silica gel or PVC (incare1 advance plus, Hollister inc,USA) T:unknown/speedicath (Conveen, ColoplastA/S Denmark)	CH12
Kjaergaard (1994) [25]	Denmark	68	M	C:no T: unknown/LoFric	Unknown

[a]Gender: M/ F (male/ female)

[b]T: hydrophilic coated (HC); C: non-hydrophilic catheters (NHC)

[c]PVC: polyvinyl chloride

[d]PU: polyurethane

[e]PE: polyethylene

in high power field under the microscope. There were 3 trials in 12 studies for microscopic hematuria in our study [19, 23, 24]. The incidence of microscopic hematuria was 41.7% (53/127) in patients using hydrophilic catheters and 56.3% (49/87) in patients using non-hydrophilic catheters (RR = 0.69; 95% CI, 0.52–0.90) (Fig. 5). The difference between two groups was statistically significant, indicating that the risk of microscopic hematuria with hydrophilic catheters was only 69% of that in non-hydrophilic group. There was also no evidence of heterogeneity ($p = 0.678$; $I^2 = 0.0\%$) or publication bias ($t = -0.65$, $P = 0.633$) (additional Fig. 5②). For the results of the sensitivity analysis, the included studies were all within the CI (additional Fig. 5③). In short, HC significantly improved the incidence of microscopic hematuria compared with NHC.

Urethral stricture

The method for stricture evaluation is maximum flow rate < 14 mL/s or endoscopic or radiographic examination. A total of five trials reported the number of patients with urethral stricture [14, 15, 21, 22, 25]. The incidence of urethral stricture was 3.1% (6/194) in patients using hydrophilic catheters and 11.5% (23/200) in patients using non-hydrophilic catheters (RR = 0.28; 95% CI 0.13–0.60) (Fig. 6). The difference between two groups was statistically significant,

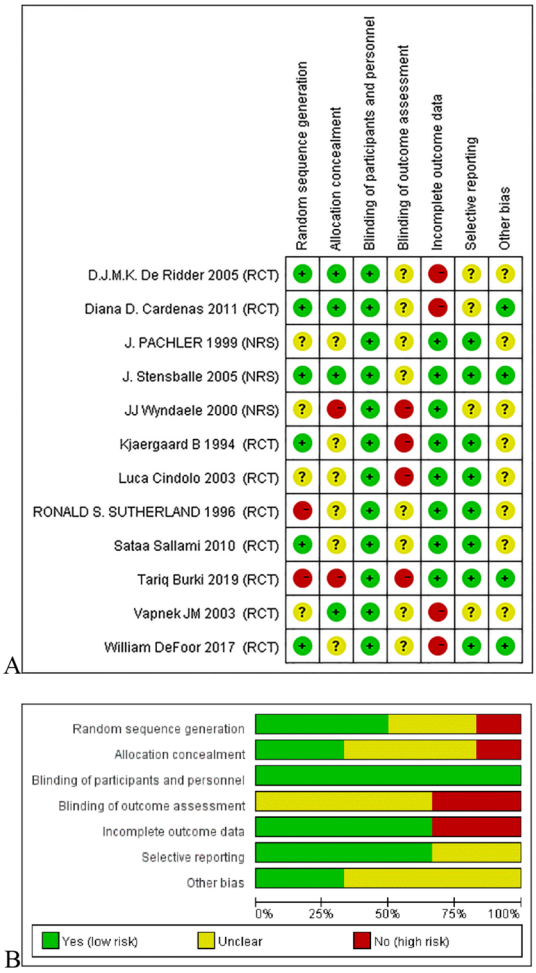

Fig. 2 **A** Risk of bias summary for RCT ($n=9$) and NRS ($n=3$); **B** risk of bias graph for all included studies ($n=12$). *RCT* randomized controlled trials, *NRS* non-randomized controlled trials

suggesting that the risk of urethral stricture with hydrophilic catheters was only 28% of that in the non-hydrophilic group. There was also no evidence of heterogeneity ($P=0.983$; $I^2=0.0\%$) or publication bias ($t=0.69$, $P=0.617$) (additional Fig. 6②). Five studies were all within the 95% CI about the sensitivity analysis (additional Fig. 6③). In a word, HC significantly improved the incidence of urethral stricture compared with NHC.

Rare adverse events

In addition to hematuria and urethral stricture, false passages and bladder stone are also rare adverse reactions after intubation in patients with bladder dysfunction. There were two studies focusing on the incidence of false passages [14, 20] and another two studies on bladder stone morbidity [18, 23]. Wyndaele [20] enrolled 39 patients who had been using NHC for IC over a number of years and switched to urocath-gel hydrophilic lubricated catheter for 1 month. It was found that only NHC group had one false passage. William [14] included children with neurogenic bladder dysfunction and divided them into 41 patients with NHC and 37 patients with HC. There were no false passages patients found in both groups. Jonathan [23] included 30 patients with HC and 31 patients with NHC for neurogenic bladder dysfunction, and found that one patient in each group had bladder stone. Tariq [18] included 101 children with spina bifida and divided them into HC and NHC groups. There were no bladder stones in the two groups. The incidences of both indicators were low after IC, and there was no difference between the two groups.

Discussion

Since Dr. Lapides proposed that using of IC as an alternative way to urinary diversion in 《Urology》 in 1972 [6], IC has become the globally recognized standard for the treatment of neurogenic bladder dysfunction and has been usually used in managements for various urinary system disease [26]. Generally, IC improves the quality of patients' life through removing long-standing drainage tubes and drainage bags [2]. Initially, catheters for IC were mainly made of latex and rubber. However, these catheters were gradually taken placed by polyvinyl chloride (PVC) catheters due to their sensitization, hardness and difficulty in catheterization [27]. In addition, the practice of re-using catheters with same tube in IC has changed over the past 10 years, for example most patients with intermittent self-catheterization (ISC) were required to use disposable catheters during catheterization [2].

Under the guidance of healthcare workers, almost all patients with bladder dysfunction could get benefits from IC [2]. IC changes the pattern of urinary management in patients with bladder dysfunction because of its various advantages. In addition to decreasing mortality caused by kidney deterioration [28], IC also reduces the harmful effects of long-term indwelling urinary catheters, including urinary tract infections (UTIs) [29], traumatic hypospadias, urinary fistula and even bladder cancer [30]. However, there are still unavoidable complications including mechanical stimulation and mucosa injuries for IC, such as pain and urethral injury. Applying external lubricant is a traditional method to reduce mucosa friction and adhesion during catheterization. Common external lubricants cover Vaseline, paraffin oil, gel, lidocaine cream, amiodarone and ketamine [31]. Nevertheless, the application of external lubricant on the surface of urinary duct has plentiful limitations such as uneven application, cumbersome operation, weak lubrication effect and short residence time. In addition, anesthetic lubricant such as

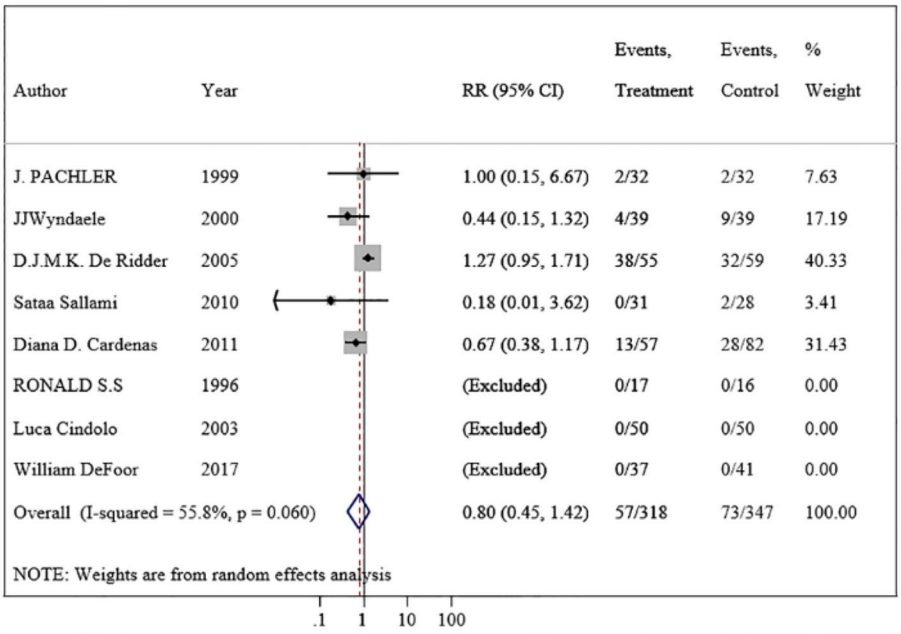

Fig. 3 Meta-analysis comparing hydrophilic catheter with non-hydrophilic catheter, evaluating gross hematuria

lidocaine cream contains additives that cause allergic reactions [32].

In recent years, water lubrication, which is an ideal solution to ultralow friction of medical catheter has received growing attentions. Hydrophilic coated catheters are usually made of PVC material and polyvinylpyrrolidone coated (PVP coated). PVP is a polymer with hydrophilic groups [33]. After the PVP hydrophilic groups are combined with a lubricating fluid (such as water or saline), the interface between the surface of catheter and the urethral mucosa forms a smooth area composed mainly of water molecules [24]. Direct contact between the surfaces is avoided during sliding process, thus greatly reducing friction coefficient and mucosal injury [24, 34, 35]. Furthermore, PVP coated possibly reduce a potential risk of urethral stricture caused by repeatedly intubation [22, 36]. Meanwhile, PVP coated is able to reduce the adsorption of fibrinogen and fibronectin, as well as the deposition of hydroxyapatite on the tube surface [34], potentially resulting in lower incidence of bladder stone.

Generally, gross hematuria is used as an indicator to estimate urethral trauma. However, the results of previous researches were contradictory in regard to whether gross hematuria could be reduced by HC [3, 12, 13]. Two meta-analyses concluded that HC was associated with a reduced risk of urethral bleeding compared with NHC [12, 13], but another research suggested a higher risk of hematuria in the HC group [3]. Simultaneously, the results from the three meta-analyses were challenged due to their inclusion, heterogeneity and bias risk analysis.

Gross hematuria is a more serious outcome indicator, so it is not a favorable indicator for reflecting the early condition of urethral damage. Innovatively, our study assessed urethral microtrauma using microscopic hematuria. Except for urethral bleeding, there are few studies evaluating whether HC reduce the incidence of adverse events, such as urethral stricture, false passages and bladder stone. In our study, HC made positive contributions to reducing the incidence of urethral microtrauma and urethral stricture compared with NHC, whereas gross hematuria was no significant difference. More studies are needed to further confirm the association between HC and these indicators in the future.

Implications for clinical practice

Due to the limitations of the study population and relevant intervention measures, the results of previous studies were contradictory and difficult to be generalized. Our study included a broad population of men and women of all ages with IC. There were no strict restrictions on the influencing factors, including catheterization frequency, self-catheterization or other-catheterization, single-use or multiple-use and the intubation environment. Therefore, our results regarding the complications of HC have broad adaptability to guide clinical practice.

Call for future studies

More high-quality, large-scale RCT studies are urgently needed. Recommendations for future research are as follows: ① The inclusion and exclusion criteria of study subjects should be clarified; ② The specific details of the intervention should be clarified including catheter material/catheter brand, the coating type and the way of lubrication; ③ key

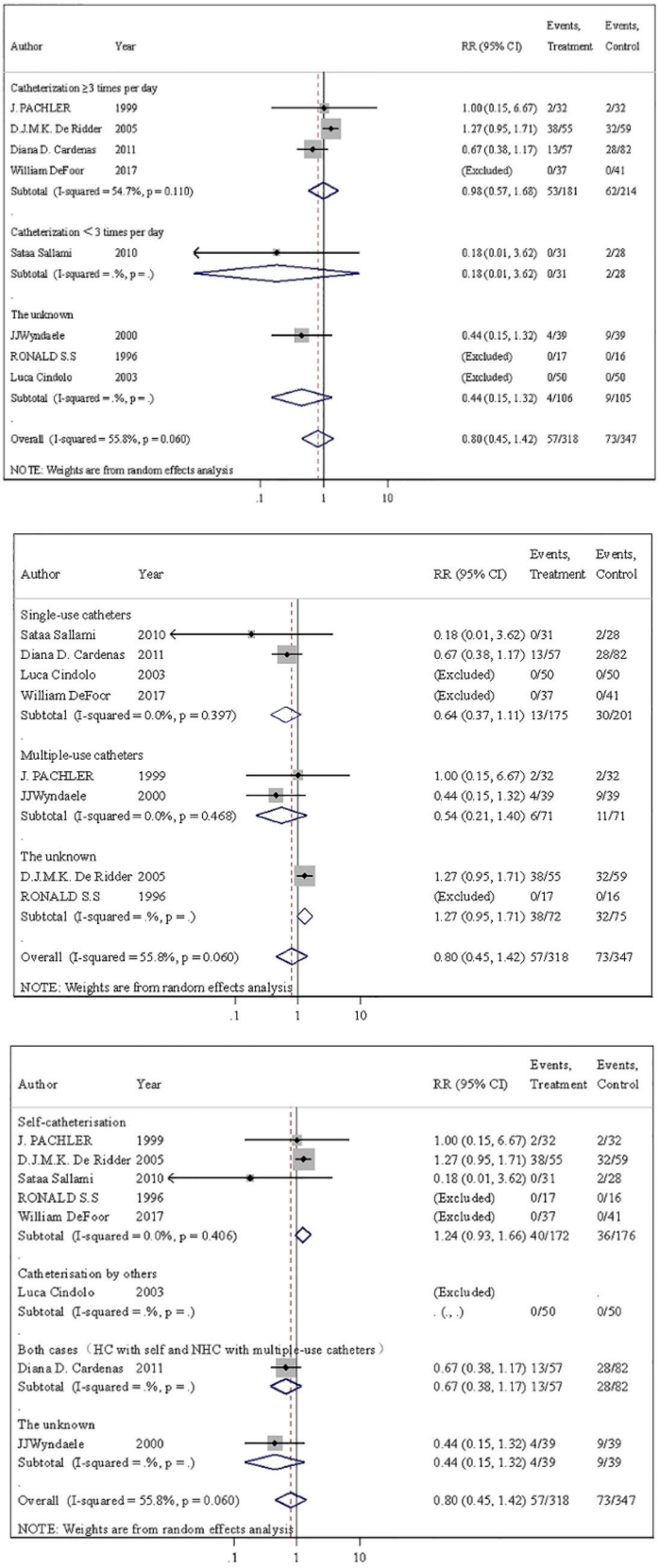

Fig. 4 Meta-analysis comparing hydrophilic catheter with non-hydrophilic catheter, evaluating subgroup analysis of gross hematuria

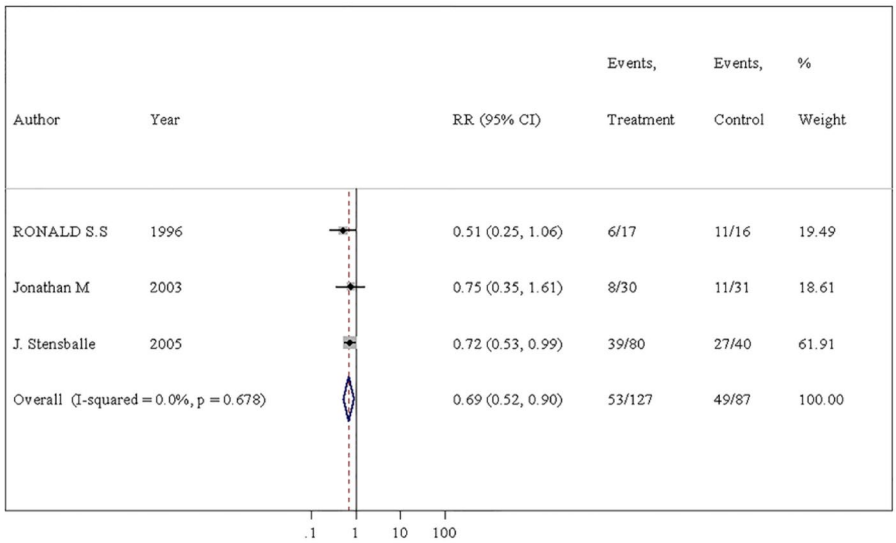

Fig. 5 Meta-analysis comparing hydrophilic catheter with non-hydrophilic catheter, evaluating microscopic hematuria

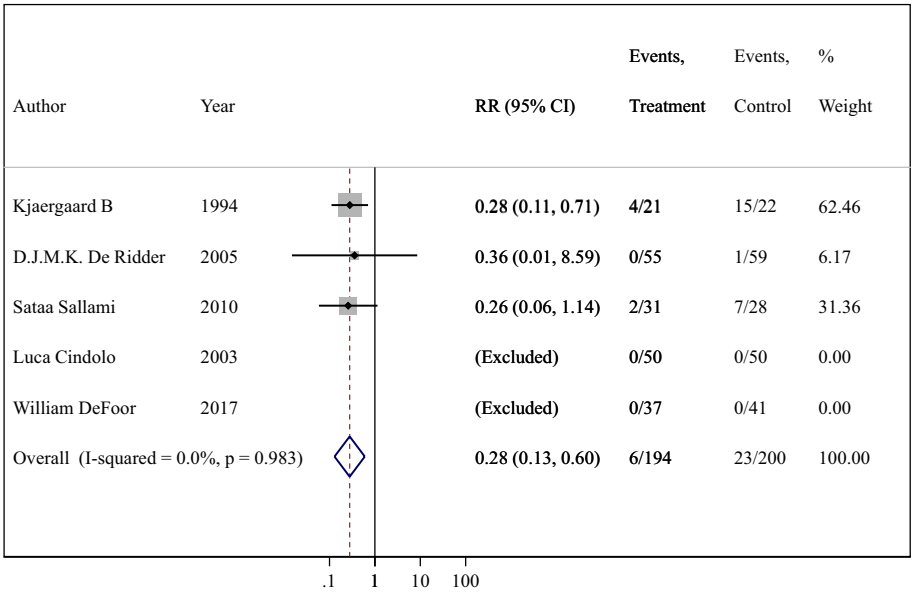

Fig. 6 Meta-analysis comparing hydrophilic catheter with non-hydrophilic catheter, evaluating urethral stricture

factors for the risk of bias need to be controlled including catheter size, total duration of intubation, time to start catheterization, self-catheterization or other catheterization, single-use or multiple-use of catheterization and catheterization frequency; ④ Call for clear definition of outcome indicators and specification of outcome measures.

Limitations

Our study still had some aspects for improving: ① Due to the wide heterogeneity of study subjects, study design, outcome measurement methods, as well as the small number of included literatures, it was difficult to conduct meta-subgroup analysis about long term adverse events such as urethral stricture. Therefore, we only performed subgroup analysis for gross hematuria; ② Risk of bias covers "little blinding of participants and interveners" and "the differences in patient drop-off between the two groups", which perhaps impact study results; ③ The majority of our data was in males and it would be a non-negligible influence factor for IC. However, the objects are only men in the current literature which was eligible for inclusion in these two indicators of microscopic hematuria and urethral stricture.

Conclusion

This meta-analysis supports the benefits of using hydrophilic coated catheters for IC in patients with bladder dysfunction, including reduced incidence of microscopic hematuria and urethral stricture. However, whether HC reduces the risk of gross hematuria has not been proven. While waiting for more evidence, it is recommended to select a more appropriate catheter type of IC combined safety, efficacy, cost effectiveness and patient satisfaction. Patients are advised to use hydrophilic coated catheter as the first treatment option when the condition permits to reduce urethral complications and offers higher comfort [20]. In this study, we evaluated the effects of HC and NHC on urethral trauma, microtrauma, urethral stricture and rare adverse events, demonstrating that HC is a better intubation method for patients with bladder dysfunction.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11255-022-03172-x.

Funding This study was funded by Key Research and Development Program from Department of Science and Technology of Sichuan Province (grant number 2021YFS0022) and the 1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University (grant number ZYJC21057).

Declarations

Conflict of interest Xi Liao declares that she has no conflict of interest. Yuwei Liu declares that she has no conflict of interest. Shiqi Liang declares that she has no conflict of interest. Ka Li declares that she has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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Acupuncture for Depression May 2026

Plain Language Summary:

Depression is treatable. Many people get better with talk therapy, medication, or both. Acupuncture is proposed as a therapy to help other treatments for depression work better.

Western medical studies show acupuncture is not helpful when treating depression. Staff recommends not adding acupuncture coverage for depression.

Staff Analysis Summary:

Significant proposed changes or discussion items:

1. Do not add acupuncture for treatment of depression based on studies done in Western healthcare settings

Changes after public comment period:

Six public comments were received on this topic from Oregon patients and providers. All commentors described their personal and/or professional benefits of acupuncture for mental health conditions. One submitted study was added to the issue summary which did not find a significant impact of auricular acupuncture on depression. These comments did not change the HERC staff assessment that acupuncture is not more clinically beneficial than control in the western medical setting.

Coverage Question:

What does the literature from studies performed in medical systems similar to the US indicate about acupuncture for depression?

Question source:

HERC

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Background:

At the March 2026 HERC meeting, HERC staff discussed a recent listening session at which two Oregon acupuncturists presented information on acupuncture for depression, anxiety and PTSD. The HERC requested that staff research the studies included in the meta-analysis presented at the May 2025 VBBS/HERC meeting that were conducted in health systems similar to the US (western Europe, Australia, Canada, or similar).

HERC staff reviewed the NICE 2022 systematic review of acupuncture for depression which concluded that there was a clinical effect, but that it was unclear whether this effect would translate into the UK medical system. The references from this NICE review were individually reviewed. 6 publications were conducted in health systems similar to the US.

Current Prioritized List/Coverage status:

Acupuncture is paired with a variety of conditions but not with depression

Evidence:

Studies included in the NICE 2022 systematic review

1) **Allen 2006** Acupuncture for Depression: A Randomized Controlled Trial
    a. United States
    b. N=157 patients
        i. N=53 specific acupuncture (N=42 at 8 weeks, 34 at 16 weeks)
        ii. N=52 non-specific acupuncture (points not intended to treat depression) (N=45 at 8 weeks, 37 at 16 weeks)
        iii. N=52 waitlist (N=44 at 8 weeks, 38 at 16 weeks)
        iv. All patients given specific acupuncture after 8 weeks
    c. Intensity of intervention: 12 acupuncture sessions over 8 weeks
    d. Hamilton rating scale for depression
        i. All subjects had significant reduction at 8 weeks
        ii. 22% of patients in specific acupuncture group, 39% of non-specific acupuncture group and 17% of waitlist group rated as responders at 8 weeks

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   e. Authors conclusions: results fail to support [TCM manual acupuncture] as a monotherapy for MDD

2) **Andreescu 2011** Acupuncture for the Treatment of Major Depressive Disorder: A Randomized Controlled Trial
   a. Australia
   b. N=53 patients
      i. N=28 electroacupuncture
      ii. N=25 control (sham acupuncture)
      iii. "Subjects remained free of psychotropic medications during the duration of the study"
   c. Intensity of intervention: 2 sessions a week for 6 weeks
   d. Both groups improved, with mean (SD) absolute HDRS score decreases of −6.6 (5.9) in the verum group and −7.6 (6.6) in the control group, corresponding to 37.5% and 41.3% relative decreases from baseline. There were no serious adverse events associated with either intervention
   e. Authors conclusions: We were unable to demonstrate a specific effect of electroacupuncture.

3) **MacPherson 2013** Acupuncture and Counselling for Depression in Primary Care: A Randomised Controlled Trial
   a. United Kingdom
   b. N=564 patients
      i. N=233 acupuncture + usual care
      ii. N=222 counseling + usual care
      iii. N=119 usual care
      iv. Usual care defined as "according to need" in the NHS system
   c. Intensity of intervention
      i. Average 8.7 acupuncture sessions over 3 months
      ii. Average 7.5 counseling sessions over 3 months
   d. The majority (68.7%) of all patients were taking antidepressants at baseline
      i. Rate comparable across study arms
   e. Compared to usual care, patients in the acupuncture arm experienced an average additional reduction in depression of -2.46 points on the PHQ-9 (p,0<001, 95% CI -3.72 to -1.21)

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f. Compared to usual care, patients allocated to the counselling arm experienced an average additional reduction in depression of -1.73 points (p = 0=008, 95% CI -3.00 to -0.45)
g. The difference between acupuncture and counselling, -0.76 points on the PHQ-9 (p= 0.41, 95% CI -0.77 to 0.25), was not statistically significant.
h. NOTE: the MCID for the PHQ-9 is -5 points
i. Authors conclusions: In this randomised controlled trial of acupuncture and counselling for patients presenting with depression, after having consulted their general practitioner in primary care, both interventions were associated with significantly reduced depression at 3 months when compared to usual care alone
j. HERC staff note: none of the PHQ-9 reductions were clinically meaningful

4) **Quah-Smith 2005** Laser acupuncture for mild to moderate depression in a primary care setting – a randomised controlled trial
    a. Australia
    b. N=25 patients
        i. N=11 inactive or sham laser
        ii. N=14 active laser
    c. Beck Depression Inventory scores
        i. Inactive group at 12 weeks: -9.1 (-14.1 to -4.1)
        ii. Active group at 12 weeks: -13.9 (-17.5 to -10.4)
        iii. Inactive group at 20 weeks: -9.4 (-13.7 to -5.1)
        iv. Active group at 20 weeks: -15.8 (-18.3 to -13.2)
        v. HERC staff note: the confidence intervals overlap between groups, indicating no significant difference
    d. Hospital Anxiety and Depression Scale (HADS) scores not significantly different at 12 or 20 weeks
    e. Authors conclusions: Conclusion Laser acupuncture may be worth further investigation as a treatment for mild to moderate depression in primary care
5) **Quah-Smith 2013** Laser acupuncture for depression: A randomised double blind controlled trial using low intensity laser intervention
    a. Australia
    b. N=43
        i. N=22 active laser

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ii. N=21 inactive laser
iii. Patients required to be “free of psychotropic drugs and herbal remedies for at least four weeks prior to trial entry”

c. Intensity of intervention: Twelve sessions of the intervention were performed: twice weekly for four weeks and once a week for another four weeks.
d. Respectively) and for QIDS-CL (P¼ o0.001 and 0.016). For QIDS-SR, although there was an overall statistically significant decrease in depression scores over time (F1, 39=4.63, p= 0.038 and F1, 42=0.013, respectively), there were no differences between groups (P=0.571 and 0.390).

Additional studies done in Western medical settings provided by experts (note: these studies were included in submitted systematic reviews)

1) **Whiting 2008** Using acupuncture to treat depression: A feasibility study
   a. United Kingdom
   b. N=19 (13 acupuncture and 6 sham acupuncture)
   c. Intensity of intervention: 12 sessions (time period not given)
   d. There was a decrease in mean scores on the BDI in both study groups, which indicates a reduction in depressive symptoms. There was also a slight increase in mean scores on the RAND in both study groups, which indicates an improvement in quality of life; however, a reduction in mean scores for the RAND categories of ‘physical functioning’ and ‘pain’ was seen in the sham-control group only
2) **Allen 1998** The Efficacy of Acupuncture in the Treatment of Major Depression in Women
   a. United states
   b. N=38 women
      i. N=12 specific acupuncture
      ii. N=11 non-specific acupuncture (control)
      iii. N=11 waitlist
      iv. Significant differences in scores existed at baseline between groups
   c. Treatment intensity: 2 sessions a week for 4 weeks then 1 session a week for 4 weeks

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d. At the conclusion of the acute (8-week) phase of treatment, by DepHRSD criteria, 50% of the participants in the specific-treatment group had remitted, whereas only 27% in the nonspecific-treatment group and 27% in the wait-list group had remitted.
    i. Remitted defined as a 50% decrease in the Hamilton Rating Scale for Depression (DepHRSD) score
e. Authors conclusions: Results from this small sample suggest that acupuncture can provide significant symptom relief in depression, at rates comparable to those of psychotherapy or pharmacotherapy.

3) **Roschke 2000** The benefit from whole body acupuncture in major depression
    a. Germany
    b. N=70 patients
        i. N=22 acupuncture
        ii. N=24 placebo acupuncture
        iii. N=24 control
        iv. All three groups were treated with an antidepressant (mianserin)
    c. Treatment intensity: three times a week over 4 weeks
    d. Both treatment and sham acupuncture groups improved slightly more than antidepressant alone group. No difference found between the treatment and sham acupuncture groups
    e. Authors conclusions: The results of our study suggest that the effect of acupuncture is unspecific and might be due to additional attention provided three times a week for nearly half an hour
4) **De Oliveira Rodigues 2023** Efficacy and Safety of Auricular Acupuncture for Depression A Randomized Clinical Trial
    a. Brazil
    b. N=47 patients
        i. N=24 specific auricular acupuncture
        ii. N=23 nonspecific auricular acupuncture (control)
    c. Treatment intensity: twice a week for 6 weeks
    d. Three months after randomization, 14 of the 24 participants (58%) randomized to the specific acupuncture group had a reduction of at least 50% in the PHQ-9 score compared with 10 of 23 participants (43%) in the

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nonspecific acupuncture group. The result was not statistically significant (risk ratio [RR], 1.34; 95% CI, 0.76-2.45; P = .38)

e. Authors conclusions: The results of this randomized clinical trial suggest that SA over 6 weeks is safe. Although there was no statistically significant difference between groups for the primary efficacy outcome, patients receiving SA did experience greater symptom remission at 3 months. A larger sample size and longer intervention are needed to further evaluate the efficacy of SA for depression

HERC staff summary:

The NICE systematic review included 5 studies in Western medical settings, 3 in Australia, 1 in the US and 1 in the UK. All 5 studies did not find a significant impact of acupuncture on depression when compared to sham acupuncture, counseling, usual care or wait list. The "dose" of acupuncture (1-2 times per week) was typical for the US healthcare system.

Four additional small studies conducted in Western medical settings (UK, US, Germany and Brazil) were found through review of references in the systematic reviews submitted by experts or were submitted by commentors. All four studies found beneficial effects of acupuncture; however, statistical significance was not reported or was not significant. Therefore, the statistical or clinical significance of the results were not determinable.

Based on the 9 studies identified conducted in Western medical settings, acupuncture does not appear to be more effective than control. The statistically and clinically significant impact seen in meta-analyses therefore was driven by studies conducted in the Chinese medical system.

HERC staff recommendation:

1) Do not add coverage for acupuncture for depression

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Public Comment Disposition: Acupuncture for Depression

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Discussion Table

IDs/#s	Summary of Issue	HERC Staff Response
A	Commentors described the beneficial effects of acupuncture on their personal and their patients mental health and recommended coverage.	Comments from providers and patients are appreciated by the HERC. One additional submitted study was included in the issue summary.

Commenters

Identification	Commenter
A	Kelly Ilseman, (Oregon provider, Oregon Acupuncturists Association Research Committee Chair) [Submitted April 16, 2026]
B	Ashley Guillen (OHP patient) [Submitted April 15, 2026]

Identification	Commenter
C	Dr. Aubrey Kelly LAc (OHP member and OHP provider) [Submitted April 7, 2026]
D	Katje Johnson Jacobs (Oregon resident) [Submitted April 2, 2026]
E	Liz Greenhill (OHP member and OHP provider) [Submitted April 3, 2026]
F	Tanya Z (OHP member, Oregon provider but not OHP provider) [Submitted April 15, 2026]

Public Comments

ID/#	Comment	Disposition
A	I fully support the Oregon Health Authority's coverage of acupuncture for depression based on both the strength of the research and clinical outcomes/experiences I have had both personally as a patient and directly with patients as an acupuncture provider. I initially sought acupuncture for women's health issues in 2004. As a person with a history of severe injury due motor vehicle accident at age 12 and someone with congenital musculoskeletal imbalances (transitional segment L4/L5 to sacrum and scoliosis) that were exacerbated by the car accident causing lifelong chronic pain, I soon realized acupuncture could help with body pain. Yet, the thing that really intrigued me about acupuncture is that it soothed my emotional experience of life. Acupuncture has effectively treated my own anxiety and depression, which are core components of PTSD. As an acupuncture practitioner working in substance use treatment, one of the	Thank you for your comments. The HERC values the perspectives of patients and providers.

ID/#	Comment	Disposition
	main benefits that I see with SUD clients is that acupuncture relieves their depression, anxiety, and PTSD, giving them the much needed resilience needed to tackle the day to day life of being substance free. Many SUD clients use substances to deal with depression, anxiety, and PTSD. They are assisted in their process of recovering from these conditions by getting regular acupuncture treatments, which in turn allows them to recover from substance use. I want to emphasize that mental health and substance use are both beneficially treated with acupuncture. Please consider OHP insurance coverage for depression, anxiety, and PTSD; this decision will beneficially impact so many Oregonians.	
B	I first received acupuncture treatment at the age of 14. Even at that early stage, I experienced a notable reduction in symptoms of social anxiety and early-onset depression. Over the years, I returned to acupuncture intermittently, particularly during periods when conventional treatments—including pharmaceutical interventions, individual psychotherapy, and group therapy—did not sufficiently address both my psychological and physical symptoms. The majority of these treatments were conducted at Working Class Acupuncture facilities. After a nine-year hiatus from therapeutic care, I reached a point where severe depression, anxiety, and accumulated complex post-traumatic stress disorder (C-PTSD) significantly impaired both my mental and physical health. At that time, I	Thank you for sharing your experiences. The HERC values patient input.

ID/#	Comment	Disposition
	began treatment at Quest Center for Integrative Health, which offers a multidisciplinary approach combining acupuncture with individual and group therapies. I enrolled in an outpatient program at Quest that incorporates acupuncture treatments two-three times per week. Within the first week of treatment, I observed meaningful improvements in both my mental state and physiological symptoms. I was able to attend group therapy sessions without experiencing debilitating social anxiety and noticed a reduction in depressive episodes during non-treatment days. Within the first month, my physical health improved substantially, and I developed the capacity to set and pursue both short- and long-term goals. My C-PTSD symptoms also showed significant improvement, and I began to experience a renewed sense of stability and hope. In addition to supporting my mental health, acupuncture has played a critical role in regulating my nervous system and mitigating the physiological effects of chronic stress. I have developed several autoimmune-related conditions that are exacerbated by stress. Through ongoing acupuncture treatment, I have experienced a marked decrease in the frequency of flare-ups, and when they do occur, both their duration and severity are significantly reduced. Overall, acupuncture has been a central component in my recovery and long-term health management. It has contributed not only to symptom reduction but also to an improved quality of life, enabling me to	

ID/#	Comment	Disposition
	function more effectively and engage meaningfully with my personal and social environment.	
C	I have worked with PTSD depression and anxiety for many years. My capstone project in 2016 was on acupuncture and PTSD. Since then, I have seen many patients dealing with all sorts of trauma related issues and helped them work through it. Aspects that have improved are self perception, sleep quality, managing emotional swings and relational dynamics, and of course pain of any kind.	Thank you for sharing your clinical experience.
D	I believe that Acupuncture can help those who suffer from anxiety and depression (including PTSD). Having this service covered by OHP will enable more folks to benefit from acupuncture. I work with a non profit who helps breast cancer patients. We have partnered with local health care providers who provide acupuncture and have seen first hand how acupuncture has helped them first hand. Many breast cancer survivors/thrivers have anxiety/depression and some PTSD before and after treatment and acupuncture has helped ease those for many of the people we serve. We have been lucky that the health providers have partnered with us and offer low to no cost but so many others are not as lucky. If OHP covered acupuncture for anxiety, depression and PTSD, imagine the amount of people who could be helped.	Thank you for sharing your experiences and for sharing your thesis on acupuncture and PTSD. Unfortunately, the HERC cannot accept reports of professional experience as evidence.

ID/#	Comment	Disposition
E	I have been an acupuncturist for nearly 20 years. Before that I was a patient who's life was dramatically improved by acupuncture for the treatment of anxiety and PTSD. That's how I decided I wanted to study it. In 2001, I was in my early twenties living in New York City. After 9/11 many of us were suffering from PTSD, anxiety, grief, and depression. At times, the PTSD was so bad it was impacting my ability to function. This went on for months and months. I sought help from various sources: EMDR therapy led me to Acupuncture and Chinese Medicine. I cannot begin to express to you the impact of acupuncture on my body. My panic attacks resolved. I was able to sleep again. I got my energy back. It felt like my soul was healing. In a sense, I had become soulsickened. It was like my nervous system had gotten fried. With acupuncture it was coming back to life and healing. After six months of acupuncture regular acupuncture, I felt enormously better and was so moved and wowed by the experience that I left my career and enrolled in graduate school for acupuncture and herbal medicine. I have practiced in Portland, Oregon since 2009, and done thousands of sessions for emotional pain as well as physical pain. This medicine is exemplary for people struggling with significant mental health issues with few options that effectively bring improvement. Pharmaceuticals can treat the symptoms and reduce them, but they do not treat the root issue in the nervous system. Acupuncture is repairative	Thank you for sharing your personal and professional experiences.

ID/#	Comment	Disposition
	by nature. It restores the body and mind and heals rifts in the soul. It helps keep people off of opioids and other dangerous drugs people reach for to numb their feelings. It has been proven over and over in studies that it statistically reduces suicide rates and symptoms of Anxiety, Depression, and PTSD. By making it billable for OHP, you are providing deep and meaningful access to this valuable medicine. Oregon has the opportunity here to be a leading state, modeling the need to prioritize mental-emotional health care, employing methods that are unconventional (to some) and that are proven time and time again to work. People need effective mental health care. What we currently have is not enough. Imagine a society where people have less anxiety, depression, and PTSD. What would you do to make that happen?	
F	As an acupuncturist, I have treated depression and seen the benefits for patients and their families. Outside of anecdotal evidence, there is research that shows acupuncture performing as well as standard practice. Also, the safety of acupuncture provides an alternative to medication, which often carries unwanted side effects. I am not asking for acupuncture to replace other therapies, but that is is offered as an option alongside allopathic practices. Oregon should set a standard of best practices utilizing evidence-based medicine, for which acupuncture has shown to be as beneficial as any other medical care.	Thank you for your comments and for the provided literature. The first link provided is the website for the American Academy of Medical Acupuncture. The de Oliveira Rodrigues 2023 RCT was added to the issue summary. The Armour 2019 article was a systematic review and meta-analysis of acupuncture for depression. The included studies had a high

ID/#	Comment	Disposition
		degree of overlap with the NICE 2022 systematic review already considered by the Commission. The Wong 2021 study was conducted in Hong Kong and this review was focused on non-Chinese type medical system studies.

References Provided by Commenters

ID	References
A	No references submitted
B	No references submitted
C	Thesis document provided
D	No references submitted
E	No references submitted
F	https://medicalacupuncture.org/conditions/depression-anxiety/ https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2812388 https://pmc.ncbi.nlm.nih.gov/articles/PMC6722678/ https://pmc.ncbi.nlm.nih.gov/articles/PMC8804104/

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Author manuscript

J Clin Psychiatry. Author manuscript; available in PMC 2023 September 28.

Published in final edited form as:

J Clin Psychiatry. 2011 August ; 72(8): 1129–1135. doi:10.4088/JCP.10m06105.

Acupuncture for the Treatment of Major Depressive Disorder: A Randomized Controlled Trial

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Abstract

Background: Over 50% of patients with major depressive disorder (MDD) either do not tolerate or do not respond to antidepressant medications. Several preliminary studies have shown the benefits of acupuncture in the treatment of depression. We sought to determine whether a 2-point

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Trial Registration:
clinicaltrials.gov Identifier: NCT00071110

Potential conflicts of interest:
Drs Andreescu and **Glick** and **Mss Emeremni** and **Houck** have no conflicts of interest relative to the subject of this article.

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electro-acupuncture protocol (verum acupuncture) would be beneficial for MDD, in comparison to needling at nonchannel scalp points with sham electrostimulation (control acupuncture).

Method: Fifty-three subjects aged 18–80 years, recruited via advertisement or referral, were included in the primary analysis of our randomized controlled trial, which was conducted from March 2004 through May 2007 at UPMC Shadyside, Center for Complementary Medicine, in Pittsburgh, Pennsylvania. Inclusion criteria were mild or moderate MDD (according to the Structured Clinical Interview for *DSM-IV* Axis I Disorders) and a score of 14 or higher on the Hamilton Depression Rating Scale (HDRS). Exclusion criteria included severe MDD, seizure disorder or risk for seizure disorder, psychosis, bipolar disorder, chronic MDD, treatment-resistent MDD, and history of substance abuse in the prior 6 months. Patients were randomized to receive twelve 30-minute sessions of verum versus control acupuncture over 6 to 8 weeks. The HDRS was the primary outcome measure. The UKU Side Effect Rating Scale was used to assess for adverse effects.

Results: Twenty-eight subjects were randomized to verum electroacupuncture and 25 to control acupuncture. The 2 groups did not differ with regard to gender, age, or baseline severity of depression. Both groups improved, with mean (SD) absolute HDRS score decreases of −6.6 (5.9) in the verum group and −7.6 (6.6) in the control group, corresponding to 37.5% and 41.3% relative decreases from baseline. There were no serious adverse events associated with either intervention, and endorsement of adverse effects was similar in the 2 groups.

Conclusions: We were unable to demonstrate a specific effect of electroacupuncture. Electro-acupuncture and control acupuncture were equally well tolerated, and both resulted in similar absolute and relative improvement in depressive symptoms as measured by the HDRS.

Depression is a common problem affecting as much as 20% of the adult population during their life-time.[1] Depression is associated with reduced quality of life, increased suicide risk, and increased morbidity and mortality of common conditions such as heart disease[1] and is often resistant to treatment, with over 50% of patients either not tolerating or not responding to antidepressant medications.[2,3] In addition, many Americans refuse conventional treatments for depression, or they discontinue them prematurely.[4,5] Other barriers to adequate antidepressant treatment involve perceived stigma associated with mental illness and minimization of the need for somatic treatment.[6]

Thus, a growing number of Americans have been turning to complementary and alternative modalities for the treatment of depression.[7] In a large survey, depression was among the 10 most frequently reported medical conditions for which respondents sought alternative treatments.[8]

These alternatives might be used as adjuncts to, or substitutes for, conventional acute treatments or as maintenance or preventive treatments following remission. A 2005 Cochrane review[9] found 7 published reports[10–16] on controlled studies of the efficacy of acupuncture for major depressive disorder (MDD). Overall, these 7 trials included a total of 547 patients, but they used a variety of designs and acupuncture interventions, and most of them had significant methodological flaws.[9] We identified 2 additional reports[17,18] published since 2004, for a total of 9 published studies: In 5 studies, all conducted in China, acupuncture or electroacupuncture was as efficacious as, or more efficacious

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than, amitriptyline (150–400 mg/d)[10–13] or maprotiline (75–250 mg/d).[15] By contrast, in the 2 US studies,[14,18] acute response and remission rates did not differ significantly among subjects randomized to depression-specific acupuncture protocols according to the principles of traditional Chinese medicine (TCM), nonspecific ("control") acupuncture, or a wait-list condition.[14,18] Finally, in a small Australian study[17] (N = 30), there was greater improvement in depressive symptoms with active laser acupuncture than with control laser acupuncture.

In a recent meta-analysis,[19] the efficacy of monotherapy acupuncture was comparable to that of an antidepressant alone—and not different from control acupuncture. A recent update of the Smith et al Cochrane review[20] included all randomized controlled trials comparing acupuncture with control acupuncture, no treatment, pharmacologic and psychotherapeutic treatment, or standard-of-care treatment. On the basis of a total of 30 trials involving over 2,800 participants, the authors concluded that there was insufficient evidence of a consistent beneficial effect of acupuncture.[20] However, a recent randomized controlled trial[21] found depression-s pecific acupuncture to be more beneficial than nonspecific control acupuncture in depressed pregnant women,[21] supporting the possibility that acupuncture could be a valuable alternative to pharmacotherapy given the risks and side effects of antidepressants during pregnancy.[21,22]

We used a randomized parallel-group design to compare the efficacy and tolerability of electroacupuncture and control ("sham") acupuncture for the treatment of mild or moderate MDD. We hypothesized that (1) depressed subjects randomized to 12 sessions of electroacupuncture would have a significantly higher decrease in their scores on the Hamilton Depression Rating Scale (HDRS)[23] than subjects randomized to control acupuncture, (2) a higher proportion of subjects randomized to electroacupuncture would experience clinical response, (3) a significantly higher proportion of depressed subjects randomized to electro acupuncture than to control acupuncture would experience an improvement in functioning, and (4) there would be no significant difference between subjects randomized to electroacupuncture and control acupuncture with regard to adverse events.

METHOD

Subjects

Patients aged 18–80 years who met the criteria for mild or moderate MDD, according to the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID),[24] and who presented with an HDRS score of 14 or above were recruited via advertisement or referral. Patients with severe MDD (as per SCID criteria) or with acute suicidality were excluded from the study. Other exclusion criteria included (1) a seizure disorder or significant risk factors for a seizure disorder (history of brain trauma, recent stroke, brain tumor); (2) psychosis; (3) bipolar disorder; (4) chronic MDD (as per SCID criteria, ie, duration of 2 years or longer); (5) treatment-resistant MDD, defined as having failed at least 1 prior adequate antidepressant trial according to the criteria of the Antidepressant Treatment History Form[25]; and (6) history of substance abuse in the 6 months prior to enrollment.

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The trial was conducted from March 2004 through May 2007 at UPMC Shadyside, Center for Complementary Medicine, in Pittsburgh, Pennsylvania, and was registered at www.clinicaltrials.gov (Identifier: NCT00071110). The protocol was approved by the Institutional Review Board of the University of Pittsburgh, Pittsburgh, Pennsylvania, and all subjects provided written informed consent.

Active and Control Interventions

Treatment regimen.—Both the active and control intervention consisted of 12 sessions (2 sessions/wk), with each session lasting 30 minutes.

Cointerventions.—All antidepressants and other psychotropic medications were tapered prior to randomization. Subjects remained free of psychotropic medications during the duration of the study. No other cointerventions (eg, herbs, exercises, life-style advice) were used.

Needling procedures.—For subjects randomized to the active electroacupuncture intervention, 0.22 × 30-mm sterile stainless steel needles were inserted at the following 2 points: Du 20 (top of the scalp, located at the intersection of the midsaggital plane and an imaginary line drawn between the apexes of the ears) and Yintang (midpoint between the eyebrows). These points were selected on the basis of the protocol reported by Luo et al.[26] At Du 20, the needle was inserted obliquely in the frontal direction beneath the scalp for 2 cm. At Yintang, the needle was inserted obliquely and downward for 2 cm. An Electro-Stimulator 4-C (Pantheon Research, Venice, California) was connected to the needles with a current of 3–5 mA and a frequency of 2 Hz. At this current intensity, subjects typically felt a slight but not uncomfortable twitching. Current was applied for 30 minutes.

The control intervention consisted of needling at nonchannel scalp points with sham electrostimulation. For subjects randomized to this control acupuncture intervention, the procedures closely followed the procedures used for the active electroacupuncture intervention except that (1) needles were inserted at 2 points that are remote from any classically described meridian or extraordinary acupuncture point and (2) no current was applied to the needles. These 2 points were located as follows: the anterior superior aspect of each ear where the helix meets the temporal region was identified, and the 2 control points were 3 cun (a Chinese word that translates to “anatomical inch”) superior bilaterally. These points correspond to the area of the coronal suture and the inferior temporal line. The location of these points on the head enhanced the similarity between the control acupuncture and the electroacupuncture and the believability of the control procedures.[27,28] The needles were inserted obliquely approximately 1 cm, which was the minimum needed to allow a stable connection to the electroacupuncture leads. We used a control electro-stimulator identical to the one used for the electroacupuncture intervention, with the lead modified so that no electrical stimulation was administered when the stimulator was turned on.

Practitioner background.—A licensed acupuncturist provided both the active and controlled interventions. The acupuncturist had 4 years of schooling, completing a Masters of Acupuncture and Traditional Chinese Medicine, was certified by the National

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Certification Commission for Acupuncture and Oriental Medicine (NCCAOM), was a licensed acupuncturist, and had been in the practice of acupuncture and TCM for 5 years prior to the start of the study. His clinical practice included the treatment of anxiety disorders and depression. He monitored the subjects periodically throughout the session for both active and control conditions, but he did not engage the subjects in conversation.

Outcome Measures and Other Assessments

Ratings were performed at the initial screen, at baseline prior to the first intervention session, weekly during the intervention, and 2 weeks postintervention. All ratings were performed by a trained research associate who was blind to the subject's randomized assignment.

The primary outcome measure was defined a priori as the absolute change in HDRS score. In addition, we also compared the proportions of responders in each group, with response defined as both a final HDRS score of 10 or less and a relative decrease of at least 50% from baseline. The UKU Side Effect Rating Scale (UKU)[29] was used weekly to assess tolerability. The Medical Outcomes Study 36-Item Short-Form Health Survey (MOS-SF-36)[30] was used at baseline and completion to assess functional improvement. Response rates, the UKU, and the MOS-SF-36 were a priori–defined secondary outcome measures. The Global Assessment of Functioning[31] was also completed at baseline and 2 weeks postintervention. In addition, an exploratory analysis was conducted to determine whether acupuncture had a meaningful impact on anxiety or sleep symptoms that have been shown to be frequently present with MDD and to respond to antidepressant treatment.[32,33] We assessed the change in scores for 2 HDRS subscales: HDRS anxiety (items 9, 10, 11, and 15 for agitation, psychic anxiety, somatic anxiety, and hypochondriasis, respectively) and HDRS sleep (items 4, 5, and 6 for early, middle, and late insomnia, respectively).[33]

At baseline, the Cumulative Illness Rating Scale[34] was completed to assess for comorbid physical illnesses, and the Mini-Mental State Examination[35] was complete to assess cognitive status.

Statistical Analysis

Randomized subjects who completed at least 1 follow-up assessment were included in the intent-to-treat analysis. We used a hierarchical linear model to assess the difference in baseline mean HDRS scores between the 2 groups (electro-acupuncture and control acupuncture). The significance of the treatment effect and rate of change was compared using a mixed-effects model with random intercepts to detect time and group-by-time differences that were treated as fixed-effects study factors in the mean-response mixed-model analysis. The dependent variable was the HDRS score at each time point. We assumed an unstructured covariance structure to account for correlation among different intervention assessment points. The significance of the treatment effect was assessed using the likelihood ratio statistic using a type I error of $\alpha = .05$. The analysis was performed using SAS Version 9.2 PROC MIXED.[36] Proportions of responders in each group were compared with χ^2 statistics; tolerability (measured by the UKU) and functional improvement (measured by the MOS-SF-36) were compared using 2-sample *t* tests. Changes

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in the scores for the HDRS anxiety and sleep subscales were analyzed using a hierarchical linear model as described above.

On the basis of the results of studies that had been published at the time this study was designed,[12,14] we predicted that we would observe a mean (SD) improvement in HDRS scores of approximately 12.2 (5.4) points in the electroacupuncture group and 2.9 (7.9) points in the control acupuncture group. Thus, we estimated that with at least 20 subjects in each group we would have a 91% power to detect a significant difference between the 2 groups.

RESULTS

Figure 1 summarizes the recruitment and retention of study subjects. Of 83 persons screened, 57 subjects who met all eligibility criteria were randomized—28 to electro-acupuncture and 29 to control acupuncture. Over the first 4 months of the study, the primary acupuncturist erred in treating the first 4 control acupuncture subjects. Although he correctly used the control electricity procedure (ie, no current was applied to the needles), he placed needles into the verum electroacupuncture points of Du 20 and Yintang for these 4 subjects randomized to control acupuncture. Therefore, we excluded them from the primary analysis, resulting in the inclusion of 28 subjects treated with electro-acupuncture and 25 treated with control acupuncture in the intent-to-treat analysis. Of these, 24 subjects in the electro-acupuncture group completed the protocol (21 of whom received at least 10 sessions), and 22 in the control acupuncture group completed the protocol (all of whom received at least 10 sessions).

Table 1 presents the demographic and baseline clinical characteristics of the 53 subjects included in the analysis. The 2 groups did not differ with regard to gender, age, education, baseline HDRS scores, and cognitive or functional status.

The absolute and relative decreases in mean (SD) HDRS scores observed in the 2 groups did not differ significantly (Table 2). In the mixed-model analysis including all subjects, the absolute decreases were −6.6 (5.9) for electroacupuncture versus −7.6 (6.6) for control acupuncture (t_{48} = 0.59, P = .56); the mean relative decreases were 37.5% (32.8) vs 41.3% (34.3), respectively (t_{48} = 0.41, P = .69). The mixed model revealed no differences between the rates of change (group-by-time interaction estimate = 0.13, SE = 0.23; P = .47), and there was no statistically significant difference between the HDRS scores in the 2 groups at end-point or at any evaluation point (Figure 2). Similarly, the proportion of responders did not differ significantly in the 2 groups (40.0% for electro-acupuncture vs 44.0% for control acupuncture; χ^2_1 = 0.08, P = .77).

We also conducted a sensitivity analysis that included in each study group the 4 subjects who were randomized to control acupuncture but who had the needles inserted into the verum points. Again, the absolute and relative decreases observed in the 2 groups and the proportion of responders did not differ significantly between the groups: (1) When we included these 4 subjects in the control acupuncture group, the mean HDRS absolute decreases were −6.6 (5.9) for electroacupuncture and −8.3 (6.4) for control

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acupuncture (t_{52} = −0.96, P = .34); the mean relative decreases were 37.5% (32.8) versus 45.9% (34.4), respectively (t_{52} = 0.91, P = .36); and the proportions of responders were 40.0% versus 48.3%, respectively (χ^2_1 = 0.37, P = .54). (2) When we included these 4 subjects in the electroacupuncture group, the mean absolute decreases were −7.3 (5.9) for electroacupuncture and −7.6 (6.6) for control acupuncture (t_{52} = −0.19, P = .85); the mean relative decreases were 42.5% (33.6) versus 41.3% (34.3), respectively (t_{52} = −0.13, P = .90); and the proportions of responders were 44.8% versus 44.0%, respectively (χ^2_1 = 0.0037, P = .95).

There were no serious adverse events in either group. Endorsement of adverse effects and endpoint UKU scores did not differ between the 2 groups (see Table 2). Similarly, there was no difference in functional improvement, as measured by the MOS-SF-36 (see Table 2). The 2 groups had similar baseline HDRS sleep subscale scores (see Table 1), and a second mixed model revealed that both groups experienced a significant decrease in their HDRS sleep subscale scores over time (t_{253} = −2.04, P = .04), with no difference between the groups. The 2 groups had similar baseline HDRS anxiety subscale scores (see Table 1), and both groups also experienced a significant decrease in their HDRS anxiety subscale scores over time (t_{253} = −4.99, P < .001), with no significant difference between the groups.

DISCUSSION

We conducted a randomized controlled trial to compare the efficacy and tolerability of electroacupuncture and control acupuncture for the treatment of mild or moderate MDD. Electroacupuncture was well tolerated and resulted in close to a 50% reduction in depressive symptoms as measured by the HDRS. However, there was no significant difference between the absolute or relative changes in HDRS score observed in the electroacupuncture and the control acupuncture groups. Similarly, the 2 groups did not differ with regard to functional improvement or improvement in anxiety or sleep symptoms. These results differ from the reports in the Chinese literature[10–12,26] but are similar to reports from other trials conducted in North America.[14,18,37]

Our negative results need to be considered in the context of some potential limitations in the design and conduct of our study: an error in the treatment of 4 subjects, the selection of our control (“sham”) condition, and a standardized protocol using only 2 needles.

Inadvertently, the acupuncturist treated the first 4 subjects in the control group with the verum points without electricity. As a result, these subjects did not fit with either group, and they were excluded from the analysis. A sensitivity analysis showed that including them in either group would not appreciably change the study results.

One possible interpretation of our results is that the beneficial effect of electroacupuncture we observed is due solely to a placebo effect. However, there are many complexities in conducting acupuncture research. Similar to research on pharmacotherapy, studies of acupuncture commonly find that a believable control intervention improves clinical outcomes comparably to the active (verum) acupuncture treatment but to a greater extent than no-treatment, wait-list, or other nonneedle controls.[38,39] A placebo is defined as being

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inert and *believable*.[40] Extensive studies and commentaries have indicated problems with both of these assumptions.[41] As with the use of placebo pills, needling at nonacupuncture points can be associated with physiologic effects that can be detected by functional neuroimaging.[42] Even sham or nonpenetrating needles display these properties. For our control condition, the needles were inserted far from any specific acupuncture meridian. However, in both TCM and Japanese approaches, the entire scalp is considered a microsystem, with any point corresponding to an area of the body and having some effect.[38,43] The control points we used are located on the scalp and thus might not offer a viable inert control to the verum points. Therefore, we might have in fact tested 2 potentially effective treatments, explaining why we did not detect any differences between our active and control interventions. Also, care was taken in our study and other studies to maintain the blind; however, given the difference in technique and the fact that the treating acupuncturist cannot be blinded, it is difficult to have the same level of concealment as in a placebo-drug study.

There has been extensive research and discussion in the literature regarding the optimal design of acupuncture trials, including the above issues pertaining to placebo.[40,41,43,44] Considerations include the use of nonpenetrating, telescoping needles; the use of a multigroup design with comparison of verum acupuncture, a needle control, and some other control such as wait-list; and options for providing a more individualized acupuncture intervention.[28,40,43]

Another factor that has an impact on acupuncture trials is the use of a standardized treatment. In clinical practice, an acupuncturist will individualize treatment on the basis of the TCM diagnosis, which includes evaluation of constitutional symptoms, pulses, and the tongue. This evaluation leads to the use of specific points for treatment and to modulation of the intensity of stimulation of the needles, all based on the TCM diagnosis. Conversely, most Western-designed randomized controlled trials, including this study, have utilized a standardized protocol for all subjects, which may minimize the treatment efficacy.

Finally, dosage of the treatment may also have contributed to this study's negative results. The use of only 2 acupuncture points reflects a minimalist approach. We selected this approach on the basis of the positive results of previous studies published by Luo et al[11,26] that used the same 2 acupuncture points. However, their study used a much higher dose of electroacupuncture (6 sessions per week for 6 weeks) than our protocol, which consisted of twelve 30-minute sessions—a dosage that has been commonly used in other studies and that is considered adequate to determine an acute effect. A number of other acupoints have been described in the TCM literature as being useful for the treatment of depression, anxiety, and sleep problems. Consequently, one could consider a "dose-finding study" comparing our active protocol, 1 or 2 additional conditions with a greater number of points to be treated, and a control condition. However, such a multigroup design would require a much larger sample size. Moreover, recruitment into our study was hindered by the exclusion of anyone taking any psychotropic medications. To conduct a larger study, investigators could include and stratify subjects who are currently taking a selective serotonin reuptake inhibitor or other antidepressant.

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In conclusion, our data support the tolerability of electro-acupuncture in the treatment of mild or moderate MDD. Both the subjects treated with electroacupuncture and those who received control acupuncture experienced a significant and comparable decrease in HDRS scores from baseline to end-of-intervention. Thus, we were not able to demonstrate a specific effect of electroacupuncture. Future studies might consider different designs, such as a 3-group design com paring our 2-acupoint protocol, a more extensive TCM-based acupuncture intervention, and a control condition using noninserted placebo needles.

Acknowledgment:

The authors acknowledge Richard D. Day, PhD, of the Department of Biostatistics, University of Pittsburgh, for his contribution to the original statistical design of the study. Dr Day has no conflicts of interest relative to the subject of this article.

Dr Mulsant has received grants/research support from the National Institutes of Health (NIH), the Canadian Institutes of Health Research, AstraZeneca, Bristol-Myers Squibb, Corcept, Eisai, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Pfizer, and Wyeth; has been a consultant for AstraZeneca, Bristol-Myers Squibb, Eisai, Eli Lilly, Forest, Fox Learning Systems, GlaxoSmithKline, Janssen, Lundbeck, and Pfizer; has been a member of the speakers bureaus for and has received honoraria from AstraZeneca, Eisai, Forest, GlaxoSmithKline, Janssen, and Pfizer and has also received honoraria from Lundbeck; has directly held stocks (all less than $10,000) of Akzo-Nobel, Alkermes, AstraZeneca, Biogen Idec, Celsion, Elan, Eli Lilly, Forest, General Electric, Orchestra Therapeutics, and Pfizer; and has received other financial or material support from Forest and Janssen.

Funding/support:

Supported by grants R21 AT001218 from the National Center for Complementary and Alternative Medicine, NIH, Bethesda, Maryland, and K23 MH086686, K24 MH069430, and P30 MH071944 from the National Institute of Mental Health, NIH, Bethesda, Maryland; a NARSAD Young Investigator Award, Great Neck, New York (Dr Andreescu); and the John A. Hartford Foundation Center of Excellence in Geriatric Psychiatry, University of Pittsburgh, Pittsburgh, Pennsylvania.

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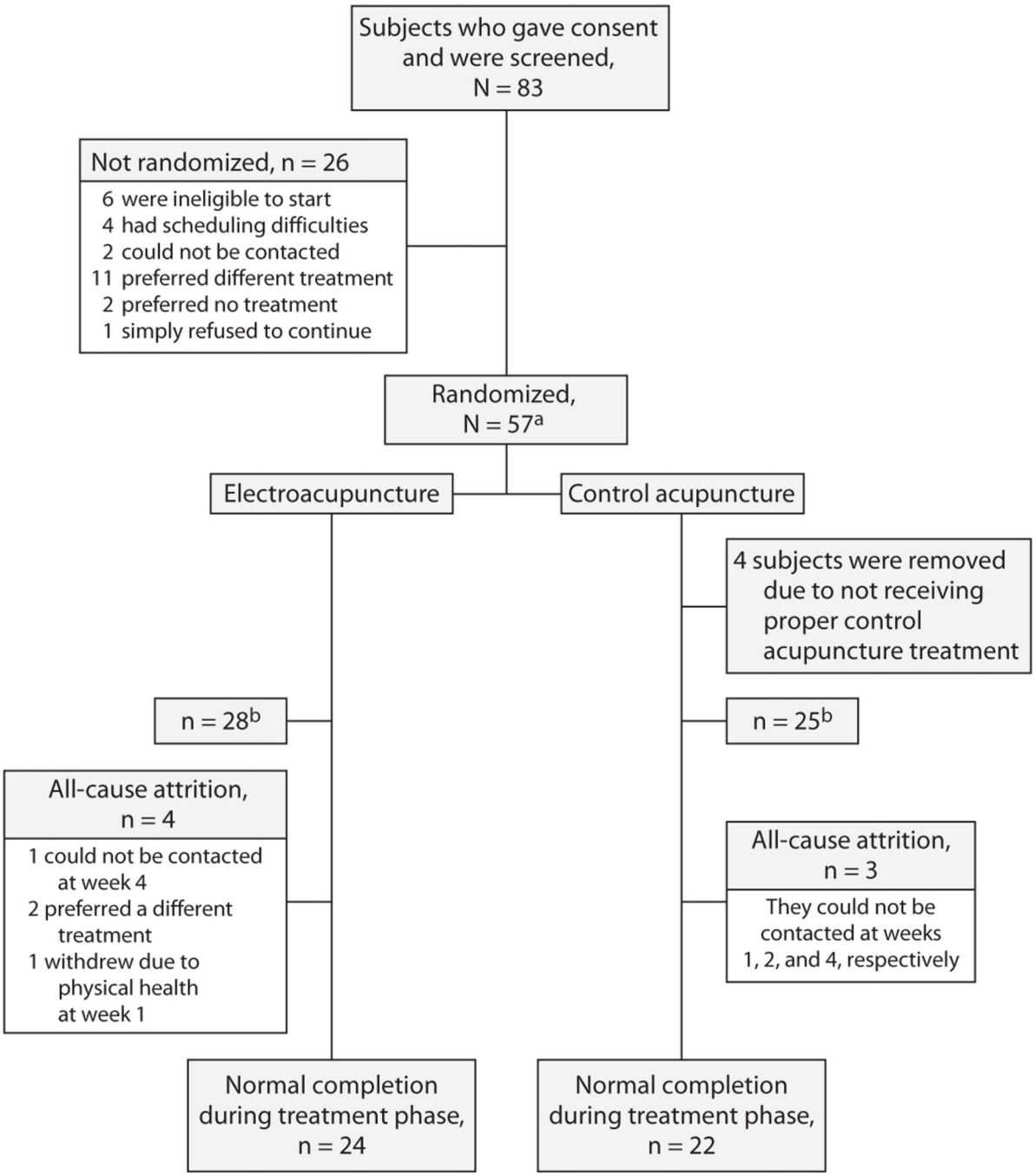

Figure 1.

Flowchart of Recruitment and Retention of Study Subjects

[a]These 57 subjects were included in the sensitivity analysis.

[b]These 53 subjects were included in the primary analysis.

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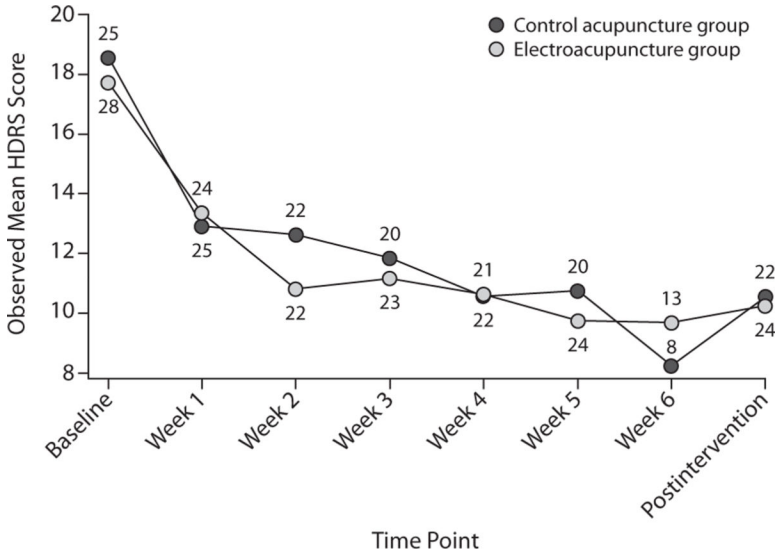

Figure 2.

Hamilton Depression Rating Scale (HDRS) Weekly Scores (main efficacy findings)[a]

[a]Plot of observed mean depression scores by week, with the frequency at each point labeled.

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Table 1.

Demographic and Baseline Clinical Characteristics of Study Subjects (N = 53)[a]

Characteristic	Electroacupuncture Group (n = 28)	Control Acupuncture Group (n = 25)	Statistic (*t* or χ^2)	*P* Value
Age at consent, y	46.0 (11.5)	49.1 (14.0)	0.88	.38
Sex, male, n (%)	7 (25.0)	8 (32.0)	0.32	.57
Race, white, n (%)	21 (75.0)	22 (88.0)	1.46	.23
Education, y	15.4 (2.7)	15.3 (2.8)	0.10	.92
Hamilton Depression Rating Scale score	17.7 (3.9)	18.6 (2.9)	0.89	.36
UKU Side Effect Rating Scale score	13.4 (5.0)	15.9 (6.0)	1.74	.09
Mini-Mental State Examination score	29.6 (0.6)	26.7 (0.6)	0.53	.60
Cumulative Illness Rating Scale score	2.6 (2.2)	3.8 (3.0)	1.68	.10
Medical Outcomes Study 36-Item Short-Form Health Survey score				
Physical component	48.8 (9.9)	48.8 (11.8)	0.00	1.00
Mental component	27.1 (9.0)	25.8 (10.9)	−0.45	.66
Bodily pain index	62.5 (24.8)	60.3 (23.7)	−0.31	.75
Global Assessment of Functioning score	60.5 (6.1)	59.2 (5.2)	−0.84	.41
Hamilton Depression Rating Scale sleep subscore	2.5 (1.5)	1.8 (1.7)	−1.58	.12
Hamilton Depression Rating Scale anxiety subscore	4.8 (1.7)	4.5 (1.6)	−0.52	.61

[a]All results are reported as mean (SD) unless otherwise indicated.

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Table 2.

Score Changes From Baseline to Postintervention Evaluation (N = 45)[a]

Measure	Electroacupuncture Group (n = 23)	Control Acupuncture Group (n = 22)	Statistic (*t*)	*P* Value
Hamilton Depression Rating Scale	−7.4 (6.2)	−7.9 (7.4)	.24	.81
UKU Side Effect Rating Scale	−4.0 (4.6)	−7.0 (6.3)	1.59	.12
Medical Outcomes Study 36-Item Short-Form Health Survey				
Physical component	0.5 (6.9)	−1.7 (8.0)	−1.00	.32
Mental component	6.2 (13.6)	14.1 (17.5)	1.56	.09
Bodily pain index	−1.0 (18.3)	6.8 (19.7)	1.40	.17
Global Assessment of Functioning	10.3 (10.3)	11.4 (8.8)	.39	.70

[a]All results are reported as mean (SD).

Acupuncture and Counselling for Depression in Primary Care: A Randomised Controlled Trial

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Abstract

Background: Depression is a significant cause of morbidity. Many patients have communicated an interest in non-pharmacological therapies to their general practitioners. Systematic reviews of acupuncture and counselling for depression in primary care have identified limited evidence. The aim of this study was to evaluate acupuncture versus usual care and counselling versus usual care for patients who continue to experience depression in primary care.

Methods and Findings: In a randomised controlled trial, 755 patients with depression (Beck Depression Inventory BDI-II score ≥20) were recruited from 27 primary care practices in the North of England. Patients were randomised to one of three arms using a ratio of 2:2:1 to acupuncture (302), counselling (302), and usual care alone (151). The primary outcome was the difference in mean Patient Health Questionnaire (PHQ-9) scores at 3 months with secondary analyses over 12 months follow-up. Analysis was by intention-to-treat. PHQ-9 data were available for 614 patients at 3 months and 572 patients at 12 months. Patients attended a mean of ten sessions for acupuncture and nine sessions for counselling. Compared to usual care, there was a statistically significant reduction in mean PHQ-9 depression scores at 3 months for acupuncture (−2.46, 95% CI −3.72 to −1.21) and counselling (−1.73, 95% CI −3.00 to −0.45), and over 12 months for acupuncture (−1.55, 95% CI −2.41 to −0.70) and counselling (−1.50, 95% CI −2.43 to −0.58). Differences between acupuncture and counselling were not significant. In terms of limitations, the trial was not designed to separate out specific from non-specific effects. No serious treatment-related adverse events were reported.

Conclusions: In this randomised controlled trial of acupuncture and counselling for patients presenting with depression, after having consulted their general practitioner in primary care, both interventions were associated with significantly reduced depression at 3 months when compared to usual care alone.

Trial Registration: Controlled-Trials.com ISRCTN63787732

Please see later in the article for the Editors' Summary.

Citation: MacPherson H, Richmond S, Bland M, Brealey S, Gabe R, et al. (2013) Acupuncture and Counselling for Depression in Primary Care: A Randomised Controlled Trial. PLoS Med 10(9): e1001518. doi:10.1371/journal.pmed.1001518

Academic Editor: Vikram Patel, London School of Hygiene & Tropical Medicine, United Kingdom

Received February 25, 2013; **Accepted** August 14, 2013; **Published** September 24, 2013

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Funding: This article presents independent research funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research Programme (RP-PG-0707-10186). The views expressed are those of the author(s) and not necessarily those of the National Health Service, the NIHR or the Department of Health. The funders, and the University of York in its role as sponsor for the study, had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

Abbreviations: ANCOVA, analysis of covariance; AUC, area under the curve; SD, standard deviation.

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Introduction

Depression will be the second leading cause of disease burden worldwide by 2020, according to the Global Burden of Disease Study [1]. An estimated 2·6 million cases of depression were reported in England in 2000 [2]. It is the third most common reason for primary care consultations [3]. The economic burden is estimated to exceed UK£9 billion per annum in England, with direct costs of treatment being approximately UK£370 million [2]. Anti-depressants are the front-line treatment in primary care, yet an inadequate response to antidepressant treatment has been reported in up to 60% of patients [4] and lack of adherence to medication in 30% [3]. The effectiveness of newer anti-depressants for mild to moderate depression has recently come under question [5]. Patients have been concerned about an over-reliance on prescribed antidepressant medications and are keen to have access to non-pharmacological treatment options [6].

Acupuncturists commonly treat depression [7], but it is rarely provided within the UK's mental health services or primary care [8]. A Cochrane review found insufficient data on whether or not acupuncture is an effective intervention for depression, in part because of the high risk of bias in the majority of studies [9]. This review recommended the use of comparative designs in future research, comparing acupuncture to structured psychotherapies such as counselling or standard care. A widely used intervention for patients with depression is counselling, which is provided in approximately half of the 9,000 primary care practices in England [10]. Most counsellors provide a humanistic style of counselling. Recent National Institute for Health and Care Excellence (NICE) guidance is equivocal in recommending counselling for mild to moderate depression, identifying uncertainty regarding its effectiveness [11]. A Cochrane review, which identifies short-term but not long-term benefits from counselling, recommends extending the evidence base to include comparisons not just with usual care but also other interventions, including acupuncture, as this would have the potential to increase patient choice [12].

The primary aim of this study was to determine the clinical effectiveness and cost-effectiveness of short courses of either acupuncture or counselling when compared to usual care for patients with moderate to severe depression, with the secondary aim to compare acupuncture and counselling on the basis that there is structural equivalence regarding time and attention. The health economic results will be reported separately.

Methods

Ethics Statement

Ethical approval was obtained on 21st September 2009 from the York NHS Research Ethics Committee (ref: 09/H1311/75).

Design

The design was that of an open parallel-arm randomised controlled trial with patients randomised by the York Trials Unit to one of three arms using the allocation ratio of 2:2:1, respectively: acupuncture plus usual care; counselling plus usual care; and usual care alone, as detailed in the published protocol [13]. Patient details were recorded by the Trials Unit prior to using Structured Query Language (SQL) software for computer-generated block randomisation, with block sizes of five and ten, conducted by an investigator with no clinical involvement in the trial. This ensured that the allocation was securely concealed from the researchers who subsequently informed patients of their allocation.

Population

Patients who had consulted with depression in primary care within the past 5 years, and were continuing to experience moderate to severe depression were recruited. Identified from general medical practice databases, potential participants were aged 18 or over. Patients returned written consent forms and baseline questionnaires and were eligible if scoring 20 or above on the Beck Depression Inventory-II [14]. Thus all participants would be recognised as having depression. We used a different screening questionnaire from our chosen outcome measurement of depression, PHQ9 [15], because we did not want to use a screening questionnaire with a cut-off as the baseline measure in our analysis, to avoid problems of regression towards the mean. We did not want to give people the same questionnaire twice in fairly rapid succession, hence our choice of a second, also well-established, questionnaire for screening. We excluded patients who were receiving acupuncture or counselling at the time, who had terminal illness, significant learning disabilities, haemophilia, hepatitis, HIV, were pregnant, or who had confounding psychiatric conditions (bipolar disorder, postpartum depression, adjustment disorder, psychosis, dementia, or personality disorder). Patients who had suffered a close personal bereavement or given birth during the previous 12 months were excluded. Spoken English was a requirement.

Interventions

Patients allocated to the acupuncture and counselling groups were offered up to 12 sessions usually on a weekly basis. Participating acupuncturists were registered with the British Acupuncture Council with at least 3 years post-qualification experience. An acupuncture treatment protocol was developed [16] and subsequently refined in consultation with participating acupuncturists. It allowed for customised treatments within a standardised theory-driven framework. Counselling was provided by members of the British Association for Counselling and Psychotherapy who were accredited or were eligible for accreditation having completed 400 supervised hours post-qualification. A manualised protocol, using a humanistic approach, was based on competences independently developed for Skills for Health [17]. Practitioners recorded in logbooks the number and length of sessions, treatment provided, and adverse events. Further details of the two interventions are presented in Tables S2 and S3. Usual care, both NHS and private, was available according to need and monitored for all patients in all three groups for the purposes of comparison.

Outcome Measures

Our primary outcome measure was the PHQ-9 [15] at 3 months. In addition, we evaluated the overall impact over a 12-month period. PHQ-9 scores range from 0 to 27, with depression considered mild (5–9), moderate (10–14), moderately severe (15–19), or severe (20 and above). The EQ-5D was used as a preference-based measure of health outcome [18]. The use of medication was ascertained by asking patients whether they had taken any prescribed medication for depression or any prescribed analgesics/painkillers. Patients were asked to report health service use, including the number of times they had consulted a health professional because of their depression. Out-of-pocket costs included patient reports on spending on acupuncture, counselling, or psychotherapy including cognitive behavioural therapy. These data were collected at baseline and by postal questionnaire at 3, 6, 9, and 12 months These data were self-reported by patients

independent of the research team, thereby avoiding problems of potential differentials between trial arms, such as unblinding, that could lead to bias. BDI-II was collected at baseline and 12 months. We collected baseline demographic data and patients' prior preferences and expectations of the interventions. For both acupuncture and counselling groups, we measured patients' perceptions of their practitioners' empathy at 3 months using the Consultational and Relational Empathy (CARE) measure [19]. A reimbursement of UK£5 was enclosed with the final questionnaire to enhance response rate [20]. In-depth interviews were used to explore the experiences and perspectives of patient and practitioner, the results of which will be reported separately.

Sample Size

An effect size of 0·39 on the PHQ-9 was sought when comparing either acupuncture versus usual care alone or counselling versus with usual care alone. An allocation ratio of 2:2:1 was chosen in order to increase power to detect statistically significant differences between acupuncture and counselling. As a result, a smaller effect size of 0·32 was sought when comparing acupuncture and counselling. Anticipated differences between the treatments were likely to be smaller but not clinically meaningful. With 90% power and a two-sided significance level of 5%, the required group sizes were 204, 204, and 102 participants in the acupuncture, counselling, and usual care alone arms, respectively. Allowing for 20% attrition, the total sample size required was 640 (i.e., groups of 256, 256, 128, respectively).

Analysis

The primary effectiveness comparisons were between acupuncture plus usual care versus usual care alone, and counselling plus usual care versus usual care alone. A secondary comparison was between acupuncture plus usual care versus counselling plus usual care. The primary outcome was PHQ-9 at 3 months, for which we used analysis of covariance (ANCOVA), with baseline PHQ-9 score as covariate. Multiple imputation by chained regression was used for missing data using treatment group, baseline measures (PHQ-9, BDI-II, SF-36, EQ-5D Anxiety/Depression), and demographics (age and gender). The primary analysis was based on the imputed rather than raw data in order to take account of the profile of non-responders.

To assess the overall clinical impact at 12 months, we evaluated area under the curve (AUC) for PHQ-9 over that period by linear regression, predicting average AUC while controlling for baseline PHQ-9. We also explored PHQ-9 outcomes across all time points in more detail using random intercept linear mixed models with fixed effects for treatment arm, time, and arm by time interaction for each treatment comparison. The models nested time points within patients and controlled for baseline PHQ-9 and potential mediators including patients' prior expectations and preferences regarding the treatments. These were identified by univariate regressions ($p<0·1$) of PHQ-9 at 3 months for the whole patient sample, controlling for baseline PHQ-9. When comparing acupuncture and counselling, we controlled for treatment time (combined length of sessions) and quality of attention (CARE empathy score). Treatment differences between BDI-II depression scores at 12 months were analysed by ANCOVA, controlling for BDI-II baseline scores and covariates for depression as identified above. Missing data were multiply imputed as for the PHQ-9.

All analyses were carried out in Stata (version 12.1) on an intention-to-treat basis. Statistical tests were at a two-sided 0·05 significance level. Analysis of residuals was undertaken for all regression models in order to assess model assumptions.

Results

Participants

Patient flow in the trial is presented in Figure 1. In total 755 patients were recruited, 18% over target, from 27 general medical practices between December 2009 and April 2011 in Yorkshire and northeast England. General practices recruited an average of 28 patients (range 0 to 122). Baseline patient characteristics were balanced between the trial arms and are presented in Table 1. These characteristics included data on expectations of the treatments, which were lowest for acupuncture (68% were undecided) and preferences, for which the majority (58%) would have preferred to have been allocated acupuncture. These variations were taken into account in the linear mixed model analysis. Comparison of baseline data between patients with and without missing data at 3 months is presented in Table S1.

Interventions

In the acupuncture arm, 266 patients (88.1%) received one or more treatment sessions (mean = 10.3, standard deviation [SD] 3.14) with one of 23 acupuncturists. By the 3-month time point, the average number of sessions received was 8.7 (SD = 3.34), with 133 patients (50.0%) having completed all of their sessions. In the counselling arm, 231 patients (76.5%) received one or more treatment sessions (mean = 9.0, SD = 3.74) with one of 37 therapists. By the 3-month time point, the average number of sessions received was 7.5 (SD = 3.60), with 114 patients (49.4%) having completed all of their sessions. The mean time from randomisation to last treatment was 117 days in both treatment arms (SD = 47.0 and 51.2, respectively), a period that included time to first appointment. Acupuncturists were allocated an average of 13 patients each (range two to 45), and counsellors an average of eight patients each (range one to 27).

In the logbooks, we collected data on acupuncturists' and counsellors' self-reports of intervention protocol violations. We received reports of four cases of violations of the acupuncture protocol (which incidentally did not involve counselling), one of which was deemed a true case involving prescription of a herbal lotion application to reduce swelling and pain. We received seven reports of violations of the counselling protocol, of which two were deemed true cases; one case involved goal setting and in another the counsellor reported being analytical and interpretative beyond the scope of humanistic counselling.

Details of medication use over the period of the trial is reported below, and further details of all three interventions are summarised for acupuncture (Table S2) and counselling (Table S3), and, respectively, and for usual care: patients seeing a health professional (Table S4); patients attending hospital accident and emergency departments (Table S5); patients admitted to hospital (Table S6); and patients paying for private health care (Table S7). A more complete report on the acupuncture provision has now been published [21] and one on the counselling provision will follow shortly.

Clinical Outcomes

Unadjusted mean scores for the PHQ-9 at all time points are presented in Table 2 and Figure 2. For the primary outcome, Table 3 gives results for between-group differences in PHQ-9 depression at 3 months using ANCOVA. Patients for whom no data were available at that point tended to be younger with higher levels of baseline depression, and imputed data were used to take their profile into account. Compared to usual care, patients in the acupuncture arm experienced an average additional reduction in depression of −2·46 points on the PHQ-9 ($p<0·001$, 95% CI

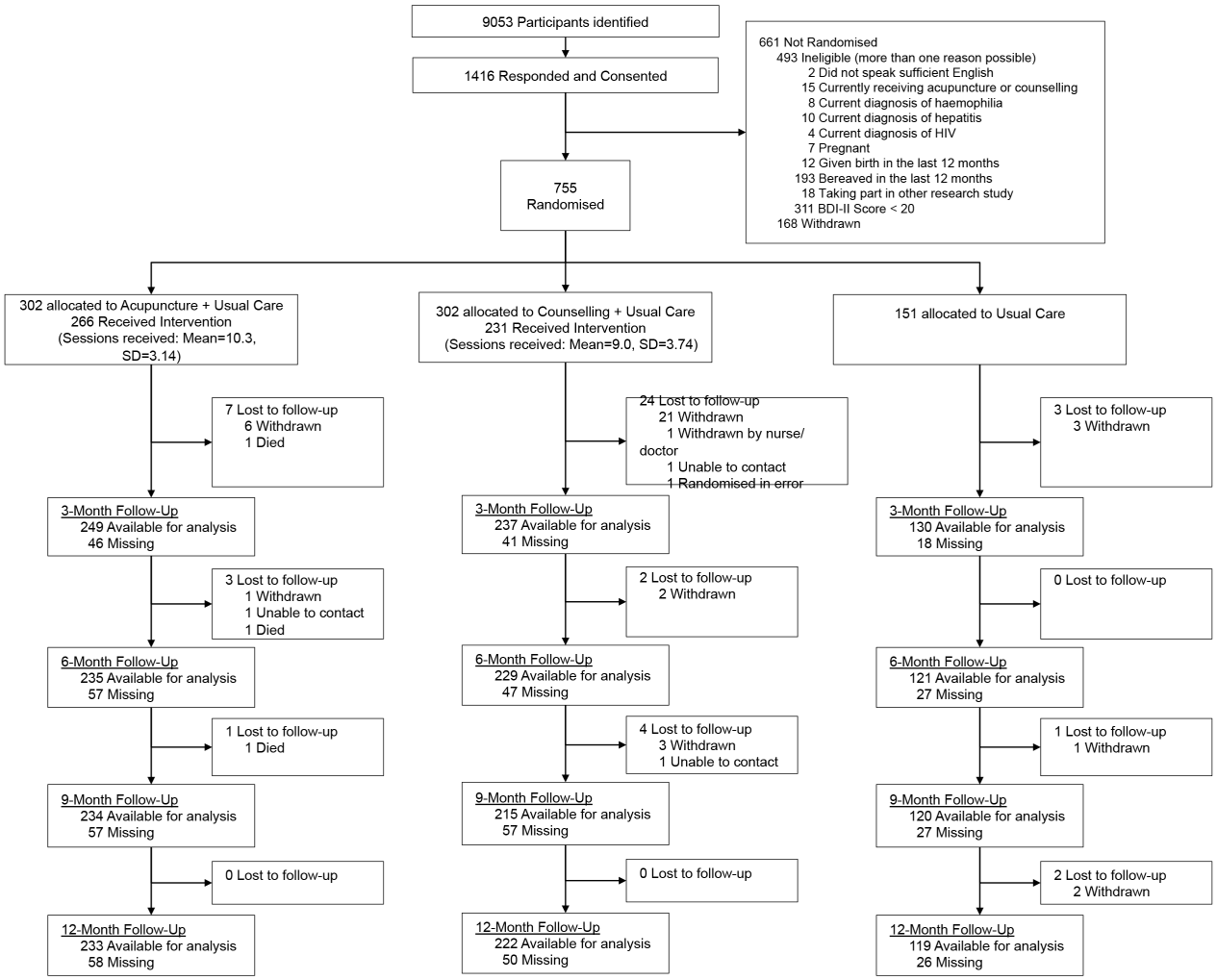

Figure 1. CONSORT flow diagram.
doi:10.1371/journal.pmed.1001518.g001

−3·72 to −1·21), an observed effect size equivalent to a Cohen's *d* of −0·39 (95% CI −0·58 to −0·19). Compared to usual care, patients allocated to the counselling arm experienced an average additional reduction in depression of −1·73 points ($p = 0·008$, 95% CI −3·00 to −0·45), equivalent to a Cohen's *d* of −0·27 (95% CI −0·47 to −0·07). The difference between acupuncture and counselling, −0·76 points on the PHQ-9 ($p = 0.41$, 95% CI −1·77 to 0·25), was not statistically significant. These data are conservative, as non-imputed data showed slightly larger treatment effects (see Table S8).

In the AUC analysis of PHQ-9 scores over 12 months, the benefit of acupuncture and counselling over usual care alone in terms of score reduction seen at 3 months remained when averaging over the 12-month trial period: acupuncture reduced PHQ-9 scores by −1·55 (95% CI −2·41 to −0·70); counselling by −1·50 (95% CI −2·43 to −0·58) (Table 3).

In secondary analyses, PHQ-9 at 3 months was associated with two factors: expectations of counselling ($p = 0·064$) and expectations about the treatment that patients were allocated to ($p = 0·015$). These factors were included as potential mediators of the effect of trial arm in further analyses. Within the acupuncture and counselling arms, additional significant factors were total session time at 3 months ($p < 0·001$) and perceived empathy of practitioners ($p < 0·001$), which were added as further covariates.

Linear mixed modelling showed reduced PHQ-9 depression in the acupuncture and counselling groups as compared to usual care at 3 and 6 months (Table 3). The scores in the usual care group continued to reduce over time, such that differences were no longer statistically significant at 9 and 12 months. There was no evidence of significant differences between acupuncture and counselling throughout.

Unadjusted mean scores for the BDI-II at baseline and 12 months are shown in Table 2. Results using ANCOVA show that depression scores on the BDI-II were reduced in the acupuncture arm (−2·88, 95% CI −5·68 to −0·08) and counselling arm (−2·74, 95% CI −5·50 to 0·02) to a greater extent than by usual care alone at 12 months, but with no statistically significant differences between the two interventions (Table 4).

Prescribed Medication

The majority (68·7%) of all patients were taking antidepressants at baseline (Table 5). The use of prescribed antidepressants decreased steadily by an average of 12% over the 12-month study period, the rate of which was comparable between trial arms. Around half (47·9%) of patients were taking analgesics at baseline,

Table 1. Demographics and variables of interest at bastline.

Characteristic	Acupuncture + Usual Care	Counselling + Usual Care	Usual Care	Total
n	302	302	151	755
Age				
Mean (SD)	43·4 (13·24)	43·5 (13·26)	43·5 (13·93)	43·5 (13·37)
Median (min, max)	43 (18–86)	43 (18–93)	42 (18–89)	43 (18–93)
Inter-quartile range	34–52	33–52	32–54	33–53
Missing	–	–	–	–
Sex				
Male	88 (29·1%)	69 (22·9%)	44 (29·1%)	201 (26·6%)
Female	214 (70·9%)	233 (77·1%)	107 (70·9%)	554 (73·4%)
Missing	–	–	–	–
Age left education				
Mean (SD)	18·0 (4·69)	18·0 (3·92)	18·1 (4·62)	18·0 (4·37)
Median (min, max)	16 (13–54)	16 (14–48)	16 (14–54)	16 (13–54)
Inter-quartile range	16–18	16–19	16–19	16–19
Missing	17 (5·6%)	7 (2·3%)	7 (4·6%)	31 (4·1%)
Employment				
Full-time education	13 (4·4%)	5 (1·7%)	5 (3·3%)	23 (3·1%)
Working full-time	112 (38·0%)	107 (36·4%)	62 (41·3%)	281 (38·0%)
Working part-time	57 (19·3%)	59 (20·1%)	28 (18·7%)	144 (19·5%)
Unable to work	38 (12·9%)	42 (14·3%)	15 (10·0%)	95 (12·9%)
Looking after home	37 (12·5%)	32 (10·9%)	14 (9·3%)	83 (11·2%)
Retired	23 (7·8%)	30 (10·2%)	12 (8·0%)	65 (8·8%)
Other	15 (5·1%)	19 (6·5%)	14 (9·3%)	48 (6·5%)
Missing	7 (2·3%)	8 (2·6%)	1 (0·7%)	16 (2·1%)
Depression				
In last 2 wk	224 (75·7%)	235 (78·6%)	115 (77·7%)	574 (77·3%)
Missing	6 (2·0%)	3 (1·0%)	3 (2·0%)	12 (1·6%)
Not first major episode	196 (89·5%)	217 (93·5%)	100 (87·7%)	513 (90·8%)
Missing	5 (2·2%)	3 (1·3%)	1 (0·9%)	9 (1·6%)
4+ previous episodes	143 (73·0%)	165 (76·7%)	81 (82·7%)	389 (76·4%)
Missing	0 (0·0%)	2 (0·9%)	2 (2·0%)	4 (0·8%)
Age at first major depressive episode				
Mean (SD)	25·8 (12·69)	24·9 (11·73)	24·4 (12·55)	25·2 (12·28)
Median (min, max)	23 (3–79)	22 (6–71)	20 (0–78)	22 (0–79)
Inter-quartile range	16–33	16–31	16–30	16–31
Missing	9 (3·0%)	3 (1·0%)	4 (2·6%)	16 (2·1%)
Medication				
Depression medication in last 3 mo	189 (62·6%)	220 (72·9%)	110 (72·9%)	519 (68·7%)
Missing	0 (0·0%)	0 (0·0%)	0 (0·0%)	0 (0·0%)
Analgesic medication in last 3 mo	147 (48·8%)	126 (42·3%)	86 (57·3%)	359 (47·9%)
Missing	1 (0·3%)	4 (1·3%)	1 (0·7%)	6 (0·8%)
EQ-5D Anxiety/Depression				
Not anxious/depressed	8 (2·7%)	8 (2·7%)	5 (3·3%)	21 (2·8%)
Moderately anxious/depressed	219 (73·0%)	221 (73·2%)	114 (75·5%)	554 (73·6%)
Extremely anxious/depressed	73 (24·3%)	73 (24·2%)	32 (21·2%)	178 (23·6%)
Missing	2 (0·7%)	0 (0·0%)	0 (0·0%)	2 (0·3%)
PHQ-9				
Mean (SD)	15·3 (5·33)	16·6 (5·27)	16·2 (5·09)	16·0 (5·29)
Median (min, max)	15 (3–27)	17 (4–27)	16 (5–27)	16 (3–27)

Table 1. Cont.

Characteristic	Acupuncture + Usual Care	Counselling + Usual Care	Usual Care	Total
Inter-quartile range	11–19	13–21	13–20	12–20
Missing	1 (0·33%)	0 (0·0%)	0 (0·0%)	1 (0·1%)
PHQ Group				
None (0–4)	4 (1·3%)	2 (0·7%)	0 (0·0%)	6 (0·8%)
Mild (5–9)	44 (14·6%)	29 (9·6%)	14 (9·3%)	87 (11·5%)
Moderate (10–14)	97 (32·2%)	74 (24·5%)	46 (30·5%)	217 (28·8%)
Moderately severe (15–19)	88 (29·2%)	96 (31·8%)	47 (31·1%)	231 (30·6%)
Severe (20–27)	68 (22·6%)	101 (33·4%)	44 (29·1%)	213 (28·3%)
BDI-II				
Mean (SD)	32·0 (8·54)	33·3 (9·11)	31·8 (8·17)	32·5 (8·72)
Median (min, max)	31 (20–57)	32 (20–60)	30 (20–56)	31 (20–60)
Inter-quartile range	25–37	26–39	25–37	26–38
Missing	–	–	–	–
BDI-II Group				
Moderate (20–28)[2]	124 (41·1%)	104 (34·4%)	56 (37·1%)	284 (37·6%)
Severe (29–63)	178 (58·9%)	198 (65·6%)	95 (62·9%)	471 (62·4%)
SF-36 Bodily Pain				
Mean (SD)	58·8 (27·99)	58·0 (29·17)	54·4 (27·83)	57·6 (28·44)
Median (min, max)	62 (0–100)	62 (0–100)	51 (0–100)	52 (0–100)
Inter-quartile range	41–84	31–84	31–74	32–84
Missing	1 (0·3%)	3 (1·0%)	0 (0·0%)	4 (0·5%)
Expectation acupuncture				
Very ineffective	10 (3·3%)	6 (2·0%)	1 (0·7%)	17 (2·3%)
Fairly ineffective	9 (3·0%)	11 (3·7%)	6 (4·0%)	26 (3·5%)
Can't decide	187 (61·9%)	204 (68·0%)	103 (68·2%)	494 (65·6%)
Fairly effective	66 (21·9%)	44 (14·7%)	29 (19·2%)	139 (18·5%)
Very effective	30 (9·9%)	35 (11·7%)	12 (8·0%)	77 (10·2%)
Missing	0 (0·0%)	2 (0·7%)	0 (0·0%)	2 (0·3%)
Expectation counselling				
Very ineffective	23 (7·7%)	18 (6·0%)	15 (9·9%)	56 (7·5%)
Fairly ineffective	50 (16·7%)	43 (14·3%)	21 (13·9%)	114 (15·2%)
Can't decide	101 (33·8%)	100 (33·2%)	39 (25·8%)	240 (32·0%)
Fairly effective	95 (31·8%)	97 (32·2%)	65 (43·1%)	257 (34·2%)
Very effective	30 (10·0%)	43 (14·3%)	11 (7·3%)	84 (11·2%)
Missing	3 (1·0%)	1 (0·3%)	0 (0·0%)	4 (0·5%)
Expectation usual care				
Very ineffective	29 (9·6%)	34 (11·3%)	6 (4·1%)	69 (9·2%)
Fairly ineffective	60 (19·9%)	62 (20·7%)	44 (29·7%)	166 (22·1%)
Can't decide	108 (35·8%)	92 (30·7%)	50 (33·8%)	250 (33·3%)
Fairly effective	95 (31·5%)	97 (32·3%)	46 (31·1%)	238 (31·7%)
Very effective	10 (3·3%)	15 (5·0%)	2 (1·4%)	27 (3·6%)
Missing	0 (0·0%)	2 (0·7%)	3 (2·0%)	5 (0·7%)
Expectation of actual treatment randomised to				
Very ineffective	10 (3·3%)	18 (6·0%)	6 (4·1%)	34 (4·5%)
Fairly ineffective	9 (3·0%)	43 (14·3%)	44 (29·7%)	96 (12·8%)
Can't decide	187 (61·9%)	100 (33·2%)	50 (33·8%)	337 (44·9%)
Fairly effective	66 (21·9%)	97 (32·2%)	46 (31·1%)	209 (27·8%)
Very effective	30 (9·9%)	43 (14·3%)	2 (1·4%)	75 (10·0%)
Missing	0 (0·0%)	1 (0·3%)	3 (2·0%)	4 (0·5%)

Table 1. Cont.

Characteristic	Acupuncture + Usual Care	Counselling + Usual Care	Usual Care	Total
Treatment preference				
Acupuncture	177 (58·8%)	171 (57·6%)	82 (54·7%)	430 (57·5%)
Counselling	55 (18·3%)	75 (25·3%)	34 (22·7%)	164 (21·9%)
Usual Care	2 (0·7%)	7 (2·4%)	1 (0·7%)	10 (1·3%)
No preference	67 (22·3%)	44 (14·8%)	33 (22·0%)	144 (19·3%)
Missing	1 (0·3%)	5 (1·7%)	1 (0·7%)	7 (0·9%)
Treatment concordance				
Randomised to preferred treatment	177 (58·8%)	75 (25·3%)	1 (0·7%)	253 (33·8%)
Randomised to non-preferred treatment	57 (18·9%)	178 (59·9%)	116 (77·3%)	351 (46·9%)
No preference	67 (22·3%)	44 (14·8%)	33 (22·0%)	144 (19·3%)
Missing	1 (0·3%)	5 (1·7%)	1 (0·7%)	7 (0·9%)

Percent given out of non-missing data, percent missing given out of applicable group total.
A BDI-II score of 20 or above was required to be eligible for the trial.
doi:10.1371/journal.pmed.1001518.t001

which decreased on average to 41·0% over 12 months. Patients in the acupuncture arm showed a marked decrease in the use of analgesics in the first 3 months, which was not sustained following the end of the intervention.

Adverse Events

The number of patients experiencing a serious adverse event (SAE) over the 12 months, as judged by a clinician (IW), was 16 (5·3%) of 302, 26 (8·6%) of 302, and nine (6·0%) of 151 from the acupuncture, counselling, and usual care groups, respectively, of whom nine had more than one SAE (range 2–4). No SAEs, including three deaths, were known to be related to treatment. The number of patients experiencing a non-serious adverse event (NSAE) was 56 (18·5%), 47 (15·6%), and 40 (26·5%), respectively, of whom 17 had more than one NSAE (range 2–4).

Discussion

Principal Findings

In this first randomised trial of acupuncture and counselling for patients continuing to experience depression in primary care, we found statistically significant benefits at 3 months associated with both interventions when provided alongside usual care. This population can be characterised as having experienced recurring bouts of depression (76% having had four or more episodes), with the first episode on average at age 25, some 19 years previously, and 69% were on anti-depressant medication. Moreover significant benefits were observed over the 12-month period as a whole in an AUC analysis. Over time, the usual care group improved such that by 9 and 12 months the benefits of acupuncture and counselling were no longer significantly better than usual care in our primary outcome measure, the PHQ-9. No serious adverse events related to treatment were reported.

Strengths and Limitations

This study had a clear and practical research question with an appropriate trial design, namely a pragmatic randomised controlled trial, which modelled closely what would happen if patient referrals to acupuncturists and counsellors were routine. Pragmatic trials have an emphasis on external validity with the intention that findings are generalisable to typical patients and settings. We recruited patients in primary care from those who had consulted with depression and continued to be moderately or severely depressed, thereby excluding patients whose symptoms had been

Table 2. Unadjusted depression outcomes.

Outcome Measures	Acupuncture + Usual Care		Counselling + Usual Care		Usual Care		Total	
	n	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)
PHQ-9								
Baseline	301	15·3 (5·33)	302	16·6 (5·27)	151	16·2 (5·09)	754	16·0 (5·29)
3 mo	249	9·4 (6·33)	237	10·9 (6·45)	128	12·7 (6·47)	614	10·7 (6·51)
6 mo	235	9·1 (6·51)	228	10·1 (6·87)	120	12·0 (6·85)	583	10·1 (6·80)
9 mo	234	9·7 (6·90)	215	10·1 (7·03)	120	11·9 (7·04)	569	10·3 (7·02)
12 mo	233	9·3 (6·68)	220	10·1 (6·86)	119	11·5 (6·98)	572	10·1 (6·85)
BDI-II								
Baseline	302	32·0 (8·54)	302	33·3 (9·11)	151	31·8 (8·17)	755	32·5 (8·72)
12 mo	226	20·4 (13·19)	211	21·4 (13·64)	151	23·8 (12·63)	550	21·4 (13·29)

doi:10.1371/journal.pmed.1001518.t002

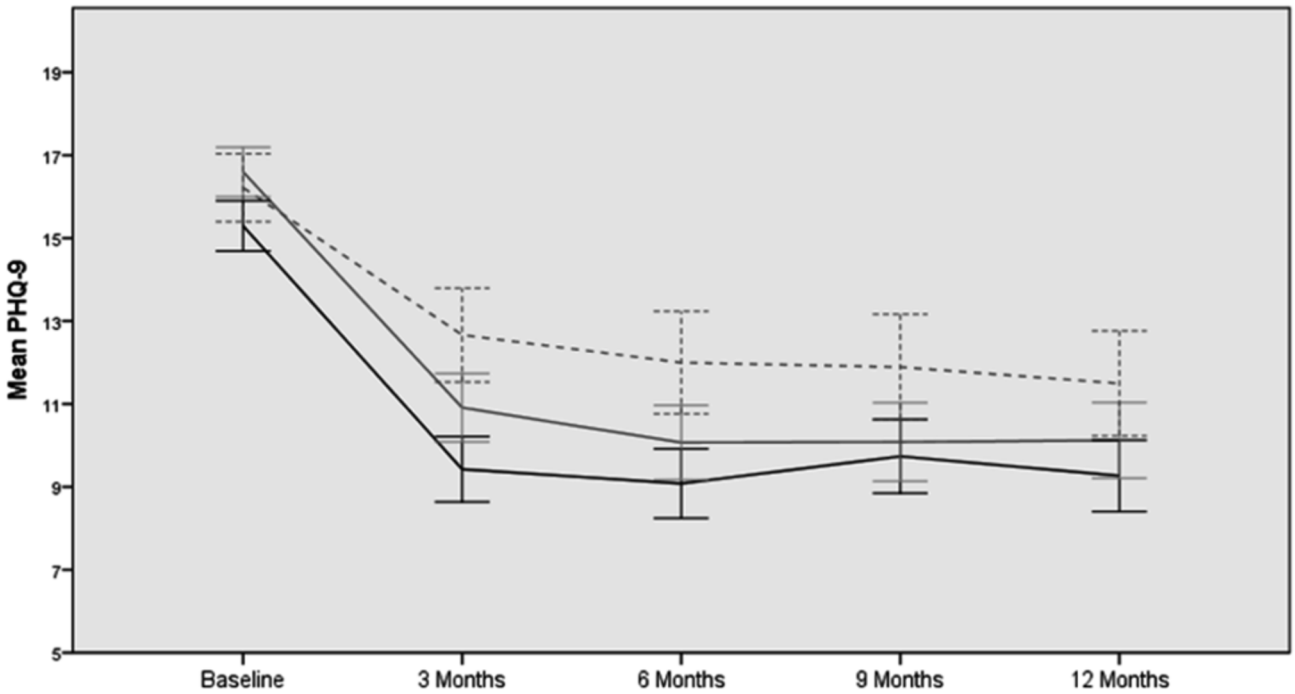

Figure 2. Unadjusted PHQ-9 mean scores from baseline to 12 months. Acupuncture, black line; counselling, grey line; usual care, dashed line.
doi:10.1371/journal.pmed.1001518.g002

alleviated sufficiently by other treatment. Using a different screening measure (BDI-II) from the one we used for measuring outcome (PHQ-9) had the advantage that we avoided the well-known problems of regression towards the mean that occur when we choose people as being above a cut-off. The natural variation in responses to questionnaires produced a few scores below the cut-off for depression on the PHQ9 measurement, 0.8% of participants being below 5, which would have them classified as not depressed, and 11.5% between 5 and 9, which would be mild depression. This is an inevitable consequence of the difficulty of measuring depression. A single PHQ9 below 5 does not mean that someone is not depressed and a single BDI above 20 does not mean that they are depressed, these scores occurring in the same individuals for six participants. Each of these scores is only an uncertain estimate of the person's position on a continuum.

The attrition between invitation to participate and randomisation at baseline was typical of trials that recruit via primary care databases. Multiple imputation was used to compensate to some degree for the limitations related to the loss of follow-up data. The randomisation into groups provided a control for temporal effects and other factors across all patients that might have influenced outcomes beyond the treatment itself. We provided standardised treatment protocols for the acupuncturists and counsellors that were designed to reflect routine practice, allowing individualisation to match patient variability, while ensuring all practitioners met appropriate standards of qualification and experience. While no attempt was made to standardise usual care, it was however provided to patients in all arms of the trial, with a majority of patients continuing with anti-depressants, and differences between groups in usual care at all time points were minimal (see Tables S4–S7). Accordingly, we can assume that the differences between arms can largely be ascribed to the treatments provided by the acupuncturists and the counsellors.

Pragmatic trials, however, tell us less about which aspects of the interventions might be most or least beneficial. Such trials are not designed to separate out relative contributions from treatment components that are specific or non-specific to the intervention. With regard to two treatment components in the acupuncture and counselling groups that are often considered "non-specific," namely session time and quality of therapist attention, we found that specific treatment effects remained when these were accounted for. Despite the limitation that a pragmatic approach has in ascribing outcomes to different treatment components, exacerbated by some loss to follow-up, this design nevertheless provides a useful estimate of overall effects of complex interventions, an estimate of most interest to patients, practitioners and providers.

Relationship to the Literature

In a recent Cochrane review of acupuncture for depression, no studies focussed on moderate to severe depression. The only comparator equivalent to the usual care of our study was a wait list comparator, which involved two trials by the same research team [22–23]. The Cochrane review's meta-analysis involving 94 patients in these two trials showed a reduction in standardised mean difference (SMD) of −0·73 (95% CI −1·18 to −0·29). This is a larger effect size than we found, however we need to be cautious in the interpretation of the result, as the patients were less depressed and the numbers analysed were small. Regarding counselling, we found no trial based in primary care that evaluated counselling for moderate to severe depression. From a Cochrane review, there is evidence from six trials of counselling for mild to moderate depression with 772 patients that counselling is more effective than usual care in terms of mental health outcomes over 1 to 6 months (SMD −0·28, 95% CI −0·43 to −0·13). These advantages were not shown to endure over the longer term from 7

Table 3. Effect of trial arm on PHQ-9 depression.

Analysis	Month	*n*	Group 1		Group 2		Group Difference			
			Mean	SE	Mean	SE	Mean	SE	95% CI	*p*-Value
			Acupuncture		Usual Care					
ANCOVA[a]	3	452	9·8	0·41	12·3	0·58	−2·46	0·636	−3·72 to −1·21	<0·001
Mixed[b]	3	372	9·8	0·27	12·1	0·38	−2·29	0·475	−3·22 to −1·36	–
	6	350	9·6	0·33	11·5	0·46	−1·90	0·569	−3·02 to −0·79	–
	9	348	10·2	0·39	11·1	0·54	−0·83	0·671	−2·15 to 0·49	–
	12	347	9·7	0·45	10·7	0·64	−0·99	0·785	−2·53 to 0·55	–
AUC[c]	3–12	407	10·9	0·25	12·5	0·35	−1·55	0·435	−2·41 to −0·70	–
			Counselling		Usual Care					
ANCOVA	3	453	11·1	0·40	12·8	0·58	−1·73	0·648	−3·00 to −0·45	0·008
Mixed	3	362	10·9	0·28	12·8	0·38	−1·83	0·477	−2·76 to −0·90	–
	6	345	10·4	0·33	12·2	0·47	−1·78	0·576	−2·91 to −0·65	–
	9	332	10·5	0·40	11·8	0·55	−1·26	0·688	−2·61 to 0·08	–
	12	336	10·4	0·47	11·4	0·65	−1·00	0·805	−2·58 to 0·57	–
AUC	3–12	402	11·6	0·28	13·1	0·38	−1·50	0·470	−2·43	−0·58
			Acupuncture		Counselling					
ANCOVA	3	603	10·0	0·41	10·8	0·40	−0·76	0·514	−1·77 to 0·25	0·140
Mixed	3	402	9·5	0·29	9·4	0·32	0·11	0·439	−0·75 to 0·97	–
	6	371	9·6	0·35	9·1	0·38	0·45	0·527	−0·58 to 1·49	–
	9	360	10·0	0·41	9·0	0·45	0·97	0·621	−0·25 to 2·19	–
	12	361	9·6	0·48	9·0	0·53	0·59	0·721	−0·82 to 2·01	–
AUC	3–12	531	11·1	0·27	11·2	0·27	−0·06	0·378	−0·81 to 0·68	–

[a]ANCOVA, effect of trial arm on imputed PHQ-9 at 3 months (adjusting for baseline PHQ-9).
[b]Mixed, effect of trial arm on PHQ-9 over 12 months, (mixed effects model, including time, trial arm x time, baseline PHQ-9, baseline expectation of counselling and baseline expectation of allocated treatment. For the comparison between acupuncture and counselling, treatment time by 3 months and practitioner's empathy were additionally included.)
[c]AUC, effect of trial arm on average PHQ-9 depression over 12 months (adjusting for Baseline PHQ-9).
SE, standard error.
doi:10.1371/journal.pmed.1001518.t003

to 12 months (SMD −0·09, 95% CI −0·27 to 0·10). Their number-needed-to-treat for short-term benefit was 6, somewhat less than the 10 we found for moderate to severely depressed patients. In another review of psychological interventions, four cognitive behaviour therapy studies based in primary care covering 259 patients with depression found a similar short-term effect (SMD −0·33, 95% CI −0·60 to −0·06) [24]. In our rigorously conducted large-scale trial, we present the first evidence on acupuncture and counselling for patients in primary care who are representative of those continuing to experience symptoms of moderate to severe depression. Both interventions are shown to be effective treatments at 3 months when compared to usual care

Table 4. Effect of trial arm on BDI-II depression.

Analysis	Month	*n*	Group 1		Group 2		Group Difference		
			Mean	SE	Mean	SE	Mean	SE	95% CI
			Acupuncture		Usual Care				
ANCOVA[a]	12	445	22·8	1·34	25·7	1·82	−2·88	1·419	−5·68 to −0·08
			Counselling		Usual Care				
ANCOVA	12	449	22·7	1·47	25·4	1·74	−2·74	1·399	−5·50 to 0·02
			Acupuncture		Counselling				
ANCOVA	12	401	22·5	0·92	21·9	1·02	0·59	1·281	−1·93 to 3·11

[a]ANCOVA, effect of trial arm on imputed BDI-II at 12 months (adjusting for baseline BDI-II, baseline expectation of counselling and baseline expectation of allocated treatment. For the comparison between acupuncture and counselling, treatment time by 3 months and practitioner's empathy were additionally included.)
doi:10.1371/journal.pmed.1001518.t004

Table 5. Number of patients taking prescribed medication in the preceding 3 months.

Prescribed Medication	Acupuncture + Usual Care			Counselling + Usual Care			Usual Care			Total		
	n	Percent[a]	Change from Baseline	Percent	Percent	Change from Baseline	*n*	Percent	Change from Baseline	*n*	Percent	Change from Baseline
Antidepressants												
Baseline	189	62·6%	–	220	72·9%	–	110	72·9%	–	519	68·7%	–
3 mo	147	60·7%	−0·9%	155	69·2%	−3·7%	80	66·7%	−6·2%	382	65·2%	−3·5%
6 mo	126	54·6%	−8·0%	145	65·3%	−7·6%	75	63·6%	−9·3%	346	60·6%	−8·1%
9 mo	123	54·0%	−8·6%	124	60·8%	−12·1%	74	66·1%	−6·8%	321	59·0%	−9·7%
12 mo	121	52·4%	−10·2%	124	58·2%	−14·7%	69	61·6%	−11·3%	314	56·5%	−12·2%
Analgesics												
Baseline	147	48·8%	–	126	42·3%	–	86	57·3%	–	359	47·9%	–
3 mo	73	30·8%	−18·0%	93	42·5%	+0·2%	57	48·3%	−9·0%	223	38·9%	−9·0%
6 mo	99	43·4%	−5·4%	84	38·5%	−3·8%	52	46·4%	−10·9%	235	42·1%	−5·8%
9 mo	82	36·8%	−12·0%	71	34·8%	−7·5%	55	50·0%	−7·3%	208	38·7%	−9·2%
12 mo	84	36·8%	−12·0%	87	41·0%	−1·3%	54	49·5%	−7·8%	225	41·0%	−6·9%

[a]All percentages given out of total number of patients with valid responses.

doi:10.1371/journal.pmed.1001518.t005

alone, with evidence that there are benefits over the 12-month period in terms of clinical symptoms.

Implications for Clinical Practice and Future Research

If treatment success is defined as improvement from a depressed PHQ-9 score (≥10) to a non-depressed score (≤9) with an improvement of at least 50% [25], then 33% of acupuncture patients, 29% of counselling patients, and 18% of usual care patients achieved this. These percentages apply to the total number of patients with a baseline PHQ-9 score of 10 or above and for whom data were available at 3 months. The number-needed-to-treat for one additional treatment success, as defined above, was 7 for acupuncture (95% CI 4·3–17·4) and 10 for counselling (95% CI 5·3–47·3). The patient experience can be further illustrated in terms of "depression free days" [26], an approximate summary measure derived from PHQ-9 cut-off scores averaged over the period between measurements. The mean number of depression free days over 3 months was 34 (95% CI 31–38) for the acupuncture group, 27 (95% CI 24–30) for the counselling group, and 23 (95% CI 19–27) for the usual care group.

Further research into the optimal populations and treatment regimens for acupuncture and counselling is merited. The characteristics of patients one recruits to trials of interventions for depression in primary care will depend on the recruitment methods used. Patients recruited at the point of consultation will be different from those recruited via databases, as we did in this trial, and different again from those with depression who are not consulting at all. In the trial we report here, what was important was that patients had consulted in primary care, continued to be depressed, and were seeking other interventions that might help with their depression. A different recruitment method could be used to assess whether the interventions would be more effective for patients referred at the onset of their first episode of depression, rather than after many episodes, as was the case in the present study in which 76% had had four or more previous episodes.

We recruited patients using the Beck Inventory (BDI-II) with scores greater or equal to 20, which is classified by this measure as "moderate to severe." However other classifications systems, such as DSM, have different categories of severity. What our trial does not tell us is whether acupuncture or counselling performs better or worse for the more mild forms of depression. Nor do we know whether patients not receiving anti-depressant medication (one third of our sample) do better or not, or whether fewer sessions would be sufficient for mild to moderate depression, or more sessions would improve outcomes for those with severe depression (approximately 60% of our sample). For those randomised to acupuncture, it was usually their first experience of this intervention, whereas many randomised to counselling had received this intervention before; however, it is not clear whether this difference impacted on outcomes.

With regard to the acupuncture provision, there is some evidence from the literature that a uniform combination of points can work for depressed patients [27,28]; however, a head-to-head trial or large individual patient data meta-analysis would be required to determine whether a uniform approach was more beneficial than an individualised approach.

A full economic analysis is needed to combine the costs and effects of each treatment option to determine the cost-effective treatment. Although no other trial data are available on the costs and effects of acupuncture for these primary care patients, other trials exist for counselling in primary care and, to guide policy, these should be synthesized into cost-effectiveness estimates.

Conclusion

To our knowledge, our study is the first to rigorously evaluate the clinical and economic impact of acupuncture and counselling for patients in primary care who are representative of those who continue to experience depression in primary care. We have provided evidence that acupuncture versus usual care and counselling versus usual care are both associated with a significant reduction in symptoms of depression in the short to medium term, and are not associated with serious adverse events.

Supporting Information

Protocol S1 Trial protocol.
(PDF)

Table S1 Baseline characteristics for patients with and without missing data at 3 months.
(DOC)

Table S2 Details of the acupuncture treatment based on STRICTA reporting guidelines.
(DOC)

Table S3 Details of the competences that underpinned the delivery of counselling.
(DOC)

Table S4 Usual care provided: number of patients seeing a health professional and average number of visits (total and specifically for depression) for these patients in the preceding 3 months.
(DOC)

Table S5 Usual care provided: number of patients attending hospital accident and emergency departments and number of attendances in the preceding 3 months.
(DOC)

Table S6 Usual care provided: number of patients admitted to hospital and number of overnight stays in the preceding 3 months.
(DOC)

Table S7 Usual care provided: number of patients paying for private health care & money spent in the preceding 3 months.
(DOC)

Table S8 Effect of trial arm on PHQ-9 depression at 3 months and BDI-II depression at 12 months (non-imputed data).
(DOC)

Text S1 CONSORT statement checklist.
(DOC)

Acknowledgments

We acknowledge the patients, counsellors, acupuncturists, and general medical practitioners; Sylvia Schroer for conducting the pilot study; Mike Bennett and David Smith from York & District Mind; and from the ACUDep research team, Matthew Bailey, Richard Blackwell, Sally Brabyn, Ben Cross, Janet Eldred, David Geddes, Simon Gilbody, Pauline Holloway, Hillary Marshall, Stephen Morley, Karen Overend, Lucy Revell, Val Wadsworth, and Kerry Wheeler. We especially acknowledge Peter Bower who chaired our Independent Steering Group.

Author Contributions

Conceived and designed the experiments: HM SR MB MS DT IW. Performed the experiments: HM SR MB SB AH HL SP MS DT IW. Analyzed the data: MB RG AK MS ES. Wrote the first draft of the manuscript: HM AK RG ES. Contributed to the writing of the manuscript: HM SR MB SB RG AH AK HL SP MS ES DT IW. ICMJE criteria for authorship read and met: HM SR MB SB RG AH AK HL SP MS ES DT IW. Agree with manuscript results and conclusions: HM SR MB SB RG AH AK HL SP MS ES DT IW. Enrolled patients: SR AH.

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Editors' Summary

Background. Depression–overwhelming sadness and hopelessness–is responsible for a substantial proportion of the global disease burden and is a major cause of suicide. It affects more than 350 million people worldwide and about one in six people will have an episode of depression during their lifetime. Depression is different from everyday mood fluctuations. For people who are clinically depressed, feelings of severe sadness, anxiety, hopelessness, and worthlessness can last for months and years. Affected individuals lose interest in activities they used to enjoy and sometimes have physical symptoms such as disturbed sleep. Clinicians can diagnose depression and determine its severity by asking patients to complete a questionnaire (for example, the Beck Depression Inventory [BDI-II] or the Patient Health Questionnaire 9 [PHQ-9]) about their feelings and symptoms. The answer to each question is given a score and the total score from the questionnaire ("depression rating scale") indicates the severity of depression. Antidepressant drugs are usually the front-line treatment for depression in primary care.

Why Was This Study Done? Unfortunately, antidepressants don't work for more than half of patients. Moreover, many patients would like to be offered non-pharmacological treatment options for depression such as acupuncture–a therapy originating from China in which fine needles are inserted into the skin at specific points of the body–and counseling–a "talking therapy" that provides patients with a safe, non-judgmental place to express feelings and emotions and that helps them recognize their capacity for growth and fulfillment. However, it is unclear whether either of these treatments is effective in depression. In this pragmatic randomized controlled trial, the researchers investigate the clinical effectiveness of acupuncture or counseling in patients with depression compared to usual care in primary care in northern England. A randomized controlled trial compares outcomes in groups of patients who are assigned to different interventions through the play of chance. A pragmatic trial asks whether the intervention works under real-life conditions. Patient selection reflects routine practice and some aspects of the intervention are left to the discretion of clinician, By contrast, an explanatory trial asks whether an intervention works under ideal conditions and involves a strict protocol for patient selection and treatment.

What Did the Researchers Do and Find? The researchers recruited 755 patients who had consulted their primary health care provider about depression within the past 5 years and who had a score of more than 20 on the BDI-II–a score that is defined as moderate-to-severe depression on this depression rating scale–at the start of the study. Patients were randomized to receive up to 12 weekly sessions of acupuncture plus usual care (302 patients), up to 12 weekly sessions of counseling plus usual care (302 patients), or usual care alone (151 patients). Both the acupuncture protocol and the counseling protocols allowed for some individualization of treatment. Usual care, including antidepressants, was available according to need and monitored in all three groups. Compared to usual care alone, there was a significant reduction (a reduction unlikely to have occurred by chance) in the average PHQ-9 scores at both 3 and 6 months for both the acupuncture and counseling interventions. The difference between the mean PHQ-9 score for acupuncture and counseling was not significant. At 9 months and 12 months, because of improvements in the PHQ-9 scores in the usual care group, acupuncture and counseling were no longer significantly better than usual care.

What Do These Findings Mean? These findings suggest that, compared to usual care alone, both acupuncture and counseling when provided alongside usual care provided significant benefits at 3 months in primary care to patients with recurring depression. Because this trial was a pragmatic trial, these findings cannot indicate which aspects of acupuncture and counseling are likely to be most or least beneficial. Nevertheless they do provide an estimate of the overall effects of these complex interventions, an estimate that is of most interest to patients, practitioners, and health care providers. Moreover, because this trial only considers the effect of these interventions on patients with moderate-to-severe depression as classified by the BDI-II; it provides no information about the effectiveness of acupuncture or counseling compared to usual care for patients with mild depression. Importantly, however, these findings suggest that further research into optimal treatment regimens for the treatment of depression with acupuncture and counseling is merited.

Additional Information. Please access these Web sites via the online version of this summary at http://dx.doi.org/10.1371/journal.pmed.1001518.

- The US National Institute of Mental Health provides information on all aspects of depression (in English and Spanish)
- The UK National Health Service Choices website provides detailed information about depression, including personal stories about depression, and information on counseling and acupuncture
- The UK charity Mind provides information on depression, on talking treatments, and on complementary and alternative therapies including acupuncture; Mind also includes personal stories about depression on its website
- More personal stories about depression are available from Healthtalkonline
- MedlinePlus provides links to other resources about depression and about acupuncture (in English and Spanish)

Laser acupuncture for mild to moderate depression in a primary care setting

– a randomised controlled trial

Joo Im Quah-Smith, Wai Mun Tang, Janice Russell

Abstract

Objective Depression is a major public health problem. There is some evidence supporting the effectiveness of needle acupuncture in its treatment. Laser stimulation, regarded here as a modality of acupuncture, is non-invasive and therefore free of infection risk; and it is acceptable to patients with needle phobia. The technique is relatively easily learned by community-based general practitioners. It is also amenable to sham control and therefore double-blinding in clinical trials. A double-blind randomised controlled trial was conducted to test the efficacy of low level laser acupuncture in mild to moderate depression.

Methods Thirty patients with depression were randomised to receive either active or inactive laser treatment. The laser unit could be switched to one of two settings. One switch position delivered active laser acupuncture and the other was inactive (sham). In the active mode, 0.5J was delivered to each of six to eight individually tailored acupuncture sites per visit. All patients were treated twice weekly for four weeks then weekly for a further four weeks. The patients and the acupuncturist were both blinded to conditions. Outcome was assessed using the Beck Depression Inventory at baseline, weeks four and eight during treatment, and at 4 and 12 weeks following the treatment.

Results At the end of the treatment period, Beck Depression Inventory scores fell from baseline by 16.1 points in the intervention group and by 6.8 points in the sham control group ($P<0.001$). The difference showed only a trend four weeks later, but was again significant after 12 weeks ($P=0.007$). Laser acupuncture was well tolerated with transient fatigue as the most common adverse effect.

Conclusion Laser acupuncture may be worth further investigation as a treatment for mild to moderate depression in primary care.

Keywords

Depression, acupuncture, low level laser therapy, depressive disorder.

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Introduction

Clinical depression is defined as a syndrome with symptoms of low mood, loss of pleasure and interest, sleep disturbances, weight and appetite changes, fatigue, feelings of worthlessness or guilt, poor concentration and (when severe) suicidal thoughts and gestures, that persist for at least two weeks.[1] Depression commonly impacts not only on the patient but their families, workplace and the community. In 2000 the World Health Organisation assessed the global burden of unipolar depressive disorders, and estimated that depression accounted for 11.9% of years lived with a disability, compared with 10.7% in 1990. Depression remained the fourth leading cause of total disease burden accounting for 4.4% of Disability Adjusted Life Years, a measure of future lost years of healthy life.[2;3] The economic burden of depression in the USA has been estimated at $83.1 billion annually, 30% in direct health care and the remainder from impaired workplace productivity and premature death. Depressed workers have an estimated 20% decrease in productivity.[4;5]

Only 40% of people with depressive symptoms seek professional help, and less than half of these receive evidence-based treatments.[6] The National Institute of Mental Health (NIMH) has published the largest study to date on pharmacological and

psychotherapy treatments of depression in which health outcomes of known clinical interventions were examined.[7] Thirty two percent of patients dropped out of therapy prior to completion and of those who did complete 16 weeks of active treatment, 30% to 49% failed to respond. A significant proportion of responders were found to be depressed again within 18 months. Premature termination of treatment was attributed to adverse effects, dissatisfaction with treatment effectiveness or preference for other therapies, particularly use of complementary therapies.[8;9] Thus, there is need to explore these clinical alternatives and to establish their effectiveness in primary and tertiary care settings.

A review of the available evidence on acupuncture for depression was recently conducted within the framework of the Cochrane Collaboration.[10] Seven trials fulfilled inclusion criteria and were evaluated to determine whether acupuncture was more effective than sham acupuncture, no treatment, standard treatments (pharmacotherapy and psychological intervention) and to determine the adverse effects of acupuncture. One included study tested the effectiveness of overall acupuncture and specific acupuncture points in the management of depression.[11] Acupuncture was shown to be effective in the management of depression with a significant effect of specific acupuncture points. Six months later, relapse rates were comparable to those of established therapies.[12] There was adequate randomisation and blinding of the participant, acupuncturist and outcome assessor but no mention of blinding of the statistical analyst. There was no intention-to-treat analysis performed and the sample population was small. In the trials by Luo et al and Han et al, electroacupuncture was found to be as effective as pharmacotherapy,[13-16] although the group treated with pharmacotherapy alone in the trial of Luo et al (1998) reported a greater reduction in depression compared to the combined acupuncture and pharmacotherapy group.[16] Roschke compared pharmacotherapy with needle acupuncture, pharmacotherapy with placebo acupuncture, and pharmacotherapy alone. Acupuncture intervention was superior to pharmacotherapy alone but there was no measurable difference between the effects of placebo and true acupuncture.[17] Xiujuan found classical needle acupuncture to be no different from pharmacotherapy in the reduction of depression.[18] Together, these trials demonstrate that acupuncture may be effective in depression management but methodological issues are of major concern. Outcomes were confounded by small sample sizes, randomisation and blinding issues, lack of specific inclusion and exclusion criteria, statistical analytical issues and variable dosages of pharmacotherapy. Adverse events were not always reported.

The efficacy of laser acupuncture has been demonstrated in a variety of medical conditions,[19-28] but not in depression. Again methodological issues including the depth of transmission of the laser beam have been problematic.[29] The generalisability of results is limited due to the relatively small number of studies performed, and the lack of widespread clinical experience. Laser acupuncture was selected for this study as it allows blinding of treatments more easily than does needle acupuncture. Other advantages of laser acupuncture over needling include the facts that it has shorter treatment times, is not invasive, has no infection concerns, is ideal for the needle phobic patients, and should be relatively easy for primary care doctors to use as a treatment option for depressed patients.

The aims of this study were to examine the efficacy of laser acupuncture in the treatment of mild to moderate depression in a double blind controlled trial and to report on any adverse effects from the treatment.

Methods

Recruitment and Study Design

We performed a randomised controlled trial comparing laser acupuncture with sham laser acupuncture. Patients were invited to participate through advertisements placed in local newspapers and referral from medical practitioners in the North Shore area of Sydney. Interested participants were then interviewed via telephone by a research assistant to assess their eligibility. Details recorded included age, sex, marital status, previous diagnoses with depression and treatment received. Those who fulfilled the recruitment criteria then completed the Beck Depression Inventory (BDI) and Hospital Anxiety and Depression Scale (HADS) by mail. Potential participants with BDI scores between 12 and 30 were then examined by a psychiatrist (JR or WMT) to confirm the diagnosis of mild to moderate depression. Those with scores outside this range were referred to a general practitioner.

The treatment period was eight weeks. Treatment commenced within two weeks of completion of the screening BDI, which also served as baseline score. The BDI was then completed by participants after four weeks and eight weeks of treatment, and four and a further eight weeks following termination of the treatment course, ie 12 and 20 weeks from randomisation. Participants were given a $20 rebate upon completion of the final post intervention questionnaire in order to offset their travel expenses.

Instruments

The BDI is a self-reporting questionnaire with 21 questions relevant to depression.[30] Each question has four options scoring 0 to 3. The clinical threshold score for 'caseness of depression' (ie a diagnosis of depression in an individual) is 12, with scores of 12-20 signifying mild depression, 20-30 moderate depression and over 30 severe depression. The HADS is a self-reported questionnaire with 14 questions concerning anxiety and depression.[31] The scores for anxiety and depression are scored separately on a four point Likert scale (0-3). Scores of less than eight are considered below the clinical threshold for anxiety, 8-10 doubtful and 11 and above indicative of definite anxiety. Patients who scored 11 or more for anxiety at baseline were treated with an additional, anxiety specific acupuncture point (see below). HADS was administered at baseline and postal follow ups at 12 and 20 weeks. An Adverse Events Questionnaire was sent to all participants who completed the final treatment session.

Inclusion criteria

Participants were suitable for inclusion in the trial if they had depressive symptoms with a BDI score of 12 to 30, if they agreed to being included and to participate in follow up for three months after the completion of acupuncture intervention, and if they were able to give informed consent.

Exclusion criteria

Participants were excluded if they were diagnosed as suffering from chronic dysthymia, ie chronic depression of over two years duration, hypomania, psychosis or substance abuse, if they had been taking psychotropic drugs including prescribed drugs or herbal supplements for depression within the last three months. Other exclusion criteria were history of neurological disorders, endocrine disorders, pregnancy or active suicidal tendencies.

Withdrawal criteria

Participants were withdrawn from the study if any of the aforementioned exclusion criteria became apparent, as decided by the participant or treating doctor.

Randomisation and blinding

Equal numbers of red and green beans were placed in a closed jar with a small hole in its lid. Upon entry into the study, the research assistant randomly selected one of the coloured beans from the jar to indicate group allocation. The colour corresponded to position 1 or 2 on the laser, as decided by a flip of a coin and only known to the manufacturer until the data had been analysed.

The participants and the acupuncturist were both blinded. The laser did not cause any sensory effect and the indicator light on the control panel flashed during treatment for both the inactive and active laser. The acupuncturist was not allowed access to the BDI scores during the eight week intervention. At the outset, she was told when the baseline HAD-A (anxiety) was equal to or greater than 11. She was not allowed to interact with the participant apart from greeting them. The time spent with each participant at each treatment was less than five minutes. The research assistant collecting the data and the statistical analyst were blind to group assignment.

Intervention

Practitioner background and acupuncture point selection

The medical acupuncturist is a fellow of the Australian Medical Acupuncture College (AMAC). She is in full time medical acupuncture practice. Her training was with AMAC, Professor Jean Bossy (Montpelier University), Associate Professor Steven Aung (University of Alberta), Dr Stephen Birch (LA, PhD) and Dr Raphael Nogier of Groupe Lyonnaise d'Etudes Medicale (GLEM).

Acupuncture point selection was based on classical syndromes as defined in Traditional Chinese Medicine. The treatments were individualised, and the predominant syndromes were found to be either liver Qi stagnation or liver Qi deficiency. To facilitate recovery, classical 'alarm points' were chosen for

treatment as these are traditionally believed to be the fastest acting points. Six primary acupuncture points were routinely used for all participants: LR14 on the right, CV15 and CV14 in the anterior midline (all being alarm points), HT7 at the wrists (for calming) and LR8 on the left (Liver Yin). LR8 was also believed to be a faster-acting acupuncture point. Secondary acupuncture points were selected by the acupuncturist and were only used when the HADS anxiety score was 11 or greater. The most important site was KI10. Other acupuncture points infrequently used were LI4, SP6, GV20.

Treatment regimen

Twelve laser acupuncture sessions in total were given, twice weekly for the first four weeks then weekly for the following four weeks. There were no co-interventions. The participants were made aware at initial telephone interview that herbal or pharmaceutical psychotropic preparations were not permitted during the study, and reminded at the first session. The participants were also told to check with the research assistant if there were other therapies being considered and that these should be avoided until the final assessment.

Laser unit

The low level infrared laser acupuncture unit was adapted for the study. A flick switch was installed, numbered '1' and '2' by the manufacturer. One of these two options was sham laser, but at both positions the laser would beep and flash at the control panel during 'treatment'. None of the participants in either group reported any sensation when the laser was applied to the skin.

The low level laser acupuncture unit used was the Meyer 100mW, (Meyer, Melbourne, Australia) which is in common use by medical practitioners in Australia. The laser was applied to each acupuncture point for five seconds to deliver 0.5J per point. The instrument was recalibrated during preparation for this research project. At each acupuncture point, the probe was held lightly in contact with the skin for five seconds to deliver 0.5J of laser energy so each participant received in total 3-4J of laser energy per session.

Ethical approval

The study was approved by the Monash University Standing Committee on Ethical Research on Humans. All participants gave written informed consent at study entry and were also given information regarding the clinical use of laser acupuncture, the mechanism of action and its safety. They were also assured of the confidentiality of their participation and their right to withdraw at any stage.

Statistical Analysis

A multivariate analysis of variance (MANOVA) was performed on all completers to compare group effects. The main effects were time (baseline, weeks 4, 8, 12 and 20), switch setting (1 or 2) and the interaction term was time by switch setting. The primary outcome measure was the change in BDI score at each assessment point (baseline minus the BDI at each time point). In addition, caseness (ie BDI score >11) in the active laser and sham control groups was compared using chi square analysis. An intention-to-treat analysis (ITT) was also carried out using the last observation carried forward method for imputing missing values.

Results

Of the 234 people who responded to advertisements, 129 did not meet inclusion criteria when screened by telephone (see Figure 1). Of the 105 participants sent an invitation package, 30 participants (29%) were eligible to participate with BDI scores between 12 and 30. Seventy five respondents with BDI scores suggesting they had major depression (>30) were referred to a general practitioner.

Of the 30 participants entering the study, 16 patients were allocated to receive active laser treatment and 14 were randomised into the control arm. The mean age was 38.5 years (range 21-49 years) and women comprised 77% of the participants (13 active arm and 10 in the inactive arm). Other baseline data are presented in Table 1. For half the patients, the patient's general practitioner or psychiatrist had made the diagnosis of depression, in 10% there was a history of postpartum depression and in 37% antidepressants had been used previously. Four patients (13%) dropped out of the study before completing the eight week intervention, two from each arm of the study. The reasons giving for dropping out were acute illness, relocation or deterioration in mood. No patient dropped out because of adverse effects from the treatment. One control participant did not return the questionnaires

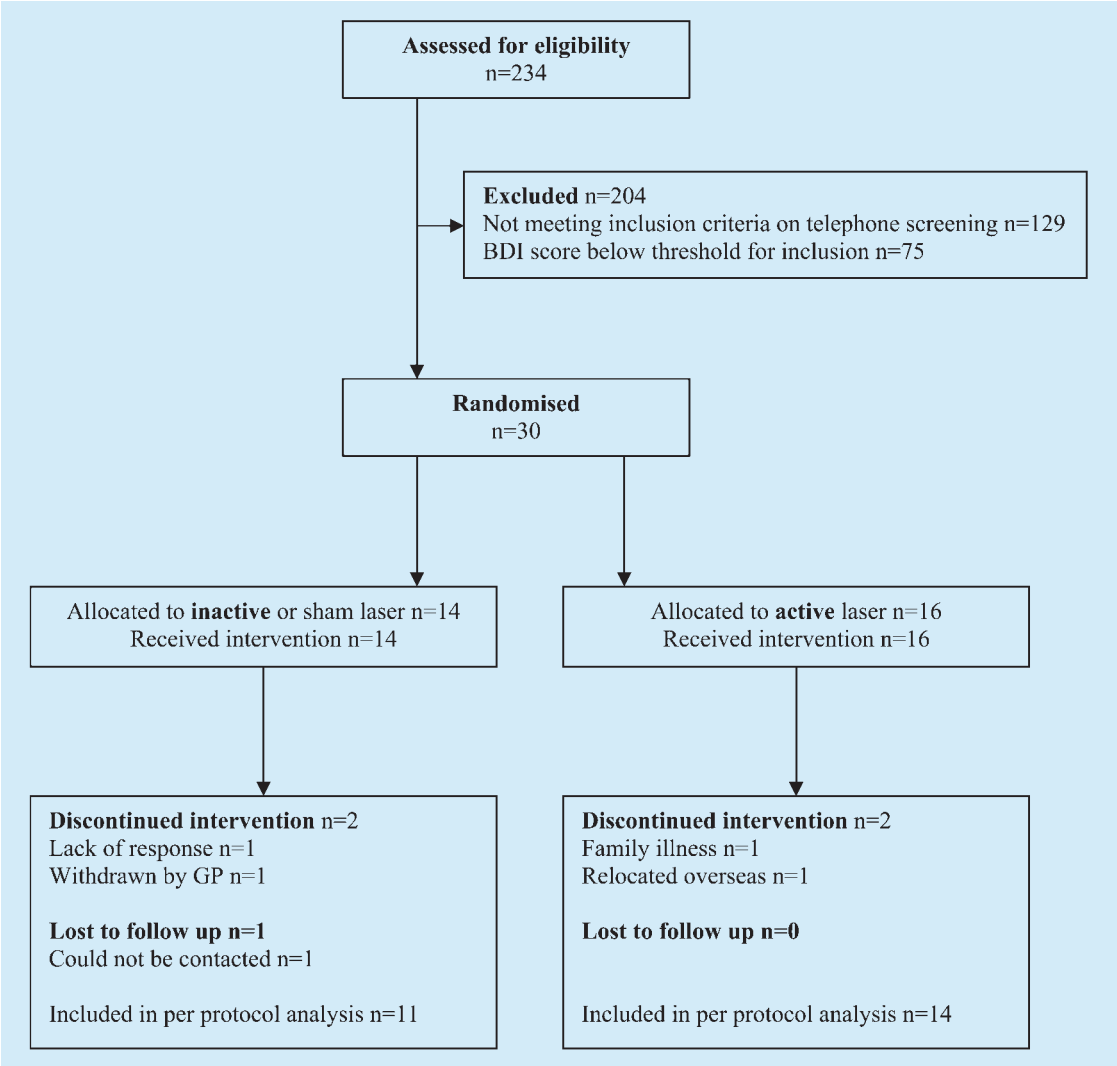

Figure 1 Patient flow through RCT of laser acupuncture for depression.

post treatment. Thus, 25 participants completed the study as per protocol (14 participants from the active group and 11 participants from the inactive arm).

Table 2 shows the baseline and change in BDI scores over the study period. A repeated measures ANOVA of BDI scores for the completers (n=25) demonstrated a significant effect of time (F=44.23, DF=4, 92, P<0.001) and switch setting by time interaction (F=4.30, DF=4, 92, P=0.003) but not for the switch setting (F=2.70, DF=1, 23, P=0.114). Subsequent post-hoc tests at each time point showed significantly improved BDI scores for the active laser group at eight weeks (P=0.006) and a strong trend at week 20 (P=0.07).

With reference to Table 2, change in BDIs from baseline were calculated and compared between active and control groups in a per protocol analysis. The changes in BDI ratings were not significantly different at four weeks, but at eight weeks the difference was significantly different between the groups receiving active versus the inactive laser treatment (P<0.001). At 12 weeks the change in BDI was not significantly different (P=0.088). However at 20 weeks the change in BDI was significantly different between groups (P=0.007). An intention to treat analysis using the last observation carried forward showed a significant group difference for change in BDI scores at the eight weeks (P=0.003) and a trend three months after the intervention (P=0.046).

Table 2 also presents the numbers of patients in each group with BDI scores greater than 11 (ie caseness of probable depression) at each time point. For the inactive laser group, 64% fulfilled the criteria for depression at the end of the study (20 weeks)

Table 1 **Baseline characteristics of patients included in RCT of laser acupuncture**

Variable	Inactive laser group (n=14)	Active laser group (n=16)	Total (n=30)
Females (n)	10	13	23 (77%)
Mean age, years (SE)	38.1 (2.3)	38.9 (1.5)	38.5 (1.3)
Age range, years	21-49	23-48	21-49
Unmarried	4	5	9
Married	8	7	15
Divorced or separated	2	4	6
Reported never previously diagnosed with depression	7	8	15
Depression diagnosed by GP or psychiatrist	7	8	15
Previously taken Antidepressants?	5	6	11
BDI score, mean + SD (range)	21.2 + 6.6 (12-34)	22.8 + 3.5 (18-30)	22.0 + 5.1
HADS depression score, mean + SD	9.1 + 2.4	9.5 + 2.5	9.3 + 2.4
Non-case, score <8	4	4	8
Doubtful case, score 8-10	4	4	8
Definite case, score >10	6	8	14
HADS anxiety score, mean + SD	12.7 + 2.6	12.4 + 2.8	12.5 + 2.7
Definite case, score >10	11	13	24

Table 2 **Beck Depression Inventory (BDI) scores**

	Inactive laser group (n=14)	Active laser group (n=16)	Between group comparison
BDI score at baseline, mean ± SEM	21.2 ± 1.8 (n=14)	22.8 ± 0.9 (n=16)	
Change at 4 wks	-6.2 (-10.3 to -2.0) (n=13)	-10.8 (-15.6 to -5.9) (n=15)	P=0.130
Change at 8 wks	-6.8 (-11.3 to -2.4) (n=12)	-16.1 (-18.5 to -13.8) (n=14)	P<0.001
Change at 12 weeks	-9.1 (-14.1 to -4.1) (n=11)	-13.9 (-17.5 to -10.4) (n=14)	P=0.088
Change at 20 weeks	-9.4 (-13.7 to -5.1) (n=11)	-15.8 (-18.3 to -13.2) (n=14)	P=0.007
Cases of depression (BDI >11)			
At recruitment	14/14 (100%)	16/16 (100%)	
4 weeks	8/13 (62%)	6/15 (40%)	
8 weeks	9/12 (75%)	5/14 (36%)	
12 weeks	6/11 (55%)	5/14 (36%)	
20 weeks	7/11 (64%)	2/14 (14%)	

BDI scores at baseline, changes (95% CI) at each measurement point, and numbers of patients scoring >11 in each group. Negative scores indicate an improvement in depression.

whilst in the active group only 14% had BDI scores greater than 11 (chi square 6.51, df=1, P<0.025).

The main aim of administering the HADS was to identify patients with anxiety and treat them at additional acupuncture points. The change in depression and anxiety subscales were not significantly different between the active and inactive laser groups (Table 3).

In response to the Adverse Effect Questionnaire, 17% of the placebo group recorded adverse effects and 29% of the active laser group. Fatigue was the main complaint in the active group. Insomnia, dry mouth and headache were also recorded. Participants reported that the side effects were mild and transient, resolving in less than 24 hours after treatment.

Table 3 **Hospital Anxiety and Depression Scale (HADS) scores**

	Inactive laser group	Active laser group	Between group comparison
HADS Depression at baseline, mean ± SEM	9.1 ± 0.6 (n=14)	9.5 ± 0.6 (n=16)	
Change at 12 weeks	-2.3 (-5.5 to 0.8) (n=11)	-4.9 (-6.7 to -3.0) (n=14)	P=0.113
Change at 20 weeks	-2.6 (-5.0 to -0.2) (n=11)	-4.9 (-6.8 to -3.0) (n=14)	P=0.110
HADS Anxiety at baseline, mean +SEM	12.7 ± 0.7 (n=14)	12.4 ± 0.7 (n=16)	
Change at 12 weeks	-2.7 (-4.8 to -0.6) (n=11)	-4.4 (-6.6 to -2.2) (n=14)	P=0.245
Change at 20 weeks	-3.4 (-5.0 to -1.7) (n=11)	-4.9 (-7.2 to -2.5) (n=14)	P=0.295
Diagnostic Severity (HADS-D) categories	0-7, 8-10, 11+	0-7, 8-10, 11+	
Baseline	4, 4, 6	4, 4, 8	
12 weeks	8, 1, 2	12, 2, 0	
20 weeks	8, 2, 1	12, 1, 0	
Responders	n=5	n=7	
Non-responders	n=3	n=1	

HADS scores at baseline, changes (95% CI) and numbers of patients in each category at various measurement points.

Discussion

Laser acupuncture was shown to be effective in the treatment of mild to moderate depression at the end of treatment and at the three month follow up. The findings were supported by a trend in reduced caseness for depression from 100% at baseline to 36% at eight weeks and 14% at 12 weeks post intervention, compared to 64% of controls at this time point.

Limitations of this study include: small sample size; recruitment method; use of a single assessment instrument; short time period of the trial; and lack of acceptability assessment. The selection of laser acupuncture facilitated the conduct of a randomised double blind controlled trial. In planning the study, the simplicity of recruitment by advertisement was thought to outweigh the risk of selection bias. In order to compensate for this, the potential participants who passed both the telephone interview and the BDI screening were interviewed by a team psychiatrist. The small study population was of concern, as was the brevity of the trial period due to lack of funding. There were difficulties with recruitment: the large numbers of respondents (234) did not translate into a large number of participants (13%). To increase recruitment numbers, a longer recruitment period over 12 months or more or a multicentre trial might have been preferable. The dropout rate was low at 13% compared to the 30% reported by Elkin et al.[7] This might have been partly due to acceptability of the modality used and partly to the fact that the participants had the regular attention of a single practitioner resulting in a better therapeutic alliance.

The improvement in BDI score was not significant at four weeks post intervention even though it was significant at the end of the study and at 12 weeks post intervention. This suggests that the positive effect was delayed until the completion of treatment, or that the sample size was too small. In the follow up phase of the study by Allen,[9] the positive effect from needle acupuncture was no longer present by six months post intervention. If this study indicated that the effect was still present at three months, further follow up questionnaires at four, five and six months would have been useful. This would be of practical utility in making maintenance treatment plans to improve the quality of life of the depressed patient.

The HADS was poorly utilised. It would have been useful to explore anxiety as a co-morbidity and to have applied the HADS alongside the BDI at each time point. Another, possibly better measure could have been the Beck Anxiety Index, an observer rated instrument. However, the simplicity of the self-reporting BDI was a major advantage in this primary care based study.

It is not clear why the BDI was more sensitive to change than the HAD. There are two possibilities to

be considered. First, that the HADS may have been more appropriate for measuring the interrelationship between depression and anxiety, and not so appropriate for measuring depression changes alone. Secondly, as the acupuncture points were specific for depression, the BDI may have been the more sensitive instrument. One anxiety related acupuncture point was used regularly (KI10) but only in those participants who had a positive HADS scale for anxiety. Another problem identified was the lack of recording of the number of participants needing the anxiety specific acupuncture points. This should be addressed in future studies.

The adverse effect profile was reassuring in that although 29% experienced adverse effects in the active laser group, 60% of these being fatigue, the effects were transient and persisted for less than 24 hours. When compared to adverse effects from pharmacotherapy which may persist and affect patient compliance, these transient adverse effects were better tolerated .

Conclusion

Persisting alleviation of mild to moderate depressive symptoms was demonstrated in a randomised controlled sample of a primary care population treated with an eight week course of laser acupuncture. In order to confirm this positive result, a study with a larger sample is required using an observer rated depression instrument. The fact that the BDI produced a significant result but not the HADS needs to be further evaluated. This form of laser acupuncture was not designed to treat anxiety, so the HADS scale might not be as appropriate. More research is warranted to investigate acupuncture point specificity in both depression and anxiety. The prevalence of poorly managed depression in the population highlights the need for a safe, effective and well tolerated treatment appropriate for use in primary care. With minimal adverse effects, a time frame of efficacy comparable to conventional methods and high user friendliness, laser acupuncture could prove to be an important addition to the clinical armamentarium for the treatment of depression in primary care.

Acknowledgements

The author wishes to thank Dr Glenn Hunt for his advice and statistical analysis on the project; Ms Helen Bezer, research assistant, for her patience and diligence; Associate Professor Peter Schattner for his help toward completion of this study.

Summary points

- Mild to moderate depression is commonly under treated
- A double blind RCT tested the efficacy of an eight week course of laser acupuncture
- Laser acupuncture was significantly superior to sham at two measurement points
- Adverse effects were minimal, mostly transient fatigue
- The conclusions from this study are limited by small sample size

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Journal of Affective Disorders 148 (2013) 179–187

Contents lists available at SciVerse ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

Laser acupuncture for depression: A randomised double blind controlled trial using low intensity laser intervention ☆

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ARTICLE INFO

Article history:
Received 4 June 2012
Received in revised form
26 November 2012
Accepted 27 November 2012
Available online 19 January 2013

Keywords:
Laser acupuncture
Depression
Randomised controlled trial

ABSTRACT

Introduction: Trials of acupuncture for the treatment of depression have produced mixed results. We examined the effectiveness of laser acupuncture compared with placebo acupuncture for the treatment of major depression.

Methods: A randomised, double blinded, placebo controlled trial was conducted in Sydney, Australia. Participants aged 18–50 years with DSM-IV major depressive disorder were eligible to join the study. Forty-seven participants were randomised to receive laser acupuncture or placebo laser at acupoints LR14, CV14, LR8, HT7 and KI3. The intervention was administered twice a week for 4 weeks and once a week for another four weeks, for a total of 12 sessions. The primary outcome assessed the change in severity of depression using the Hamilton-Depression Rating Scale (HAM-D), and secondary outcomes assessed the change in severity of depression using the Quick Inventory for Depression-Self Reporting (QID-SR), the Quick Inventory for Depression-Clinician (QIDS-CL), with outcomes assessed at eight weeks. The treatment response (greater than 50% improvement in HAM-D) and remission (HAM-D <8) were analysed.

Results: At eight weeks participants showed greater improvement in the active laser group on the primary and clinician-rated secondary outcome measures (HAM-D (mean 9.28 (SD 6.55) vs. mean 14.14 (SD 4.78 $p<0.001$); QIDS-CL (mean 8.12 (SD 6.61 versus 12.68 (mean SD 3.77)) $p<0.001$). The self-report QIDS-SR scores improved in both groups but did not differ significantly between the groups. In the active laser group, QIDS-SR scores remained significantly lower than baseline at 3 months follow-up. Response rates (active laser, placebo laser) on ITT (intention to treat) analyses were 72.0% and 18.2% ($p<0.001$), respectively. Remission rates on ITT analyses (active laser, placebo laser) were 56.0% and 4.5% ($p<0.001$). Transient fatigue was the only adverse effect reported.

Limitations: There was no follow-up for the placebo group at one and 3 months.

Conclusion: Laser acupuncture showed a clinically and statistically significant benefit with reducing symptoms of depression on objective measures.

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1. Introduction

Clinical depression has been identified as one of the top health priorities worldwide. The World Health Organization quantifies unipolar depression as the fourth leading cause of total disease burden worldwide (Lopez, 2005). In addition to lost productivity, depression has a major impact on the quality of life of the sufferer. In spite of growing community awareness and attempts to destigmatise depression, 60% of the depressed population avoids professional help, seeking only symptomatic relief. Of the remainder, less than half receive evidence-based care (Ellis and Smith, 2002). Many patients with depression either refuse antidepressant drugs or discontinue them owing to side-effects, and turn to complementary and alternative medicines (CAMs) (MacPherson et al., 2006). The latter are perceived as being "natural", holistic, free of adverse effects and more nurturing than standard medical therapies. Amongst CAMs, herbal remedies such as St John's Wort and acupuncture are two of the most popular therapies (Kessler et al., 2001; Jorm et al., 2002).

Recent evaluation of the use of pharmacotherapy in depression found that only 7% of patients remitted on antidepressants (Pigott et al., 2010). The majority discontinued due to adverse effects. There was also concern that, for those who continued pharmacotherapy, the adverse effects actually increased the placebo response (Pigott et al., 2010). This sobering report raises concerns for the future

☆ Trial registration: Australian New Zealand Clinical Trials Registry ANZCTR #12610000340033.

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http://dx.doi.org/10.1016/j.jad.2012.11.058

management of major depression in the community. There is therefore some urgency to evaluating non-drug treatments of depression.

There been much clinical interest in acupuncture for the treatment of depression over the last decade, with the current scientific evidence base being inconclusive. Four systematic reviews (Mukaino et al., 2005; Leo and Ligot, 2007; Halbreich, 2008; Smith et al., 2010) found acupuncture to be no more effective than sham or waitlist control strategies. The efficacy of acupuncture as an adjunct to standard treatment is also unclear. Methodological issues have plagued many of these investigations.

There are many acupuncture techniques, most of which traditionally use needle puncture. However there are other modalities utilised such as acupressure and low intensity laser. Laser acupuncture (LA) has emerged as a well-accepted technique due to its ease of application, and being both needle and pain-free, it is non-invasive and presents no risk of infection.

Laser is an acronym for Light Amplification by Stimulated Emission of Radiation. In brief, the chosen lasing medium (in this study, this is a semiconductor made from gallium–aluminium-arsenide or GaAlAs) is excited by an external energy source (battery pack consisting of AA alkaline batteries) to a higher energy state and a portion of this is released as the laser output from the laser unit (Baxter, 1994). The laser output is usually measured in milliwatts in low intensity laser acupuncture units.

Being pain-free and non-invasive, low intensity laser lends itself to clinical applications in paediatrics. LA in the treatment of children with headaches significantly reduced the number of headache days ($p < 0.001$) with active laser compared to placebo laser ($p < 0.22$) (Gottschling et al., 2008). LA to acupoint PC 6 also significantly reduced postoperative vomiting in children undergoing strabismus surgery (Schlager et al., 1998) and when this modality was used in school age children with asthma, there were significantly less days of febrile infections and reduction in bronchial hypersensitivity (Stockert et al., 2007). An earlier study on low intensity laser (with lasing medium GalAlAs) described the relationship between pain attenuation and significant change ($p < 0.001$) in serotonin plasma ratios after laser application (Mizokami et al., 1993). Endogenous opiate like peptides and serotonin plasma levels were found to increase with laser puncture analgesia (Zhong et al., 1989).

There has been one pilot laser acupuncture study (Quah-Smith et al., 2005) that reported LA as efficacious compared to placebo laser (PA) ($p < 0.001$) in the treatment of mild to moderate depression in a primary care setting, and the treatment response persisted for 3 months following laser intervention ($p < 0.01$). This improvement in mood was more significant at the end of the series of LA, with data showing only a trend for improvement at 4 weeks post LA and then was very significant again at 12 weeks post LA. This fluctuation may be attributable to, possibly, a delay before the longer- term effect of acupuncture (in this case, mood improvement) was evident (Quah-Smith et al., 2012). There were no significant adverse effects. It has also been shown, using functional magnetic resonance imaging (fMRI), that LA produces significant activation and deactivation in fronto-limbic-striatal brain regions compared to placebo (Quah-Smith et al., 2010). In this study, we examined the efficacy of acupuncture with reducing the symptoms of depression compared with a placebo control Fig. 1.

2. Methods

A double blinded, randomised, placebo controlled clinical trial was undertaken at the Black Dog Institute and a private acupuncture clinic in Sydney, Australia. Participants were recruited from the media and online advertising. Individuals aged 18–50 years were eligible to join the trial if they were diagnosed with major depressive disorder meeting DSM-IV (American Psychiatric Association, 1993) criteria for current major depression, a score of ≥ 14 on the Hamilton Depression Rating Scale (HAM-D_{17}) (Hamilton, 1960), and a score > 10 on the Quick Inventory of Depressive Symptomatology – Clinician (QIDS-CL) and Quick Inventory of Depressive Symptomatology – Self Reporting (QIDS-SR) (Rush et al., 2003). Participants needed to be free of psychotropic drugs and herbal remedies for at least four weeks prior to trial entry, and no co-interventions were permitted during the trial. Participants were not eligible if the duration of depression was greater than two years, or there was a history of hypomania or mania, substance abuse disorders, known central nervous system lesions, known uncontrolled endocrine disorders, pregnancy or potential pregnancy, or active suicidal tendencies. Suitability was confirmed by clinician screening. Participants provided written informed consent and the study was approved by the Human Research Ethics Committee of the University of New South Wales (HREC No. 07258).

Following recruitment, participants were randomised to either laser acupuncture (LA) or placebo acupuncture (PA). Randomisation was computer-generated. Only the project manager (JAH) was privy to this sequence to allow allocation of participants to LA or PA. Switch 'A' or 'B' was identified for each participant and this was kept in an envelope in each participant's folder (identifiable by the recruitment code alone of initials and recruitment number). The medical acupuncturist was not allowed access to each participant's folder.

All participants received treatment at selected putative 'depression' acupoints (unilateral right sided Qimen LR14, Juque Ren14, left sided Ququan LR8, left sided Shenmen HT7) and unilateral (right side) Taixi KI3. Twelve sessions of the intervention were performed: twice weekly for four weeks and once a week for another four weeks. The choice of acupoints administered to both groups included – Qimen LR14, Ququan LR8, Juque CV14, Shenmen HT7 and Taixi KI3 – was based on the principles of TCM (Macioca, 1994; Aung and Chen, 2007), No TCM differential diagnosis was undertaken as the selected acupoints have been trialled successfully in our pilot study (Quah-Smith et al., 2005). Qimen LR14 and Juque CV14 are "alarm points" empirically known to act rapidly. LR14 and LR8 are useful in mood disorders and stressful states. CV14 is useful where somatic changes occur including pectoral pain, headaches, epigastric pain and nausea. HT7 is a classical acupoint used to calm the individual and help in insomnia. KI3 is useful for addressing fatigue and reducing anxiety.

KI3 replaced CV15 in the pilot study, for the purposes of treating the anxiety component found in 85% of depressives (Tiller, 2012). Empirically, CV14 is used more frequently than CV15 and the former is the "alarm point" as previously mentioned on the Heart meridian (Aung and Chen, 2007).

This clinical study is part of a series of clinical and biological investigations into LA in depression: KI3 on the right had side was treated and LR8 on the left hand side so laterality could be tested (whether acupoint stimulation with LA activates ipsilateral or contralateral brain regions) in our associated functional magnetic resonance (fMRI) investigations mentioned above (Quah-Smith et al., 2010, 2012).

Acupoint location followed the guidelines documented by the World Health Organisation were applied (World Health Organization, 2008). IQS administered the LA: she is a Fellow of the Australian Medical Acupuncture College and has been teaching and practising acupuncture for 21 years.

For those receiving LA, 100 mW low intensity infra red (808 nm) units were produced, based on the Moxla^{R} protocol, by Advantage Health Care, Victoria, Australia for this study. The

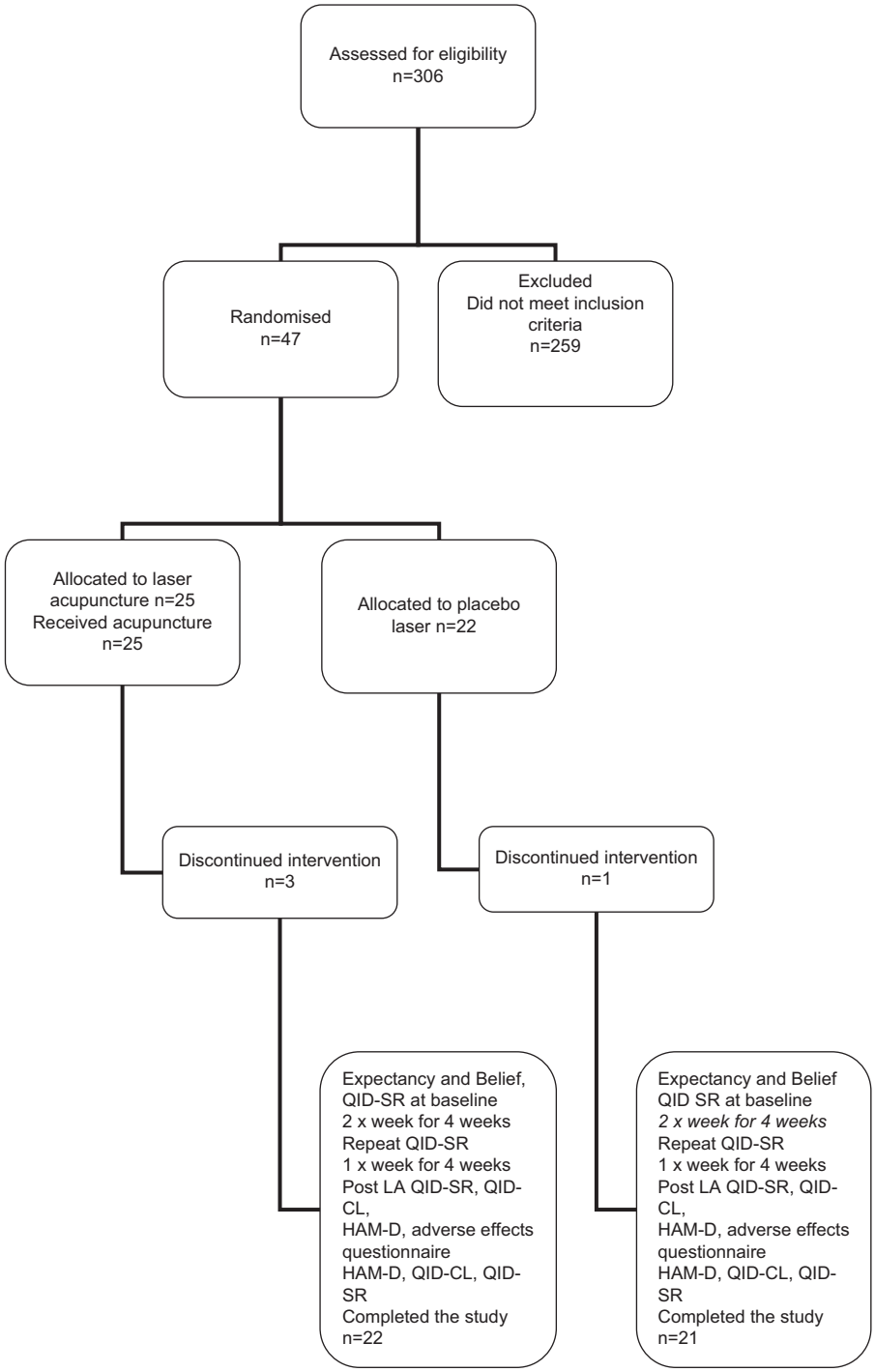

Fig. 1. Recruitment and participant flow through the trial.

laser beam is infra-red in frequency range (808 nm) and is not visible to the naked eye. The laser probe is fully in contact (perpendicular to the skin surface) to avoid scatter of the laser beam. Both laser units had a concealed section with a flick switch numbered by the manufacturer as 'A' and 'B', one of which was the placebo option, known only to the project manager (JAH) and the manufacturer. The control panel of the laser units beeped and a red light flashed when the laser probe button was on either A or B. Each unit was separately set up for placebo or laser options.

None of the participants reported any sensation apart from a light touch of the laser probe when it was applied to the skin. The flick switches were concealed with wide fabric strip (velcrose) bands. The prepared unit was handed to the medical acupuncturist at the time of treatment and retrieved immediately after.

The laser was applied to each acupoint for 10 s to deliver one joule of laser energy at each acupoint, giving a total of 5 J for 5 acupoints per session. For those in the placebo group the laser infra- red beam did not come on when the switch was pressed. Each participant wore black lensed laser protective glasses supplied by the manufacturer and was treated in a brightly lit environment. The laser probe was in direct contact with the participant's skin surface perpendicularly before commencement of laser delivery. The participants and acupuncturist were blind to group allocation.

The primary endpoint was measured at the 2 months mark after the last treatment (HAM-D). Secondary endpoints were measured at the one month mark (QID-SR), at the two months mark after the last treatment (QID-SR, QID-CL), one month post treatment (QID-SR) and three months post treatment (QID-SR). The primary outcome measured a reduction in the severity of depression defined as a $>50\%$ reduction in score, of the 17-item HAM-D. The secondary outcome measured remission at the end of treatment defined as a score of ≤ 7 on HAM-D or ≤ 5 on QIDS-CL and QIDS-SR. The structured interviews for rating were conducted by trained clinicians blind to group allocation. Inter-rater reliability of the rating clinicians was high prior to trial commencement. Practice ratings were conducted to ensure reliability. The raters were (MH designated main rater), IQS (for emergencies) and for screening only, JAH.)

We evaluated the baseline expectations and beliefs of the participants and whether there might be any contributory bias (positive effect) to their scores, using a self report 6-item Expectancy and Belief scale, adapted from the University of Michigan study on acupuncture and fibromyalgia (Harris et al., 2005). Upon completion of the 12 sessions of acupuncture, JH asked all participants to complete a 6-item scale with score range of 0 to 6 (6 being maximum intensity) to assess any adverse effects:1. dizziness, 2.aches, 3.transient fatigue, 4.prolonged fatigue, 5.vagueness, and 6.nausea). An assessment of blinding was made from each participant and the medical acupuncturist.

The results of the pilot study showed a large effect size (Cohen's d) of approximately 0.90, based on differences between the placebo and active groups in the change in the Beck Depression Inventory (BDI) scores (Beck et al., 1961). To detect a similar effect size for measures used in the present study, with power of 80% and $\alpha=0.05$, we estimated that a total sample of 44 participants would be required, assuming approximately equal number of participants in placebo and active groups.

The analysis was carried out by JC. Repeated measures ANCOVA was used to examine differences between the active and placebo groups in changes in the HAM-D, QIDS-CL and QIDS-SR measures. Control variables were age, sex and expectancy. The Expectancy variable was calculated as the first principal component (Question1: "In general, do you think acupuncture works?") of the six expectancy items and was rated from 1 (very negative) to 7 (very positive). The remaining 5 questions in the Expectancy and Beliefs Questionnaire were rated 0% to 100% by the participants: (Questions 2: Do you want LA to improve your mood and help your depression; Question 3: Do you want LA to help your general wellbeing: Question 4: How confident are you that LA will improve your mood; Question 5: How confident are you that it will improve your fatigue; Question 6: How confident are you LA will alleviate your other symptoms for (physical complaints).). Mean values were calculated for Questions 2 to Question 6.

Per-protocol analyses were performed using only those participants with both pre- and post-treatment ratings, as well as Intention to Treat (ITT) analyses in which last observed value carried forward for missing post-treatment ratings. In order to better understand which domain of depression was most affected by the laser acupuncture intervention, the repeated measures ANCOVA was also performed with each of the items in HAM-D and QIDS-CL as dependent variables. Only the clinician based assessments were selected for the latter analysis in order to better evaluate items such as somatic symptoms, psychomotor agitation and retardation, as well as general interaction. Response and remission rates based on HAM-D and QIDS scores at post-test were calculated. Remission was at HAM-D <8 or QIDS-CL <6 and QID-SR <6 (Insel, 2006). The statistical significance of differences between active and placebo groups in response and remission rates were investigated using the chi-squared test. Number-needed-to-treat (NNT) values were calculated for remission rates. An assessment of blinding was examined using the Chi-square test.

3. Results

Recruitment commenced in mid-August 2007 and continued until the end of August 2009. In total, 306 potential participants were assessed for eligibility. The majority of those excluded had chronic depression of more than 2 years or were on antidepressant therapy and did not wish to stop their medication. Forty-seven were randomised. Twenty-two recruited subjects completed laser acupuncture (LA) and 21 completed the placebo acupuncture (PA). There were four dropouts (LA 3; PA 1). The reasons for dropout were: LA group—one participant withdrew after 2 weeks LA, the subject felt her mood was not improving and may be deteriorating and chose to return to pharmacotherapy, one was unable to keep up attendance and withdrew, and the last completed the series of LA but was too unwell to continue with post LA QID-SR. The dropout in the PA group withdrew for personal reasons after completing the treatment series.

The baseline characteristics are presented in Table 1. Thirty-four participants were female (72%), thirty-five were working (74%). Twenty-six (55%) had previously sought needle acupuncture treatment. Participants had clinically significant depression with a DSM-IV diagnosis of major depressive disorder and were drug free or drug naive at the time of their entry into the trial. Clinical depression scores included mean scores on the HAM-D of 20.03 (SD 4.2), QIDS-CL 20.6 (SD 4.3), and QIDS-SR 18.40 (SD 4.6). Twenty-seven participants reported duration of depression of greater than three months (57%), and thirty-two reported a previous episode of depression (68%). No statistically significant differences between LA and PA were found at baseline. There was no statistical difference between groups for expectancy ($p=0.412$). All participants completed all scheduled intervention sessions.

In addition to the baseline characteristics, mean values for the remaining questions in the expectancy and belief questionnaire were: wanting LA to help their depression (92.0%), wanting LA to help their general wellbeing (42.7%), confident that LA will improve their mood (30.5%), confident that LA will alleviate their fatigue (28.8%) and confident that LA will alleviate all their other physical complaints (28.0%).

3.1. Treatment effects

Table 2 Statistically significant group by occasion interactions were found with both per-protocol and ITT analyses for HAM-D ($P=0.001$ and 0.013, respectively) and for QIDS-CL ($P=<0.001$ and 0.016). For QIDS-SR, although there was an overall statistically significant decrease in depression scores over time (F1, $39=4.63$, $p=0.038$ and F1, $42=0.013$, respectively), there were no differences between groups ($P=0.571$ and 0.390). In these analyses, no statistically significant interactions with occasion were observed with any of the control variables, sex, age or expectancy, except for the per-protocol analysis for changes in QIDS-CL, in which greater reductions in scores were found for those with higher expectancy scores (F1, $38=5.61$, $p=0.023$).

3.2. Ancillary analyses

In the analyses of depression symptoms HAM-D item-by-item analyses, five items showed statistically significant group by occasion interactions, after controlling for age, sex and expectancy. These were: depressed mood ($P=0.044$), late insomnia

Table 1
Baseline characteristics of participants.

	Laser acupuncture group		Placebo laser group		t	p
	N	Mean (SD)	N	Mean (SD)		
Age in years	25	40.08 (9.37)	22	36.27 (10.13)	1.34	.187
Expectancy	25	−0.11 (1.19)	22	0.13 (0.74)	0.82	.412
	N	n (%)	N	n (%)	χ^2 (d.f.)	p[a]
Sex (female)	25	20 (80.0%)	22	14 (63.6%)	1.566 (1)	.328
Marital status:	25		22		3.623(2)	1.000
Never married		12 (48.0%)		15 (68.2%)		
Married		11 (44.0%)		4 (18.2%)		
Divorced/separated		2 (8.0%)		3 (13.6%)		
Career status (active)	25	19 (76.0%)	22	17 (77.3%)	0.011 (1)	1.000
Education	25		22		1.103 (2)	1.000
Completed secondary		5 (20.0%)		3 (13.6%)		
Completed tertiary		17 (68.0%)		14 (63.6%)		
Currently studying		3 (12.0%)		5 (22.7%)		
Employment status	25		22		5.294 (3)	1.000
Full time		10 (40.0%)		14 (63.6%)		
Part time		9 (36.0%)		2 (9.1%)		
Home duties		2 (8.0%)		3 (13.6%)		
Unemployed		4 (16.0%)		3 (13.6%)		
Depressions diagnosis	25	15 (60.0%)	22	17 (77.3%)	1.607 (1)	.230
How long depressed this time?	23		22		0.341 (3)	1.000
Less than 3 months		9 (39.1%)		9 (40.9%)		
3 to 6 months		4 (17.4%)		3 (13.6%)		
6 to 12 months		4 (17.4%)		3 (13.6%)		
More than 12 months		6 (26.1%)		7 (31.8%)		
Medication for depression	25	1 (4.0%)	22	0 (0.0%)	0.899 (1)	1.000
Herbs for depression	25	0 (0.0%)	22	0 (0.0%)	-	-
Other medications	25	6 (24.0%)	20	3 (15.0%)	0.563 (1)	.710
Type of previous acupuncture	12		16		2.520 (2)	1.000
Needle		12 (100.0%)		13 (81.3%)		
Laser		0 (0.0%)		2 (12.5%)		
Both needle and laser		0 (0.0%)		1 (6.3%)		

[a] p values derived from Fisher's Exact test.

Table 2
Baseline and post-treatment values on HAM-D and QID measures by treatment group.

	Placebo laser			Laser acupuncture			F($df1$, $df2$))	p
	N	Baseline mean (SD)	Post-treatment mean (SD)	N	Baseline mean (SD)	Post-treatment mean (SD)		
Per-protocol analyses								
HAM-D	21	20.71 (3.38)	13.48 (3.74)	22	20.98 (3.62)	7.64 (4.94)	14.44 (1.38)	.001
QID-CL	21	20.57 (4.87)	12.24 (3.22)	22	20.68 (4.03)	6.55 (5.27)	15.78 (1.38)	.0003
QID-SR	21	18.57 (5.26)	10.67 (4.48)	23	17.91 (4.35)	11.22 (6.67)	0.33 (1.39)	.571
ITT analyses								
HAM-D	22	21.05 (3.65)	14.14 (4.78)	25	21.02 (3.51)	9.28 (6.55)	6.69 (1.42)	.013
QID-CL	22	20.64 (4.77)	12.68 (3.77)	25	20.56 (3.84)	8.12 (6.61)	6.25 (1.42)	.016
QID-SR	22	18.64 (5.14)	10.55 (4.41)	25	18.20 (4.28)	12.04 (7.00)	0.75 (1.42)	.390

F and p values are for statistical tests for interactions between group and occasion, with control variables age, sex and Expectancy. 17-item Hamilton-Depression Rating Scale HAM-D; Quick Inventory for Depression-Self Reporting QIDS-SR; Quick Inventory for Depression-Clinician QIDS-CL.

(P=0.014), anorexia (P=0.035), somatic symptoms (P=0.00021), somatic anxiety (P=0.013) and agitation (P=0.035). [Supplementary Table 1]. In the QIDS-CL, five items with significant group by occasion interactions. These were: waking up too early (p=0.002), increased or decreased appetite (p=0.002), view of self (p=0.042), general interest (p=0.007) and energy level (p=0.021). After Bonferroni's correction for multiple comparison, somatic symptoms (heaviness in limbs, back and head; backache, headache and muscle aches; loss of energy and fatigability) were still highly significant (p=0.00021). [Supplementary Table 1].

Statistical analyses were undertaken to ensure there was no significant difference between raters. Statistical analyses were undertaken on pre- and post-LA-treatment scores only. In the rater comparisons, there was a constant trend for MH to rate lower than QS but the only statistically significant difference was for pre treatment QID-CL (means 18.17 and 21.13, p=0.041) [Supplementary Table 2].

Table 3
Response and remission rates, and numbers needed to treat (NNT) for per-protocol and intention to treat (ITT) analyses by treatment group.

	Placebo laser n/N (%)	Laser acupuncture n/N (%)	χ^2 ($df=1$)	P	NNT
Per-protocol analyses					
HAM-D > 50% reduction	4/21 (19.0%)	18/22 (81.8%)	18.94	.00005	1.59
HAM-D < 8 at post-test	1/21 (4.8%)	14/22 (63.7%)	16.40	.00005	1.70
QID-CL < 6 at post-test	0/21 (0.0%)	12/22 (54.5%)	15.89	.00006	1.83
QID_SR < 6 at post-test	1/21 (4.8%)	5/23 (21.7%)	2.69	.188	5.89
ITT analyses					
HAM-D > 50% reduction	4/22 (18.2%)	18/25 (72.0%)	13.61	.0004	1.86
HAM-D < 8 at post-test	1/22 (4.5%)	14/25 (56.0%)	14.26	.0001	1.94
QID-CL < 6 at post-test	0/22 (0.0%)	12/25 (48.0%)	14.18	.0001	2.08
QID_SR < 6 at post-test	1/22 (4.5%)	5/25 (20.0%)	2.51	.194	6.47

Hamilton-Depression Rating Scale (HAM-D_{17}); Quick Inventory for Depression-Self Reporting (QIDS-SR); Quick Inventory for Depression-Clinician (QIDS-CL).

3.3. Treatment response rate, treatment Effects on remission Rates, and Numbers needed to treat (Table 3)

Response rates (> 50% reduction in HAM-D scores) were 81.8% in the active group and 19.0% in the placebo group ($p < 0.001$) for the per-protocol analysis, and for the ITT analyses these were 72.0% and 18.2% ($p < 0.001$), respectively. The numbers needed to treat (NNT) to achieve a response over 8 weeks of LA were 1.59 for per-protocol analysis and 1.86 for the ITT analysis. Remission rates were significantly different between the two groups based on a criteria of HAM-D < 8 or QIDS-CL < 6, for both per-protocol and ITT analyses ($p < 0.001$), but not based on a criteria of QIDS-SR < 6 ($p=0.188$ and 0.194). For HAM-D < 8 criteria, remission rates in the active group were 63.7% and 56.0% for the two types of analyses, and for the placebo group, 4.8% and 4.5%. Based on the criterion of QIDS-SR < 6, remission rates in the active group were 21.7% and 20.0%, and in the placebo group 4.8% and 4.5%, respectively. NNT for remission based on the HAM-D < 8, QIDS-CL < 6 and QIDS-SR < 6 criteria were 1.70. 1.83 and 5.89, respectively, for the per-protocol analyses, and 1.94, 2.08 and 6.47, for the ITT analyses, respectively Table 3.

3.4. Follow up at one and three Months post treatment for laser acupuncture group

QIDS-SR follow-up scores were obtained for the laser acupuncture group at one month ($n=18$), and at 3 months after study completion ($n=16$). Repeated measures ANCOVA, controlling for age, sex and expectancy, showed statistically significant differences between pre-test scores and each of end of LA, and 1-month post LA and 3 months post LA follow-up scores (all $P=0.001$). No statistically significant differences were found between the post-test and 1 and 3 months QID-SR scores.

3.5. Integrity of blinding

The percentage of participants in the active group that offered guesses 'active', 'placebo' and 'unsure' were 65.2%, 30.4% and 4.3%. For participants in the placebo group, the corresponding percentages were 60.0%, 30.0% and 10.0%. These differences were not statistically significant between groups (Chi-square=0.537, $df=2$, $p=0.765$). Overall, the acupuncturist's patterns of response for the three options (active vs. placebo vs. unsure) were evenly distributed with no significant difference in proportion of guesses (Chi-squared=0.125, $df=1$; $p=0.723$).

3.6. Adverse effects

There were no significant inter-group differences in adverse effects. Out of a maximum score of 6, the only adverse effects with mean scores > 0.50 were: in the LA group, minimal transient fatigue (0.67); and in the PA group, aches (0.11), transient fatigue (1.0), days of fatigue (0.71) and vagueness (0.52).

4. Discussion

This is the first adequately sized double blind controlled trial of LA in depression. LA was associated with a clinically and statistically significant reduction in HAM-D scores, and a significant number of patients with major depression responded or remitted on this measure after 8 weeks of treatment. This result was supported by analysis of the secondary clinician-rated measure, but not by the self-rated measure. Although this positive effect was found in the earlier pilot study at 3 months post LA compared to PA (as recorded using the self reporting Beck Depression Inventory Scale (BDI)), we cannot make any conclusive comments that this was the case in this study. In the LA group, the positive effect was still measurable at the third month post treatment (QID-SR $p < 0.001$ compared to baseline) but we did not follow up the QID-SR in the PA group after completion of intervention due to our ethical responsibility (a condition of our ethical approval) to break the blinding and offer the PA group active laser upon completion of intervention. Clinician ratings at the 3-month post treatment mark, which were not carried out due to resource limitations, would have overcome this limitation. There were no significant adverse effects of LA.

The results of this trial must be examined in light of the accumulating literature on acupuncture in depression. A recent Cochrane Review (Smith et al., 2010) examined 30 trials of acupuncture in depression and concluded that the evidence of the effectiveness of acupuncture in depression, relative to sham acupuncture, was inconclusive. The majority of trials compared acupuncture with drug treatment and found no group differences. Two trials found acupuncture to have an additional beneficial effect when co-administered with medication. Most studies used either manual acupuncture or electro-acupuncture, with the exception of one small study that examined laser acupuncture (Quah-Smith et al., 2005), the latter finding LA to be superior to placebo in its anti-depressant effect. There are three possible explanations to justify the large clinical effect observed in this trial. First, the double blind study design allowed an evaluation of the efficacy of laser acupuncture compared with a placebo and therefore reduced the potential for effects arising from the use of

active sham points seen in manual acupuncture studies. Our findings have been supported by our fMRI study (Quah-Smith et al., 2005) on healthy subjects where we demonstrated significant brain activation patterns greater than rest or placebo with active laser. Second, there was a significant improvement in the debilitating somatic changes that accompany depression including somatic symptoms (muscle aches and pains, headaches, digestive changes), and sleep patterns. Consequently participants' quality of life improved. Third, there were little or no adverse effects using the low intensity laser. This clinical study returned a transient mild fatigue (for only a few minutes after each laser session which appeared and resolved within the couple of hours after the laser intervention).

The lack of significant inter-group difference in the self-report measure in our study is worthy of comment. The high expectancy of being in the LA group by all subjects (60% in both LA and PA groups thought they were in the LA group when asked by JH which group they were in upon completion of the intervention) may be a factor. Also at baseline, the mean Expectancy Score for wanting LA to improve their mood and help their depression (Question 2) by all the subjects was very high (mean score of 92%). This desire for LA to work did not, however, carry through to wanting LA to help their wellbeing (42.7%), confidence their mood will improve (30.5%), confidence their fatigue will get better (28.8%) nor alleviate other physical symptoms they might also have (28.0%). Another factor may be that the HAM-D and QID-CL rated different items of depression to the QID-SR and the acupuncture effect in depression is better measured by the first two scales. We did not foresee that changing the self-rating instrument from BDI in our pilot study to the QID-SR in this study would be of concern. Unfortunately, this was not the case. The BDI correlated well with the HAM-D in the assessment of depression (Schotte et al., 1997; Hotopf et al., 1998; Kim et al., 2009). For this reason, we used the BDI as the primary measure in the pilot study as we did not then have the resources to use the HAM-D. Our finding in the pilot study that the change in score for BDI from baseline was significant ($p < 0.001$) in the LA group has been replicated in this study with the change in score of the HAM-D ($p < 0.001$). Our secondary measure in the pilot study, the Hospital Anxiety and Depression Scale (HADS) did not record this significant improvement at all (Zigmund and Snaith, 1983).

Upon further evaluation at the item-by-item level, we examined items of depression in the HAM-D, the BDI (as it was our primary measure in the pilot study) and the QID-SR: the HAM-D measured somatic changes (Questions 8, 9, 13) and the QID-SR had no clearly defined somatic symptoms questioning. Irritability is measured in the HAM-D (Question 12) and interestingly, also by the BDI (Question 11) in the pilot study, but does not feature as an item in the QID-SR. Although psychomotor agitation is measured by all three instruments, psychomotor retardation is only measured by the HAM-D (Question 16). Furthermore, the QIDS-SR did not correlate well with its sister scale the QIDS-CL in this study and the primary measure the HAM-D, while the latter two correlated well. The somatic items (Q 3,Q 6,Q 7,Q 14 in QIDS-CL) (Supplementary Table 1) were found to show a significant change in LA; these items were measures of pain, appetite, speech and agitation, which are possibly better assessed by a clinician. In the QIDS-CL, improvement in sleep (Q 1) and appetite (Q 7) were greater in the LA group. These differences may be attributed to laser acupuncture induced somatisation effects as described previously, including autonomic modulation (Haker et al., 2000; Agelink et al., 2003; Wu et al., 2009; Napadow et al., 2012; Quah-Smith et al., 2012). After correction for multiple comparisons, the HAM-D item on change in somatic symptomatology was still highly significant ($p = 0.00021$) reflecting the most important positive physical changes from active laser acupuncture resulting in improved quality of life. In spite of the participants' lack of confidence in LA alleviating their fatigue or their physical symptoms such as headaches and back aches, those who received active laser certainly benefited as measured by the HAM-D item on somatic changes. It is apparent now that the choice of primary and secondary measures including the self-reporting measure is important if we want to better measure the acupuncture effect.

In this study, not being able to follow up at one and three months post intervention with the QID-SR in the PA group imposes a limitation- if there was a delayed or prolonged effect of LA we have missed the opportunity to measure this effect compared to the PA group. However there is emerging evidence of this prolonged or delayed effect as measured by fMRI (Rheu et al., 2011; Quah-Smith et al., 2012).

An important strength of the trial was that blinding was successfully maintained for study participants. Not only does LA lend itself to blinding easily because of the lack of skin sensation from laser stimulation, the allocation, administration and evaluation aspects of the trial were kept separate. Unforeseen circumstances necessitated IQS to be a rater as well. However analysis of the ratings by MH and IQS did not show any significant difference between the two raters for the post treatment scores, only a tendency for MH to overall rate a lower baseline QID-CL compared to IQS. This lower baseline QID-CL would have exerted a conservative effect by lowering post treatment scores. Post-treatment questioning of participants and IQS did not suggest that blinding had been compromised.

We therefore explain the discrepancy between objective and subjective ratings to be due two possibilities: (a) the objective measures of depression improved to a greater extent than the subjective measures. An item-analysis of HAM-D revealed 5 items as being significantly affected by treatment: depressed mood, late insomnia, anorexia, somatic symptoms, somatic anxiety and agitation, partially supporting this possibility; (Supplementary Table 1). (b) our choice of self rating scale the QID-SR in this study did not measure some of the items of depression which improve with LA (for example, irritability and psychomotor retardation). In addition, the somatic symptoms changes with LA were also highly significant ($p = 0.00021$) in the HAM-D item-by-item analysis.

In studies of major depression, it has been found that the placebo response is significant regardless of the treatment type being tested and is related to the study design and study population (Brunoni et al., 2009). The frequent visits for treatment and the contact with the supportive research team are likely to have exaggerated the placebo effect, especially at a subjective level. JAH also recorded the relatively long periods of time (20–30 min) some of the subjects would stay on in her office to chat (unsolicited by JAH) or arrange appointment times. The conditioning effects of repeated visits leading to increased learning and increased placebo response have previously been described (Colloca et al., 2010).

The mechanism of action of LA, and indeed all acupuncture as a potential anti-depressant treatment, is poorly understood. Various mechanisms have been suggested for needle acupuncture, which include stimulation of large peripheral nerves, neurovascular bundles, mechanoreceptors, or free nerve endings, but no neuroanatomical structure or pathway has been clearly established as mediating the therapeutic effect (Napadow et al., 2008). More recent attention has been on the intermuscular/intramuscular loose connective tissue, as many meridians and acupuncture points align with this (Langevin and Yandow, 2002). Acupuncture meridians have also been reported to have lower electrical impedance and higher capacitance compared to adjacent controls, which may justify the use of electroacupuncture, although the data on this are not conclusive (Ahn et al., 2008). In relation to the use of laser, the mechanisms are poorly understood.

The choice of acupoints for this trial was based on recommendations in TCM for the treatment of depression (Macioca, 1994; Aung and Chen, 2007), the highly significant results of our pilot study and the neuroimaging evidence we have gathered with regards to this suite of acupoints in depression (Quah-Smith et al., 2012). In practice, acupoint efficacy is not specific, and one acupoint can be used for several different conditions, just as one medical condition can be managed with several acupoint locations. Empirical basis for the choice of acupoints is therefore weak and requires further evaluation. There is however some emerging evidence for acupoint specificity (Jin et al., 2004; Yan et al., 2005; Campbell, 2006). For example, in a functional magnetic resonance imaging (fMRI) investigation of acupoints considered to be useful in depression performed in a healthy sample, HT7, considered to be an anti-anxiety acupoint in TCM, did not have any significant brain response (Quah-Smith et al., 2010). The neuroanatomical pathways by which laser stimulation produces its effect are also not known, although a role has been postulated for unmyelinated C fibres (Olausson et al., 2002).

There is further evidence that acupuncture produces brain changes that are consistent with a potential therapeutic effect. Some neuroimaging and neuroendocrine studies have suggested that needle acupuncture affects hypothalamic as well as extra-hypothalamic functions and modulates mood (Hsieh et al., 2001; Napadow et al., 2007). Laser acupuncture of a foot acupoint, classically used for treating visual problems, was demonstrated to cause activation of the occipital cortex (Siedentopf et al., 2002). More recently, our group showed in an fMRI study that LA stimulation of the acupoints used in the current study lead to activation of frontal-limbic-striatal brain regions, with the pattern of neural activity being somewhat different for each acupuncture point (Quah-Smith et al., 2010). This argued for the plausibility of LA as an anti-depressant treatment, although the relative merits of the various acupoints, or their combinations, are unknown.

The promise of improved efficacy, in particular, the clinically and statistically significant improvement of somatic symptomatology and lack of adverse effects is a potent combination for improving the quality of life for the depressed. The efficacy of LA relative to established treatments is not known, and it is therefore difficult to suggest a place for it in today's repertoire of anti-depressant treatments. A recent study did however use acupuncture as augmentation therapy in antidepressant partial and non-responders (Yeung et al., 2011). Our study also does not further our understanding of potential mechanisms by which the response occurs.

5. Conclusion

Low intensity laser acupuncture was associated with objective improvement in depression. Further studies are needed to replicate this finding, and larger trials will help determine the predictors of good response. It is also important to examine longer-term effects, and whether repeated applications are necessary to maintain such benefit.

Role of funding source

This study was funded by the Black Dog Foundation and a grant from a private philanthropist.

Conflict of interest

The authors have no conflict of interest to declare.

Acknowledgements

We wish to thank Scientia Professor Gordon Parker, the Black Dog Foundation and Mr Charles Scarf for their support and generosity, Scientia Professor Perminder Sachdev for his support, Associate Professor Vijaya Manicavasagar for her counsel, Julie Ann Ho (JAH) for her role as the research project manager, Dr. Mark Horowitz for his role in pre and post acupuncture assessments, Matthew Hyett (BDI) for his role in helping establish inter-rater reliability for the project, BDI staff for their kind support and enthusiasm always and the staff at Albert Medical Acupuncture for their support. Thanks also to Professor Rick Harris (University of Michigan) for his permission to modify his expectancy and belief measures for acupuncture in pain for our study.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2012.11.058.

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Complementary Therapies in Medicine (2008) **16**, 87—91

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SHORT COMMUNICATION

Using acupuncture to treat depression: A feasibility study

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Available online 29 September 2007

KEYWORDS
Depression;
Acupuncture;
Sham control

Summary
Objectives: To establish the feasibility of conducting a randomised controlled trial to evaluate the efficacy of acupuncture in the treatment of mild-to-moderate depression. Control group intervention, blinding of treatment, outcome measures and the acceptability of such a trial amongst participants were key factors to be addressed. The findings from this study will be used to determine the design of a phase III randomised controlled trial.
Design: Nineteen participants were recruited through general practices in London, UK. Participants were randomly assigned on a 2:1 basis to either 12 sessions of verum acupuncture or 12 sessions of sham acupuncture (control). Sham acupuncture involved actual needling but at sites considered to be unrelated to depression.
Main outcome measures: The Beck's Depression Inventory (BDI) and the RAND 36 Item Health Survey 1.0 (RAND) were completed at baseline and at the end of treatment or at treatment dropout. All participants also attended a brief qualitative interview at the end of the study.
Results: Treatment dropout was low and there were high levels of patient enthusiasm for a study of acupuncture. Referrals from General Practitioners (GPs) were lower than expected. The sham control method successfully maintained participant blinding to treatment and enabled the specific (or active) component of an acupuncture intervention to be isolated and its efficacy assessed. The outcome measures were sensitive enough to record changes in depressive symptoms and quality of life and are appropriate for use in a larger trial.
Conclusions: This feasibility study has provided important information that can be used to guide the design and methodology of a full-randomised controlled trial.
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Introduction

Depressive disorders are expected to become the second highest cause of disease burden worldwide by 2020.[1] Around 70% of all primary care consultations are reported to involve individuals with depressive disorder.[2]

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0965-2299/$ — see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ctim.2007.07.005

Acupuncture may be a promising treatment in primary care for individuals with depressive disorders[3–5]; however, the evidence for use of this technique in such cases is inconsistent or inconclusive, and further trials are required.[5–7] The objective of this study was to establish the feasibility of conducting a randomised controlled trial to evaluate the efficacy of acupuncture in the treatment of mild-to-moderate depression. Previous report has highlighted the need for greater methodological rigour in acupuncture trials[6]; therefore, this feasibility study was designed to focus on patient recruitment, to identify a suitable control group intervention, to explore treatment blinding, and to ascertain suitable outcome measures.

Materials and methods

Accrual of participants

Participants were recruited in seven general practices in North London, UK. General Practitioners (GPs) provided information to eligible participants during routine consultations and posters and leaflets describing the study (and inviting contact) were displayed in practice waiting rooms. Participants were screened using a self-completion Beck's Depression Inventory (BDI) and those who scored at least 14 were contacted.

Following referral or expression of interest, the participants were screened for eligibility.

Inclusion criteria

(1) Aged at least 18 years; (2) ''mixed anxiety and depression'' or ''mild-to-moderate depressive episode with or without somatic syndrome''[8] as diagnosed using the Clinical Interview Schedule—Revised.[9]

Exclusion criteria

(1) Pregnancy; (2) history of substance abuse or brain damage; (3) other psychiatric disorder preceding the onset of depression; (4) in receipt of concurrent alternative treatments or a talking therapy for repression; (5) in receipt of pharmacological treatments for more than 3 months in the past year.

Randomisation and treatment blinding

Participants with confirmed eligibility attended a diagnostic session with the acupuncturist and were then randomised. The acupuncturist elicited the underlying imbalances of the participants without reference to 'depression'. A member of the research team (S.A.) was independently responsible for randomisation off-site, and used a block method on a 2:1 ratio with two-thirds of participants receiving verum acupuncture.

The member of the research team responsible for randomisation informed the acupuncturist by telephone of each patient's randomisation after they had completed their diagnostic session. All other researchers, including assessors, and the participants were blinded to treatment. The acupuncturist received training from a member of the research team who has extensive clinical trial experience. The training included advice on how to maintain professionalism and confidentiality about assignment of treatment.

Intervention

Participants were randomised to receive either 12 sessions of manual verum acupuncture or 12 sessions of manual sham acupuncture (control). Each session lasted 40 min and was provided during usual clinic hours by an accredited TCM Healthcare practitioner with 10 years' clinical experience.

Verum acupuncture—rationale and method

A formula combined with two additional discretionary points was used in the acupuncture treatment. Box 1 (published in online version at http://sciencedirect.com/ as supplementary data) shows the points used in the verum group, the range of needling depth, and the dimensions of the needles used. Choice of points and needling depth was individualised according to TCM Healthcare principles[10] and body mass of the participant.

Sham acupuncture—rationale and method

Sham acupuncture involves actual needling but at sites considered to be unrelated to depression. The same sham points were used on all participants in the sham group (Box 1, published in online version at http://sciencedirect.com/ as supplementary data). In addition, only shallow needling was undertaken, there was no needle stimulation after insertion and *de-qi* was avoided.

Needle retention time was 20 min for both verum and sham control treatments.

Outcome assessment

The primary outcome measure was the BDI.[11] The secondary outcome measure was the RAND 36 Item Health Survey 1.0 (RAND).[12] Both the BDI and the RAND were completed at baseline and at the end of treatment or at treatment dropout. All participants also attended a brief qualitative interview at the end of the study. The interview was designed to explore the participant's experiences of the study. The participants were also asked to indicate to which study group they believed they had been assigned. All baseline outcome measures were assessed face-to-face at the participant's general practice. Where possible, end point assessments were also conducted face-to-face. In cases where this was not possible, end point assessments were conducted by telephone.

Analysis

Brief descriptive analysis of the BDI and the RAND was used to examine changes in mean scores. Qualitative data were coded into the categories 'acupuncture treatment had a positive impact', 'acupuncture treatment had a negative impact' and 'acupuncture treatment was ineffective'.

Ethical approval was obtained from Barnet, Enfield and Haringey Local Research EthicsCommittee. All participants provided signed informed consent.

Results

Enrolment

Twenty patients were recruited into the study over a period of 15 months. One patient withdrew from the study before randomisation. Thirteen participants were randomised into the verum group and six into the sham-control group. Endpoint data were available for all 13 participants in the verum group and for four of the six participants in the sham-control group. The flow of participants through each stage of the study is shown in Fig. 1. Most participants were self-referred.

Baseline characteristics

The mean age of participants was 39.9 years (S.D. = 12.1) in the verum group (nine female, four male) and 48.5 years (S.D. = 10.2) in the sham-control group (five female, one male). Participants in the verum group had slightly higher depression scores on the BDI and slightly lower wellbeing scores on the RAND than participants in the sham-control group (Table 1). The TCM Healthcare diagnosis of each participant's condition at enrolment is given in Box 2 (published in online version at http://sciencedirect.com/ as supplementary data).

Adherence to treatment

Treatment adherence was good: 11 of 19 participants (58%) completed all 13 study sessions and 16 of 19 participants (84%) completed at least 6 study sessions (Table S1, published in online version at http://sciencedirect.com/ as supplementary data). There was no correlation between early treatment dropout of participants and the treatment they were receiving.

Outcome scores

There was a decrease in mean scores on the BDI in both study groups, which indicates a reduction in depressive symptoms. There was also a slight increase in mean scores on the RAND in both study groups, which indicates an improvement in quality of life; however, a reduction in mean scores for the RAND categories of 'physical functioning' and 'pain' was seen in the sham-control group only.

Qualitative interviews

All participants welcomed the opportunity to participate in the current study. There were no differences between the verum and sham-control groups with regard to self-

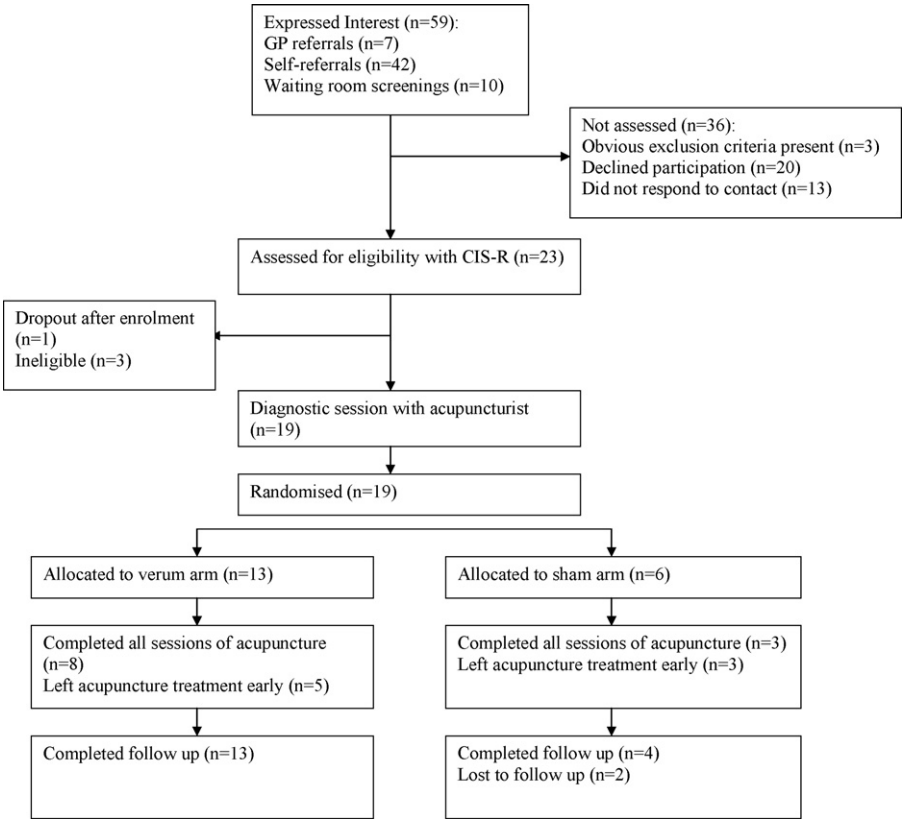

Figure 1 Flow of participants through the trial.

Table 1 Mean scores (S.D.) in BDI and RAND 36 Item Health Survey 1.0 at baseline and end point

	Verum baseline ($n = 13$)	Verum end point ($n = 13$)	Sham baseline ($n = 6$)	Sham end point ($n = 4$)
BDI	30.7 (5.3)	21.3 (10.5)	24.7 (8.4)	13.5 (11.6)
RAND 36 Item Health Survey				
Physical functioning	63.2 (27.8)	64.6 (33.9)	73.5 (24.2)	61.1 (41.8)
Role limitations physical	26.9 (29.8)	50.7 (48.5)	54.2 (40.1)	75.0 (35.4)
Role limitations emotional	2.6 (9.6)	47.2 (43.7)	27.8 (39.0)	73.3 (43.5)
Energy/fatigue	21.0 (12.5)	35.3 (22.9)	25.3 (33.2)	62.3 (23.0)
Emotional well-being	29.8 (11.1)	50.2 (23.7)	30.7 (13.5)	55.2 (29.3)
Social functioning	25.0 (15.3)	46.9 (23.9)	31.3 (29.5)	55.0 (36.0)
Pain	51.7 (32.3)	63.3 (35.5)	63.3 (29.3)	56.0 (21.0)
General health	34.2 (16.1)	46.3 (15.8)	50.8 (28.9)	60.0 (12.4)

reported positive or negative impacts of acupuncture. Eleven participants (eight verum, three sham) reported that the acupuncture treatment had a positive impact on their wellbeing, particularly on levels of stress and energy. One participant in the verum group reported that needle insertion caused pain, and two participants in the verum group reported that the acupuncture process had made their depressive symptoms worse. Three other participants (two verum, one sham) considered acupuncture to be ineffective.

Treatment blinding

There was no correlation between a participant's ability to judge correctly their study group and the treatment they were receiving.

Discussion

This feasibility study has increased our understanding of the challenges associated with conducting a full trial of the efficacy of acupuncture in the treatment of depression, and has provided important guidance on how to proceed. The study has been particularly useful in providing information about recruitment, control group design and outcome measures. The outcome measures used in this study appear to be suitable for use in a larger trial. In such a trial, the BDI and RAND will be completed following an extended follow-up period to clarify the long-term efficacy of verum acupuncture. The main purpose of this feasibility study was to provide methodological guidance for future work. The study comprised only a small population; therefore, the findings of the study need to be treated with caution and no definitive conclusions about the efficacy of acupuncture in the treatment of depression can be drawn. The number of GP referrals into this study was lower than expected, which is consistent with other trials,[13] and may be a problem related to time pressures and workload priorities[14,15] rather than a lack of commitment to the study. Most participants were self-referred after seeing an advertisement for the study in their practice waiting rooms. More consistent referral channels will need to be established for recruitment of participants into a full trial. Retrospective recruitment methods have been used successfully in Complementary and Alternative Medicine (CAM) trials[16]; however, these methods were not used in the current study because many recorded patients may be on alternative treatments that would exclude them from the study, and retrospective recruitment would exclude patients who have not yet been diagnosed with depression by the GP. Recruitment of participants into a large phase III trial is recommended to occur through a combination of patient screening in general practice waiting rooms and targeted advertising in primary care settings.

The use of a sham control method is recommended in a definitive randomised controlled trial. However, non-acupuncture points should also be used to show that the sham control needling sites are completely ineffective in the treatment of depression.

There are several concerns about the use of sham control interventions in acupuncture studies. For example, sham control methods may be perceived to reduce the experience of acupuncture solely to needling, rather than enabling the holistic nature of acupuncture to be assessed.[17] Also, the possibility that 'expectation' of treatment has a physiological effect on the brain, thus mediating a potentially powerful non-specific clinical response to acupuncture, has been suggested during pain trials.[18]

The study described here was designed to separate the non-specific effects of the intervention from the effects of needling at the correct depth in the correct place and with manual stimulation, all of which are specific to acupuncture treatment. Furthermore, the study showed that the sham method was a plausible intervention for the control group and successfully maintained participant blinding to treatment, an issue that is central to improving the methodological quality of trials assessing the effects of acupuncture in individuals with depression.[6]

The use of a sham-control group also enabled the specific (or active) component of an acupuncture intervention to be isolated and its efficacy assessed.

Although practitioner engagement is an essential part of acupuncture,[19] correct needling must be considered the most important factor. Examination of the impact of inserting needles into specific energy points in the body is imperative and will provide valuable evidence about the efficacy of acupuncture.

Conclusion

This feasibility study has provided important information that can be used to guide the design and methodology of a full-randomised controlled trial.

Acknowledgements

The authors would like to thank the acupuncturist, study participants and GPs. The North Central London Community Research Consortium funded this study.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ctim.2007.07.005.

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The Efficacy of Acupuncture in the Treatment of Major Depression in Women
Author(s): John J. B. Allen, Rosa N. Schnyer and Sabrina K. Hitt
Source: *Psychological Science*, Sep., 1998, Vol. 9, No. 5 (Sep., 1998), pp. 397-401
Published by: Sage Publications, Inc. on behalf of the Association for Psychological Science
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Research Report

THE EFFICACY OF ACUPUNCTURE IN THE TREATMENT OF MAJOR DEPRESSION IN WOMEN

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Abstract—*The effectiveness of acupuncture as a treatment for major depression was examined in 38 women, randomly assigned to one of three treatment groups. Specific treatment involved acupuncture treatments for symptoms of depression; nonspecific treatment involved acupuncture for symptoms that were not clearly part of depression; a wait-list condition involved waiting without treatment for 8 weeks. The nonspecific and wait-list conditions were followed by specific treatment. Five women terminated treatment prematurely, 4 prior to the completion of the first 8 weeks. Following treatments specifically designed to address depression, 64% of the women* (n = *33) experienced full remission. A comparison of the acute effect of the three 8-week treatment conditions* (n = *34) showed that patients receiving specific acupuncture treatments improved significantly more than those receiving the placebo-like nonspecific acupuncture treatments, and marginally more than those in the wait-list condition. Results from this small sample suggest that acupuncture can provide significant symptom relief in depression, at rates comparable to those of psychotherapy or pharmacotherapy. Acupuncture may hold sufficient promise to warrant a larger scale clinical trial.*

Depression is an unfortunately common condition for which people often seek alternative treatment (Eisenberg et al., 1993). Lifetime-prevalence estimates of major depression (American Psychiatric Association, 1994) have ranged from 3% to 6% (Horwath & Weissman, 1995; Myers et al., 1984; Robins et al., 1984), with recent estimates (Kessler et al., 1994) notably higher, in the range of 17%. The costs of major depressive disorder exceed those of other chronic diseases such as diabetes and hypertension in terms of personal distress, lost productivity, interpersonal problems, and suicide (Gotlib & Beach, 1995; Hirshfield & Schatzberg, 1994).

Conventional treatments for depression, such as psychotherapy and pharmacotherapy, provide significant relief for approximately 50% to 70% of patients who complete treatment. Unfortunately, of those enrolling in treatment, about one third terminate treatment prematurely (Elkin et al., 1989), citing factors such as dissatisfaction with their current treatment or intolerable side effects. If both noncompleters and nonresponders are taken into account, more than half of all depressed persons who enter treatment fail to recover. Even among those who recover from an episode of major depression, more than one third show clinical relapse within 18 months (Shea et al., 1992).

These statistics suggest that alternative treatments may be welcomed by individuals with depression. Such alternatives might serve as adjuncts to or substitutes for existing treatments, or as maintenance or preventive treatments following remission. A recent survey (Eisenberg et al., 1993) revealed that depression was among the 10 most frequently reported medical conditions for which respondents sought treatment, and among those with self-reported depression, seeking alternative treatments (with or without traditional treatment) was more common than seeking the services of a traditional provider alone.

The present study therefore sought to assess the efficacy of an alternative treatment—acupuncture—for major depression. Although abstracts of several reports from China and the former Soviet Union suggest that acupuncture may assist in the treatment of emotional disorders, including those for which depression is a prominent symptom (Chengying, 1992; Cherkezova & Toteva, 1991, 1993; Dudaeva, 1990; Frydrychowski, Landowski, Watrobski, & Ostrowska, 1984; Han, 1986; Polyakov, 1988; Suobin, 1991), there exist no controlled studies of acupuncture's effectiveness for depression in the refereed literature in English.

Acupuncture treatments derive from the principles of Chinese medicine. Strictly speaking, depression does not exist as a disease category in Chinese medicine, because Chinese medicine does not focus on the diagnosis and treatment of disease, but rather on the detection of energetic imbalances. Chinese medicine views health as a balance between the yin and the yang forces, which depends on the proper circulation of the vital energy Qi (pronounced "chee") along energetic pathways or meridians. Within the Western framework, many different symptom patterns are subsumed under the diagnosis major depression (e.g., a depression with overeating, hypersomnia, and psychomotor retardation vs. a depression with loss of appetite, insomnia, and psychomotor agitation); by contrast, these different symptom constellations would signify different patterns of disharmony from the perspective of Chinese medicine, and would require different treatments. The rationale of Chinese medicine has been well described (Kaptchuk, 1983), and we have elsewhere discussed in greater detail its application to assessing and treating depression (Allen & Schnyer, 1998). In brief, acupuncture can be seen as providing a framework for understanding heterogeneous symptom patterns, and for providing treatments individually tailored to address these distinct patterns.

In the present study, patients with major depression received acupuncture treatments that were individually tailored, according to the principles of Chinese medicine, to specifically address each individual's pattern of symptoms. Some patients, prior to receiving these specific treatments, received superficially similar placebo-like treatments designed to treat symptoms other than depression (nonspecific treatments) or entered a wait list. This design allowed us to test whether acupuncture designed to specifically treat symptoms of depression would demonstrate efficacy compared with a wait-list control and nonspecific acupuncture treatments.

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METHOD

Patients

Thirty-eight women between the ages of 18 and 45 were recruited through newspaper advertisements. Advertisements mentioned treatment for depression, but not acupuncture. Patients were included if they met the diagnostic criteria for current major depression as outlined in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV; American Psychiatric Association, 1994). They were assessed using the Structured Clinical Interview for DSM-III-R (SCID; Spitzer, Williams, Gibbon, & First, 1990), which was administered by interviewers with a master's in psychology under the supervision of the first author. Patients were excluded if any of the following criteria were present: (a) dysthymia or chronic (duration greater than 2 years) major depression, (b) any current Axis I diagnosis besides major depressive disorder, (c) history of psychosis or mania, (d) substance abuse or dependence within the past 4 months, (e) any current treatment, (f) endocrine abnormalities, (g) history of central nervous system lesions or any medical disorder or treatment that could cause depression, (h) active suicidal potential necessitating immediate treatment, or (i) pregnancy. Five women (13%) dropped out of the study prior to completing it,[1] resulting in a final sample of 33 women who received treatment specifically for depression.

To assess the women's depression, we administered a 31-item, modified version of the Hamilton Rating Scale for Depression (HRSD) modeled after the revision of the HRSD by Gelenberg et al. (1990). Because only 19 of the items in this version address DSM-IV symptoms of depression, we report in this article scores for this subset of items, which we refer to as the DepHRSD.[2] The 33 women in the final sample had mild to moderate depression, with a mean DepHRSD score of 25.1 (SD = 6.8, range: 13–41). The mean duration of their current episodes was 9.2 months (SD = 6.9), and they had on average 2.5 (SD = 2.9) prior episodes. Additionally, 82% of the patients reported having previously received psychotherapy, 53% reported previous trials of antidepressants, and 11% reported no previous treatment. Fifty-nine percent of these patients reported that one or more first-degree relatives also had depression of comparable severity. All participants provided informed consent to participate, and had their rights protected by procedures approved by the University of Arizona's human subjects committee.

General Design and Data Analysis

Factors not specific to acupuncture or the points selected can have therapeutic impact. Such factors include, among others, the patient–acupuncturist relationship and actively engaging in activity believed to improve depression. Our design therefore provided for the development of two types of acupuncture treatments for each patient: a treatment individually tailored to treat the patient's specific symptoms of depression (specific treatment) and a placebo-like treatment designed to treat a pattern of disharmony that was not related to the individual's depression, but was characteristic of the individual (nonspecific treatment; e.g., targeting back pain). The nonspecific treatment was not, strictly speaking, a placebo because it was an active treatment and may therefore have had more impact than a truly inert placebo treatment. We reasoned that if specific treatments outperformed these active nonspecific treatments, it is likely that they would also outperform a truly inert placebo treatment. Active nonspecific treatments were employed, however, to keep the acupuncturists' expectancies of efficacy comparable between the two treatments. Moreover, the specific and nonspecific treatments were similar from the perspective of the patients—involving points in the same general body regions—and patients were unaware of which treatment they were receiving. If specific treatments demonstrated greater efficacy than nonspecific treatments, it would be reasonable to conclude that the effect of acupuncture per se was responsible.

The specific and nonspecific treatment plans were developed according to our treatment manual (Schnyer & Allen, 1998) by an assessing acupuncturist (R.N.S.), and were administered by four other trained and board-certified acupuncturists. Because the nonspecific treatments involved valid acupuncture points, the treating acupuncturists perceived that they were providing a valid treatment, a belief that they would not have held if sham points had been used as a control. The treating acupuncturists were blind to the experimental hypotheses and the method by which the specific and nonspecific treatments were devised, and were not informed of which treatment plan they received. Nonetheless, it may not be appropriate to consider this study fully double-blind because it remains possible that the acupuncturists developed some awareness of the differences between the treatments. There is evidence, however, that the acupuncturists were effectively blinded. They rated their beliefs about the efficacy of the treatment[3] following the first treatment session, and these ratings did not differ between specific and nonspecific treatments, $F(1, 22) < 1$, n.s.

Patients were randomly assigned to one of three conditions (specific treatment: n = 12, nonspecific treatment: n = 11,[4] or wait list: n = 11) and to one of the acupuncturists. All women received the specific treatment. Patients in the specific-treatment group received 8 weeks of specific treatment immediately. Patients in the nonspecific-treatment group received 8 weeks of nonspecific treatment first, and then 8 weeks of specific treatment. Patients in the wait-list group waited 8 weeks before receiving 8 weeks of specific treatment. Each 8-week treatment regimen (both specific and nonspecific) comprised 12 treatment sessions: 2 sessions a week for the first 4 weeks followed by 1 per week thereafter.

1. Two dropped out for reasons unrelated to treatment (pregnancy, moving out of state), 2 left because of discomfort with the treatment, and 1 left because she was not losing weight and believed that she would lose weight with a pharmacological treatment.

2. The 19 items included in the DepHRSD are depressed mood, suicidal thinking, suicidal behavior, difficulty falling asleep, middle-of-the-night awakening, early-morning awakening, hypersomnia, loss of interest, loss of pleasure, psychomotor retardation, psychomotor agitation, loss of energy, appetite change, weight change during the past month, loss of sexual interest, decreased concentration, helplessness, hopelessness, and worthlessness-failure. The non-included items on the HRSD reflect symptoms such as anxiety (psychic anxiety, somatic anxiety, obsessive-compulsive symptoms) and other nondepressive symptoms (e.g., paranoia, depersonalization).

3. The acupuncturists used a 9-point Likert scale to rate the following two items: "To what extent do you feel you have helped this client?" and "Predict the extent to which the client will benefit from the specific treatment we are offering."

4. Among the 5 patients who left the study prematurely, 2 dropped out from specific treatment, 2 from nonspecific treatment, and 1 from the wait list. The patient who dropped out because she wanted to lose weight had completed nonspecific treatment but had not begun specific treatment, and is therefore included in analyses involving the nonspecific treatment.

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Assessments

Interviews

All patients were interviewed by trained raters blind to treatment condition using the previously described 31-item version of the HRSD. Patients were interviewed before treatment (baseline), after 4 weeks, after 8 weeks, and if in the wait-list and nonspecific groups, after 12 weeks and after 16 weeks. An intraclass correlation of .96 was obtained for a sample of 22 interviews comparing the original interviewers' HRSD scores with consensus (original interviewer excluded) HRSD scores. The questions from the depression section of the SCID were also administered at the end of each 8-week treatment regimen.

Self-report measures

The Inventory of Depressive Symptomatology (IDS; a self-report version of the HRSD; Rush, Giles, Schlesser, & Fulton, 1986), the Beck Depression Inventory (BDI; Beck, Rush, Shaw, & Emery, 1979), and the Beck Hopelessness Scale (BHS; Beck, Weissman, Lester, & Trexler, 1974) were filled out weekly by patients during treatment, but not during the wait-list period. Although the interview data were available for all 33 patients, self-report data were available for 29 women.

RESULTS

First, to test for the efficacy of the specific treatment compared with the nonspecific treatment and the wait list, we examined the reduction in depressive symptoms after Week 8 for all three groups. Second, to estimate the clinical significance of treatment, we calculated the percentage of patients experiencing remission. In all cases, parametric tests are reported, unless the test could not be run because of violations of the normality assumption, in which case the comparable nonparametric test is reported (χ^2 with Friedman repeated measures analysis of variance [ANOVA] on ranks for repeated measures analyses, H with Kruskal-Wallis ANOVA on ranks for nonrepeated measures analyses). All post hoc tests used the Student Newman-Kuels procedure.

Comparative Efficacy of Specific Acupuncture Treatments

To determine whether specific treatment was comparatively more effective than nonspecific treatment or the wait list, we examined change scores from baseline to Week 8. Change scores were selected because, despite random assignment to group, there were significant differences between the groups at baseline on the DepHRSD, $F(2, 31) = 4.6$, $p < .05$: The nonspecific group (mean score = 20.5, $SD = 4.5$) was significantly less depressed ($p < .05$) than both the wait-list group (mean score = 27.7, $SD = 6.8$) and the specific group (mean score = 26.9, $SD = 6.7$), which did not differ from one another.

Figure 1 shows the mean change in DepHRSD scores for the three groups over the course of the study. A one-way ANOVA revealed a significant difference in symptom reduction between the groups on the DepHRSD, $H(2) = 7.2$, $p < .05$. The symptom reduction in the specific group ($M = -11.7$, $SD = 7.3$) exceeded that of the nonspecific group ($M = -2.9$, $SD = 7.9$). In addition, there was a nonsignificant trend ($p < .12$) for symptom reduction in the specific group to exceed

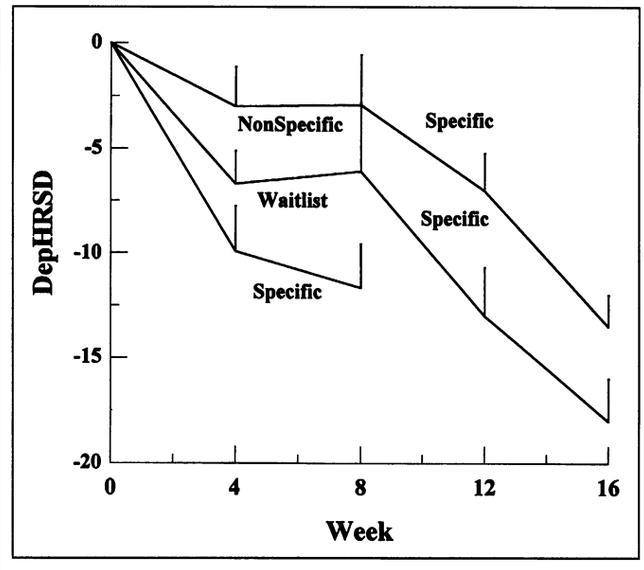

Fig. 1. Mean (±*SE*) change on the depression items from the Hamilton Rating Scale for Depression (DepHRSD) for patients in the specific-treatment ($n = 12$), nonspecific-treatment ($n = 11$), and wait-list ($n = 11$) groups by week. Note that after 8 weeks, patients in the nonspecific-treatment and wait-list groups began receiving specific treatment.

that of the wait-list group ($M = -6.1$, $SD = 10.9$). Similar results were obtained over the 8-week interval with the self-report measures for those patients undergoing treatment. On the BDI, patients in the specific group demonstrated larger changes ($M = -10.7$, $SD = 7.8$) than those in the nonspecific group ($M = -3.4$, $SD = 7.4$), $F(1, 20) = 5.2$, $p < .05$. On the IDS, patients in the specific group also demonstrated larger changes ($M = -18.5$, $SD = 11.8$) than those in the nonspecific group ($M = -8.5$, $SD = 9.0$), $F(1, 20) = 5.0$, $p < .05$. No differences emerged on the BHS, $F(1, 20) = 1.3$, n.s. Because self-report measures were completed only in the context of treatment, no comparisons with the wait-list condition were possible using self-report measures.

To determine whether the results would be the same for the original intent-to-treat sample, we conducted two analyses. The simple intent-to-treat analysis took the last available DepHRSD score of each participant who dropped out and carried that score forward to count as the subsequent observation. DepHRSD scores again differed significantly between participants in the three treatment groups, $H(2) = 6.4$, $p < .05$. The second strategy used a random regression model (Gibbons et al., 1993, implemented with BMDP 5V), which imputes missing values based on maximum-likelihood estimates of missing parameters, thereby allowing for the analysis of all intent-to-treat subjects. The model examined DepHRSD scores at intake, 4 weeks, and 8 weeks, and revealed a significant Group × Time interaction ($\chi^2[4, N = 38] = 9.70$, $p < .05$), which indicated that the rate of change differed significantly between the specific- and nonspecific-treatment groups ($\chi^2[2, N = 26] = 9.95$, $p < .01$), but not between the nonspecific-treatment and wait-list groups ($\chi^2[2, N = 24] = 0.76$, n.s.). The specific-treatment and wait-list groups showed a trend for rates of change to differ, $\chi^2(2, N = 26) = 4.28$, $p < .12$.

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Clinical Significance

We used two measures to ascertain whether treatment resulted in clinically significant remission: DSM-IV diagnoses and at least a 50% reduction in scores on the DepHRSD. Full remission in terms of DSM-IV diagnoses was defined as absence of both core symptoms of depression (depressed mood and anhedonia).

At the conclusion of the acute (8-week) phase of treatment, by DepHRSD criteria, 50% of the participants in the specific-treatment group had remitted, whereas only 27% in the nonspecific-treatment group and 27% in the wait-list group had remitted. By DSM-IV criteria, 42% of those in the specific-treatment group, 9% of those in the nonspecific-treatment group, and 20% of those in the wait-list group had experienced full remission.

After completion of specific treatment (pooled across all patients), by DepHRSD criteria, 70% of women had remitted. Using the DSM-IV remission criteria, 64% of women experienced full remission.

DISCUSSION

These findings from a small sample of women with major depression suggest that acupuncture may hold sufficient efficacy to warrant a larger clinical trial. Moreover, it appears that acupuncture induces remission at rates roughly comparable to those of conventional treatments[5] (Elkin et al., 1989). Additionally, the dropout rate of 13% in this sample compares favorably with the rates of more than 30% reported in other studies (Elkin et al., 1989), although such a finding could be due to many factors that may or may not be related to the modality of treatment. It is important to note that all women in this study were outpatients, free of psychosis or acute suicidal ideation. However, 29% of them met criteria for suicidal ideation (but without acute risk), based on the SCID. The efficacy of acupuncture for more severe depressions is unknown.

The present data also suggest that acupuncture has a specific effect above and beyond the nonspecific therapeutic factors related to regular visits to an acupuncturist. Patients receiving specific treatment improved more over 8 weeks than patients receiving nonspecific treatment. Although expectancy effects cannot be completely ruled out as a factor in the comparative efficacy of the treatments, the design minimized the possible role of these effects. Patients were blind to which treatment they received. Moreover, the treating acupuncturists implemented treatment plans provided by the assessing acupuncturist, and both the specific and the nonspecific treatments involved active and valid acupuncture points. Furthermore, the acupuncturists' beliefs about the efficacy of the treatment—which were assessed following the first treatment session—did not differ between specific and nonspecific treatments, reducing the likelihood that the acupuncturists' expectancies were responsible for the observed superiority of the specific treatment. Although it remains possible that the treating acupuncturists' expectations changed across the 8 weeks of delivering treatment, it would be impossible to determine whether differential beliefs about the effectiveness of specific and nonspecific treatment—if such beliefs had been assessed later in the progression of treatment—would indicate unblinding or simply be the result of differential improvement in the specific- and nonspecific-treatment groups.

Because specific treatment did not produce significantly greater improvement than the wait list, it remains possible that the improvement during specific treatment was due to spontaneous remission. Several findings suggest, however, that the specific treatment may have provided improvement above and beyond that expected by spontaneous remission alone. First, spontaneous remission was equally likely to affect patients in all groups, and specific treatment provided greater improvement than nonspecific treatment. Moreover, an examination of the effect sizes[6] indicates that the relative advantage of the specific treatment over the wait list ($d = 0.61$) is similar to what has been observed when other treatment modalities have been compared with a wait-list control in depression (Robinson, Berman, & Neimeyer, 1990). With greater statistical power, specific treatment would likely prove significantly more effective than a wait-list control, as the power to detect a significant difference between these two groups with the present sample size is only .31. Finally, among participants in the wait-list group, comparing the change observed during the specific-treatment phase and the wait period preceding it yields an effect size ($d = 0.52$) of similar magnitude. In other words, even after 8 weeks of a wait list, specific treatment provided change that was notably larger than that seen in these same patients during the wait period. Similarly, specific treatment produced larger change than the nonspecific treatment preceding it ($d = 0.79$) for patients in the nonspecific-treatment group (see Fig. 1).

These findings are, of course, preliminary. Larger scale studies are required to provide corroboration. If additional research corroborates that acupuncture is an effective treatment for depression, further research should address several issues. First, acupuncture's effectiveness remains to be determined for severe or chronic depressions (e.g., chronic major depression, dysthymia), as well as for persons with comorbid disorders (e.g., anxiety disorders, substance dependence). Second, the long-term prognosis of patients who respond to acupuncture treatment is unknown. Therefore, future research can address whether the treatment gains are maintained or whether less-frequent continuation or maintenance treatments are required after the initial set of treatments. Evidence from studies of other treatments for depression suggests the importance of maintenance treatments (Hirshfield & Schatzberg, 1994). Third, a direct comparison of the efficacy of acupuncture and psychotherapy or pharmacotherapy—within the same study—needs to be performed. Fourth, investigation of the mechanisms by which acupuncture achieves its effects is required. Finally, and perhaps most important, future research is required to determine whether acupuncture can assist individuals who fail to respond to traditional treatments, and whether traditional treatments will assist those who fail to respond to acupuncture.

5. Remission criteria vary somewhat from study to study. Very few studies have used interview-based DSM diagnoses as a measure for remission because the interviews are expensive and labor-intensive. Most studies use a joint criterion of reduction of 50% in HRSD score and a final score less than or equal to 6. The present data cannot be compared with data from studies using this criterion because we used a version of the HRSD that is different from the version most studies use. BDI scores, however, can provide a clear comparison between the results in this study and those reported in the literature. After the 33 patients had completed specific treatment, their mean BDI score was 12.1, which compares favorably with the mean score of 11.8 from 22 studies of psychotherapy (Robinson, Berman, & Neimeyer, 1990).

6. Effect sizes were calculated using Cohen's (1977) d, which expresses the differences in treatment means as a proportion of the pooled standard deviation: $(\bar{x}_1 - \bar{x}_2)/s$, where $\bar{x}_1$ is the first treatment mean, $\bar{x}_2$ is the second treatment mean, and s is the pooled standard deviation.

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Acknowledgments—Portions of the present data were presented at the Third Annual Symposium of the Society for Acupuncture Research, Washington, D.C., September 1995; at the annual meeting of the American Psychological Association, Toronto, Ontario, August 1996; and at the meeting of the North American Society for Psychotherapy Research, Tucson, Arizona, December 1997.

This work was supported, in part, by an Exploratory/Development Grant from the National Institutes of Health (1 R21 RR09492-01), through the Office of Alternative Medicine. The authors wish to thank Della Estrada, Leslie McGee, Bob Stagnitto, and MaryAnn Tully for their tireless efforts and for making the controlled study of the efficacy of acupuncture possible. The authors also thank Karen Moriah for her consultation, Varda Shoham and Karen Moriah for their assistance in the planning of this project, and Richard R. Bootzin, Richard D. Lane, Varda Shoham, and Connie J.A. Beck for helpful comments on an earlier draft of this manuscript.

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Journal of Affective Disorders 57 (2000) 73–81

JOURNAL OF AFFECTIVE DISORDERS

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Research report

The benefit from whole body acupuncture in major depression

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Received 22 January 1998; received in revised form 31 January 1999; accepted 22 March 1999

Abstract

Background: In a single-blind placebo-controlled study design we investigated the efficacy of acupuncture additionally applied to drug treatment in major depression. *Methods:* We randomly included 70 inpatients with a major depressive episode in three different treatment groups: verum acupuncture, placebo acupuncture and a control group. All three groups were pharmacologically treated with the antidepressant mianserin. The verum group received acupuncture at specific points considered effective in the treatment of depression. The placebo group was treated with acupuncture at non-specific locations and the control group received pharmacological treatment plus clinical management. Acupuncture was applied three times a week over a period of 4 weeks. Psychopathology was rated by judges blind to verum/placebo conditions twice a week over 8 weeks. *Results:* Patients who experienced acupuncture improved slightly more than patients treated with mianserin alone. *Conclusions:* Additionally applied acupuncture improved the course of depression more than pharmacological treatment with mianserin alone. However, we could not detect any differences between placebo and verum acupuncture. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Acupuncture; Depression; Mianserin

1. Introduction

In various different records and books acupuncture (Mann, 1973; Zhang, 1988; Bullock et al., 1989; Youbang and Liangyue, 1989), an ancient Chinese art of healing, is considered to alleviate or cure physical or mental diseases by simply piercing the skin with a fine needle at defined acupuncture points. In detail, symptoms of depression reoccur frequently in traditional Chinese works (Hubei Zuhonggyi Xueyuan, 1979; Nguyen Van Nghi, 1983) as well as newer literature on acupuncture (Porkert, 1983; Ross and Zang, 1985; Requena, 1989; Ots, 1990), suggesting whole body acupuncture is beneficial in the treatment of depressive patients.

The present study was designed to explore the efficacy of acupuncture in treating depression. Up to now, a single placebo-controlled clinical study of acupuncture as a treatment for depression has been reported. Yang et al. (1994) published data on acupuncture employed in the case of 41 patients suffering from various types of depression. The

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PII: S0165-0327(99)00061-0

diagnostic assignment was quite heterogeneous ranging from bipolar affective disorders and dysthymia to involutional depression of in- and outpatients. One group received acupuncture with individually determined needle points, the controls were pharmacologically treated with amitriptyline ranging between 150 and 300 mg/day. After 6 weeks no significant difference in psychopathology between the two methods of treatment was found, suggesting acupuncture to be as effective as antidepressant medication.

The aim of our study was to evaluate the efficacy of whole body acupuncture additionally applied to drug treatment of depression in a single-blind placebo-controlled study design. The hypotheses tested were: (a) additionally applied acupuncture improves the course of the illness more than pharmacological treatment by itself; (b) the effect of needling defined acupuncture points is specific, meaning in the case of verum acupuncture, the improvement of the course of depression is much higher than in the case of placebo acupuncture.

2. Methods

2.1. Study design

From October 1993 to October 1995 we studied 70 consecutive inpatients suffering from a major depressive episode and randomly assigned the patients to one of three different treatment groups:

1. mianserin treatment (90–120 mg/day);
2. mianserin treatment (90–120 mg/day) plus verum acupuncture; and
3. mianserin treatment (90–120 mg/day) plus placebo acupuncture.

In all treatment groups a benzodiazepine comedication up to 20 mg/day diazepam was allowed if required. The criteria for inclusion into the study were: cross-sectional diagnosis of a major depressive episode according to DSM-III-R (American Psychiatric Association, 1987), a score ≥ 18 points on the 21-item Hamilton depression scale (HAMD, Hamilton, 1976), and age of the patients between 20 and 70 years. Entry into the study was limited to patients without acute suicidality, longitudinal diagnosis of schizoaffective or bipolar affective disorder as well as delusions. Furthermore, patients with coagulation-disease, wound healing disease, emphysematous thorax, abnormal blood cell count, serious liver and kidney diseases, and epilepsy were excluded.

Because of the wide range of age for participants, we selected mianserin as the standardized antidepressant medication, which is not accompanied by anticholinergic side effects (Swinkels and de Jonghe, 1995). The dosage regimen was 30–30–30 or 30–30–60 mg/day. Written informed consent was obtained from all patients.

Psychopathology was rated at entry to the study and twice a week over a period of 8 weeks by two independent experienced judges not informed about verum/placebo acupuncture. The following observer rating scales were used to determine the psychopathological course of the illness: Global assessment scale (GAS, Endicott et al., 1976), Bech–Rafaelsen Melancholia scale (BRMS, Bech and Rafaelsen, 1980), Clinical global impressions scale (CGI, National Institute of Mental Health, 1976). For evaluation of depressive states in longitudinal studies we employed a self-rating scale (Bf-S, von Zerssen et al., 1974).

2.2. Subjects

Table 1 summarizes the age, gender and psychiatric diagnosis according to DSM-III-R of the patients participating in the study. The DSM-III-R number 296.2 represents a single episode, 296.3 a recurrent episode of a major depressive disorder.

2.3. Acupuncture protocol

Acupuncture was practised by two clinicians experienced in traditional Chinese acupuncture. They were excluded from the clinical management. For both groups, verum and placebo acupuncture, each patient was treated with a standardized whole body acupuncture treatment, applied three times a week over four consecutive weeks at 18 different locations. The duration of each acupuncture session was nearly 30 min. Each individual patient was needled over the treatment period by the same clinician. However, both clinicians did the acupuncture in both groups. The distribution verum/placebo acupuncture

Table 1
Psychopathological characteristic of the patients according to DSM-III-R

Control-group			Verum acupuncture			Placebo acupuncture		
DSM-III-R	Age	Sex	DSM-III-R	Age	Sex	DSM-III-R	Age	Sex
296.3	28	m	296.3	44	f	296.3	55	f
296.3	64	f	296.3	51	m	296.2	45	f
296.3	65	f	296.3	56	f	296.3	50	f
296.2	53	m	296.3	32	f	296.2	32	f
296.3	53	m	296.3	68	f	296.3	36	m
296.2	44	f	296.2	44	m	296.2	53	m
296.2	32	m	296.3	57	f	296.3	56	f
296.2	36	f	296.3	55	f	296.2	65	m
296.3	47	m	296.3	65	f	296.3	41	m
296.2	47	f	296.3	35	f	296.3	56	f
296.3	59	f	296.3	64	f	296.2	49	f
296.2	38	m	296.3	53	f	296.3	55	m
296.3	63	m	296.3	53	f	296.2	63	m
296.2	58	f	296.3	21	f	296.3	52	f
296.2	38	m	296.2	65	f	296.3	42	f
296.2	53	f	296.3	50	f	296.2	32	f
296.3	63	f	296.3	26	m	296.3	44	f
296.2	59	f	296.2	41	f	296.3	44	m
296.2	41	f	296.3	30	f	296.2	54	m
296.3	59	m	296.3	53	f	296.3	38	f
296.3	53	f	296.3	51	f	296.2	45	f
296.3	53	m	296.3	55	f	296.3	43	m
296.3	42	f	–	–	–	296.2	33	f
296.3	37	f	–	–	–	296.2	50	f

was equal for both clinicians. In case of verum acupuncture we needled bilaterally at the positions: U.B.15, U.B.17, U.B.18 (back), H7 (wrist), P6 (forearm), St40 (lower leg), Sp5, Sp6 (foot), and Lu1 (upper part of the body). Skin was pierced at the acupuncture points with a fine stainless steel needle (0.3×25 mm) to a depth of a few millimeters which was withdrawn after the lapse of a few minutes (Nguyen Van Nghi, 1983; Ross and Zang, 1985; Bullock et al., 1989). The electric skin resistance was measured to accurately determining the acupuncture points where resistance was reduced. In the case of placebo acupuncture we needled at non-specific locations in the neighbourhood of the loci cited above merely pricking the skin superficially.

2.4. Statistical analysis

Values in tables are presented as means±S.D. Categorical variables were analyzed by means of χ^2-tests. Baseline differences were evaluated with one-way ANOVA. Between group differences in outcome parameters were analyzed following an intention-to-treat-analysis with repeated measures ANOVA using treatment as between subjects factor (control vs. placebo vs. verum acupuncture) and assessments 1–16 (week 1–8) as repeated measures. For adjustment of degrees of freedom due to heterogeneity of variance–covariance matrices the procedure of Huynh and Feldt (1976) was applied. The level of statistical significance was set at $\alpha = 0.05$.

3. Results

3.1. Patients' characteristics

Table 2 summarizes the number of patients, gender, mean age and the HAMD score at the beginning of the study for the different treatment groups. According to χ^2-test (gender) and ANOVAs (age, HAMD), no differences between the groups under study could be found. It is obvious that all

Table 2
Number, sex ratio, mean age and HAMD score of the patients

Group	Number	Male:female	Mean age	HAMD
Control group	24	10:14	49±11	28±7
Verum acupuncture	22	3:19	49±13	28±5
Placebo acupuncture	24	9:15	47±9	29±5

patients suffered from a severe depression (mean score on HAMD = 28). An additionally applied one-way ANOVA did not show any difference in the number of former hospitalizations between the groups. Thus, the distribution of the patients' severity score, age, and gender ratio was quite homogeneous across the groups.

3.2. Differences between the three different treatments under study

Figs. 1–5 show the course of the depression according to the observer rating scales GAS, BRMS, CGI, and the self rating scale Bf-S over a time period of 8 weeks. In all cases there was greater improvement when acupuncture (placebo or verum) was applied compared to plain pharmacological treatment. In case of GAS (the higher the score, the better the psychopathology) the different groups under study improved homogeneously within the first 4 weeks of treatment (Fig. 1). However, during the last 4 weeks patients who had experienced acupuncture reached a higher score than patients treated with mianserin alone. For the observer ratings BRMS and CGI, respectively, again the three groups improved equally during the first half of the study (the lower the scores the better the psychopathology), whereas during the second half patients previously treated with acupuncture showed greater benefit (Figs. 2–4). According to the self rating scale Bf-S (the lower the score the better the psychopathology) we observed the same course of depression over time: patients who had experienced acupuncture showed more rapid progress than patients with mianserin alone (Fig. 5).

For each rating instrument Table 3 summarizes the results of the two-way ANOVA with between subjects factor group (control vs. placebo vs. verum acupuncture) and within-subject factor time (repeated measure design of ratings 1–16). We could not detect any statistically significant main effect for the factor group, but in all instruments a highly significant

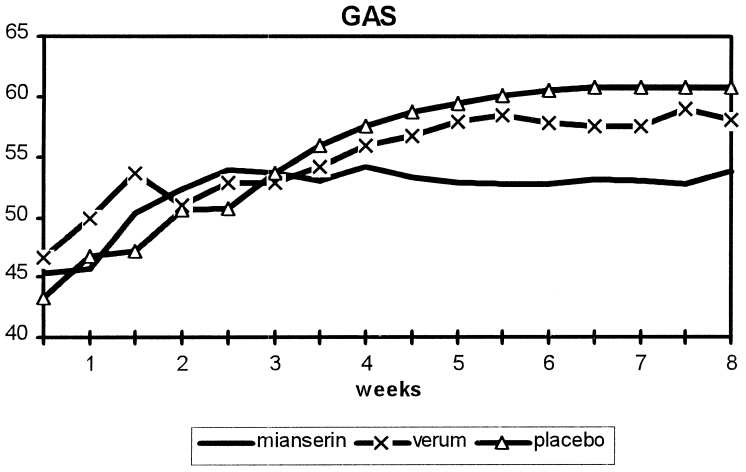

Fig. 1. GAS ratings (global assessment) over time (the better the score, the better the psychopathology).

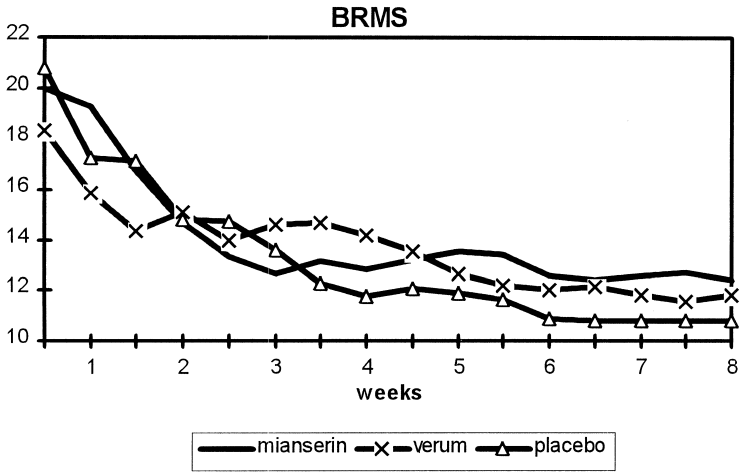

Fig. 2. BRMS ratings (melancholia scale) over time (the lower the score, the better the psychopathology).

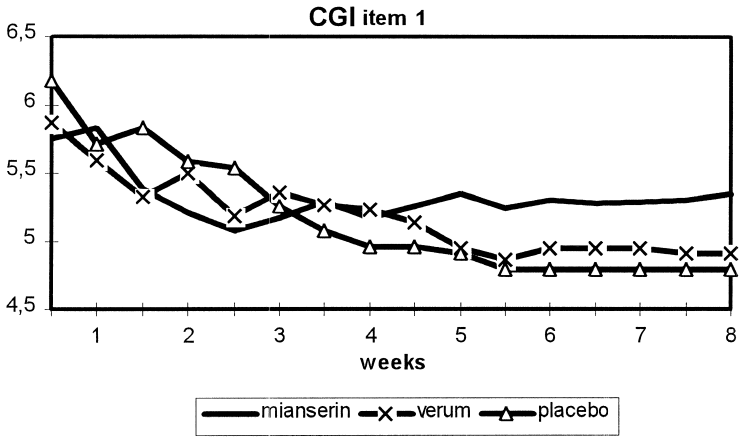

Fig. 3. CGI ratings (item 1 = psychopathological state) over time (the lower the score, the better the psychopathology).

effect for the factor time. In case of CGI item 2 (measuring the improvement of psychopathology) we found a statistically significant interaction of group by time ($P = 0.048$).

Additionally, we investigated the differences in mianserin dosage and diazepam comedication (if required) between the three treatment groups. Fig. 6 shows the mianserin medication and the diazepam dosage during the study period. Table 4 summarizes the results of a two-way ANOVA for both mianserin and diazepam. No main effect for the factor group nor any statistically significant interaction of group by time could be observed. Thus, the significant interaction of group by time for CGI (item 2) is not due to influence by different medication.

3.3. Differences between control and acupuncture treatment

In order to detect differences between the drug treatment and both acupuncture conditions (placebo as well as verum acupuncture), we performed a

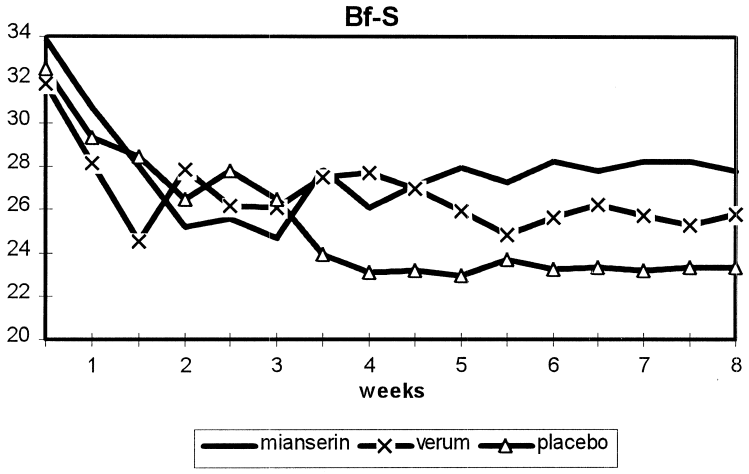

Fig. 5. Bf-S self ratings (depressive mood) over time (the lower the score, the better the psychopathology).

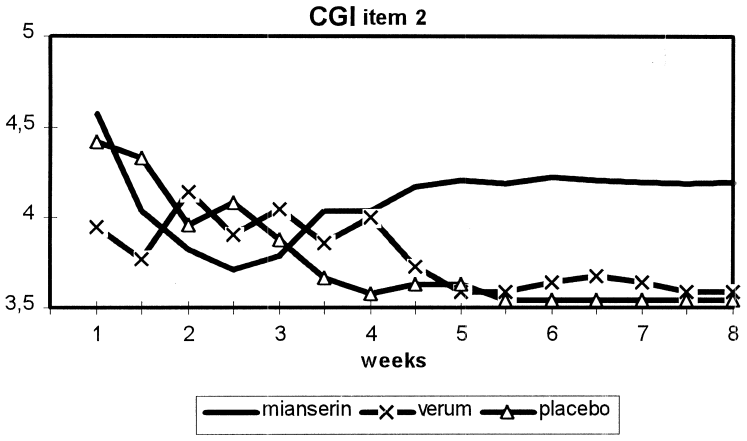

Fig. 4. CGI ratings (item 2 = improvement) over time (the lower the score, the better the psychopathology).

Table 3
Summary of two-way ANOVA for each of the rating instruments (Huynh–Feldt adjusted P values)

Instrument	ANOVA (between the three treatment groups)		
	Group	Time	Interaction
CGI item 1	$F_{2,67} = 0.12$ $P = 0{,}889$	$F_{15,1005} = 12.36$ $P = 0.0001$	$F_{30,1005} = 1.94$ $P = 0.092$
CGI item 2	$F_{2,67} = 0.84$ $P = 0.435$	$F_{15,1005} = 48.23$ $P = 0.0001$	$F_{30,1005} = 2.36$ $P = 0.048$
BRMS (sumscore)	$F_{2,67} = 0.10$ $P = 0.906$	$F_{15,1005} = 23.79$ $P = 0.0001$	$F_{30,1005} = 1.39$ $P = 0.226$
GAS	$F_{2,67} = 0.65$ $P = 0.525$	$F_{15,1005} = 19.18$ $P = 0.0001$	$F_{30,1005} = 2.16$ $P = 0.052$
Bf-S	$F_{2,67} = 0.25$ $P = 0.782$	$F_{15,1005} = 4.99$ $P = 0.0001$	$F_{30,1005} = 1.22$ $P = 0.296$

two-way ANOVA with between-subject factor group (control vs. acupuncture) and within-subject factor time. Table 5 summarizes the results. No main effect for the factor group could be found. However, for the instruments CGI (item 2) and GAS statistically a significant interaction was shown.

Therefore, according to the observer ratings CGI (item 2) and GAS patients treated with acupuncture (placebo or verum) showed higher benefit than patients treated only with mianserin. However, we could not detect any difference between patients who had experienced verum acupuncture and those who had placebo acupuncture. A two-way ANOVA with

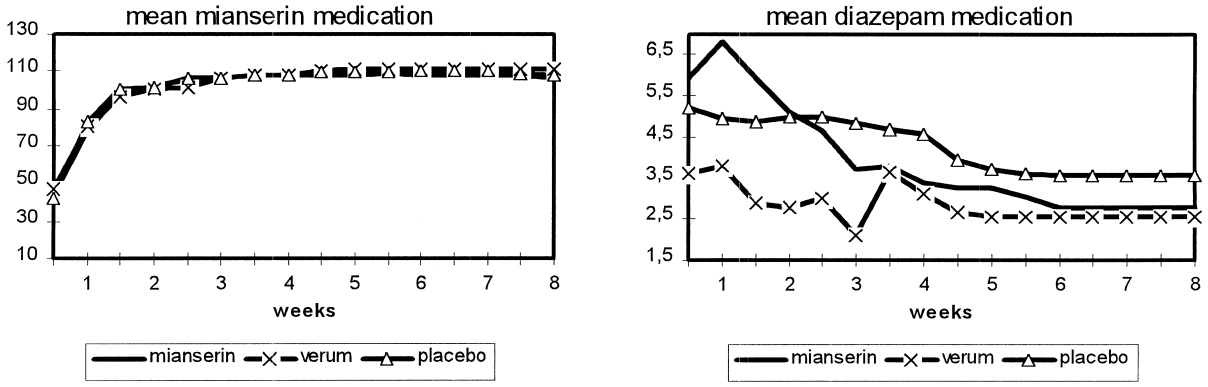

Fig. 6. Mianserin and diazepam medication during the study period.

Table 4
Results of ANOVA for mianserin and diazepam medication

Medication	ANOVA (between the three treatment groups)		
	Group	Time	Interaction
Mianserin	$F_{2,67} = 0.06$ $P = 0.940$	$F_{15,1005} = 201.28$ $P = 0.0001$	$F_{30,1005} = 0.65$ $P = 0.693$
Diazepam	$F_{2,67} = 0.70$ $P = 0.502$	$F_{15,1005} = 6.07$ $P = 0.001$	$F_{30,1005} = 1.25$ $P = 0.288$

Table 5
Results of the ANOVA with between-subject factor group (control vs. acupuncture) and within-subject factor time (Huynh–Feldt adjusted P values)

Instrument	ANOVA (mianserin versus both acupuncture groups)		
	Group	Time	Interaction
CGI item 1	$F_{1,68} = 0.24$ $P = 0.628$	$F_{15,1020} = 8.95$ $P = 0.0001$	$F_{15,1020} = 2.63$ $P = 0.065$
CGI item 2	$F_{1,68} = 1.71$ $P = 0.195$	$F_{15,1020} = 44.60$ $P = 0.0001$	$F_{15,10200} = 3.14$ $P = 0.026$
BRMS (sumscore)	$F_{1,68} = 0.15$ $P = 0.702$	$F_{15,1020} = 21.64$ $P = 0.0001$	$F_{15,1020} = 1.09$ $P = 0.348$
GAS	$F_{1,68} = 1.30$ $P = 0.257$	$F_{15,1020} = 14.20$ $P = 0.0001$	$F_{15,1020} = 3.03$ $P = 0.049$
Bf-S	$F_{1,68} = 0.35$ $P = 0.558$	$F_{15,1020} = 4.21$ $P = 0.005$	$F_{15,1020} = 1.14$ $P = 0.336$

factor group (placebo vs. verum acupuncture) and within-subject factor time did not come out with any statistically significant main effect for the factor group or any significant interaction. Therefore, we could demonstrate an improvement of the depressive psychopathology when acupuncture had been applied, but this effect appeared to be nonspecific.

3.4. Responder analysis

According to GAS scale we defined a low improvement when GAS score at the end of the study was less than 25 points above the baseline value. A medium or high improvement was defined when GAS score at the end was more than 25 points above baseline value. Following this definition we observed a statistically significant difference between the three groups under study ($\chi^2 = 6.75$, df = 2, $P = 0.034$). Comparing placebo and verum acupuncture we could not detect any significant difference in responder rate. However, comparing both verum and placebo acupuncture with control conditions we found a higher responder rate in case of acupuncture ($\chi^2 = 5.01$, df = 1, $P = 0.025$). Table 6 summarizes the responder rate for control, placebo, and verum conditions.

Table 6
Responder analysis according to GAS score

GAS	Control group	Verum acupuncture	Placebo acupuncture
No or low improvement (≤ 25 points)	$n = 23$ 96%	$n = 18$ 82%	$n = 16$ 67%
Medium or high improvement (> 25 points)	$n = 1$ 4%	$n = 4$ 18%	$n = 8$ 33%

4. Discussion

In this single-blind placebo-controlled study we investigated the effectiveness of additionally applied whole body acupuncture in the treatment of severe depression. For this reason three different treatment procedures were selected, having a standardized pharmacological treatment with mianserin in common. The first group experienced verum acupuncture with needling points, which are proposed for the treatment of depressive symptoms (Mann, 1973). In the second group placebo acupuncture was applied with needling points not being regarded as any specific acupuncture locations and not inserted in the recommended depth. In the third group (control) we did not apply any acupuncture technique. The first hypothesis tested could be confirmed: additionally applied acupuncture did improve the course of depression more than pharmacological treatment with mianserin did by itself. The second hypothesis, however, had to be rejected: we could not detect any differences between placebo and verum acupuncture. Thus, our results point to the view that there is no specific effect of needling defined acupuncture points in the treatment of major depression (Wolf et al., 1995).

This outcome did not correspond to a ceiling effect due to highly sufficient pharmacological medication. In each treatment group the patients suffered from a severe major depressive disorder according to DSM-III-R. During the study period of 8 weeks the patients did not experience a full remission, neither in the control group nor in the acupuncture groups. Therefore, the medication dosage chosen did not appear highly potent and verum acupuncture should have shown a measurable improvement if effective. However, patients additionally treated with either verum or placebo acupuncture experienced a statistically significant higher benefit than patients in the control group. There was no difference in mianserin dosage or diazepam comedication between the groups. The responder rate was higher when acupuncture was applied and the differences observed did not depend on different numbers of drop-outs. A more complete analysis revealed a complete rate of the acupuncture groups in the same order as under control conditions. One might discuss whether our placebo condition was really placebo (Patell, 1987; Vincent and Lewith, 1995). It might be the case that the effect of acupuncture does depend on the needling itself and that it is not necessary to needle specific acupuncture locations.

Another reason for the missing effectiveness and superiority of verum acupuncture might be the severity of depression and the operationally defined major depressive episodes according to DSM-III-R criteria, which, of course, were not subject to traditional Chinese proposals in the treatment of mood disorders. It is not excluded that needling of other points would come out with other results. Particularly from the traditional point of view it appears suitable to needle individually selected points for each patient and not performing a standardized acupuncture design as presented here.

The results of our study suggest that the effect of acupuncture is unspecific and might be due to additional attention provided three times a week for nearly half an hour. Patients under acupuncture treatment experienced a calm environment with a high degree of relaxation. Moreover, we cannot exclude that the clinicians performing the acupuncture and necessarily being informed about verum and placebo conditions, intensively cared for in particular the patients receiving placebo acupuncture. This phenomenon might explain why patients under placebo acupuncture improved slightly more than those under verum conditions.

Acknowledgements

This work was supported by Rut- und Klaus-Bahlsen-Stiftung, Germany. It contains essential parts of the doctoral dissertation of S. Bech.

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Efficacy and Safety of Auricular Acupuncture for Depression
A Randomized Clinical Trial

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Abstract

IMPORTANCE Depression is a leading cause of disability worldwide, and there is increasing interest in nonpharmacological treatments. Auricular acupuncture (AA) is a simple, low-cost, and well-tolerated option, but further studies are needed to establish its efficacy and safety.

OBJECTIVE To estimate the efficacy and safety of auricular acupuncture as a treatment for depression.

DESIGN, SETTING, AND PARTICIPANTS This randomized clinical trial was conducted at 4 university research centers in Brazil, from March to July 2023. Eligible patients were adults aged 18 to 50 years whose score on the Patient Health Questionnaire–9 (PHQ-9) indicated moderate depression (score 10-14) or moderately severe depression (score 15-19). Exclusion criteria included previous application of AA, risk of suicidal ideation, or severe depression (PHQ-9 score >20). An intent-to-treat analysis and modified intent-to-treat analysis were conducted.

INTERVENTION Participants were randomized into 2 treatment groups, which included specific AA (SA) and nonspecific AA (NSA). Both groups received 12 sessions of AA with semipermanent needles with daily stimulation twice a week over 6 weeks and were followed-up for 3 months. All participants continued with their usual care for ethical reasons. The SA group's treatment protocol consisted of 6 acupuncture points on the auricular pavilion chosen according to the diagnosis of depression by traditional Chinese medicine (Shenmen, subcortex, heart, lung, liver, and kidney). The NSA group's acupuncture points were the external ear, the cheek and face area, and 4 nonspecific points in the helix region unassociated with mental health symptoms. A locator device was used to confirm which areas had neuroreactive points.

MAIN OUTCOMES AND MEASURES The primary outcome was a reduction of at least 50% in the PHQ-9 score (ie, depression recovery) at 3 months. Secondary outcomes included depression recovery at 4 and 6 weeks; depression remission (PHQ-9 score < 5) at 4 weeks, 6 weeks, and 3 months); and adverse events.

RESULTS A total of 304 participants were screened, and 74 participants (62 women [84%]; median [IQR] age, 29 [23-27] years) were included in the intention-to-treat analysis, with 37 participants randomized to each group (SA and NSA). A total of 47 participants (64%) were followed-up through 3 months. The results showed no statistically significant difference in depressive recovery between the groups at 3 months (14 of 24 participants in the SA group [58%] vs 10 of 23 participants in the NSA group [43%]; risk ratio [RR], 1.34; 95% CI, 0.76-2.45; P = .38). The proportions of depression recovery and remission at 4 and 6 weeks based on the PHQ-9 were higher in the SA group (except for depression recovery at 6 weeks) with no statistically significant differences. However, a statistically significant difference was observed in symptom remission at 3 months (11 of 24 participants in the SA

(continued)

Key Points

Question Is auricular acupuncture a safe and effective treatment for depression?

Findings This randomized clinical trial of 74 patients with depression undergoing 6 weeks of auricular acupuncture found no significant differences in adverse event rates between the intervention (specific auricular acupuncture) and control (nonspecific auricular acupuncture) groups, evidencing the intervention's safety. No significant differences were found in depression recovery (50% reduction in Patient Health Questionnaire–9 score from baseline).

Meaning These findings suggest that auricular acupuncture is safe for patients with depression, but additional studies with larger samples and longer interventions are needed for confirmation.

+ Visual Abstract

+ Supplemental content

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Abstract (continued)

group [46%] vs 3 of 23 participants in the NSA group [13%]; RR, 1.99; 95% CI, 1.16-3.34; *P* = .02) in favor of SA. There were no significant differences in adverse event rates between the groups, evidencing the intervention's safety. Most participants reported mild pain at the needle application site (33 patients [94%] in the SA group vs 32 patients [91%] in the NSA group). Five participants dropped out of the study due to adverse events.

CONCLUSIONS AND RELEVANCE The results of this randomized clinical trial suggest that SA over 6 weeks is safe. Although there was no statistically significant difference between groups for the primary efficacy outcome, patients receiving SA did experience greater symptom remission at 3 months. A larger sample size and longer intervention are needed to further evaluate the efficacy of SA for depression.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT05855421

JAMA Network Open. 2023;6(11):e2345138. doi:10.1001/jamanetworkopen.2023.45138

Introduction

Depression is one of the leading causes of disability worldwide, affecting more than 300 million people (4.4% of the global population).[1] In 2019, depressive disorders represented the highest proportion of disability-adjusted life-years among mental disorders (37.3%).[2] In Brazil, the prevalence depression is among of the highest in the world, affecting 5.8% of the Brazilian population and accounting for 10.3% of years of life lost by Brazilians.[3] However, less than 10% of those affected by the disease receive appropriate treatment.[1,4] Nonadherence to antidepressant treatment is a concern for health care professionals; adherence to antidepressant therapy ranges from 40% to 90% across different studies, with a mean adherence rate of 65%.[5]

Research has shown that Australians and North Americans prefer integrative treatments for depression.[6-8] In this sense, auricular acupuncture (AA), a type of acupuncture in which thin semipermanent needles are inserted into specific points on the auricular pavilion, may be a therapeutic option. AA is easier to implement in clinical settings than body acupuncture owing to its short application time, low technique complexity, relative safety, and daily continuous physiological stimulation.[9]

Several nerves are distributed in the auricular pavilions. The concha area has a rich distribution of the vagus nerve.[10] Anatomical studies have shown that the auricular pavilion is the only place on the human body's surface with a distribution of the afferent vagus nerve.[11] Thus, needle stimulation on the auricular pavilion appears to lead to specific activation in the brain, mainly through the auricular branch of the vagus nerve.[12,13] A systematic review[14] found little evidence of the efficacy of AA for depression. The methodological quality scores showed that most analyzed studies indicated considerable methodological flaws. Additionally, no study in the review[14] used semipermanent needles in the groups. Therefore, this study aims to estimate the efficacy and safety of AA for depression recovery and remission at 4 weeks, 6 weeks, and 3 months.

Methods

Study Design

This randomized clinical trial was approved by the Hospital das Clínicas ethics committee, the University of São Paulo, and the University of Southern Santa Catarina and was monitored by an independent data and safety monitoring board. We followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline and the Standards for Reporting Interventions in

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Clinical Trials of Acupuncture (STRICTA)[15] for the design and reporting of this study. We recruited patients from the community at 4 university research centers in Santa Catarina, Brazil, from March to April 2023. All patients provided written informed consent before participation, and participants did not receive incentives or compensation to be part of the study. The study protocol and statistical analysis plan can be found in Supplement 1.

Participants

The research participants were adults aged 18 to 50 years. Eligible participants were those whose score on the Patient Health Questionnaire–9 (PHQ-9)[16] indicated moderate depression (score of 10-14) or moderately severe depression (score of 15-19). Exclusion criteria included previous application of AA, risk of suicidal ideation, or severe depression (PHQ-9 score ≥20) (eTable 1 in Supplement 2). Demographic characteristics, including gender and race and ethnicity, were collected via self-report on electronic tablets using the REDCap platform. Race and ethnicity categories included Black, White, and multiracial; race and ethnicity were included in this study to align with current research.

Randomization and Blinding

A computer program performed block randomization in a 1:1 ratio, in different block sizes (4, 6, and 8), corresponding to the 2 study groups. The experimental group received specific AA (SA) for depression and usual care, and the control group received nonspecific AA (NSA) and usual care. All participants continued with their usual care for ethical reasons. Participant allocation was concealed and delivered to the acupuncturists in individual opaque sealed envelopes. Participants, evaluators, data managers, and the statistician were blinded to treatment assignment. Neither the study participants nor the investigators had any influence on randomization and allocation concealment, which an independent statistician performed. Participants were informed that there were 2 treatment protocols.

Procedures

The study assessors were trained to approach participants similarly to avoid recruitment biases. The study used a protocol of questions and procedures for all phases: prescreening, screening, data collection, and application of protocols.

Participants with severe depression levels (PHQ score ≥20) or suicidal ideation did not participate in the study and were followed and consulted by a psychiatrist. The sessions of AA application occurred twice weekly, alternating the application on the right and left auricular pavilions, over 6 weeks, totaling 12 sessions, with a duration of 15 minutes each, in reserved rooms. The acupuncturists instructed the participants to stimulate each point manually (de qi stimulation) 3 times a day (morning, afternoon, and evening) for 30 seconds or until the auricular pavilion became red or sensitive to pressure. In this study, the acupuncturists had specific training in the field, with a minimum of 1200 hours in acupuncture and a minimum of 10 years of experience. They received standardized training before the study began.

All participants answered the PHQ-9 questionnaires 4 weeks, 6 weeks, and 3 months after the study initiation and reported adverse events before each AA session (eFigure 1 in Supplement 2). Patients were asked to complete the blinding assessment and treatment efficacy perception assessment and were requested to guess which treatment they received to test the success of blinding after 3 months of the study. More details about AA procedures and outcome assessment can be found in Supplement 1.

SA Treatment

The SA group's treatment consisted of a protocol of acupuncture points chosen according to the diagnosis of depression by traditional Chinese medicine. All SA participants used 6 preestablished points on the auricular pavilion: Shenmen, subcortex, heart, lung, liver, and kidney[17,18] (eFigure 2 and

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eTable 2 in Supplement 2). The EL11 device (NKL) was used to find the exact location of the points; the device searches on the skin for areas of lower electrical resistance, indicating more neuroreactive points (ie, true acupuncture points).[19] The size of the semipermanent needle (Complementar) used was 0.2 mm wide and 2.5 mm long. The semipermanent needles were inserted to a depth of 2.5 mm.

NSA Treatment

The existing literature acknowledges the difficulty in establishing protocols to be used as a control because of the high responsiveness and innervation of the auricular pavilion (ie, sham needling is not physiologically inert).[19-21] As a control group strategy, our study opted for superficial needling at nonpoints or irrelevant true points, aiming to reach other neural segments. The NSA group points were the external ear, the cheek and face area, and 4 nonspecific points in the helix region (eFigure 3 in Supplement 2), which are points that are not associated with mental health symptoms (eTable 2 in Supplement 2). The EL11 locator device was used to confirm that the sham areas were not neuroreactive points. The size of the needle (Complementar) used in the control group was 0.2 mm wide and 1.0 mm long, aiming for more superficial needling. The semipermanent needles were inserted to a depth of 1.0 mm.

Outcomes

The primary outcome was the proportion of participants who showed improvement of 50% or more in depressive symptoms (ie, depression recovery) between the groups, as assessed by the PHQ-9 at 3 months. Secondary outcomes included the difference in the proportion of participants reaching depression recovery at 4 and 6 weeks; the proportion of participants who achieved a score of less than 5 on the PHQ-9 (indicating depression remission) and differences in depression scores at 4 weeks, 6 weeks, and 3 months; the difference in the proportion of reported adverse events (ie, those arising from the AA technique) and reported adverse effects (ie, the worsening of depression symptoms or the onset of suicidal ideation); and the difference in the proportion of patient blinding to randomization and perception of treatment efficacy (eTable 3 in Supplement 2).

Statistical Analysis

Data analysis in this clinical trial was conducted by an independent hired statistician, blinded to treatment groups. The sample size was designed to detect a 30% difference (experimental group, 60% and control group, 30%) in depression symptom recovery between the 2 groups. A minimum sample of 36 participants per group was estimated, considering the test as 2-tailed, with 80% power and a significance level of $P < .05$. An additional 10% was added, considering segment losses, totaling 40 participants in each group, for 80 participants.

Initially, a baseline comparison between the SA and NSA groups was performed with median and IQR descriptions for continuous variables and frequencies and percentages for categorical variables. Subsequently, intent-to-treat and modified intent-to-treat analyses were conducted to compare the proportions of depression recovery and remission at different time points in the study using Fisher exact test. The effect size for dichotomous variables was calculated as relative risk.

Scores were subjected to a normality test that rejected the normality hypothesis to verify sample normality. Therefore, nonparametric tests were adopted. The reduction of depression scores over time in both groups was evaluated using the median and IQR. The statistical analysis of these data was conducted using the Wilcoxon-Mann-Whitney *U* test.

Cochran *Q* and Friedman analysis of variance tests were also used to verify statistically significant differences in depression scores over time within each group. These tests were followed by post hoc tests to identify significant differences at specific time points. We performed a sensitivity analysis with missing data imputation to evaluate the robustness of the results. Multiple imputation methods were explored, including last observation carried forward, imputation using the generalized estimating equations model, and multiple imputation through the expectation-maximization lag algorithm for categorical variables; the generalized estimating equations model was applied

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specifically to PHQ-9 depression scores. All analyses were conducted with a significance level of $P < .05$. Relative and absolute frequency were used to assess treatment safety and identify adverse events. The success of blinding and the perception of treatment efficacy were assessed using Fisher exact test. Statistical analyses were performed using R statistical software version 4.1.0 (R Project for Statistical Computing).

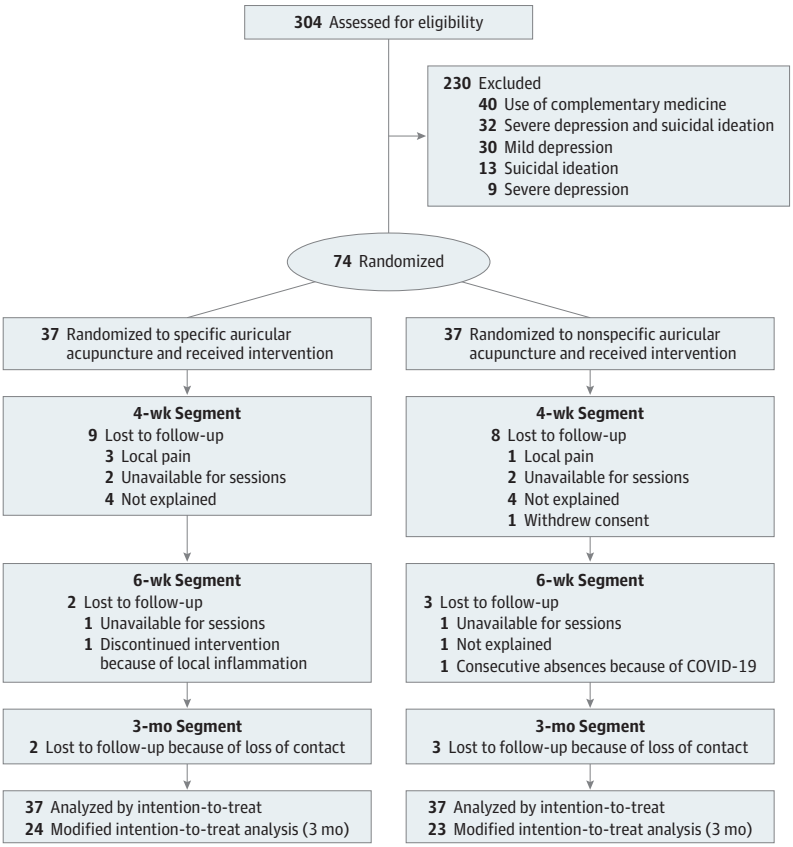
Results

Of the 304 screened volunteers, 230 were excluded for various reasons, resulting in a cohort of 74 participants (62 women [84%]; median [IQR] age, 29 [23-37] years; 5 Black participants [7%]; 61 White participants [82%]; 8 multiracial participants [10%]) comprising the intent-to-treat sample with 37 participants randomized to SA treatment and 37 participants randomized to NSA treatment (**Figure 1**). At 3 months, 27 patients (36%) were lost to follow-up; a total of 47 patients (64%), including 24 patients in the SA group and 23 participants, in the NSA group, comprised the modified intent-to-treat sample. There was no difference between the study groups in the number of patients lost to follow-up (eTable 4 in Supplement 2). We conducted a comparison of baseline depression scores according to the PHQ-9 among the individuals lost to follow-up (eTable 5 in Supplement 2). The groups were similar regarding demographic characteristics, clinical diagnosis, pharmacological treatments, and health characteristics at the study's outset, except for race and ethnicity (**Table 1**).

Primary Outcome

Three months after randomization, 14 of the 24 participants (58%) randomized to the SA group had a reduction of at least 50% in the PHQ-9 score compared with 10 of 23 participants (43%) in the

Figure 1. Flowchart of Screening, Randomization, and Follow-Up



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NSA group. The result was not statistically significant (risk ratio [RR], 1.34; 95% CI, 0.76-2.45; *P* = .38) (**Table 2**).

Secondary Outcomes

The proportions of patients with depression recovery and remission based on the PHQ-9 at 4 weeks was higher in the SA group, but not at 6 weeks, and there were no statistically significant differences between the groups at 4 or 6 weeks. A statistically significant difference in favor of the SA group was observed in depression remission after 3 months (11 of 24 participants [46%] in the SA group vs 3 of 23 participants in the NSA group [13%]; RR, 1.99; 95% CI, 1.16-3.34; *P* = .02) (Table 2). The median PHQ-9 scores decreased after 4 weeks, 6 weeks, and 3 months in both groups, with no statistically significant differences. Lower scores were observed in the SA group than in the NSA group (eTable 6 in Supplement 2 and **Figure 2**).

The modified intent-to-treat analyses showed the similar results as the intention-to-treat analyses. Intragroup analysis was performed using the Cochran *Q* test, with no statistically significant differences (eTable 7 in Supplement 2). Intragroup analysis was performed using the Friedman analysis of variance test followed by post hoc tests for the differences in PHQ-9 scores at each time

Table 1. Baseline Demographic and Clinical Characteristics at the Time of Randomization in the Intention-to-Treat Analysis

Variable	Participants, No. (%) (N = 74)	
	SA group (n = 37)	NSA group (n = 37)
Age, median (IQR), y	28 (22-37)	30 (23-36)
Patient Health Questionnaire-9 Score, median (IQR)[a]	14.0 (12.0-16.0)	16.0 (14.0-18.0)
Gender		
Male	5 (13)	6 (16)
Female	32 (87)	30 (81)
Nonbinary	0	1 (3)
Race and ethnicity		
Black	0	5 (14)
Multiracial	2 (5)	6 (16)
White	35 (95)	26 (70)
Income[b]		
≤3 times the monthly minimum wage	14 (38)	11 (30)
>3 times the monthly minimum wage	23 (62)	26 (70)
Marital status		
Single	22 (59)	17 (46)
Not single	15 (41)	20 (54)
Education		
Less than high school up to completed high school	10 (27)	10 (27)
Incomplete college education or higher	27 (73)	27 (73)
Weekly working hours, median (IQR) (n = 49)	42 (27-44)	44 (22-44)
Previous diagnosis of depression or other mental illness	16 (43)	16 (43)
Participant used any medication for depression	8 (22)	4 (11)
Participant used medication in the last 3 mo		
No	21 (57)	27 (73)
Antidepressant	8 (22)	5 (13)
Tranquilizer or sedative	5 (13)	4 (11)
Anxiolytic	7 (19)	3 (8)
Participant consumes alcoholic beverages	26 (70)	20 (54)
Participant smokes any cigarette		
No	35 (95)	35 (96)
Yes	2 (5)	1 (2)
Former smoker	0	1 (2)

Abbreviations: NSA, nonspecific auricular acupuncture; SA, specific auricular acupuncture.

[a] A score of 10 to 14 indicates moderate depression; 15 to 19, moderately severe depression; and 20 to 25, severe depression.

[b] The monthly minimum wage in Brazil is equivalent to $250 in 2023.

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point compared with baseline, which revealed statistically significant differences in all evaluations, in both groups, at different assessment points (eTable 8 and eFigure 4 in Supplement 2).

Sensitivity Analyses

The sensitivity analyses revealed that there were no statistically significant differences in depression recovery across the visits (eTable 9 in Supplement 2). These analyses confirmed the statistically significant results in favor of the SA group regarding depression remission after 3 months (eTable 10 in Supplement 2). As for PHQ-9 scores, the generalized estimating equations model demonstrated favorable effect sizes of SA, and the visits had a statistically significant effect on the scores (eTable 11 and 12 in Supplement 2).

Safety

Most participants reported mild pain at the needle application site (33 patients [94%] in the SA group vs 32 patients [91%] in the NSA group). One participant had mild local inflammation in 1 of the auricular points and received appropriate treatment. Regarding adverse events, an increase in

Table 2. Primary and Secondary Efficacy Outcomes in the Intention-to-Treat Analysis

Outcomes	Participants, No./Total No. (%)		RR (95% CI)[a]	*P* value[b]
	SA group	NSA group		
Primary outcome, depression recovery at 3 mo vs baseline (n = 47)[c,d]	14/24 (58)	10/23 (43)	1.34 (0.76-2.45)	.38
Secondary outcomes				
Depression recovery at 4 wk vs baseline (n = 57)	12/28 (43)	9/29 (31)	1.28 (0.74-2.14)	.42
Depression recovery at 6 wk vs baseline (n = 51)	10/26 (38)	10/25 (40)	0.96 (0.53-1.65)	>.99
Symptom remission at 4 wk vs baseline (n = 57)[e]	8/28 (28)	5/29 (17)	1.35 (0.72-2.20)	.36
Symptom remission at 6 wk vs baseline (n = 51)	7/26 (27)	5/25 (20)	1.19 (0.61-2.00)	.74
Symptom remission at 3 mo vs baseline (n = 47)	11/24 (46)	3/23 (13)	1.99 (1.16-3.34)	.02

Abbreviations: NSA, nonspecific auricular acupuncture; RR, risk ratio; SA, specific auricular acupuncture.

[a] Effect size was calculated as RR for dichotomous data.

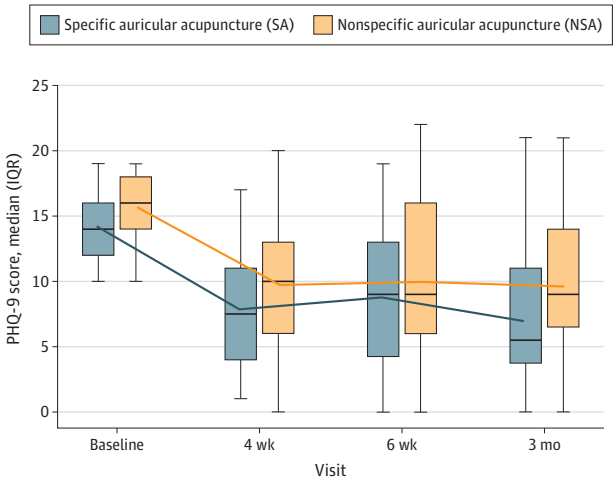
[b] Statistical significance was calculated with Fisher exact test.

[c] The primary outcome (improvement in depression symptoms) was defined as a reduction of 50% or more from baseline Patient Health Questionnaire-9 (PHQ-9) scores. The number of cases and proportions are based on observed data.

[d] Depressive symptoms measured by PHQ-9 scores range from 0 (least) to 27 (greatest) symptom burden.

[e] Participants who achieved a score less than 5 on the PHQ-9, indicating symptom remission.

Figure 2. Median Depression Scores by Intention-to-Treat Analysis



The figure shows the median Patient Health Questionnaire-9 (PHQ-9) scores of patients receiving specific auricular acupuncture (SA) and nonspecific auricular acupuncture (NSA) at baseline, 4 weeks, 6 weeks, and 3 months. A score of 10 to 14 indicates moderate depression; 15 to 19, moderately severe depression; and 20 to 25, severe depression. The lines inside the boxes reflect the medians, with the upper and lower ends of the boxes reflecting the IQRs. The error bars reflect the minimum and maximum values. The line plot reflects means.

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depression scores was observed during data collection in 3 participants, and 7 individuals responded positively to question 9 of the PHQ-9, which addresses suicidal ideation. These cases were carefully monitored, and the independent data monitoring and safety committee did not consider these events related to the intervention. No statistically significant difference was found between the groups in the proportion of participants with adverse effects (ie, those arising from AA) and adverse events (ie, worsening of depression symptoms or suicidal ideation). Five participants withdrew from the study as a result of adverse effects. No severe adverse events were reported (**Table 3**). The study participants did not change their medications or psychotropic medication dosages throughout the data collection.

Blinding Quality

For results on the success of blinding, see eTable 13 in Supplement 2. No difference was found between groups in the proportion of patients who guessed correctly what kind of AA they had received and their perception of efficacy in symptom relief after the 3 months.

Discussion

The results of this randomized clinical trial showed no difference in depression recovery between the groups at 3 months. However, depression remission at 3 months was significantly higher in the SA group. In addition, no significant differences were observed in the rates of adverse events and adverse effects, and no severe adverse events were recorded, evidencing practice safety. To our knowledge, this is the first randomized clinical trial on the effectiveness of SA using a semipermanent needle with NSA directed at depression as the comparator group. However, previous studies[22-28] using other AA techniques found favorable results in depressive symptoms, but with shorter study duration and different comparators.

Table 3. Adverse Effects and Adverse Events Listed by Treatment Group

Adverse event or adverse effect	Participants, No. (%) (N = 74)	
	SA group (n = 37)	NSA group (n = 37)
Mild and transient adverse effects		
Mild pain	33 (94)	32 (91)
Intense pain	1 (3)	0
Punctate bleeding	3 (9)	2 (6)
Itching in the auricle	11 (31)	14 (40)
Increased appetite	1 (3)	0
Headache	1 (3)	0
Hot flashes	0	1 (3)
Difficulty sleeping	0	2 (6)
Sensitivity to pressure	1 (3)	2 (6)
Facial skin hypersensitivity	0	1 (3)
Moderate adverse effect: local inflammation	1 (3)	0
Moderate adverse events		
Worsening of depressive symptoms (4 wk)	0	0
Worsening of depressive symptoms (6 wk)	0	1 (6)
Worsening of depressive symptoms (3 mo)	1 (3)	1 (6)
Emergence of suicidal ideation (4 wk)	0	2 (6)
Emergence of suicidal ideation (6 wk)	0	2 (6)
Emergence of suicidal ideation (3 mo)	2 (6)	2 (6)
Any severe adverse events and adverse effects	0	0
Discontinuation due to adverse effects		
Local pain	3 (9)	1 (3)
Local inflammation	1 (3)	0

Abbreviations: NSA, nonspecific auricular acupuncture; SA, specific auricular acupuncture.

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These preliminary findings are promising and support the use of SA in depression treatment. The rates of recovery (58%) and remission (46%) from depression in the present study are similar to those observed in meta-analyses of pharmacological treatments[29,30] and superior to those for psychotherapy.[31] The 33% difference in symptom remission between the groups (ie, 46% remission in the SA group vs 13% in the NSA group) was clinically meaningful; depression remission is crucial for patients, providing better psychosocial functioning and long-term prognosis, not just symptom improvement.[32]

The absence of statistically significant differences between the groups for depression recovery can be explained. First, the small sample size resulted in insufficient power and may have underestimated true efficacy. Second, considering the economic cost of time and participant adherence, we provided only 12 sessions over 6 weeks in this study. Therefore, adding AA doses by increasing the treatment duration (eg, 16-18 sessions over 8-12 weeks) may be an effective way to streamline the treatment program. Third, the manual stimulation of the semipermanent needle (known as de qi induction) is a factor that affects the efficacy of AA. To maintain the blinding of the study, the NSA group also used this daily stimulation, which may have contributed to an increased effect size of the technique in this group. Fourth, the study's follow-up loss (36%) may have impacted the results. However, adherence to depression treatment remains a relevant and common challenge to overcome in clinical trials. A study by Olfson et al[33] found that 36.4% of patients discontinued antidepressant treatment within the first 30 days. A meta-analysis[34] reported a 36.4% dropout rate for cognitive behavioral therapy. A study[35] on acupuncture in depression treatment observed a dropout rate similar to the present study. This trend of treatment discontinuation seems to be associated with the characteristics of the disease itself (apathy, hopelessness, and lethargy). Regardless of the chosen treatment, patients with depression are likely to discontinue treatment.[36]

First-line therapy for depression is medication, but several factors interfere with treatment access and adherence, such as system barriers and clinical and individual factors.[37] Therefore, it is necessary to offer a wide range of evidence-based therapies to treat depression, aiming at person-centered mental health care.[38] AA may be an option for patients who reject medication or psychotherapy because it has fewer adverse effects than pharmacological treatment. A systematic review[39] of adverse events associated with AA found that most were transient, mildly intense, and tolerable. No severe adverse events were identified in our study, indicating that AA is a safe treatment.

Besides the technique's safety, patients in the SA group had increased rates of symptom remission between 6 weeks and 3 months, which may be associated with the delayed effects of AA treatment.[40] We should underscore that in AA, part of the technique's effect is attributed to stimulating the auricular branch of the vagus nerve, increasing parasympathetic activity while simultaneously decreasing sympathetic nervous system activity.[41,42] This effect may lead to an improvement in depression-related symptoms.[13] A systematic review[43] concluded that trigeminal nerve stimulation and transcutaneous vagus nerve stimulation improve the treatment of specific neuropsychiatric disorders, such as depression.

An additional hypothesis is that AA may reduce serotonin depletion by inhibiting the hyperactive hypothalamic-pituitary-adrenal axis, which would explain the technique's prolonged effect at the 3-month follow-up.[44] Experimental studies confirmed this hypothesis, showing that the antidepressant effect of AA is possibly associated with the normalization of this axis' hyperactivity.[45] Additionally, some studies[10,13]observed that AA can trigger cardioinhibitory effects similar to vagus nerve stimulation. It is essential to highlight that participants in the NSA group may have also experienced temporary inhibition of this axis due to the perception of having received adequate treatment. However, this effect tends to decrease gradually after the end of the treatment sessions.

This study has strengths. First, the research addressed the selection of AA points, providing a solid foundation for future large-scale studies. In addition, the study included a more extended study period and experienced acupuncturists who used semipermanent needles, which are considered

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more effective than other stimuli. The control group received needling in nonspecific areas, and blinding measures were implemented for assessors, participants, and the statistician.

Limitations

The present study also has limitations. The predominance of women in the sample precluded the detection of possible gender differences in the results. Using self-report instruments to measure the primary outcome may also introduce bias into the results. Other major limitations include the limited sample size and the relatively high loss of participants during the follow-up period. Additionally, an NSA group with positive results indicates the need to investigate better the mechanisms of action and nonspecific outcomes associated with AA.

Conclusions

The results of this randomized clinical trial suggest that SA over 6 weeks is feasible and safe. Although the differences between SA and NSA groups did not reach statistical significance for the primary outcome, SA did produce greater symptom remission at 3 months. A more extensive sample size study, more protracted intervention, and objective evaluation of the results are necessary to further investigate the efficacy of SA for depression.

ARTICLE INFORMATION

Accepted for Publication: October 14, 2023.

Published: November 30, 2023. doi:10.1001/jamanetworkopen.2023.45138

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Author Contributions: Drs de Oliveira Rodrigues and Faisal-Cury had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Rodrigues, Silotto, Heps, Faisal-Cury.

Critical review of the manuscript for important intellectual content: Rodrigues, Menezes, Sanches, Schveitzer, Faisal-Cury.

Statistical analysis: Menezes.

Obtained funding: Rodrigues, Faisal-Cury.

Administrative, technical, or material support: Rodrigues, Silotto, Heps, Sanches.

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Conflict of Interest Disclosures: Dr Rodrigues reported receiving grants from the Education Department of the Government of Santa Catarina, Brazil outside the submitted work. Dr Silotto reported receiving grants from São Paulo Research Foundation (FAPESP) and CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior) outside the submitted work. Dr Heps reported receiving grants from FAPESP and CAPES outside the submitted work. No other disclosures were reported.

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Funding/Support: This study was supported by FAPESP grant 2018/8117469-5 to Drs Rodrigues, Sanches, and Faisal-Cury.

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 3.

Additional Contributions: We thank the undergraduate scholarship holders (research scholarship under Article 171 of the Education Department of the Government of Santa Catarina, Brazil) Isabel Transferetti Pose (University of Southern Santa Catarina), Joana Loudes Lawless (University of Southern Santa Catarina), Gabriela Chaves Reis (University of Southern Santa Catarina), Beatriz Inez Dalsasso (University of Southern Santa Catarina), Juliana Vasconcelos (University of Southern Santa Catarina), Fabiana Tyminski (University of Southern Santa Catarina), and Bruna Caminha Ferreira (University of Southern Santa Catarina) for their recruitment and outreach support. We also thank Maria Eduarda Antunes, BA (University of Southern Santa Catarina) for assistance with data collection; Pedro Henrique de Mesquita Pacheco, BA (Butantan Institute) for statistical analysis; Roberto Ferreira, BA (Albert Einstein Hospital) for data management and data monitoring; and Alexandre Biasi Cavalcanti, MD, PhD (HCor Research Institute) for suggestions on data analysis. These individuals did not receive additional compensation for their support.

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Section 8.0

Coverage Guidances

Hypoglossal Nerve Stimulation for Obstructive Sleep Apnea

Plain Language Summary:

This is a small device placed inside the body for people with certain types of sleep apnea. It is meant to work with the airway and breathing during sleep. The device is one option that may be considered to treat people with this condition.

Staff Analysis Summary:

Significant proposed changes or discussion items:

Recommendation to cover HGNS for adults 21 and older diagnosed with obstructive sleep apnea who meet criteria listed below.

Coverage Question:

Should hypoglossal nerve stimulation be covered for adults with moderate to severe obstructive sleep apnea?

Question source:

Evidence-based guideline subcommittee

Background:

EbGS approved a coverage guidance regarding hypoglossal nerve stimulator devices for obstructive sleep apnea at the 4/16/26 meeting. EbGS previously reviewed this topic on 9/19/24 and voted to table the draft coverage report for 1 year. Staff monitored the release of newly published studies and a newly approved HGNS device prior to bringing the report back to EbGS meeting on 9/11/25 where it was referred for a 30-day comment period and returned the EbGS meeting on 2/5/26 where the approved motion was to post the modified report for an additional 21-day comment period.

The “blue box” wording is shown below:

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SHOULD HYPOGLOSSAL NERVE STIMULATION BE COVERED FOR ADULTS WITH MODERATE TO SEVERE OBSTRUCTIVE SLEEP APNEA?

We recommend coverage of hypoglossal nerve stimulation (HGNS) for symptomatic adults age 21 and older when all of the following criteria are met:

1) **A polysomnography study is performed within 24 months of first consultation for HGNS implant that shows both**
   a. **Moderate to severe sleep apnea (apnea-hypopnea index (AHI) 15 to 100 events per hour using the 4% oxygen desaturation threshold for hypopneas; AHI4); *AND***
   b. **Predominantly obstructive events (defined as central and mixed apneas less than 25% of the total AHI4); *AND***
2) **Have a body mass index (BMI) 35 kg/m^2 or less; *AND***
3) **Not responsive to continuous positive airway pressure (CPAP) therapy, defined as either of the following (as documented by a sleep specialist):**
   a. **Inability to use CPAP greater than 5 nights per week of at least 4 hours per night; *OR***
   b. **Have a lack of adequate response to CPAP therapy (i.e., AHI4 of greater than 15 despite CPAP usage; *AND***
4) **Drug induced sleep endoscopy (DISE) findings consistent with the absence of concentric collapse at the soft palate level (per FDA labeling); A*ND***
5) **No other anatomical findings that would compromise performance of device (e.g., tonsil size 3 or 4 per standardized tonsillar hypertrophy grading scale); *AND***
6) **Do not have any contraindications to the device.**

Previous HSC/HERC reviews:

No prior review of HGNS.

Current Prioritized List/Coverage status:

DIAGNOSTIC GUIDELINE D8, DIAGNOSTIC TESTING FOR OBSTRUCTIVE SLEEP APNEA (OSA)

For adults over the age of 18 years:

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Hypoglossal Nerve Stimulation for Obstructive Sleep Apnea

A) For patients with clinical signs and symptoms consistent with obstructive sleep apnea (OSA), a home sleep study is the first-line diagnostic test for most patients, when available.
    1) For portable devices, Type II-III are included on this line. Type IV sleep testing devices must measure three or more channels, one of which is airflow, to be included on this line. Sleep testing devices that are not Type I-IV and measure three or more channels that include actigraphy, oximetry, and peripheral arterial tone, are included on this line.
B) Polysomnography in a sleep lab is indicated as a first-line test for patients with significant cardiorespiratory disease, potential respiratory muscle weakness due to a neuromuscular condition, awake hypoventilation or suspicion of sleep related hypoventilation, chronic opioid medication use, history of stroke or severe insomnia.
C) If a patient has had an inconclusive (or negative) home sleep apnea test and a clinical suspicion for OSA remains, then attended polysomnography is included on this line. Split night diagnostic protocols are required when a diagnosis of OSA is confirmed in the first portion of the night.
D) Repeat sleep studies are covered up to twice a year when one of the following has occurred since the most recent test:
    1) recurrence of OSA symptoms
    2) weight change of more than 10% of body weight
    3) new or worsening health conditions related to OSA
    4) upper airway surgical procedures or initial treatment with oral appliances

For children age of 18 or younger:

A) Obstructive sleep apnea (OSA) must be diagnosed by
    1) nocturnal polysomnography with an AHI >5 episodes/h or AHI >1 episodes/h with history and exam consistent with OSA, OR
    2) nocturnal pulse oximetry with 3 or more SpO2 drops <90% and 3 or more clusters of desaturation events, or
        i) alternatives desaturation (>3%) index >3.5 episodes/h,OR
    3) use of a validated questionnaire (such as the Pediatric Sleep Questionnaire or OSA 18), OR
    4) consultation with a sleep medicine specialist.

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B) Polysomnography and/or consultation with a sleep medicine specialist to support the diagnosis of OSA and/or to identify perioperative risk is recommended for
   1) high-risk children (i.e., children with cranio-facial abnormalities, neuromuscular disorders, Down syndrome, etc.)
   2) children with equivocal indications for adenotonsillectomy (such as discordance between tonsillar size on physical examination and the reported severity of sleep-disordered breathing), children younger than three years of age

C) Drug-induced sleep endoscopy (CPT *42975) is only covered when ALL of the following criteria are met:
   1) The patient is under 21 years of age; AND
   2) The patient has OSA diagnosed by polysomnography; AND
   3) The patient is being evaluated for upper airway surgery for OSA; AND
   4) The patient has at least one of the following:
      a) A high-risk condition including but not limited to trisomy 21 (Down's syndrome), craniofacial anomalies, hypotonia, or neurological disorder; OR
      b) A known physical airway anomaly.

The development of this guideline note was informed by a HERC coverage guidance. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx

GUIDELINE NOTE 27, TREATMENT OF SLEEP APNEA

Line 201

For adults over the age of 18 years:

CPAP is covered initially when all of the following conditions are met:

12 week 'trial' period to determine benefit. This period is covered if apnea-hypopnea index (AHI) calculated using the CMS definition of hypopnic episode of at least 4% oxygen desaturation or respiratory disturbance index (RDI) is greater than or equal to 15 events per hour; or if between 5 and 14 events with additional symptoms including one or more of the following:

excessive daytime sleepiness defined as either an Epworth Sleepiness Scale score >10 or daytime sleepiness interfering with ADLs that is not attributable to another modifiable sedating condition (e.g. narcotic dependence), or

documented hypertension, or

ischemic heart disease, or

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history of stroke
Additionally:
Providers must provide education to patients and caregivers prior to use of CPAP machine to ensure proper use; and
Positive diagnosis through polysomnogram (PSG) or Home Sleep Test (HST).
CPAP coverage subsequent to the initial 12 weeks is based on documented patient tolerance, compliance, and clinical benefit. Compliance (adherence to therapy) is defined as use of CPAP for at least four hours per night on 70% of the nights during a consecutive 30-day period.
Mandibular advancement devices (oral appliances) are covered for those for whom CPAP fails or is contraindicated.
Surgery for sleep apnea in adults is not included on this line (due to lack of evidence of efficacy). Surgical codes are included on this line only for children who meet criteria below
Hypoglossal nerve stimulation for treatment of obstructive sleep apnea is not included on this line due to insufficient evidence of effectiveness and evidence of harm.
For children age of 18 years or younger:

A) Adenotonsillectomy is an appropriate first line treatment for children with OSA. Adenoidectomy without tonsillectomy is only covered when a child with OSA has previously had a tonsillectomy, when tonsillectomy is contraindicated, or when tonsillar hypertrophy is not present. More complex surgical treatments are only included on this line for children with craniofacial anomalies.
B) Intranasal corticosteroids are an option for children with mild OSA in whom adenotonsillectomy is contraindicated or for mild postoperative OSA.
C) CPAP is covered for a 3-month trial for children through age 18 who have
    1) undergone surgery or are not candidates for surgery, AND
    2) have documented residual sleep apnea symptoms (sleep disruption and/or significant desaturations) with residual daytime symptoms (daytime sleepiness or behavior problems)
D) CPAP will be covered for children through age 18 on an ongoing basis if:
    1) There is documentation of improvement in sleep disruption and daytime sleepiness and behavior problems with CPAP use, AND
    2) Annual re-evaluation for CPAP demonstrates ongoing clinical benefit and compliance with use, defined as use of CPAP for at least four hours per night on 70% of the nights in a consecutive 30-day period

The development of this guideline note was informed by a HERC coverage guidance. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx

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HERC staff summary:

The coverage guidance contains criteria that require clarification in order to be implemented:

1) CPAP criteria: "Not responsive to CPAP" is defined as either of the following (as documented by a sleep specialist):
    a. Inability to use CPAP greater than 5 nights per week of at least 4 hours per night; *OR*
    b. Have a lack of adequate response to CPAP therapy (i.e., AHI4 of greater than 15 despite CPAP usage
2) Multiple hypoglossal nerve stimulation devices are FDA approved and may be covered for adults 21 and older with a diagnosis of obstructive sleep apnea with an AHI between 15-100 and a BMI of 35 or less who are not responsive to CPAP therapy.
3) Drug-induced Sleep Endoscopy (DISE): Per FDA labeling, DISE is required prior to placement of an Inspire device, but not Genio.

HERC staff recommendation:

1) Modify Diagnostic Guideline D8 as shown below to address Drug-induced Sleep Endoscopy when required prior to HGNS device placement per FDA labeling
    a) Consider whether to allow DISE for 19-20 year olds according to the adult criteria
2) Modify Guideline Note 27 as shown below

DIAGNOSTIC GUIDELINE D8, DIAGNOSTIC TESTING FOR OBSTRUCTIVE SLEEP APNEA (OSA)

For adults over the age of 18 years:

A) For patients with clinical signs and symptoms consistent with obstructive sleep apnea (OSA), a home sleep study is the first-line diagnostic test for most patients, when available.
    1) For portable devices, Type II-III are included on this line. Type IV sleep testing devices must measure three or more channels, one of which is airflow, to be included on this line. Sleep testing devices that are not Type I-IV and measure three or more channels that include actigraphy, oximetry, and peripheral arterial tone, are included on this line.

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B) Polysomnography in a sleep lab is indicated as a first-line test for patients with significant cardiorespiratory disease, potential respiratory muscle weakness due to a neuromuscular condition, awake hypoventilation or suspicion of sleep related hypoventilation, chronic opioid medication use, history of stroke or severe insomnia or being evaluated for placement of a hypoglossal nerve stimulator.

C) If a patient has had an inconclusive (or negative) home sleep apnea test and a clinical suspicion for OSA remains, then attended polysomnography is included on this line. Split night diagnostic protocols are required when a diagnosis of OSA is confirmed in the first portion of the night.

D) Repeat sleep studies are covered up to twice a year when one of the following has occurred since the most recent test:
   1) recurrence of OSA symptoms
   2) weight change of more than 10% of body weight
   3) new or worsening health conditions related to OSA
   4) upper airway surgical procedures or initial treatment with oral appliances
   5) an evaluation for placement of hypoglossal nerve stimulator has become necessary

E) Drug-induced sleep endoscopy is covered when the patient is 21 years of age or older and recommended for placement of a hypoglossal nerve stimulator where FDA labeling requires drug-induced sleep endoscopy prior to placement.

For children age of 18 or younger:
Obstructive sleep apnea (OSA) must be diagnosed by
nocturnal polysomnography with an AHI >5 episodes/h or AHI >1 episodes/h with history and exam consistent with OSA, OR
nocturnal pulse oximetry with 3 or more SpO2 drops <90% and 3 or more clusters of desaturation events, or
alternatives desaturation (>3%) index >3.5 episodes/h,OR
use of a validated questionnaire (such as the Pediatric Sleep Questionnaire or OSA 18), OR
consultation with a sleep medicine specialist.
Polysomnography and/or consultation with a sleep medicine specialist to support the diagnosis of OSA and/or to identify perioperative risk is recommended for
high-risk children (i.e., children with cranio-facial abnormalities, neuromuscular disorders, Down syndrome, etc.)

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children with equivocal indications for adenotonsillectomy (such as discordance between tonsillar size on physical examination and the reported severity of sleep-disordered breathing), children younger than three years of age

Drug-induced sleep endoscopy (CPT *42975) is only covered when ALL of the following criteria are met:

The patient is under 21 years of age; AND

The patient has OSA diagnosed by polysomnography; AND

The patient is being evaluated for upper airway surgery for OSA; AND

The patient has at least one of the following:

A high-risk condition including but not limited to trisomy 21 (Down's syndrome), craniofacial anomalies, hypotonia, or neurological disorder; OR

A known physical airway anomaly.

The development of this guideline note was informed by a HERC coverage guidance. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx

GUIDELINE NOTE 27, TREATMENT OF SLEEP APNEA

Line 201

For adults over the age of 18 years:

A) CPAP is covered initially when all of the following conditions are met:
   1) 12 week 'trial' period to determine benefit. This period is covered if apnea-hypopnea index (AHI) calculated using the CMS definition of hypopnic episode of at least 4% oxygen desaturation or respiratory disturbance index (RDI) is greater than or equal to 15 events per hour; or if between 5 and 14 events with additional symptoms including one or more of the following:
      a) excessive daytime sleepiness defined as either an Epworth Sleepiness Scale score >10 or daytime sleepiness interfering with ADLs that is not attributable to another modifiable sedating condition (e.g. narcotic dependence), or
      b) documented hypertension, or
      c) ischemic heart disease, or
      d) history of stroke
   2) Additionally:
      a) Providers must provide education to patients and caregivers prior to use of CPAP machine to ensure proper use; and

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b) Positive diagnosis through polysomnogram (PSG) or Home Sleep Test (HST).

B) CPAP coverage subsequent to the initial 12 weeks is based on documented patient tolerance, compliance, and clinical benefit. Compliance (adherence to therapy) is defined as use of CPAP for at least four hours per night on 70% of the nights during a consecutive 30-day period.

C) Mandibular advancement devices (oral appliances) are covered for those for whom CPAP fails or is contraindicated.

D) Surgery for sleep apnea in adults is not included on this line (due to lack of evidence of efficacy). Surgical codes are included on this line only for children who meet criteria below

E) Hypoglossal nerve stimulation for treatment of obstructive sleep apnea is included on this line when the following criteria are met for symptomatic adults age 21 and older when:~~not included on this line due to insufficient evidence of effectiveness and evidence of harm.~~

1) A polysomnography study is performed within 24 months of first consultation for HGNS implant that shows both
   a) Moderate to severe sleep apnea (apnea-hypopnea index (AHI) 15 to 100 events per hour using the 4% oxygen desaturation threshold for hypopneas; AHI4); AND
   b) Predominantly obstructive events (defined as central and mixed apneas less than 25% of the total AHI4); AND
2) Have a body mass index (BMI) 35 kg/m^2 or less; AND
3) Not responsive to continuous positive airway pressure (CPAP) therapy, defined as either of the following (as documented by a sleep specialist):
   a) Inability to use CPAP greater than 5 nights per week of at least 4 hours per night; OR
   b) Have a lack of adequate response to CPAP therapy (i.e., AHI4 of greater than 15 despite CPAP usage; AND
4) Drug induced sleep endoscopy (DISE) findings consistent with the absence of concentric collapse at the soft palate level (per FDA labeling); AND
5) No other anatomical findings that would compromise performance of device (e.g., tonsil size 3 or 4 per standardized tonsillar hypertrophy grading scale); AND
6) Do not have any contraindications to the device.

For children age of 18 years or younger:

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A) Adenotonsillectomy is an appropriate first line treatment for children with OSA. Adenoidectomy without tonsillectomy is only covered when a child with OSA has previously had a tonsillectomy, when tonsillectomy is contraindicated, or when tonsillar hypertrophy is not present. More complex surgical treatments are only included on this line for children with craniofacial anomalies.
B) Intranasal corticosteroids are an option for children with mild OSA in whom adenotonsillectomy is contraindicated or for mild postoperative OSA.
C) CPAP is covered for a 3-month trial for children through age 18 who have
    1) undergone surgery or are not candidates for surgery, AND
    2) have documented residual sleep apnea symptoms (sleep disruption and/or significant desaturations) with residual daytime symptoms (daytime sleepiness or behavior problems)
D) CPAP will be covered for children through age 18 on an ongoing basis if:
    1) There is documentation of improvement in sleep disruption and daytime sleepiness and behavior problems with CPAP use, AND
    2) Annual re-evaluation for CPAP demonstrates ongoing clinical benefit and compliance with use, defined as use of CPAP for at least four hours per night on 70% of the nights in a consecutive 30-day period

The development of this guideline note was informed by a HERC coverage guidance. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx

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HEALTH EVIDENCE REVIEW COMMISSION (HERC) COVERAGE GUIDANCE

HYPOGLOSSAL NERVE STIMULATION FOR OBSTRUCTIVE SLEEP APNEA

DRAFT for May 14, 2026 HERC meeting materials

QUESTION 1

SHOULD HYPOGLOSSAL NERVE STIMULATION BE COVERED FOR ADULTS WITH MODERATE TO SEVERE OBSTRUCTIVE SLEEP APNEA?

We recommend coverage of hypoglossal nerve stimulation (HGNS) for symptomatic adults age 21 and older when all of the following criteria are met:

1) **A polysomnography study is performed within 24 months of first consultation for HGNS implant that shows both**
   a. **Moderate to severe sleep apnea (apnea-hypopnea index (AHI) 15 to 100 events per hour using the 4% oxygen desaturation threshold for hypopneas; AHI4); *AND***
   b. **Predominantly obstructive events (defined as central and mixed apneas less than 25% of the total AHI4); *AND***
2) **Have a body mass index (BMI) 35 kg/m^2 or less; *AND***
3) **Not responsive to continuous positive airway pressure (CPAP) therapy, defined as either of the following (as documented by a sleep specialist):**
   a. **Inability to use CPAP greater than 5 nights per week of at least 4 hours per night; *OR***
   b. **Have a lack of adequate response to CPAP therapy (i.e., AHI4 of greater than 15 despite CPAP usage; *AND***
4) **Drug induced sleep endoscopy (DISE) findings consistent with the absence of concentric collapse at the soft palate level (per FDA labeling); A*ND***
5) **No other anatomical findings that would compromise performance of device (e.g., tonsil size 3 or 4 per standardized tonsillar hypertrophy grading scale); *AND***
6) **Do not have any contraindications to the device.**

Rationale:

We recommend coverage because the improvement in sleep-related quality of life and OSA severity outweighs the risk of the procedure in selected patients. We have added coverage criteria for this treatment consistent with inclusion criteria in the reported studies, additionally informed by certain Medicare criteria and on supplemental data.

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RATIONALE FOR DEVELOPMENT OF COVERAGE GUIDANCES AND MULTISECTOR INTERVENTION REPORTS

Coverage guidances are developed to inform coverage recommendations for public and private health plans in Oregon as plan administrators seek to improve patients' experience of care, population health, and the cost-effectiveness of health care. In the era of public and private sector health system transformation, reaching these goals requires a focus on maximizing the benefits and minimizing the harms and costs of health interventions.

The Health Evidence Review Commission (HERC) uses the following principles in selecting topics for its reports to guide public and private payers:

- Represents a significant burden of disease or health problem
- Represents important uncertainty with regard to effectiveness or harms
- Represents important variation or controversy in implementation or practice
- Represents high costs or significant economic impact
- Topic is of high public interest

HERC bases its reports on a review of the best-available research applicable to the intervention(s) in question. For coverage guidances that focus on diagnostic and clinical interventions, evidence is evaluated using an adaptation of the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) methodology. For more information on coverage guidance methodology, see Appendix A.

Multisector interventions can be effective ways to prevent, treat, or manage disease at a population level. In some cases, HERC has reviewed evidence and identified effective interventions, but has not made formal coverage recommendations when these policies are implemented in settings other than traditional health care delivery systems, as effectiveness could depend on the environment in which the intervention is implemented.

GRADE

HERC develops recommendations by using the concepts of the GRADE approach. GRADE is a transparent and structured process for developing and presenting evidence and for performing the steps involved in developing recommendations. The tables below list the elements that determine the strength of a recommendation. HERC reviews the evidence and assesses each element, which in turn is used to develop the recommendations presented in the coverage guidance box. Estimates of effect are derived from the evidence presented in this document. Assessments of confidence are from published systematic reviews and meta-analyses, where available and judged to be reliable. The level of confidence in the estimate is determined by HERC based on the assessment of 2 independent reviewers from the Center for Evidence-based Policy (Center; see Figure 1).

In some cases, no systematic reviews or meta-analyses encompass the most current literature. In those cases, HERC may describe the additional evidence or alter the assessments of confidence in light of all available information. Such assessments are informed by clinical epidemiologists from the Center. Unless

otherwise noted, statements regarding resource allocation, values and preferences, and other considerations are the assessments of HERC, as informed by the evidence reviewed, public testimony, and subcommittee discussion.

FIGURE 1. GRADE TABLE KEY

OUTCOMES	TABLE KEY				
Confidence in Estimate:	NO DATA ○○○○	VERY LOW ●○○○	LOW ●●○○	MODERATE ●●●○	HIGH ●●●●
Direction of Effect:	No Data, Unclear, No Effect, Benefit, Harm, Mixed				

Notes. Recommendations for coverage are based on the balance of benefit and harms, resource allocation, values and preferences, and other considerations. See Appendix A for more details about the factors that constitute the GRADE table.
Abbreviation. GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach.

GRADE TABLE

GRADE TABLE

HYPOGLOSSAL NERVE STIMULATION FOR ADULTS WITH MODERATE TO SEVERE OBSTRUCTIVE SLEEP APNEA

CRITICAL OUTCOMES

Quality of Life

BENEFIT

Evidence summary

Three studies, which investigated the only FDA-approved hypoglossal nerve stimulation (HGNS) device for adults with moderate to severe obstructive sleep apnea (OSA) who were intolerant to or unable to eliminate OSA with continuous positive airway pressure (CPAP), reported sleep-related quality of life (QoL) outcomes. The studies were 2 randomized controlled trials (RCTs) and 1 cohort study (N = 485). The 2 RCTs enrolled people who had a previous implantation of the HGNS device with a positive response and randomized participants to inactivation of the device or subtherapeutic stimulation. Participants in the cohort study did not begin using HGNS until after enrollment. When reported, there were no significant differences between study groups in terms of baseline sleep-related QoL scores.

Across these studies, groups who received HGNS therapy had better sleep-related QoL compared with controls (i.e., inactive device, subtherapeutic stimulation, no treatment) at follow-up (range, 2 weeks to 6 months), as indicated by significantly higher mean scores on the Functional Outcomes of Sleep Questionnaire (FOSQ). Differences in mean follow-up FOSQ scores between study groups also exceeded the established minimal clinically important difference (MCID; ≥ 1 point).

- EFFECT RCT (2 weeks): 17.0 vs. 14.9 points; $P < .001$
- STAR RCT (1 month): 17.9 vs. 15.0 points; $P < .001$
- ADHERE Comparative Cohort (6 months): 17.1 vs. 12.4 points; $P < .001$

No eligible studies of FDA-approved HGNS devices reported measures of general QoL.

Confidence rating

Low confidence that HGNS improves sleep-related QoL compared with controls.

3 studies (2 RCTs, 1 comparative cohort); N = 485

- Risk of bias concerns: limited methods reporting, selection bias in RCTs, industry funding, and author conflict of interest
- Indirectness: study design heterogeneity; study populations more limited than current FDA indication for HGNS and lack of demographic generalizability to Medicaid
- Other: short follow-up periods relative to intended length of intervention

Device-Related Severe Adverse Events

Evidence summary

Thirteen studies (2 RCTs, 1 comparative cohort study, 3 noncomparative cohort studies, 6 registry studies, and 1 systematic review) investigating the only FDA-approved HGNS device reported on device-related serious adverse events (SAEs). In general, device-related SAEs were infrequently reported in the 13 studies.

Device explants and device revisions were reported most frequently:

GRADE TABLE

HYPOGLOSSAL NERVE STIMULATION FOR ADULTS WITH MODERATE TO SEVERE OBSTRUCTIVE SLEEP APNEA

Revisions and Explants

HARM

- In 3 studies on total device revisions for participants, the rate of device revisions ranged from 0.4% to 6.3% of study participants.
- In 3 studies on total device explants for participants, the rate of device explants ranged from 0.05% to 5.2% of study participants.

Other Device-Related SAEs

HARM

Confidence rating

Studies reported actual harms (i.e., SAEs), but there is moderate (device revisions and explants) and low (other device-related SAEs) confidence of the scope and magnitude of the harms due to:

- Risk of bias concerns: industry funding and author conflict of interest, reporting bias, selection bias, and, for the systematic review, risk of bias methods
- Indirectness: study populations were more limited than current FDA indication for HGNS and lack demographic generalizability to Medicaid (concern for other device-related SAEs, not a concern for device revisions or explants), range of SAEs reported, differences in categorizing outcomes as SAEs versus AEs
- Other: Generally short follow-up periods that limit the ability to consider SAEs that may develop over the course of the intervention

IMPORTANT OUTCOMES

OSA Severity (Polysomnography Outcomes)

BENEFIT

Evidence summary

Five studies, which investigated the only FDA-approved HGNS device for adults with moderate to severe OSA who were intolerant to or unable to eliminate OSA with CPAP, reported OSA severity as measured by polysomnography. The studies included 3 RCTs and 2 cohort studies. The 3 RCTs enrolled people who had a previous implantation of the HGNS device with a positive response and randomized participants to inactivation of the device or subtherapeutic stimulation. Participants in the cohort studies did not begin using HGNS until after enrollment. There were no significant differences in baseline severity between study groups.

Compared with patients with an inactive device, subtherapeutic stimulation, or no treatment (3 RCTs and 1 cohort study; N = 547), patients who received HGNS therapy had significantly lower OSA severity, as indicated by significantly lower apnea-hypopnea index (AHI4) and oxygen desaturation index (ODI4) scores across all follow-up timepoints (range, 2 weeks to 6 months). In 3 studies, the differences in mean follow-up AHI4 and ODI4 scores between study groups exceeded the established MCID (≥ 5 events per hour).

- EFFECT RCT (2 weeks): AHI4, +0.6 vs. +16. (change scores); ODI4, +0.6 vs. +12.7 (change scores); $P < .001$ for both
- STAR RCT (1 month): AHI4, 8.9 vs. 25.8; ODI4, 8.0 vs. 23.0; $P < .001$ for both
- CARDIOSA-12 RCT (10 weeks): AHI4: 18.1 vs. 23.0; ODI4 NR; *P* value NR
- ADHERE Comparative Cohort (6 months): AHI4, 14.7 vs. 26.8; ODI4, 14.1 vs. 25.5; $P < .001$ for both

In the 3 studies that reported mean scores at follow-up, scores in the HGNS groups were generally indicative of mild OSA severity (i.e., ≥ 5 to < 15 events per hour)

whereas scores in the control groups indicated moderate OSA severity (i.e., ≥ 15 to < 30 events per hour).

Compared with patients who received CPAP therapy (i.e., were not CPAP intolerant) (1 cohort study; N = 126), patients who were CPAP intolerant and received HGNS therapy did not exhibit a significant difference in OSA severity, as measured by mean AHI4 at the 12-month follow-up (8.1 vs. 6.6; *P* = .08). However, both study groups had clinically significant AHI4 score reductions from baseline (i.e., ≥ 5 events per hour) and similar proportions of participants had an AHI below the clinical threshold for OSA (i.e., AHI < 5) at follow-up (51% vs. 59%; *P* = .27).

Confidence rating

Low confidence that HGNS reduces OSA severity compared with controls and provides similar benefit to CPAP in people with CPAP intolerance.

5 studies (3 RCTs and 2 cohort studies); N = 673

- Risk of bias concerns: limited methods reporting, selection bias in RCTs, industry funding and author conflict of interest
- Indirectness: study design and comparator heterogeneity; study populations more limited than current FDA indication for HGNS and lack of demographic generalizability to Medicaid
- Other: short follow-up periods relative to intended length of intervention

Daytime Sleepiness

BENEFIT

Evidence summary

Four studies, which investigated the only FDA-approved HGNS device for adults with moderate to severe OSA who were intolerant to or unable to eliminate OSA with CPAP, reported daytime sleepiness outcomes. The studies included 2 RCTs and 2 cohort studies. The 2 RCTs enrolled people who had a previous implantation of the HGNS device with a positive response and randomized participants to inactivation of the device or subtherapeutic stimulation. Participants in the cohort studies did not begin using HGNS until after enrollment. When reported, there were no differences between study groups in terms of baseline daytime sleepiness scores.

Compared with patients with an inactive device, subtherapeutic stimulation, or no treatment (2 RCTs and 1 cohort study; N = 485), groups who received HGNS therapy reported less daytime sleepiness at follow-up, as indicated by significantly lower Epworth Sleepiness Scale (ESS) scores (*P* < .01 for all). The differences in mean follow-up ESS scores between study groups also exceeded the established MCID (≥ 2 points).

- EFFECT RCT (2 weeks): +0.2 vs. +3.5 points (change scores); *P* < .001
- STAR RCT (1 month): 5.6 vs. 10.0 points; *P* = .005
- ADHERE Comparative Cohort (6 months): 7.2 vs. 12.8 points; *P* < .001

In the 2 studies that reported mean scores at follow-up, ESS scores in the HGNS groups were below the excessive sleepiness threshold (i.e., ESS > 10 points), whereas scores in the control groups were at or above the threshold.

Compared with patients who received CPAP therapy (i.e., were not CPAP intolerant) (1 cohort study; N = 126), patients who were CPAP intolerant and received HGNS therapy did not report a significant difference in daytime sleepiness as indicated by

mean ESS scores (7.5 vs. 10.8; $P = .27$). Both groups experienced reductions in ESS scores from baseline that met MCID (≥ 2 points) and scores were generally indicative of normal levels of daytime sleepiness.

Confidence rating

Low confidence that HGNS reduces daytime sleepiness compared with controls and provides similar benefit as CPAP therapy for patients with CPAP intolerance.

4 studies (2 RCTs and 2 cohort studies); N = 611

- Risk of bias concerns: limited methods reporting, selection bias in RCTs, industry funding, and author conflict of interest
- Indirectness: study design heterogeneity; study populations more limited than current FDA indication for HGNS and lack of demographic generalizability to Medicaid
- Other: short follow-up periods relative to intended length of intervention

Major Adverse Cardiac Events

NO DATA

There were no eligible studies that reported MACE outcomes.

Balance of benefits and harms

We have low confidence there is a clinically important improvement in sleep-related quality of life and in apnea severity as measured by AHI4 with HGNS in select patients. The degree of confidence is low because the included studies have a high degree of selection bias and indirectness. Additionally, these RCTs only enrolled people who had a positive initial response to HGNS. We have low to moderate confidence that the full scope and magnitude of harms are described. Overall, these benefits appear to outweigh the reported risk of harms.

Resource allocation

HGNS requires a high level of resource use. Before being eligible for device implantation, patients would need to undergo drug-induced sleep endoscopy (DISE), an invasive procedure requiring anesthesia. The HGNS implantation itself involves surgery, and the follow-up involves an in-lab sleep study. Long-term maintenance of this intervention requires surgical battery replacement every 7–10 years. Patients undergoing HGNS would likely need to continue CPAP therapy if they can tolerate CPAP, resulting in a lack of cost savings from CPAP discontinuation. An economic modeling study did not identify net cost-savings in reductions of OSA complications (stroke, myocardial infarction, or car crashes).

Values and preferences

Many patients who have not adequately responded to first-line OSA therapies would value a second-line treatment that may improve their sleep-related quality of life and reduce their sleep apnea symptoms. Other patients would not value an invasive surgical procedure, especially if it does not reduce their sleep apnea symptoms or eliminate the need for daily CPAP usage.

Other considerations

There are few other available treatments for moderate and severe OSA for patients who cannot tolerate or do not respond sufficiently to CPAP therapy.

Notes. GRADE table elements are described in Appendix A; a corresponding GRADE Evidence Profile for each outcome is in Appendix B.
Abbreviations. AE: adverse event(s); AHI4: Apnea-Hypopnea Index (with 4% blood oxygen desaturation threshold for hypopneas); COI: conflict of interest; CPAP: continuous positive airway pressure; DISE: Drug-induced sleep endoscopy; ESS: Epworth Sleepiness Scale; FDA: US Food and Drug Administration; FOSQ: Functional Outcomes of Sleep Questionnaire; HGNS: hypoglossal nerve stimulation; MACE: major adverse cardiac events; MCID: minimal clinically important difference; ODI4: Oxygen Desaturation Index (with 4% blood oxygen desaturation threshold); OSA: obstructive sleep apnea; QoL: quality of life; RCT: randomized controlled trial; RoB: risk of bias; SAE serious adverse event(s); UAS: upper airway nerve stimulation; US: United States; vs.: versus.

GENIO APPROVAL UPDATE

The FDA approved a new HGNS device, the Nyxoah Genio System 2.1 (Genio System), in August 2025 after the prior coverage guidance update searches were conducted (July 2025).[1] To ensure that coverage guidance evidence was aligned with the current clinical context during deliberation by the Evidence-based Guidelines Subcommittee, and subsequently by HERC, we undertook a targeted update of this coverage guidance that included the following actions:

- Incorporated newly published eligible clinical studies that supported the Genio System FDA approval
- Searched clinical trial registries for the post-approval study of the Genio System as required by the FDA in the approval notice
- Reviewed and compared the FDA labels of all currently approved HGNS devices
- Reviewed included clinical practice guidelines (CPGs) for updated guidance specific to the Genio System
- Reviewed payer policies for changes in HGNS coverage criteria specific to the Genio System

Updated findings are highlighted in call-out boxes at the beginning of each major report section and all results incorporate the new information. This document reflects the most current and updated findings.

Although our updated search resulted in the inclusion of new evidence, the findings ultimately did not alter the original conclusions of this coverage guidance.

2025 UPDATE

Following the presentation of this coverage guidance on September 9, 2024, HERC's Evidence-based Guidelines Subcommittee (EbGS) voted to table this report for 1 year and perform an updated evidence search at that time. In July 2025, we conducted a series of searches and reviews to update this report in advance of the 1-year re-presentation to EbGS (i.e., September 11, 2025):

- Searched clinical databases for eligible studies published after the original coverage guidance search dates (new search range, May 15, 2024–July 1, 2025)
- Searched clinical trial registries for new ongoing studies
- Reviewed the label and recall status of the FDA-approved HGNS device and looked for new FDA approvals
- Reviewed previously included CPGs for updated HGNS recommendations and conducted targeted searches for new relevant CPGs
- Reviewed payer policies for changes in HGNS coverage criteria
- Contacted subject matter experts for information about key industry developments and new important publications

Updated findings are highlighted in call-out boxes at the beginning of each major report section and all results incorporate the new information. This document reflects the most current and updated findings.

Although our updated search resulted in the inclusion of new evidence, the findings ultimately did not alter the original conclusions of this coverage guidance.

BACKGROUND

Genio Approval Update

In the Background section, we reviewed the FDA label for the newly approved Genio System as compared with the previously approved Inspire UAS device, and updated information regarding HGNS device indications, candidate evaluation, and device implantation procedures.

- The Genio System is surgically implanted in the chin and is a leadless, externally powered device that delivers bilateral stimulation of the genioglossus muscle, as compared with Inspire UAS (i.e., the other FDA approved HGNS device), which provides unilateral stimulation.
- The approved Genio System indication criteria largely align with the original approval criteria for the Inspire UAS device (i.e., adults age 22 years and older; confirmed failure or inability to use first-line OSA treatments; AHI 15 to 65; upper BMI warning limit of 32 kg/m^2)
- Compared with Inspire UAS, candidate evaluation for the Genio System does not require DISE

2025 Update

In the Background section, we reviewed the label and recall status for the FDA-approved HGNS device and looked for new FDA approvals between May 2024 and July 2025.

- Inspire UAS remains the only FDA-approved HGNS device and there have been no changes to the indication criteria specified on the label since 2023.
- The class 1 recall of the Inspire IV implantable pulse generator (initiated in June 2024) remains active, but no new injuries or deaths have been reported.
- No new HGNS devices have been approved by the FDA.

Obstructive sleep apnea (OSA) is the most common sleep-related breathing disorder.[2] OSA is caused by recurrent partial or complete collapse of the upper airway, which interferes with the flow of air during sleep.[3] This leads to interrupted sleep, a low oxygen level in the blood, or both.[3] Untreated or undertreated OSA can contribute to poor quality of life, is associated with chronic illnesses such as heart disease, and can cause life-threatening complications.[4-7] OSA is a common condition, affecting an estimated 9% to 38% of the general population.[8,9]

Causes and Consequences of OSA

Anatomy of OSA

The upper airway (i.e., pharynx) is mostly surrounded by soft tissues and is not supported by a bony structure, making it especially vulnerable to collapse.[3] Many factors can contribute to upper airway collapse during sleep, including irregularities in anatomical structures and loss of neuromuscular control.[3]

Symptoms and Complications

Signs and symptoms of OSA may include excessive daytime sleepiness, early morning headaches, and snoring, choking, or gasping during sleep.[10] Due to the frequent interruptions in sleep, excessive daytime

sleepiness is the most common symptom reported by individuals with OSA.[9] Excessive daytime sleepiness from OSA is associated with impaired work performance[11,12] and increased risk of motor vehicle crashes while driving.[13] OSA is also associated with other medical complications including cardiovascular complications such as high blood pressure, congestive heart failure, coronary artery disease, stroke, pulmonary hypertension, atrial fibrillation and other irregular heart rhythms, and sudden cardiac death.[3,6,7,10]

OSA Diagnosis

Diagnostic Testing

Sleep apnea testing is required for a diagnosis of OSA.[10] The American Academy of Sleep Medicine (AASM) recommends testing for OSA in individuals with excessive daytime sleepiness and other clinical features of OSA, such as loud snoring or gasping.[14] Home sleep apnea testing and in-laboratory polysomnography are the most common diagnostic tests for OSA.[2] Home sleep apnea testing typically involves a respiratory effort band around the chest, a nasal cannula with a pressure transducer to measure airflow and snoring, and an oximeter to measure oxygen saturation.[2] In-laboratory polysomnography generally also involves measures of sleep stages and arousals using electroencephalogram (EEG), electrocardiogram results, body position, and leg movements.[9] The diagnosis of OSA depends on the presence of sleep-associated conditions such as fatigue, insomnia, snoring, or breathing interruptions as well as counts of obstructive respiratory events during sleep.[10]

Defining Obstructive Respiratory Events

There are 2 main types of obstructive respiratory events: apneas (complete obstruction) and hypopneas (partial obstruction).[2] An apnea is an event defined as the complete cessation of airflow for 10 seconds or longer.[3] A hypopnea is an event characterized by a partial reduction in airflow.[3]

There is variation in the definition of hypopnea. A common definition of a hypopnea is evidence of a reduction in airflow of 30% or more for 10 seconds or longer accompanied by either an arousal or oxygen desaturation of 3% or more (this definition is abbreviated as AHI3a).[2] A stricter definition of a hypopnea (abbreviated as AHI4) uses an oxygen desaturation threshold of 4% instead of 3% and does not consider arousals.[2]

The Centers for Medicaid & Medicare Services (CMS) uses the AHI4 criteria to define a hypopnea.[15] The decision of which hypopnea definition to use has implications for the prevalence of OSA diagnoses and severity of OSA classification.[16,17] After changes adopted in 2023, the AASM Scoring Manual 3 recommends every accredited sleep center score hypopneas with the AHI3a definition due to evidence that hypopneas with a 3% oxygen desaturation or arousal are associated with health and quality of life deficits.[18] However, the current scoring manual allows sleep centers to also report AHI scores according to the AHI4 criteria for patients insured by a payer that requires it for treatment coverage.[18]

The Apnea-Hypopnea Index and Other Measures of OSA Severity

The apnea-hypopnea index (AHI) is a measure of the total number of apneas and hypopneas per hour of sleep.[2] Advantages of the AHI are that it is fairly objective and reproducible across a standardized context.[3] Generally, severity of OSA is defined by AHI thresholds, with greater than or equal to 5 obstructive events per hour characterized as mild OSA, greater than or equal to 15 events per hour as

moderate OSA, and greater than or equal to 30 events per hour as severe OSA (Table 1; Appendix D, Table D1).[3]

TABLE 1. CLASSIFICATION OF OSA SEVERITY

CLASSIFICATION	AHI SCORE
Mild	≥ 5 and < 15 events per hour
Moderate	≥ 15 and < 30 events per hour
Severe	≥ 30 events per hour

Source. Johnson, 2023.[2]
Abbreviations. AHI: apnea-hypopnea index; OSA: obstructive sleep apnea.

Limitations of AHI as a measure of OSA severity include:

(1) It equates apneas and hypopneas, even though the severity of physiological effects differ[19]

(2) Individual characteristics, such as age, obesity, and cardiopulmonary disease, can be confounding factors that affect the degree of oxygen desaturation[3]

(3) AHI is a continuous measure and the discrete thresholds used to define OSA severity may contribute to misclassification of overall OSA severity when scores are near a threshold[3]

(4) It is unclear whether AHI scores correspond closely to the severity of clinical symptoms of OSA or whether these are useful in predicting morbidity, mortality, or response to treatment[2,3]

Other measures of severity of OSA include the respiratory disturbance index (RDI), the respiratory event index (REI), and the oxygen desaturation index (ODI).[2] The RDI differs from the AHI because it accounts for the number of apneas, hypopneas, and arousals per hour of sleep.[2] The REI is commonly used in home sleep testing and reports the number of apneas and hypopneas per hour of monitoring time, since home sleep tests without EEG cannot account for the total time asleep.[2,20] As such, the REI is sometimes an underestimation of the AHI; in contrast, the RDI is often higher than the AHI because it accounts for arousals separately.[20] The oxygen desaturation index (ODI) counts the number of oxygen desaturations (typically either the AHI3a ≥ 3% standard or the AHI4 ≥ 4% standard) per hour of sleep time or monitoring time.[21]

Patient-Reported Measures of OSA Severity

Beyond measures based on sleep apnea, hypopnea, and desaturation testing, several patient-reported assessments help evaluate the severity of OSA, including the response to therapy. These instruments are the Epworth Sleepiness Scale (ESS), which measures daytime sleepiness, and the Functional Outcomes of Sleep Questionnaire (FOSQ), which measures sleep-related quality of life (QoL) impairments (Appendix D, Table D1).[9,22]

OSA Treatment

The aim of OSA treatment is to reduce AHI score, improve symptoms, and increase patient quality of life.[23] Complete remission of OSA is rare and lifelong treatment is usually necessary, with the exception of sustained weight loss.[9,23] Common criteria for measuring treatment success for OSA surgeries is referred

to as the Sher criteria, a compound measure defined as a greater than or equal to 50% reduction in baseline AHI and a postoperative AHI of less than 20 events per hour.[24]

Continuous positive airway pressure (CPAP) therapy is considered the standard first-line therapy for most adults with OSA.[23] CPAP devices work by creating a constant flow of air through a mask to support breathing.[3] The positive air pressure generated by the CPAP device helps to maintain an open airway during sleep.[3]

Hypoglossal Nerve Stimulation for OSA

Hypoglossal nerve stimulation (HGNS), a form of upper airway nerve stimulation (UAS), is a second-line treatment option for individuals with moderate or severe OSA who are intolerant to or unable to eliminate OSA with CPAP.[25,26]

How Does HGNS Work?

In OSA, the genioglossus—an extrinsic muscle of the tongue that helps stabilize the upper airway during sleep—tends to lose its muscle tone causing the tongue to fall backward and obstruct the upper airway.[7,27] HGNS therapy is intended to open and stiffen the upper airway.[25,26] It works primarily by monitoring a person's breathing and sending an electrical impulse to the hypoglossal nerve at the start of a breath, stimulating the genioglossus to move the tongue forward and open the airway.[28]

HGNS Devices and Indications

There are currently 2 FDA-approved HGNS devices:

- The Inspire UAS system, approved in May 2014, uses a stimulation lead implanted in the neck around a single branch of the hypoglossal nerve, and a respiratory sensing lead and pulse generator implanted in the chest wall.[25,29,30] The Inspire pulse generator batteries must be surgically replaced at an estimated interval of 7–10 years.[31] The manufacturer precautions advise considering that battery replacements may require serial reimplantation over an individual's lifetime, with the potential for future surgical complications.[31]
- The Genio System, approved in August 2025, is a leadless, externally powered device that is implanted in the chin over the genioglossus muscle targeting bilateral branches of the hypoglossal nerve.[1,32] The implanted stimulator unit is powered by a rechargeable external activation chip that is snapped onto a single-use disposable adhesive patch placed on the skin underneath a patient's chin each night.[33]

FDA indication criteria for HGNS therapy have evolved over time and vary by device (Table 2).

TABLE 2. KEY INDICATION CRITERIA FOR FDA-APPROVED HGNS DEVICES IN ADULTS WITH OBSTRUCTIVE SLEEP APNEA

	ORIGINAL INSPIRE APPROVAL (2014)[34]	SUPPLEMENTAL INSPIRE APPROVAL (2020)[34]	SUPPLEMENTAL INSPIRE APPROVAL (2023)[30,35]	ORIGINAL GENIO APPROVAL (2025)[1]
AGE	≥ 22 years	≥ 18 years	No change[a]	≥ 22 years
AHI	≥ 20 and ≤ 65 events/hour	≥ 15 and ≤ 65 events/hour	≥ 15 and ≤ 100 events/hour	≥ 15 and ≤ 65 events/hour

BMI WARNING THRESHOLD	32 kg/m^2	No change	40 kg/m^2	32 kg/m^2
PLACE IN THERAPY	Second-line ▪ Confirmed intolerance[b] or insufficient response[c] to CPAP therapy	No change	No change	Second-line ▪ Confirmed intolerance[b] or insufficient response[c] to all first-line therapies[d]
OTHER	Does not have complete concentric collapse as confirmed by DISE	No change	No change	DISE may be used to optimize therapy settings

Notes. a A 2023 supplemental expanded the Inspire indication to include children with Down syndrome (ages 13–18 years) who meet certain developmental and physiological criteria. b Unable or unwilling to use intervention more than 5 nights per week for at least 4 hours per night. c AHI greater than 15 despite confirmed intervention. d First-line therapies include lifestyle modifications, CPAP therapy, oral appliances, and pharmacotherapy.
Abbreviations. AHI: apnea-hypopnea index; BMI: body mass index; CPAP: continuous positive airway pressure; DISE: drug-induced sleep endoscopy; FDA: US Food and Drug Administration; HGNS: hypoglossal nerve stimulation.

Other HGNS devices with different configurations are under investigation, such as the aura6000 system by LivaNova (previously ImThera).[32,36]

Candidate Evaluation and Device Implantation

Potential candidates for HGNS who are intolerant or nonresponsive to CPAP therapy and meet age and BMI criteria may first be referred for drug-induced sleep endoscopy (DISE).[25,26,33] With DISE, the upper airway is evaluated endoscopically to assess for palate collapse and tongue position during light sedation to mimic sleep.[25,26] Individuals with complete concentric collapse at the level of the soft palate are generally not considered good candidates for HGNS.[33,35]

HGNS devices are typically implanted during an outpatient procedure performed under general anesthesia in an operating room.[25,30,33] Once implanted, the HGNS device is not activated until the system components are fully healed in place, approximately a month after implantation.[1,25,33] Following activation by a clinician, the patient is able to turn the device on and off during the night or adjust the strength of the stimulus using a remotely controlled device or a mobile phone app.[1,25,33] Patients usually return for a follow-up in-lab polysomnography for titration of the device settings by a clinician to maximize sleep quality and individual comfort.[1,26,33]

HGNS Device Recalls

On June 17, 2024, the FDA announced a recall of 32 devices of the Model 3028 Inspire UAS system implantable pulse generator due to a manufacturing defect.[37] This defect can lead to complications such as stimulation below normal levels, early depletion of the battery, inappropriate or inconsistent stimulation effect, painful stimulation, or perceived shocking sensation, and death.[37] This recall was designated as the most serious type by the FDA.[37] There are no open device recalls for the Genio System.

Access and Equity

Although clinicians of many specialties can play a role in identifying and referring patients for diagnostic testing for OSA, the AASM recommends that follow-up be under the supervision of a physician trained in sleep medicine.[14] However, there is an anticipated national shortage of sleep medicine specialists in the US.[38] This shortage is especially pronounced in federally designated Health Professions Shortage Areas, which may contribute to sleep health disparities for individuals with lower socioeconomic status and those from racial and ethnic minority groups.[39]

Differences and Disparities in OSA Prevalence and Diagnosis

The prevalence of OSA varies by sex, with men having higher rates of OSA than women.[10] When excluding mild OSA, US-specific estimates indicate approximately 13% of men and 6% of women have moderate or severe OSA.[40] However, the prevalence of OSA also increases in menopausal and pregnant people due to changes in hormone levels.[41]

Furthermore, the prevalence and severity at diagnosis of OSA may vary by race and ethnicity although the precise relationship is unclear. Some studies suggest that African American young adults experience a higher prevalence of OSA than White young adults, independent of body weight.[42] Other studies reveal a racial disparity in higher OSA prevalence for African American children, though evidence of a disparity is less robust for middle-aged populations.[43] At the time of diagnosis, OSA tends to be more severe among African American individuals compared with White individuals.[44,45] Another study found that South Asian individuals with severe obesity had higher prevalence and severity of OSA than White Europeans with severe obesity.[46] However, other study evidence indicates that rates of OSA are similar or lower among Asian individuals and Asian Americans compared with White individuals.[43]

Disparities in Treatment Coverage and Availability

For HGNS therapy specifically, evidence on insurance-related disparities was limited. Some evidence suggests that individuals with Medicare coverage, compared with privately insured individuals, had shorter waiting periods and fewer insurance-related delays in receiving HGNS, though individuals with private insurance received HGNS therapy at a younger average age.[47]

According to an Inspire Medical Systems, Inc. database, there are currently 18 clinicians at 10 practices listed as Inspire UAS system-trained providers in Oregon (as of August 2025) available for individuals who have been diagnosed with OSA and had difficulty using CPAP.[48] Eight practices (14 providers) are located between Portland and Salem in the Willamette Valley and 2 practices (4 providers) are located in Central Oregon, specifically in Bend. Compared with our initial review of the directory in August 2024, the Portland and Salem areas added 2 clinicians at 2 new practices, there were no changes in provider availability in Bend, and the single provider and practice formerly listed in Southern Oregon, specifically in Medford, was no longer listed.[48] Per personal communications with Inspire Medical Systems, Inc., (August 2024), clinicians must opt in to be listed in the database and, therefore, this database is likely not inclusive of all clinicians in Oregon trained on implantation of the Inspire UAS system.[48]

METHODS

Genio Approval Update

We reviewed the FDA approval packet and labeling materials for studies of the Genio System published since the prior update. We also searched clinical trial registries for new ongoing studies and reviewed policy landscape materials for Genio-related updates to cover the gap in time between the 2025 update searches and the posting of this updated coverage guidance (July 2025–January 2026).

2025 Update

We used the review methods described below to conduct this coverage guidance update. All searches and reviews were repeated to cover the gap in time between the original coverage guidance searches and this update (May 15, 2024–July 1, 2025).

The following section summarizes the overall scope of the evidence review, including Key Questions (KQs) and Contextual Questions (CQs), inclusion and exclusion criteria, and a brief overview of the methods used to conduct the review. Additional information regarding methods can be found in Appendix C.

Key Questions

KQ1. What is the effectiveness of hypoglossal nerve stimulation versus nonsurgical treatments for OSA in adults?

KQ2. What are the harms of hypoglossal nerve stimulation for OSA?

KQ3. How does the effectiveness and harms of these interventions vary by:

- a. Intervention characteristics
- b. Patient characteristics
  - i. Severity of OSA
  - ii. Race, ethnicity, culture, or language
  - iii. Gender or sex
  - iv. Age
  - v. Comorbidities
  - vi. Response to prior interventions

Contextual Questions

CQ1. What is the evidence for effectiveness of hypoglossal nerve stimulation for OSA on outcomes (e.g., all-cause mortality, major adverse cardiac events, motor vehicle crashes) from systematic reviews that include observational and nonrandomized studies?

CQ2. What is the comparative effectiveness of hypoglossal nerve stimulation for OSA from randomized controlled trials?

CQ3. What is the of hypoglossal nerve stimulation for OSA?

Study Eligibility Criteria

Table 3 summarizes the criteria used to inform study selection for the KQ evidence review. See Appendix C for more detailed selection criteria.

TABLE 3. EVIDENCE REVIEW CRITERIA OVERVIEW

CATEGORY	INCLUDED	EXCLUDED
POPULATION	■ Adults with moderate to severe OSA	■ Children and adolescents (i.e., aged < 18 years) with OSA ■ Adults with mild OSA ■ Adults with central sleep apnea
INTERVENTIONS	■ Upper airway nerve stimulation devices (i.e., hypoglossal nerve stimulation [HGNS])	■ Nonsurgically implantable nerve stimulation (e.g., transcutaneous electrical stimulation, Neuromuscular electrical stimulation
COMPARATORS	■ Nonsurgical OSA interventions (including noninvasive PAP therapy) ■ No treatment ■ Subtherapeutic stimulation (sometimes called "sham stimulation") or an inactive device	■ Other surgical airway interventions, including other HGNS devices ■ Intensive weight loss interventions
OUTCOMES	**Critical** ■ Device-related serious adverse events ■ Quality of life **Important** ■ Change in OSA severity (as measured by specific polysomnography indices: AHI, RDI, REI, or ODI) ■ Daytime sleepiness ■ Major adverse cardiac events	**Considered by HERC but not selected for review:** ■ All-cause mortality ■ Change in A1c ■ Remission of hypertension or diabetes ■ Fatigue-related injury ■ Other polysomnography outcomes ■ General harms
STUDY DESIGNS	**KQ1 (effectiveness)** ■ RCTs of any size ■ Comparative prospective cohort studies (N > 100) **KQ2 (harms)** ■ RCTs and prospective cohort studies (as defined above) ■ Systematic reviews including nonrandomized studies ■ Single-arm prospective NRS (N > 100) ■ Registry studies	■ Studies conducted in non-very-high-HDI countries ■ Individual retrospective cohort studies (including, cross-sectional studies, case series, or case reports)

Note. See Appendix C for complete inclusion and exclusion criteria. See Appendix D, Table D1 for information regarding outcome scale interpretation.
Abbreviations. A1c: glycated hemoglobin; AHI: apnea-hypopnea index; HDI: Human Development Index; HGNS: hypoglossal nerve stimulation; KQ: key question; ODI: oxygen desaturation index; OSA: obstructive sleep apnea; RDI: respiratory disturbance index; REI; respiratory event index.

Methods Overview

To answer the KQs, we searched multiple clinical evidence databases (e.g., Ovid MEDLINE, Cochrane CENTRAL) for published randomized controlled trials (RCTs), prospective nonrandomized studies (NRS), systematic reviews (SRs) of NRS, and registry studies, evaluating the effectiveness and harms of HGNS therapy for adults with moderate to severe OSA. We performed an updated database search 1 year after our initial search at the direction of the Evidence-based Guidelines Subcommittee.

In addition to the eligibility criteria described in Table 3, primary studies had to be available in English, include device implantation or follow-up of at least 12 weeks for RCTs and 6 months for NRS and registry studies, be conducted in very-high Human Development Index (HDI) countries,[49] and be published in 2000 or later (2014 for SRs).

- Notably, other forms of upper airway stimulation under investigation for OSA were excluded from this review: transcutaneous electrical nerve stimulation (TENS) devices are not FDA-approved for OSA and eXciteOSA, a neuromuscular electrical stimulation device, is only approved for adults with mild OSA.[50]
- To account for event overlap in studies analyzing datasets from the same clinical registry (e.g., FDA's Manufacturer and User Facility Device Experience [MAUDE]), we reported outcomes from the study with the most comprehensive dataset when overlap was identified.
- We included device-related adverse events when defined as "severe" or "serious" by study authors. In instances where the severity of adverse events was not explicitly defined, we applied FDA definitions of serious adverse events, which include: death, life-threatening events, inpatient hospitalization or prolongation of an existing hospitalization, persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or congenital abnormalities and birth defects.[51]

Two reviewers independently examined abstracts and full-text articles for inclusion and assessed the risk of bias of included studies. Disagreements were primarily resolved through consensus and were referred to a third reviewer when consensus could not be achieved. We assessed the overall strength of evidence using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) method, the results of which are presented in the previously described GRADE table.

We identified evidence for CQs by using results of the KQ database searches, auditing reference lists of relevant SRs, and performing targeted searches of relevant English-language sources as needed. Evidence regarding the CQs is summarized by question following the KQ review.

For the Policy Landscape section, we conducted targeted searches in Ovid MEDLINE, websites of relevant professional societies and guideline groups, and DuckDuckGo to identify relevant CPGs published since 2014 and key payer policies regarding HGNS for adults with moderate to severe OSA. Two reviewers independently assessed the quality of the included CPGs; disagreements were primarily resolved through consensus and were referred to a third reviewer when consensus could not be achieved. Relevant position statements and consensus documents from professional societies were also included for contextual purposes and were considered to have high risk of bias.

EVIDENCE REVIEW

Genio Approval Update

In the Evidence Review section, we reported on new studies of the Genio System published since the prior update. We also reported information on CQs and ongoing studies where relevant.

Key Questions

- We identified 1 new study of the Genio System that reported eligible HGNS-related serious adverse events outcomes (KQ2), but findings from this study did not change our certainty of evidence rating (i.e., GRADE) for the magnitude and range of harms.
- We did not identify any studies of the Genio System that reported eligible HGNS effectiveness outcomes (KQ1) or subgroup analyses of differential effectiveness or harms (KQ3).

Contextual Questions

- We did not identify any new eligible studies of the Genio System that reported key endpoints from systematic reviews (CQ1), comparative effectiveness of HGNS versus other surgical interventions for OSA (CQ2), or cost effectiveness of HGNS (CQ3).

Ongoing Studies

- 1 previously identified ongoing study of the Genio System published primary results, but this study has an ongoing open-label extension phase.
- We identified 1 new ongoing prospective nonrandomized post-approval study, which was mandated by the FDA for ongoing approval of the Genio System.

2025 Update

In the Evidence Review section, we searched clinical databases for new eligible studies addressing the key and contextual questions published between May 15, 2024, and July 1, 2025. We also searched clinical trial registries for new ongoing studies.

Key Questions

- We identified 3 new studies of HGNS-related serious adverse events (KQ2), but findings from these studies did not change our certainty of evidence rating (i.e., GRADE) for the magnitude and range of harms.
- We did not identify any new eligible studies reporting HGNS effectiveness (KQ1) or differential effectiveness or harms (KQ3).

Contextual Questions

- We did not identify any new eligible studies reporting key endpoints from systematic reviews (CQ1), comparative effectiveness of HGNS versus other surgical interventions for OSA (CQ2), or cost effectiveness of HGNS (CQ3).

Ongoing Studies

- We determined that none of the ongoing studies identified in the original coverage guidance were published during the update period.
- We did not identify any new eligible ongoing studies.

Key Question Review

The following results section organizes findings on the effectiveness and harms of HGNS in adults with moderate to severe OSA by outcomes:

- Quality of life (QoL)
- Device-related serious adverse events (SAE)
- OSA severity as measured by key polysomnography indices
- Daytime sleepiness
- Major adverse cardiac events (MACE)

Within each section, results are summarized by FDA-approval status of the HGNS devices.

We initially screened 476 records for eligibility and identified 17 studies[52-68] (reported in 20 publications[52-71]) on HGNS for moderate to severe OSA in adults, with publication dates ranging from 2014 to 2024 (Table 4).

- Our updated database search in July 2025 generated an additional 120 records for screening; 3 new studies met inclusion criteria (Table 3; Appendix D, Figure D1, Tables D2, D3, D4).[72-74] While the updated database search resulted in inclusion of newly published studies, the findings of these studies did not alter the GRADE ratings.

- The Genio approval update, conducted in January 2026, resulted in inclusion of 1 new study, reported in 2 publications (Table 3; Appendix D, Figure D1, Tables D2, D3, D4).[75,76] However, the findings of this study did not alter the GRADE ratings.

Six studies reported effectiveness outcomes (KQ1; none of which were identified in the updated database search or as part of the Genio approval update),[53,55,59-61,66] 19 studies reported harms outcomes (KQ2; 3 were identified in the updated database search; 1 was included in the Genio approval update),[52,54-58,60-68,72-75] and none of the studies reported effectiveness and harms of HGNS by patient or intervention characteristics (KQ3).

Four of the studies were RCTs,[53,55,60,61] along with 5 nonrandomized cohort studies (1 identified in the Genio approval update),[54,59,66,67,75] 6 registry studies (2 of which were identified in the updated database search),[56,57,64,65,72,74] and 6 SRs (1 of which was identified in the updated database search).[52,58,62,63,68,73] Within these categories of study design, significant variability exists. For example, 2 of the RCTs are crossover trials with a withdrawal design in which all participants had the HGNS device activated and are randomized to either active stimulation or subtherapeutic stimulation (i.e., low-level stimulation to deceive the participant).[60,61] Two RCTs are noncrossover withdrawal trials,[53,55] in which participants who previously had an HGNS device activated were randomized to keep the device on or turn the device off. One of the noncrossover withdrawal RCTs[53] is part of an included noncomparative cohort study reported in a separate publication.[54] Additionally, within the nonrandomized cohort studies, 2 are comparative[59,66] and 3 are noncomparative (i.e., single-arm cohort study with no comparison group).[54,67,75]

None of the included studies are low risk of bias (RoB). Specifically:

- The RCTs were rated as having moderate[61] or high RoB[53,55,60]
- The nonrandomized cohort studies were rated as having high RoB[54,59,66,67,75]
- The registry studies were all rated as having high RoB[56,57,64,65]
- The SRs were rated as having a moderate[52,62,63,68,73] or high RoB[58]

The 9 included RCTs and nonrandomized cohort studies ranged from 2 weeks to 5 years of follow-up with total sample sizes ranging from 46 to 1,849 (Appendix D, Table D2).[53-55,59-61,66,67,75] Of the 6 registry studies,[56,57,64,65,72,74] 4 reported data (with some notable data duplication) from the FDA MAUDE database,[64,65,72,74] 1 reported data from the TriNetX Research Network,[57] and 1 reported data from a post-market surveillance database (Appendix D, Table D2).[56] Data on event reports, participants, or devices was collected from 2000 to 2023, and sample sizes ranged from 132 to 20,881 (Appendix D, Table D2).[56,57,64,65,72,74] The 6 SRs, with publication dates from 2015 to 2024, included primary studies from 1997 to 2023 (Appendix D, Table D4).[52,58,62,63,68,73] There was some overlap of primary studies across the SRs.

The majority of the primary studies (n = 13 RCTs, cohort studies, and registry studies) included a US population,[53-57,61,64-67,72,74,75] with 2 other primary studies conducted in Germany[59,60] (Appendix D, Table D2). Study populations in the RCTs and nonrandomized cohort studies overwhelmingly consisted of White males between the ages of 50–70 years (Appendix D, Table D2).[53-55,59-61,66,67,75] Comorbidities and concomitant medication use were reported infrequently in these studies (Appendix D, Table D3).[53-55,59-61,66,67]

With the exception of 1 RCT,[55] 1 cohort study,[75] and 5 SRs,[58,62,63,68,73] the FDA-approved Inspire UAS system was the only HGNS device of interest in the included publications. Other HGNS devices evaluated in the 1 RCT[55] and 5 SRs[58,62,63,68,73] were the aura6000 system (not FDA approved), the Genio System (newly FDA approved),[75] and the discontinued Apnex Medical HGNS system (not FDA approved).[77] In half of the RCTs and cohort studies,[53-55,59-61,66,67] the HGNS device was implanted prior to study enrollment,[53,60,61,67] while in the other half, the HGNS device was implanted after enrollment.[54,55,59,66,75] HGNS was compared against an inactive device in 2 RCTs[53,55] and subtherapeutic stimulation in 2 included RCTs.[60,61] In the 2 comparative nonrandomized cohort studies,[59,66] individuals who were CPAP intolerant had HGNS implanted and then were compared with individuals who tolerated CPAP (and continued to use it).[59] In the other study, individuals who were intolerant to CPAP and implanted with an HGNS device were compared with individuals who were intolerant to CPAP but not implanted with an HGNS device due to insurance coverage denial.[66]

All of the RCTs and nonrandomized cohort studies considered select adults with moderate to severe OSA eligible for study participation.[53-55,59-61,66,67,75] When considering mean baseline AHI, 6 of these studies enrolled participants with severe OSA (mean baseline AHI range of 32.0 to 37.9 events per hour).[54,55,59,61,66,67] The remaining 2 studies (both RCTs) randomized participants with mild OSA.[53,60] However, these 2 RCTs contained cohorts with an HGNS device implanted before randomization occurred and had mean baseline AHI data prior to implantation indicative of severe OSA.[53,60] Additionally, all of the studies eligible for effectiveness data (KQ1) and those that reported on OSA severity outcomes indicated the use of the Centers for Medicaid & Medicare Services (CMS)'s more stringent AHI4 criteria.[15,53,55,59-61,66]

When considering the FDA criteria for implantation of the Inspire UAS system, the majority of the primary studies[53-57,59-61,64-67] did not report eligibility criteria (BMI scores, AHI scores, and age), or in the case of the registry studies, search dates, that would allow for the current FDA indication for the Inspire UAS system, which was expanded in 2023 (Appendix D, Table D5). Only 2 identified studies allowed for the possibility of participants who met the expanded FDA criteria: 1 of the MAUDE registry trials, which searched for reports of adverse events through December 2023 and the ADHERE trial, an ongoing nonrandomized cohort study with interim publications that had evidence for the FDA to expand implantation criteria (final results have not yet been published).[30,67,74]

Table 4. Characteristics of Included Studies of Adults With OSA

AUTHOR, YEAR STUDY[a] NAME, NCT NUMBER ROB	ELIGIBLE OSA SEVERITY MEAN BASELINE AHI[b] AHI CRITERIA[c]	SAMPLE SIZE TOTAL FOLLOW-UP	HGNS DEVICE TYPE(S)	COMPARATOR	OUTCOMES
RCTs					
Dedhia, 2024[61,70,d] CARDIOSA-12 NCT03359096 Moderate	■ Moderate ■ Severe Severe: 33.1 (4.9) AHI4	N = 62 10 weeks	■ Inspire UAS	Subtherapeutic stimulation	■ OSA severity ■ SAEs

AUTHOR, YEAR STUDY[a] NAME, NCT NUMBER ROB	ELIGIBLE OSA SEVERITY MEAN BASELINE AHI[b] AHI CRITERIA[c]	SAMPLE SIZE TOTAL FOLLOW-UP	HGNS DEVICE TYPE(S)	COMPARATOR	OUTCOMES
Heiser, 2021[60] EFFECT NCT03760328 High	■ Moderate ■ Severe Mild: 8.3 (8.9) Severe: 32.2 (11.4) [prior to implantation] AHI4	N = 89 2 weeks	■ Inspire UAS	Subtherapeutic stimulation	■ Daytime sleepiness ■ OSA severity ■ QoL ■ SAEs
Schwartz, 2023[55,e] THN3 NCT02263859 High	■ Moderate ■ Severe Severe: 37.9(9.8) AHI4	N = 138 12–15 months[f]	■ aura6000	Device inactivation	■ Daytime sleepiness ■ OSA severity ■ QoL ■ SAEs
Woodson, 2014[53] STAR RCT NCT01161420 High	■ Moderate ■ Severe Mild: 7.2 (5.0), HGNS group; 7.6 (4.0), Inactive Group Severe: 31.3 (12.3), HGNS group; 30.1 (11.4), Inactive Group [prior to implantation] AHI4	N = 46 6 months[g]	■ Inspire UAS	Inactive device	■ Daytime sleepiness ■ OSA severity ■ QoL
COMPARATIVE COHORT STUDIES					
Heiser, 2023[59] Upper Airway Stimulation vs. Continuous Positive Airway Pressure NCT03756805 High	■ Moderate ■ Severe Severe: 33.9 (15.1), HGNS group; 36.8 (21.6), CPAP group AHI4	N = 126[h] 12 months	■ Inspire UAS	CPAP	■ Daytime sleepiness ■ OSA severity

AUTHOR, YEAR STUDY[a] NAME, NCT NUMBER ROB	ELIGIBLE OSA SEVERITY MEAN BASELINE AHI[b] AHI CRITERIA[c]	SAMPLE SIZE TOTAL FOLLOW-UP	HGNS DEVICE TYPE(S)	COMPARATOR	OUTCOMES
Mehra, 2020[66] ADHERE Comparative NRS NCT02907398 High	■ Moderate ■ Severe Severe: 33.7 (13.4), HGNS group; 34.9 (16.4), no treatment group AHI4	N = 350 Up to 24 months	■ Inspire UAS	No treatment	■ Daytime sleepiness ■ OSA severity ■ QoL ■ SAEs
NON-COMPARATIVE COHORT STUDIES					
Boon, 2018[67,69] ADHERE NCT02907398 High	■ Moderate ■ Severe Severe: 36.0 (15.7)	N = 1,849[i] 12 months	■ Inspire UAS	No comparator	■ SAEs
Strollo, 2014[54,71] STAR NRS, NCT01161420 High	■ Moderate ■ Severe Severe: 32.0 (11.8)	N = 126 5 years	■ Inspire UAS	No comparator	■ SAEs
Woodson, 2025[75,76] DREAM NCT03868618 High	■ Moderate ■ Severe Moderate: 28.0 (11.5) AHI4	N = 115 12 months	■ Genio System	No comparator	■ SAEs
REGISTRIES					
Bellamkonda, 2021[65] MAUDE database High	NA	N = 132 reports Data collection: May 2014–Sept 2019	■ Inspire UAS	NA	■ SAEs
Bentan and Nord, 2024[74] MAUDE database High	NA	N = 1,178 reports Data collection: July 2014–Dec 2023	■ Inspire UAS	NA	■ SAEs

AUTHOR, YEAR STUDY[a] NAME, NCT NUMBER ROB	ELIGIBLE OSA SEVERITY MEAN BASELINE AHI[b] AHI CRITERIA[c]	SAMPLE SIZE TOTAL FOLLOW-UP	HGNS DEVICE TYPE(S)	COMPARATOR	OUTCOMES
Bestourous, 2020[64] MAUDE database High	NA	N = 204 reports Data collection: Jan 1, 2000–May 31, 2020	■ Inspire UAS	NA	■ SAEs
Commesso, 2025[72] MAUDE database High	NA	N = 765 reports Data collection: Jan 1, 2000–Dec 1, 2022	■ Inspire UAS	NA	■ SAEs
Lorenz, 2023[57] TriNetX Research Network High	NA	N = 1,813 participants Data collection: 2014–2021	■ Inspire UAS	NA	■ SAEs
Moroco, 2024[56] Post-market surveillance data High	NA	N = 20,881 devices Data collection: Jan 1, 2018–Mar 31, 2022	■ Inspire UAS	NA	■ SAEs
SRs					
Certal, 2015[63,e] Moderate	NR	N = 6 studies (200 participants) NR	■ Apnex Medical HGNS ■ aura6000 ■ Inspire UAS	NA	■ SAEs
Chu, 2024[73,e] Moderate	NR	N = 14 studies (1,040 participants) NR	■ Apnex Medical HGNS ■ Inspire UAS ■ NR	NA	■ SAEs
Costantino, 2020[62,e] Moderate	NR	N = 12 studies (350 participants)	■ Apnex Medical HGNS ■ aura6000	NA	■ SAEs

AUTHOR, YEAR STUDY[a] NAME, NCT NUMBER ROB	ELIGIBLE OSA SEVERITY MEAN BASELINE AHI[b] AHI CRITERIA[c]	SAMPLE SIZE TOTAL FOLLOW-UP	HGNS DEVICE TYPE(S)	COMPARATOR	OUTCOMES
		No restrictions on follow-up	■ Inspire UAS		
Kompelli, 2019[58,e] High	NR	N = 16 studies (participant n, NR) NR	■ aura6000 ■ Inspire UAS	NA	■ SAEs
Wollny, 2024[68,e] Moderate	NR	N = 17 studies (1,962 participants) ≥ 6 months	■ Apnex Medical HGNS ■ aura6000 ■ Genio System ■ Inspire UAS	NA	■ SAEs
Zhou, 2022[52] Moderate	■ Moderate ■ Severe NA	N = 30 studies (9 studies on HGNS with 1,029 participants) ≥ 6 months	■ Inspire UAS	MMA	■ SAEs

Notes. a Or registry. b Evaluated as a events/hr and reported as in mean (SD). Indicates mean baseline AHI at study initiation for entire study cohort unless otherwise specified. c For studies reporting on OSA severity outcomes that meet eligibility for KQ1. d Missing baseline characteristics for this study were extrapolated from FDA criteria for implantation of the Inspire UAS given the US population. e This study includes non-FDA-approved device(s) and is not included in GRADE. f Primary comparative follow-up is 4 months. g Primary comparative follow-up is ~1 month. h Sample size after propensity matching. N = 227 total. i As of March 2020. The most recent publication contains N = 2,755 participants as this is an ongoing trial that has not yet published final results.
Abbreviations. AHI: apnea-hypopnea index; AHI4: evidence of a reduction in airflow of 30% or more for 10 seconds or longer accompanied by either an arousal or oxygen desaturation of 4% or more; CPAP: continuous positive airway pressure; CQ: contextual question; FDA: US Food and Drug Administration; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations; HGNS: hypoglossal nerve stimulator; KQ: key question; MAUDE: Manufacturer and User Facility Device Experience; MMA: maxillomandibular advancement; NA: not applicable; NCT: national clinical trial; NR: not reported; NRS: nonrandomized study; OSA: obstructive sleep apnea; QoL: quality of life; RCT: randomized controlled trial; ROB: risk of bias; SAEs: serious adverse events; SRs: systematic reviews: UAS: upper airway stimulation.

Quality of Life

Four high-RoB studies, including 3 RCTs[53,55,60] and 1 comparative cohort study,[66] assessed QoL outcomes (Table 5).

- All studies reported sleep-related QoL using the validated Functional Outcomes of Sleep Questionnaire (FOSQ), which measures the amount of sleep-related impairment individuals experience in 5 domains of daily living: activity levels, vigilance, intimacy and sexual relationships, productivity, and social outcomes).[78] The FOSQ has a possible score range of 5–20 points, with scores of 18 points or greater indicating normal sleep-related QoL, while a change of 1 or more points between assessments is considered to be clinically meaningful.[78,79]

- One study[55] of a non-FDA-approved device additionally reported general QoL outcomes as measured by the validated EuroQoL-5D visual analogue scale (EQ-5D VAS). The EQ-5D VAS has a possible score range of 0–100, with higher scores indicating higher self-rated overall health, but no minimum clinically important difference has yet been established for this scale.[80]

Table 5 summarizes QoL outcomes at the longest comparative follow-up timepoint and full outcome details are available in Appendix D, Table D6. For a detailed description of reported QoL scales see Appendix D, Table D1.

TABLE 5. QOL OUTCOMES AT LONGEST COMPARATIVE FOLLOW-UP

AUTHOR, YEAR STUDY NAME SAMPLE SIZE	STUDY DESIGN HGNS DEVICE CONTROL GROUP	TIME POINT	MEASURE	HGNS VS. CONTROL BETWEEN-GROUP ESTIMATE	*P* VALUE
FUNCTIONAL OUTCOMES OF SLEEP QUESTIONNAIRE (score range, 5–20 points; higher scores are better; MCID ≥ 1 point[78,79])					
Heiser, 2021[60] EFFECT N = 89	RCT[a,b] ■ Inspire UAS ■ Subtherapeutic stimulation	2 wk	Mean	17.0 vs. 14.9	*P* < .001
			Change from baseline	+0.2 vs. –1.9 MD, –2.1 (95% CI, 1.4 to 2.8)	*P* < .001
Mehra, 2020[66] ADHERE Comp. N = 350	Cohort study ■ Inspire UAS ■ No treatment	6 mos	Mean	17.1 vs. 12.4[b]	*P* < .001
Schwartz, 2023[55] THN3[c] N = 138	RCT ■ aura6000 ■ Inactive device	4 mos	Change from baseline	+5.3 vs. +0.6 MD, 4.7 (95% CI, 0.9 to 8.6)	NR
Woodson, 2014[53] STAR RCT N = 46	RCT[b] ■ Inspire UAS ■ Inactive device	1 mo	Mean	17.9 vs. 15.0 MD, 2.9 (95% CI, 0.8 to 5.0)	*P* = .008
			Change from baseline	0.0 vs. –2.3 MD, –2.3 (95% CI, –3.8 to –0.9)	*P* = .001
EUROQOL-5D: VISUAL ACUITY SCALE (score range, 0–100 points; higher scores are better; MCID not established)					
Schwartz, 2023[55] THN3[c] N = 138	RCT ■ aura6000 ■ Inactive device	4 mos	Change from baseline	+2.5 vs. +1.1 MD, 1.5 (95% CI, 0.3 to 2.6)	NR

Notes. See Appendix D, Table D6 for complete QoL outcomes data. a Crossover trial. b Withdrawal RCT. c This study investigated a non-FDA-approved device and is not included in GRADE.
Abbreviations. HGNS: hypoglossal nerve stimulation; MCID: minimal clinically important difference; MD: mean difference; mo(s): month(s); QOL: quality of life; RCT: randomized controlled trial; wk: week.

Sleep-Related QoL

Three studies that reported sleep-related QoL, including 2 RCTs[53,60] and 1 cohort study,[66] investigated the FDA-approved Inspire UAS system (Table 5). Across these studies, HGNS groups had significantly higher mean FOSQ scores, indicating better sleep-related QoL, compared with nonsurgical control groups at final study follow-up ($P < .01$ for all).[53,60,66] Follow-up FOSQ scores in the HGNS groups were indicative of mild sleep-related QoL impairment (score range, 17.0–17.9 points) whereas scores in the control groups

indicated moderate impairment (score range, 12.4–15.0 points); differences in mean scores between study groups exceeded the established MCID (i.e., ≥ 1 point change in FOSQ score).[53,60,66]

- Control group participants in the 2 withdrawal RCTs[53,60] additionally exhibited statistically and clinically significant short-term reductions in sleep qualty after their Inspire UAS system devices were inactivated or adjusted to deliver subtherapeutic stimulation levels at baseline as compared with the groups who received continuous active HGNS therapy ($P < .001$ for both; Table 5).
- In the cohort study,[66] participants who received HGNS had significantly higher mean FOSQ10 (short-form) scores at 6 months compared with the no-treatment controls who did not receive HGNS due to insurance coverage denial (17.1 vs. 12.4 points; $P < .001$).[66] The FOSQ10 uses the same scoring scale as the long-form version and has been shown to have a high degree of interrater reliability.[78]

One withdrawal RCT (THN3)[55] investigated sleep-related QoL outcomes for the aura6000, a non-FDA-approved HGNS device (Table 5). As compared with the other RCTS, participants in this study were implanted with an HGNS device *after* enrollment and baseline assessment and participants were randomized after healing and device adjustment was complete.[55] At the primary 4-month follow-up, the active HGNS group reported significantly greater improvements in sleep-related QoL from baseline compared with the inactive device group (FOSQ: MD, 4.7 points [95% CI, 0.9 to 8.6]).[55] The mean difference in FOSQ between the groups also exceeded the threshold for clinical significance (i.e., ≥ 1 point change).[55,79]

General QoL

The THN3 trial,[55] which investigated the non-FDA-approved aura6000 HGNS device, was the only study that reported a general patient-reported QoL measure (Table 5). At the primary 4-month follow-up, the active HGNS group reported significantly greater improvement in general health status from baseline compared with the inactive device group (EQ-5D visual analogue scale: MD, 1.5 points [95% CI, 0.3 to 2.6]).[55] Although the mean difference in EQ-5D change between the groups was statistically significant, we were unable to assess whether the changes were clinically significant as there is no widely accepted EQ-5D MCID.

Device-Related Serious Adverse Events

Nineteen studies (in 21 publications), including 3 RCTs,[55,60,61] 1 comparative cohort study,[66] 3 noncomparative cohort studies (in 5 publications; 1 that was identified during the Genio approval update),[54,67,69,71,75,76] 6 registry studies (2 of which were identified in the updated database search),[56,57,64,65,72,74] and 6 SRs (1 of which was identified in the updated database search),[52,58,62,63,68,73] assessed device-related serious adverse events (SAEs) in adults with moderate to severe OSA. Thirteen of the studies were rated as having high risk of bias[54-58,60,64-67,72,74,75] and 6 as moderate risk of bias[52,61-63,68,73] due to concerns regarding conflicts of interest, selection bias, reporting bias and, for the SRs, methods and insufficient integration of risk of bias in study conclusions. Thirteen studies reported only on FDA-approved HGNS devices (i.e., Inspire UAS system, Genio System),[52,54,56,57,60,61,64-67,72,74,75] 5 SRs also included non-FDA-approved devices (i.e., aura6000, Apnex Medical HGNS system),[58,62,63,68,73] and 1 RCT (THN3) only evaluated a non-FDA-approved device (i.e., aura6000).[55]

In general, device-related SAEs were infrequently reported in the publications eligible for KQ2 (harms).[52,54-58,60-67,69,71-75] Device explants (n = 12 studies)[54-57,63,65,67,69,71-74] and device revisions (n = 12

studies)[52,54-57,64,66,67,69,71-73] were the most frequently reported device-related SAEs; however, rates of these events were low:

- In the 4 studies that reported on total device revisions for participants using the Inspire UAS system, the rate of device revisions ranged from 0.4% to 6.3% of study participants.[54,57,66,71,75]
- In the 4 studies that reported on total device explants for participants using the Inspire UAS system, the rate of device explants ranged from 0.05% to 5.2% of study participants.[54,57,67,69,71,75]
- The most frequently reported reasons for device revisions were discomfort (including pain)[54,64,66,68,71-73] or technical issues with the device.[54,56,64,68,71,73,75] The most frequently reported reason for device explant was infection.[54,56,65,68,71-74] However, not all studies reported on reasons for device explants or revisions.

Beyond device explants and device revisions, study authors reported infections,[57,67,69] pneumothorax,[57,67,69,72,74] and total SAEs[54,62,64,67,69,75] in at least 2 of the eligible studies (Appendix D, Table D7). Additional device-related SAEs include: stroke,[60] pleural effusion on the day of surgery,[57] treatment related SAEs,[55] serious device-related AEs,[52] hematomas,[67,69,75] obstructive events,[67,69] bleeding from the nose after intubation,[75] temporary hypoglossal nerve paralysis,[75] device extrusion,[75] anesthesia-related intraoperative arrest,[67,69] one death (cause unknown),[61] inability to implant the device on the right side (a separate procedure was conducted on the left side),[67,69] external device malfunction,[58] and internal device malfunction.[58,75] In one study, it was unclear if serious complications arose from the external and internal device malfunctions as this was not reported.[58] Study authors also have broadly reported "other" SAEs.[54,67,69,71,75]

There was significant heterogeneity in study design and categorization of SAEs across the included studies. For example, device explants and device revisions were reported as a combined outcome[55] and separately.[64] Additionally, some device-related SAEs were reported both separately and as justification for revisions or explants. For example, infection was reported as a distinct outcome in 2 studies,[57,67,69] as a reason for device explant in 2 studies,[56,65] and as a reason for device revision in 1 study.[64] Different units of analysis (i.e., participants, reports, devices, events) also were used to report rates of SAEs.

Inspire UAS Pulse Generator Class 1 Recall

In June 2024, the FDA issued a class 1 recall (the most serious recall type) for the Inspire IV implantable pulse generator, citing a manufacturer defect. This recall includes 32 devices of the Model 3028 and may require revision surgery to correct. At the time of writing this report (including during the updated database search), no injuries or death related to this recall were reported by the FDA.[37] Therefore, it is unlikely that the included studies reflect SAEs that may have occurred due to this manufacturing defect. Such SAEs may be reported in future studies, if these occur.

OSA Severity

Six studies, including 4 RCTs[53,55,60,61] and 2 comparative cohort studies,[59,66] assessed OSA severity outcomes as measured by select polysomnography indices, specifically AHI, RDI, REI, and ODI (Table 6).

Five studies were assessed as having high RoB[53,55,59,60,66] and 1 was moderate.[61]

- All 6 studies reported some measure of AHI (i.e., the frequency of apneas and hypopneas per hour of sleep); all studies[53,55,59-61,66] used the AHI4 criteria to define hypopneas (i.e., airflow reductions of ≥ 30% for at least 10 seconds with an oxygen desaturation of ≥ 4% or greater).
- Four studies[53,55,60,66] additionally reported some measure of ODI (i.e., the frequency of clinically significant oxygen desaturations per hour of sleep) and used the ODI4 criteria to define clinically significant events (i.e., desaturations ≥ 4% lasting for at least 10 seconds).
- AHI and ODI use a 3-category OSA severity grading system of mild (≥ 5 to < 15), moderate (≥ 15 to < 30), and severe (≥ 30); individuals with scores less than 5 are not considered to have OSA.[79]
- A change of 5 or more events per hour between assessments is considered clinically meaningful for AHI and ODI measures.[79]
- No studies reported RDI or REI outcomes.

Table 6 summarizes OSA severity outcomes at the longest comparative follow-up timepoint and full outcome details are available in Appendix D, Table D8. For a detailed description of OSA severity polysomnography measures, see Appendix D, Table D1.

TABLE 6. OSA SEVERITY AT LONGEST COMPARATIVE FOLLOW-UP

AUTHOR, YEAR STUDY NAME SAMPLE SIZE	STUDY DESIGN HGNS DEVICE CONTROL GROUP	TIME POINT	MEASURE	HGNS VS. CONTROL BETWEEN-GROUP ESTIMATE	*P* VALUE
APNEA-HYPOPNEA INDEX (events per hour; lower scores are better; MCID ≥ 5 events per hour[79])					
Dedhia, 2024[61] CARDIOSA-12 N = 62	RCT[a,b] ■ Inspire UAS ■ Subtherapeutic stimulation	10 wk	Mean	18.1 vs. 23.0 MD, −4.9 (95% CI, −8.8, to −1.0)	NR
Heiser, 2021[60] EFFECT N = 89	RCT[a,b] ■ Inspire UAS ■ Subtherapeutic stimulation	2 wk	Change from baseline	+0.6 vs. +16.1 MD, −15.5 (95% CI, −18.3 to −12.8)	*P* < .001
Heiser, 2023[59] N = 126	Cohort study ■ Inspire UAS ■ CPAP therapy	12 mo	Mean	8.1 vs. 6.6	*P* = .08
			Change from baseline	−20.3 vs. −30.9	*P* = .08
Mehra, 2020[66] ADHERE Comp. N = 350	Cohort study ■ Inspire UAS ■ No treatment	6 mo	Mean	14.7 vs. 26.8	*P* < .001
			Change from baseline	−19.1 vs. −8.1	*P* < .001
Schwartz, 2023[55] THN3[c] N = 138	RCT ■ aura6000 ■ Inactive device	4 mo	Mean	24.1 vs. 32.0	*P* < .002[d]

AUTHOR, YEAR STUDY NAME SAMPLE SIZE	STUDY DESIGN HGNS DEVICE CONTROL GROUP	TIME POINT	MEASURE	HGNS VS. CONTROL BETWEEN-GROUP ESTIMATE	*P* VALUE
Woodson, 2014[53] STAR RCT N = 46	RCT[b] ■ Inspire UAS ■ Inactive device	1 mo	Mean	8.9 vs. 25.8 MD, –16.9 (95% CI, –24.7 to –9.0)	*P* < .001
			Change from baseline	+1.7 vs. +18.2 MD, –16.4 (95% CI, –23.7 to –9.2)	*P* < .001
OXYGEN DESATURATION INDEX (events per hour; lower scores are better; MCID ≥ 5 events per hour[79])					
Heiser, 2021[60] EFFECT	RCT[a,b] ■ Inspire UAS ■ Subtherapeutic stimulation	2 wk	Change from baseline	+0.6 vs. +12.7 MD, -12.2 (95% CI, –14.8 to –9.6)	*P* < .001
Mehra, 2020[66] ADHERE Comp. N = 350	Cohort study ■ Inspire UAS ■ No treatment	6 mo	Mean	14.1 vs. 25.5	*P* < .001
Schwartz, 2023[55] THN3[c] N = 138	RCT ■ aura6000 ■ Inactive device	4 mo	Mean	26.3 vs. 33.8	*P* < .002[d]
Woodson, 2014[53] STAR RCT N = 46	RCT[b] ■ Inspire UAS ■ Inactive device	1 mo	Mean	8.0 vs. 23.0 MD, –15.1 (95% CI, –22.7 to –7.5)	*P* < .001
			Change from baseline	+1.6 vs. +17.0 MD, -15.4 (95% CI, –22.1 to –8.7)	*P* < .001

Notes. See Appendix D, Table D8 for complete OSA severity outcomes data. [a] Crossover RCT. [b] Withdrawal RCT. [c] This study investigated a non-FDA-approved device and is not included in GRADE. [d] The *P*- values for means were not reported in study text and were ascertained through personal email communication with the THN3 trial authors on August 2, 2024.
Abbreviations. AHI: apnea-hypopnea index; CFB: change from baseline; CPAP: continuous positive airway pressure; HGNS: hypoglossal nerve stimulation; MCID: minimal clinically important difference; MD: mean difference; mo: month; NR: not reported; ODI: oxygen desaturation index; OSA: obstructive sleep apnea; RCT: randomized controlled trial; RR: relative risk; wk: week.

AHI outcomes

Five studies that reported AHI4 outcomes, including 3 RCTs and 2 cohort studies, investigated the FDA-approved Inspire UAS system (Table 6). In the 4 studies with inactive comparators (i.e., subtherapeutic stimulation,[60,61] inactive device,[53] no treatment[66]), HGNS groups had significantly lower OSA severity compared with controls across all follow-up timepoints (range, 2 weeks to 6 months) as evidenced by statistically significant between-group differences in mean AHI4 scores[53,61,66] and changes from baseline indicating comparatively lower AHI scores in treatment groups[53,60,66] (Table 6).

- Among the studies that reported mean AHI, HGNS groups in the STAR RCT and ADHERE comparative cohort study had follow-up scores indicating mild OSA severity compared with moderate severity in the control group[53,66]; both study groups in the CARDIOSA-12 trial had

moderate-severity AHI4 scores (Table 6).[61] No study groups had a follow-up AHI4 score below the clinical threshold for OSA (i.e., < 5 events per hour).

- Control group participants in the EFFECT and STAR withdrawal RCTs exhibited clinically significant increases in AHI4 (i.e., ≥ 5 events per hour[79]) after their HGNS devices were inactivated or adjusted to deliver subtherapeutic stimulation levels at baseline, and also as compared within the groups who received continuous HGNS therapy ($P < .001$ for both; Table 6).[53,60] However, the between-group difference in mean AHI4 in the CARDIOSA-12 trial (–4.9 events per hour) was just below the threshold for clinical significance.[61]
- In the EFFECT RCT, participants in the HGNS group were significantly more likely to achieve AHI4 scores indicating mild OSA severity (i.e., < 15 events per hour) at 1-week pre-crossover assesssment period compared with subtherapeutic stimulation controls (73.3% vs. 29.5%; $P < .001$).[60] HGNS group participants also appeared to be more likely to have AHI4 scores below 10 and 5 events per hour, but tests of significance were not reported (Appendix D, Table D8).

In the 12-month cohort study (N = 126) that compared HGNS as a second-line OSA therapy in patients with CPAP intolerance and CPAP therapy as a first-line therapy in treatment-naïve patients,[59] there was no significant difference between groups in terms of change in AHI4 from baseline ($P = .08$), although both groups experienced a clinically significant reduction in AHI4, suggesting both therapies similarly improved OSA severity (Table 6).

- There were also no significant between-group differences in the rate of participants achieving AHI4 scores indicating mild OSA severity (< 15 events per hour) or scores below the clinical threshold for OSA (< 5 events per hour); however, the proportion of participants achieving these AHI4 thresholds was high in both groups (> 80% and > 50%, respectively).[59]

One study, the THN3 trial[55] (N = 138), reported AHI4 findings for a non-FDA-approved HGNS device (aura6000). At the primary 4-month follow-up, participants in the HGNS group had significantly lower mean AHI4 scores compared with the inactive device controls ($P < .002$), but scores in the HGNS group were still indicative of moderate OSA versus severe OSA in the control group (Table 6).[55]

- In accord with lower mean scores, the HGNS group was significantly more likely to have achieved the study-defined AHI4 treatment response threshold (i.e., ≥ 50% reduction and < 20 events per hour) compared with the inactive device group (52.3% vs. 19.6%; $P < .001$).[55]

ODI outcomes

Three studies (2 RCTs[53,60] and 1 cohort study[66]) that reported ODI outcomes investigated the Inspire UAS system. Across these studies, HGNS groups exhibited significantly lower OSA severity compared with controls across all follow-up timepoints (range, 2 weeks to 6 months) as evidenced by statistically significant between-group differences in mean ODI4 scores[54,66] and changes from baseline indicating comparatively lower ODI4 scores in treatment groups[53,60] ($P < .001$ for all; Table 6).

- In the single study that reported mean ODI4 at final follow-up,[66] participants in the HGNS group had mean scores indicating mild OSA at 6 months whereas participants in the no-treatment control group had scores indicating moderate OSA (Table 6). No study groups had a follow-up ODI4 score below the clinical threshold for OSA (< 5 events per hour[79]).
- Control group participants in the EFFECT and STAR withdrawal RCTs exhibited clinically significant increases in ODI4 (≥ 5 events per hour) after their HGNS devices were inactivated or

adjusted to deliver subtherapeutic stimulation levels at baseline as compared with in the groups who received continuous HGNS therapy ($P < .001$ for both; Table 6).[53,60]

One study, the THN3 trial,[55] reported ODI4 findings for a non-FDA-approved HGNS device (aura6000). At the primary 4-month follow-up, participants in the HGNS group had significantly lower mean ODI4 scores compared with the inactive device controls ($P < .002$), but scores in the HGNS group were still indicative of moderate OSA, versus severe in the control group (Table 6).[55]

- The HGNS group was significantly more likely to have achieved an ODI4 score reduction of 25% or more at 4 months compared with the inactive device group (62.5% vs. 41.3%; $P = .02$).[55]

RDI Outcomes

No studies reported RDI outcomes.

REI Outcomes

No studies reported REI outcomes.

Daytime Sleepiness

Five high-RoB studies, including 3 RCTs[53,55,60] and 2 comparative cohort studies,[59,66] assessed daytime sleepiness outcomes. All studies used the Epworth Sleepiness Scale (ESS), a validated self-report instrument that evaluates an individual's likelihood of falling asleep during 8 common daytime activities, to measure differences between groups.[81] The ESS has a possible score range of 0 to 24 points, with scores greater than 10 points indicating excessive daytime sleepiness; a change of 2 or more points between assessments is considered to be clinically meaningful.[79,81] Table 7 summarizes daytime sleepiness outcomes at the longest comparative follow-up timepoint, and full outcome details are available in Appendix D, Table D9. For a detailed description of the ESS see Appendix D, Table D1.

TABLE 7. DAYTIME SLEEPINESS OUTCOMES AT LONGEST COMPARATIVE FOLLOW-UP

AUTHOR, YEAR STUDY NAME SAMPLE SIZE	STUDY DESIGN HGNS DEVICE CONTROL GROUP	TIME POINT	MEASURE	HGNS VS. CONTROL BETWEEN-GROUP ESTIMATE	*P* VALUE
EPWORTH SLEEPINESS SCALE (score range, 0–24 points; lower scores are better; MCID ≥ 2 points[79,81])					
Heiser, 2021[60] EFFECT N = 89	RCT[a,b] ■ Inspire UAS ■ Subtherapeutic stimulation	2 wk	Change from baseline	+0.2 vs. +3.5 MD, −3.3 (95% CI, −4.4 to −2.2)	$P < .001$
Heiser, 2023[59] N = 126	Cohort study ■ Inspire UAS ■ CPAP therapy	12 mo	Mean	7.5 vs. 10.8	$P = .27$
			Change from baseline	−8.0 vs. −3.9	$P = .04$
Mehra, 2020[66] ADHERE Comp. N = 350	Cohort study ■ Inspire UAS ■ No treatment	6 mo	Mean	7.2 vs. 12.8	$P < .001$
			Change from baseline	−5.1 vs. +1.8	$P < .001$
Schwartz, 2023[55] THN3[c]	RCT ■ aura6000 ■ Inactive device	4 mo	Change from baseline	−4.4 vs. −1.1 MD, −3.3 (95% CI, −4.8 to −1.9)	NR

AUTHOR, YEAR STUDY NAME SAMPLE SIZE	STUDY DESIGN HGNS DEVICE CONTROL GROUP	TIME POINT	MEASURE	HGNS VS. CONTROL BETWEEN-GROUP ESTIMATE	*P* VALUE
N = 138					
Woodson, 2014[53] STAR RCT N = 46	RCT[b] ■ Inspire UAS ■ Inactive device	1 mo	Mean	5.6 vs. 10.0 MD, –4.5 (95% CI, –7.5 to –1.4)	*P* = .005
			Change from baseline	–0.3 vs. +3.8 MD, –4.2 (95% CI,–6.4 to –2.0)	*P* < .001

Notes. See Appendix D, Table D9 for complete daytime sleepiness outcomes. [a] Crossover trial. [b] Withdrawal RCT. [c] This study investigated a non-FDA-approved device and is not included in GRADE.
Abbreviations. CPAP: continuous positive airway pressure; HGNS: hypoglossal nerve stimulation; MCID: minimal clinically important difference; MD: mean difference; mo: month; NR: not reported; RCT: randomized controlled trial; RR: relative risk; wk: week.

Four studies that reported daytime sleepiness outcomes, including 2 RCTs[53,60] and 2 cohort studies,[59,66] investigated the FDA-approved Inspire UAS system. In 3 studies with inactive comparators (i.e., subtherapeutic stimulation[60] inactive device,[53] no treatment[66]), HGNS groups reported significantly less daytime sleepiness compared with controls across all follow-up timepoints (range, 2 weeks to 6 months) as indicated by significantly lower mean ESS scores or changes from baseline indicating comparatively lower scores ($P < .01$). Mean ESS scores in the HGNS groups were below the excessive sleepiness threshold (> 10 points[81]) whereas mean scores in the inactive comparator groups were at or above the threshold (Table 7).[53,60,66]

In 1 cohort study (N = 126) with an active comparator (CPAP therapy),[59] there was no significant difference in mean ESS scores at 12 months (7.5 vs. 10.8 points; $P = .27$). Although both study groups reported a clinically significant reduction in ESS scores (≥ 2 points),[81] the HGNS group reported a significantly greater improvement in subjective daytime sleepiness compared with the CPAP group ($P = .04$; Table 7).[59] Notably, only the HGNS group experienced a clinically and statistically significant change in daytime sleepiness from baseline ($P < .001$).[59]

One study, the THN3 trial[55] (N = 138), reported AHI findings for a non-FDA-approved HGNS device (aura6000). At the primary 4-month follow-up, participants in the HGNS group reported a statistically and clinically greater reduction in ESS compared with controls (MD, –3.3 [95% CI, –4.8 to –1.9])[55]; however, mean scores (baseline or follow-up) were not reported so the effect of the aura6000 on daytime sleepiness remains unclear.

Major Adverse Cardiac Events

No eligible studies reported comparative MACE outcomes.

Review Summary and Limitations

There is a reasonable evidence base from multiple RCTs and comparative prospective cohort studies regarding the effectiveness of HGNS devices for the treatment of moderate to severe OSA in adults and a substantial evidence base regarding associated device-related harms from SRs, large registry studies, and

other prospective nonrandomized studies. In the following summaries, low levels of confidence indicate that if new information from additional studies were published, our understanding of the evidence would likely change. Moderate levels of confidence indicate that it is unlikely, yet possible, that data from new studies would change our understanding of the evidence.

Evidence Summary

We identified 21 eligible studies (17 from our initial search, 3 from our updated database search in 2025, and 1 from the 2026 Genio approval update) that assessed the effectiveness and harms of HGNS devices in adults with moderate to severe OSA. Of these, 15 studies had evidence regarding FDA-approved HGNS devices and were included in the GRADE confidence ratings. The other 6 studies also assessed HGNS devices that have not yet been approved by the FDA and were excluded from GRADE. While the Genio approval update resulted in the inclusion of 1 additional study reporting on harms, the findings of this study did not alter the conclusions of this coverage guidance.

Effectiveness

Five studies (3 RCTs and 2 comparative cohort studies) investigated the effectiveness of the Inspire UAS system as compared with nonsurgical control groups in adults with moderate to severe OSA. All 3 RCTs compared HGNS with controls (either subtherapeutic stimulation or an inactive device) in participants who were implanted with an HGNS device and demonstrated a clinical response before enrollment. Participants in the cohort studies did not begin HGNS therapy until after enrollment. One cohort study compared HGNS with no treatment among a group of people who met the clinical criteria for HGNS, and 1 cohort study compared HGNS therapy among participants with CPAP intolerance versus a CPAP therapy among participants who were responsive to first-line CPAP therapy.

We have low confidence that HGNS therapy:

- **Improves sleep-related QoL compared with inactive controls**. This assessment was based on consistent findings of statistically and clinically higher scores on validated QoL scales in HGNS groups compared with controls (2 RCTs and 1 cohort study; N = 485).
- **Improves OSA severity compared with inactive controls and has similar benefit to CPAP therapy.** This assessment was based on consistent findings of statistically and clinically lower AHI4 and ODI4 scores from polysomnography in HGNS groups compared with controls (3 RCTs and 1 cohort study; N = 547), and no difference in mean scores between participants treated with second-line HGNS therapy versus first-line CPAP therapy (1 cohort study; N = 126).
- **Improves daytime sleepiness compared with inactive controls and has similar benefit to CPAP therapy.** This assessment was based on consistent findings of statistically and clinically lower scores on the validated ESS scale in HGNS groups compared with controls (2 RCTs and 1 cohort study; N = 485), and no difference in mean scores between participants treated with second-line HGNS therapy versus first-line CPAP therapy (1 cohort study; N = 126).
- The low-confidence ratings for these outcomes were due primarily to risk of bias concerns (e.g., limited methods reporting, selection bias, conflicts of interest) and indirectness from heterogeneity in study design and assessment timepoints, as well as limited generalizability due to more restrictive study enrollment criteria relative to the current indication for FDA-approved HGNS devices.

No eligible studies reported:

- General or overall measures of QoL
- Comparative MACE outcomes

Harms

Thirteen studies (2 RCTs, 4 cohort studies, 6 registry studies, and 1 SR) reported device-related SAEs for FDA-approved HGNS devices.

- We have **moderate confidence of the scope and magnitude of device revisions and explants** and **low confidence of the scope and magnitude of other device-related SAEs** in individuals with moderate to severe OSA who are treated with HGNS.
- These ratings are based upon generally low rates of reported device-related SAEs and availability of large sample sizes. However, there are concerns with risk of bias for the studies reporting these outcomes, specifically reporting bias and conflicts of interest. While we have some increased confidence in the scope and magnitude of device explants and revisions based on the available evidence, we are less confident in the scope and magnitude of other device-related SAEs, given additional concerns regarding generalizability to a Medicaid population.

Review Limitations

Although our evidence reviews are conducted using rigorous and systematic methods, we often encounter limitations in the literature or in the review design that are important to acknowledge. Below we describe limitations that broadly affected our GRADE ratings.

- **Discrepancy between enrolled study populations and current HGNS eligibility criteria:** As of 2023, FDA eligibility criteria for HGNS therapy with the Inspire UAS devices includes adults with AHI scores up to 100 events per hour and a BMI warning for patients with BMIs greater than 40 kg/m^2.[30] However, studies that assessed efficacy outcomes had lower AHI and BMI enrollment thresholds that more closely aligned with the initial 2014 Inspire UAS system FDA indication (AHI > 15 to ≤ 65 events per hour) and the lower BMI warning (BMI greater than 32) (Appendix D, Table D5).[30] Moreover, no eligible efficacy studies reported relevant subgroup analyses by AHI or BMI and current evidence for HGNS performance among participants with higher OSA severity scores, and higher BMI is limited to uncontrolled, nonrandomized studies.
- **Substantial industry-related conflicts of interest:** All primary studies received industry funding and many study authors reported receiving financial disbursements or study support from HGNS manufacturers, which may have increased the risk of publication bias. A 2021 retrospective analysis demonstrated a significant relationship between author conflict of interest, specifically with Inspire Medical Systems, Inc., and published position on HGNS.[82] The analysis demonstrated that 80% of authors with an Inspire Medical Systems, Inc., conflict of interest published articles with favorable views on HGNS, whereas only 10% of authors with an Inspire Medical Systems, Inc., conflict of interest published articles with neutral views on HGNS ($P < .004$).[82]
- **Highly selected study populations:** Study populations in the RCTs were limited to participants who received an HGNS device and demonstrated either tolerability or a positive treatment response before randomization. In multiple studies, participants were required to demonstrate a 50% or greater reduction in baseline AHI and have AHI below 20 events per hour before enrollment, generally exceeding the established threshold for clinically meaningful change in AHI

(≥ 5 events per hour). The substantial selection bias likely present in these studies may have resulted in larger effect sizes than would be experienced in clinical settings.

- **Study design and reporting heterogeneity:** There was substantial heterogeneity in the studies, including heterogeneity in study design and reported device-related SAEs specific to the studies eligible for harms evaluation. Important design variations included HGNS implantation timing differences for study participants (pre- or post-enrollment), RCT types (e.g., crossover studies, withdrawal), and length of follow-up with limited consistency between studies (follow-up range: 2 weeks to 12 months). These study design variations limited our ability to make direct outcome comparisons and the heterogeneity in reported device-related SAEs limited our ability to understand the scope and magnitude of this outcome.
- **Lack of long-term follow-up:** FDA-approved HGNS devices are intended to last for almost a decade, with component replacements potentially occurring throughout a patient's lifetime; yet, there was a lack of long-term comparative data for efficacy outcomes (≤ 12 months). However, 5-year results from the uncontrolled STAR NRS cohort study suggest the effectiveness of the Inspire UAS system observed in comparative studies, including the related STAR RCT, may be durable.[71] In this study, significant beneficial treatment effects were observed for OSA severity (AHI4 rate), sleep-related QoL (FOSQ scores), and daytime sleepiness (ESS scores) among trial participants at 12 months compared with baseline.[71] When assessed at the 5-year follow-up, the magnitude of these treatment effects persisted.[71] Additionally, an analysis adjusted for losses to follow-up found most participants (66%) continued to meet the composite AHI4 treatment response criteria at 5 years (i.e., reduction of ≥ 50% to below 20 events per hour) and maintain normal FOSQ and ESS scores (67% and 78%, respectively).[71] Long-term, open-label assessments of participants implanted with the Genio System are ongoing.[83]

Contextual Questions

We identified 2 studies that informed the contextual questions, both of which were identified in our initial database search.[68,84]

- **2025 update:** We did not identify any new evidence to inform the contextual questions in our updated database search
- **Genio approval update:** We did not identify any new evidence to inform the contextual questions during the Genio approval update.

CQ1. Key Clinical Endpoints From SRs of HGNS

We reviewed published literature and identified 1 SR, including 17 studies (1 RCT and 16 nonrandomized studies) of all available HGNS devices with data on 1,962 participants, that evaluated key clinical endpoints for OSA (all-cause mortality).[68] This SR was assessed as having a moderate risk of bias due to potential industry-related COI and limited statistical methods reporting. Among patients receiving HGNS therapy, 7 deaths were reported over a mean follow-up duration of 17.5 months (SD, 16.9), resulting in a weighted all-cause mortality rate of 0.01% (95% CI, 0.0 to 0.2).[68] Deaths were attributed to cancer (n = 3), cardiac events (n = 3), and homicide (n= 1), and none were related to HGNS therapy.[68] Importantly, follow-up durations were 5 years or less, a short time period to assess OSA-related mortality, and none of the studies were specifically powered to detect this outcome.

We did not identify SRs reporting any other OSA-relevant clinical endpoints, such as fatigue-related injuries (e.g., motor vehicle crashes), blood pressure control or use of antihypertensive medication, or rates of major adverse cardiac events.

CQ2. Comparative Effectiveness of HGNS Versus Other OSA Surgeries

We did not identify any RCTs comparing the effectiveness of HGNS with other OSA surgeries.

CQ3. Cost and Cost-Effectiveness of HGNS

We prepared this section in anticipation of the implementation of Senate Bill 1508 of the 2024 Oregon legislative session, effective January 1, 2025.[85] As such, we did not consider or extract any outcomes based on quality adjusted life years (QALY) and only extracted other cost measures anticipated to be compliant with the new law.[85] We reviewed published literature and identified 1 study that estimated such measures.[84]

In that study, the investigators developed a US-based model to estimate the costs and outcomes of the Inspire UAS system, as compared with no treatment, in individuals with OSA.[84] For costs, the study estimated the incremental costs of HGNS versus no treatment from a health care payer perspective.[84] This considered the costs of HGNS implantation, device and battery replacement every 11 years, and annual office visits.[84] For outcomes, the study looked at 3 key clinical endpoints: risk of myocardial infarction (heart attack), risk of stroke, and risk of motor vehicle collisions.[84] As available RCTs and comparative cohort studies on HGNS do not directly study or report the effect of HGNS on these outcomes, estimates of the effects of HGNS versus no treatment for the model were informed by observational and other related studies.[84] The study examined both costs and outcomes at a 10-year and a lifetime time horizon.[84] Both costs and outcomes were discounted at 3% per year.[84]

The only available measure for extraction was the estimated cost per outcome averted with HGNS.[84] The study did not report a full net cost analysis.[84] We extracted estimated cost per myocardial infarction averted, cost per stroke averted, and cost per motor vehicle collision averted. We adjusted the results from 2013 United States Dollars (USD) reported by the study to June 2024 USD, using the Consumer Price Index Inflation Calculator from the US Department of Labor, Bureau of Labor Statistics.[86] Table 8 shows the cost per outcome for the 3 identified outcomes at both time horizons.

TABLE 8. ESTIMATED COST PER OUTCOME AVERTED FROM A COST-EFFECTIVENESS STUDY OF HGNS

OUTCOME	ABSOLUTE RISK REDUCTION FOR HGNS VS. NO TREATMENT (A)	INCREMENTAL COST OF HGNS (B)	ESTIMATED COST PER OUTCOME AVERTED (B/A)
10-YEAR TIME HORIZON			
Myocardial infarction	0.050	$33,741	$674,820
Stroke	0.017	$33,741	$1,984,765
Motor vehicle collisions	0.313	$33,741	$107,799

LIFETIME TIME HORIZON			
Myocardial infarction	0.092	$58,602	$636,978
Stroke	0.009	$58,602	$6,511,333
Motor vehicle collisions	0.663	$58,602	$88,389

Notes. Outcome rates and costs are extracted from Pietzsch, et al.,[84] and inflation-adjusted to June 2024 USD using the Consumer Price Index.[86]
Abbreviations. HGNS: hypoglossal nerve stimulator.

This study has several limitations, as reported by the study investigators.[84] First, model inputs represent best estimates from observational and other related studies, as opposed to direct results from RCTs and comparative cohort studies of HGNS.[84] For example, the estimates of reduction in cardiovascular risk were taken from an observational study examining the association between AHI and cardiovascular risk.[84] This approach inherently assumes that reducing AHI through HGNS treatment will causally reduce cardiovascular risk, which has not been directly demonstrated. Second, by definition, model-based studies project outcomes using a simplified form of the disease process.[84] Third, a key model assumption is that long-term results can be estimated from short-term study findings.[84] Another related key assumption is that adherence remains high through an individual's lifetime (86% in the base case analysis).[84] Fourth, the study estimated outcomes based on the STAR study,[54] which may not be generalizable to the broader Medicaid-insured population potentially eligible to receive HGNS.[84] Finally, estimates of the cost of HGNS implantation were derived from clinical practice experience at the time (i.e., the percentage implanted in the outpatient versus inpatient setting) and would likely change if practice patterns changed.[84]

Ongoing Studies

We identified ongoing studies with searches of the ClinicalTrials.gov registry conducted in May 2024. Results of the ongoing studies search are summarized below. See Appendix D, Table D10 for individual study characteristics.

- **2025 update:** We evaluated all previously identified ongoing studies during our database search update in July 2025 and repeated our search for new ongoing studies. Of the 7 identified ongoing studies, none had been published and no new eligible ongoing studies were identified.
- **Genio approval update:** 1 previously identified ongoing study of the Genio System published primary 12-month study results in November 2025 (i.e., the DREAM study[75]); however, the long-term extension phase of this study is still ongoing with an estimated study completion date of February 2028. We additionally identified 1 new ongoing prospective nonrandomized post-approval study (i.e., BREATHE), which was mandated by the FDA for ongoing approval of the Genio System.

There are currently 8 ongoing studies of upper airway nerve stimulation for adults with moderate or severe OSA that are likely to meet the scoped inclusion criteria for this review, including:

- 1 RCT[87]
- 2 registry studies[88,89]
- 5 prospective nonrandomized studies (NRS), including 1 from the Genio approval update[83,90-93]

The ongoing RCT we identified is the OSPREY trial, a multicenter crossover RCT conducted in the US with a total study duration of 13 months and a primary completion date of October 2023.[87] This study enrolled

150 participants with moderate to severe OSA and a BMI of 35 kg/m^2 or less.[87] All participants are implanted with the aura6000 system; the HGNS group will receive active stimulation from months 1 through 7, whereas devices in the control group will be inactivated until outcomes are assessed at 7 months, at which point the crossover phase of the trial begins.[87] No published results of this trial are yet available.

Among the 7 remaining NRS, estimated primary completion dates range from September 2022 to April 2034 and planned study durations range from 12 months to 5 years.[83,88-93] Excluding the registry studies,[88,89] estimated study enrollments range from 110 to 229 participants.[83,87,90-93] The location of these studies are as follows (with some taking place in more than 1 country):

- 5 studies in the US[87,88,90-93]
- 4 in European countries (Belgium, France, Switzerland, Germany, or the Netherlands)[83,88-90]
- 1 in Australia[90]

Four of the ongoing NRS investigate the Genio System[83,90,92,93] and the other 3 studies, including the 2 registry studies, investigate the Inspire UAS system.[88,89,91] All 5 of the prospective NRS[83,90-93] and 1 of the registry studies[89] are noncomparative cohorts with pre-post comparison from baseline outcomes. The remaining registry has a control group of patients who were denied insurance coverage for the Inspire UAS system.[88]

While all ongoing NRS focus on adults with moderate to severe OSA, 5 studies specify an AHI threshold (e.g., 15 to 65 events/hour)[83,89,91-93] and 2 did not,[88,90] with 1 of these referring only to a likely diagnosis of moderate to severe OSA.[90] Four of the ongoing NRS specify BMI in the enrollment criteria,[83,89,92,93] with 3 studies including participants with a BMI of 32 kg/m^2 or less,[89,92,93] while the other has participants with a BMI of 35 kg/m^2 or less.[83] Notably, these inclusion criteria differ from 2023 changes to the FDA-approved indication and BMI warning for the Inspire UAS system.[30] While the Inspire UAS system is currently indicated only for individuals who do not have complete concentric collapse at the soft palate level,[30] 1 ongoing NRS of the Genio system is studying individuals with OSA who do have complete concentric collapse of the soft palate.[92]

All 8 identified ongoing studies include OSA severity (as measured by polysomnography) as an outcome of interest, though none look at major adverse cardiovascular events.[83,87-93] Four ongoing studies include quality of life outcomes,[83,87-89] 5 had procedure- or device-related severe adverse events,[83,87,90,91,93] and 5 looked at daytime sleepiness as represented by the ESS.[87-89,91,93]

POLICY LANDSCAPE

Genio Approval Update

Clinical Practice Guidelines

- We did not identify changes to HGNS recommendations related to the Genio System approval in any of the guidelines included in the original coverage guidance.

Payer Coverage Policies

- 1 payer policy released an update that newly acknowledges the Genio System approval (i.e., Regence), but HGNS coverage criteria did not change.
- We identified changes in HGNS coverage criteria in 3 payer policies reviewed in the original coverage guidance (Cigna, Moda, and Regence).

2025 Update

In the Policy Landscape section, we searched for new or updated HGNS-related recommendations in relevant CPGs and reviewed the previously included payer policies for changes in HGNS coverage.

Clinical Practice Guidelines

- We did not identify changes to HGNS recommendations in any of the guidelines included in the original coverage guidance.
- We did not identify any new eligible CPGs with HGNS-related recommendations.

Payer Coverage Policies

- We did not identify changes in HGNS coverage status or coverage criteria in any of the 6 payer policies reviewed in the original coverage guidance (i.e., Medicare, Washington Medicaid, Aetna, Cigna, Moda, Regence).

In the following section, we summarize evidence-based clinical guildelines about HGNS for OSA from professional societies and governmental health agencies and report on payer policies from select public and private organizations.

In this section, we summarize clinical guidelines from professional societies and public and private payer policies with guidance on HGNS as a treatment for moderate to severe OSA. Table 9 presents a high-level summary of HGNS recommendations and coverage (candidate selection) criteria.

- **2025 update:** All references cited in the following sections refer to the most current version as identified in our updated database search in July 2025. Of note, while some guidelines (Department of Veterans Affairs and the Department of Defense and German Sleep Society)[94,95] and payer policies (Aetna and Moda) were updated since conducting our initial search, HGNS-specific recommendations did not change.
- **Genio approval update:** We did not identify any Genio-specific changes to clinical practice recommendations or payer policy coverage criteria. To date, only 1 payer policy has released an update that explicitly acknowledges the Genio System (i.e., Regence).[96]

TABLE 9. CLINICAL RECOMMENDATIONS AND PAYER COVERAGE CRITERIA FOR HGNS

	CLINICAL GUIDELINES				PAYER POLICIES[a]				
	VA/DoD[97]	GSS[98]	ERS[99]	NICE[100]	Medicare LCD[101]	Aetna[102]	Cigna[103]	Moda[104]	Regence[96]
	2019	2017	2021	2017	2025	2026	2026	2025	2026
HGNS RECOMMENDATIONS									
Second-Line Treatment	✓	✓			✓	✓	✓	✓	✓
Recommendation Against HGNS (Conditional)			✓						
Should Only Use With Special Arrangements				✓					
HGNS CANDIDATE SELECTION									
Age (years)									
Adults	✓	✓	✓						
Adults ≥ 22					✓				
Adults ≥ 18						✓	✓	✓	✓
AHI (events per hour)									
15–100						✓	✓	✓	✓
15–65	✓	✓			✓				
15–50			✓[b]						
BMI (kg/m^2)									
< 40						✓	✓	✓	✓
< 35		✓[c]			✓				
< 32	✓		✓						
Documented PAP Failure or Intolerance	✓	✓	✓		✓	✓	✓	✓	✓
Polysomnogram Required Within 2 Years					✓	✓	✓	✓	✓
DISE to Evaluate for Concentric Collapse		✓			✓	✓	✓	✓	✓

Table Key. A check indicates the criterion is endorsed. Blank cells indicate the HGNS recommendation or HGNS candidate selection criteria is not applicable. A blank indicates specific criterion was not mentioned or specific criteria falls into a different category (for age, AHI, or BMI demographic).

Notes. a Washington Medicaid was not included in this table because the most relevant identified Health Technology Assessment (HTA) from Washington State Health Care Authority did not include any information on HGNS therapy. b The ERS recommendation specified AHI <50 events per hour (with no lower limit indicated). c The GSS recommendation specified < class I obesity [BMI < 34.9 kg/m2].

Abbreviations. AHI: apnea hypopnea index; BMI: body mass index; DISE: drug-induced sleep endoscopy; ERS: European Respiratory Society; GSS: German Sleep Society; HGNS: hypoglossal nerve stimulation; LCD: local coverage determination; NICE: National Institute for Health and Care Excellence; PAP: positive airway pressure; VA/DoD: Department of Veterans Affairs and the Department of Defense.

Evidence-Based Recommendations

We identified 4 clinical guidelines with HGNS-specific recommendations from the following organizations:

- Department of Veterans Affairs and the Department of Defense (VA/DoD)[97]
- German Sleep Society (GSS)[98]
- European Respiratory Society (ERS)[99]
- National Institute for Health and Care Excellence (NICE)[100]

As indicated in Table 9, there were 2 guidelines (VA/DoD[97] and GSS[98]) that endorsed HGNS as a second-line treatment, 1 guideline (ERS[99]) included a conditional recommendation against HGNS, and 1 guideline (NICE[100]) indicated HGNS should only be used with special arrangements (in the UK). Table 9 also details 3 of the 4 guidelines used for HGNS candidate selection criteria (age, AHI range, BMI range, documentation of PAP failure or intolerance, and DISE findings).[97-99]

In addition, we identified 2 position statements and 1 position paper with HGNS-specific recommendations.[105-107] The position paper and 1 of the position statements endorsed HGNS as a second-line treatment for OSA.[105,107] The position paper used HGNS candidate selection criteria (including AHI and BMI ranges),[107] but the 2 position statements did not.

We also identified 1 review with consensus recommendations on perioperative care of patients with OSA undergoing upper airway surgery, including HGNS.[108] Not within the scope of the identified review, recommendations for HGNS candidate selection were *not* specified.[108]

Clinical Guidelines With HGNS-Specific Recommendations

For this report, we assessed the methodological quality of the 4 identified clinical guidelines, which were from 4 distinct professional organizations[97-100]:

- A guideline from the VA/DoD had good methodological quality.[97]
- A guideline from the GSS had poor methodological quality.[98] A meaningful issue was lack of clarity regarding potential connections between recommendations given and the lengthy list of references; there were no in-text citations.[98] Related to this, a comprehensive discussion on the methods used to formulate recommendations was absent from the English language version of the guidelines.[98]
- Guidelines from the ERS had fair methodolgical quality; concerns were author conflicts of interest.[99]
- Guidelines from the NICE had fair methodolgical quality; concerns were lack of clarity regarding methods used for formulating recommendations.[100]

Department of Veterans Affairs and the Department of Defense (VA/DoD)

2019 guidelines from the VA/DoD included 12 recommendations on treatment and management of OSA.[97] One of the 12 workgroup recommendations on treatment and management of OSA was *select* patients who cannot adhere to PAP should be evaluated for surgical treatment with HGNS.[97] Using the GRADE system, the strength of the recommendation was graded by the VA/DoD workgroup as *weak*, consistent with a suggestion to *offer* (but not necessarily recommend) HGNS as an option.[97] In addition,

the 1 OSA recommendation pertaining to HGNS indicated the following HGNS candidate selection criteria[97]:

- AHI 15 to 65 events per hour
- BMI < 32 kg/m^2

German Sleep Society (GSS)

2017 GSS guidelines on sleep-related breathing disorders in adults had recommendations on non-pap therapies including HGNS and other surgeries.[98] The 1 recommendation on HGNS indicated use only in the case of CPAP intolerance or ineffectiveness and when DISE findings are consistent with no concentric obstruction.[98] Furthermore, the GSS recommended that HGNS should be used only in patients meeting both of the following criteria[98]:

- AHI 15 to 50 events per hour
- < class I obesity (BMI < 34.9 kg/m^2)

National Institute for Health and Care Excellence (NICE)

2017 NICE interventional procedures guidance on HGNS indicated that evidence on the safety and efficacy of HGNS for moderate to severe OSA was limited in quantity and quality.[100] Guidance indicated HGNS should be used only with special arrangements for clinical governance, consent, and audit or research.[100] The committee noted that DISE had been used for study participant screening in HGNS clinical trials; however, the committee emphasized DISE is not commonly used in the UK.[100] AHI and BMI candidate selection criteria were *not* given by the NICE.[100]

European Respiratory Society (ERS)

2021 ERS clinical guidelines on non-CPAP therapies for OSA were developed via systematic review.[99] One of the PICOs focused on whether HGNS during sleep should be used or if *no treatment* should be used in patients with OSA.[99] The task force conditionally recommended against the intervention based on what was assessed as *very low* quality of evidence (using GRADE).[99] Compared with *no treatment*, HGNS can be considered as a salvage treatment for patients meeting both of the following HGNS candidate selection criteria[99]:

- AHI < 50 events per hour
- BMI < 32 kg/m^2

Additionally, the ERS indicated the conditional recommendation *against* HGNS was based on limited evidence from 3 RCTs that had strict participant selection criteria (~10% of those screened participated in the 3 studies).[99]

Recently, experts from World Sleep Society's International Sleep Medicine Guidelines Committee and Sleep and Breathing Task Force reviewed the 2021 ERS guidelines for relevance and applicability to the global practice of sleep medicine.[109] In early 2024, the World Sleep Society task force published an endorsement of the ERS guidelines, specifically including the conditional recommendation *against* HGNS.[109]

Position Statements and Position Papers That Included Information on HGNS Surgery

American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS)

In 2019, the AAO-HNS revised an HGNS position statement first submitted for review in 2014. The entirety of the current statement is as follows[105]:

- "The American Academy of Otolaryngology-Head and Neck Surgery considers upper airway stimulation (UAS) via the hypoglossal nerve for the treatment of adult obstructive sleep apnea syndrome to be a safe and effective second-line treatment of moderate to severe obstructive sleep apnea in patients who are intolerant or unable to achieve benefit with positive pressure therapy."

Australasian Sleep Association (ASA)

In 2020, the ASA published a position statement on surgical management of OSA.[106] The authors noted although HGNS is commercially available internationally, at the time the statement was published, HGNS remained in clinical trial phase only in Australasia.[106] No criteria were shared pertaining to HGNS candidate selection (such as PAP failure or intolerance, DISE findings, AHI range, or BMI range).[106]

German Society of Oto-Rhino-Laryngology

In 2021, the German Society of Oto-Rhino-Laryngology published a 6-page position paper on HGNS for OSA.[107] After PAP therapy, HGNS is considered recommended as a second-line treatment.[107] DISE assessment for concentric collapse is required and the authors noted that "profound expertise" is needed to perform and evaluate a DISE.[107] In Germany, HGNS can be considered in patients meeting both of the following criteria[107]:

- AHI 15 to 65 events per hour
- BMI < 35 kg/m^2

Recommendations on Perioperative Care of Patients With OSA Undergoing Upper Airway Surgery

A 2019 review with consensus recommendations on perioperative care of patients with OSA undergoing upper airway surgery had recommendations and statements specific to a variety of procedures, including HGNS.[108] Authors were experts from the US and Europe.[108]

Two consensus recommendations specific to HGNS were as follows[108]:

- HGNS surgery can be performed in a daycare or clinical setting, depending on the clinical judgment of the surgeon and/or anesthesiologist. (Quality of evidence was considered very low and strength of the recommendation was considered strong according to the GRADE system.)
- In most cases, patients undergoing HGNS surgery should not have prolonged postoperative monitoring. (Quality of evidence was considered very low and strength of the recommendation was considered strong.)

Given these recommendations were focused on perioperative care, no recommendations were provided for HGNS candidate selection.[108]

Payer Coverage Policies

We identified 5 policies related to coverage of HGNS from Aetna, Cigna, Moda, Regence, and the Medicare local coverage determination (LCD).[96,101-104] The 5 payers cover HGNS for *select* adult patients with OSA.[96,101-104] All payers require that patients be previously insufficiently treated with CPAP and that DISE findings are consistent with absence of complete concentric collapse at the soft palate level.[96,101-104]

Additional coverage criteria include but are not limited to varying AHI ranges and BMI ranges.[96,101-104] As noted previously in this report, FDA-approved indications for use of the Inspire UAS system were expanded in June 2023 to include a higher upper limit for AHI and a higher upper limit of the warning for BMI.[34] This was based on the FDA's analysis of data from the ADHERE registry through 2022 (Appendix D, Table D11).[110] For AHI, the FDA compared 1,483 people with an AHI ≤ 65 with 57 people with an AHI of greater than 65 to 100. FDA did not find any significant difference in key outcomes: final AHI, AHI responder, final ESS, and change in ESS and determined the safety profile to be "similar."[110] For BMI, the analysis compared 1,218 people with a BMI ≤ 32 kg/m^2 with 279 people with a BMI of greater than 32 to 40 kg/m^2.[110] The FDA also did not identify a significant difference key outcomes: final AHI, change in AHI, AHI responder, AHI nonresponder, final ESS, change in ESS, and also determined the safety profile to be "similar."[110] See Table 9 for a concise visual summary of commonalities and differences in payer policy criteria, including AHI and BMI.

We also identified a 2012 Health Technology Assessment (HTA) from Washington State Health Care Authority on sleep apnea diagnosis and treatment that did *not* include any information on HGNS therapy, which is likely related to FDA approval after completion of the Washington HTA.[111]

Medicare

We identified 1 coverage determination document for Medicare with information about HGNS.[101] This LCD (L38312), shown in Table 9, covers Oregon and was revised with an effective date of March 2020.[101] Beneficiaries diagnosed with moderate to severe OSA are potential candidates for HGNS if *ALL* of the following criteria are met[101]:

- Beneficiary is 22 years of age or older
- BMI is less than 35 kg/m2
- A polysomnography study is performed within 24 months of first consultation for HGNS implant
- Beneficiary has predominantly obstructive events (defined as central and mixed apneas less than 25% of the total AHI)
- AHI is 15 to 65 events per hour
- Beneficiary has documentation demonstrating CPAP failure (defined as AHI greater than 15 despite CPAP usage) or CPAP intolerance (defined as less than 4 hours per night, 5 nights per week, or the CPAP has been returned) including shared decision making that the patient was intolerant of CPAP despite consultation with a sleep expert
- Absence of complete concentric collapse at the soft palate level as seen on a DISE procedure
- No other anatomical findings that would compromise performance of device (e.g., tonsil size 3 or 4 per standardized tonsillar hypertrophy grading scale)

HGNS is considered NOT medically reasonable and necessary when ANY of the following contraindications are present [101]:

- Beneficiaries who have central and mixed apneas that make up more than 25% of the total AHI
- Beneficiaries who have an implantable device and could experience unintended interaction with the HGNS implant system
- BMI equal to or greater than 35
- Neuromuscular disease
- Hypoglossal-nerve palsy
- Severe restrictive or obstructive pulmonary disease

- Moderate to severe pulmonary arterial hypertension
- Severe valvular heart disease
- New York Heart Association class III or IV heart failure
- Recent myocardial infarction or severe cardiac arrhythmias (within the past 6 months)
- Persistent uncontrolled hypertension despite medication use
- An active, serious mental illness that reduces the ability to carry out activities of daily living (ADLs) and would interfere with the patient's ability to operate the HNS and report problems to the attending provider
- Coexisting nonrespiratory sleep disorders that would confound functional sleep assessment
- Beneficiaries who are or who plan to become pregnant
- Beneficiaries who require magnetic resonance imaging (MRI) with model 3024
- Beneficiaries who require MRI with model 3028, and can undergo MRI on the head and extremities if certain conditions and precautions are met
- Beneficiaries who are unable or do not have the necessary assistance to operate the sleep remote
- Beneficiaries with any condition or procedure that has compromised neurological control of the upper airway

The coverage guidance includes the following caveats[101]:

- DISE: Due to documented inconsistency in determining if complete concentric collapse is present, the inserting provider shall be certified by the FDA-approved manufacturer's second opinion service of validation by video clip submissions of at least 80% agreement in at least 15 consecutive studies. Inserting providers shall have documentation to submit to this contractor if necessary.
- Provider qualifications: HGNS for the treatment of OSA must be ordered and furnished by qualified personnel. Insertion of the device must be performed by a qualified physician (MD or DO) who is a board-certified or a board-eligible otolaryngologist having completed a residency and/or fellowship program and maintains ongoing certification in otolaryngology.

The coverage policy did not provide specific rationale for coverage more restrictive than the FDA approval criteria.[101]

Private Payers (Aetna, Cigna, Moda, Regence)

Among 4 private payers (Aetna, Cigna, Moda, and Regence), coverage criteria for HGNS have commonalities and differences. As indicated above in Table 9, commonalities include these requirements[96,102-104]:

- Documentation of PAP failure or intolerance
- Polysomnography (sleep study), including AHI results, within the previous 2 years
- DISE findings consistent with the absence of concentric collapse at the soft palate level
- Also detailed above in Table 9, AHI and BMI differences in coverage criteria are nuanced. The most recent policies align with (or more closely align with) the June 2023 expanded FDA indication and BMI warning[30] for use of the Inspire UAS system.

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Coverage guidance is prepared by the Health Evidence Review Commission (HERC), HERC staff, and subcommittee members. The evidence summary is prepared by the Center for Evidence-based Policy at Oregon Health & Science University (Center). This document is intended to guide public and private purchasers in Oregon in making informed decisions about health care services.

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Suggested citation: Durbin S, Bachhuber M, Cooper C, Ryan JJ, Young E, King V. *Coverage guidance: hypoglossal nerve stimulation for obstructive sleep apnea*. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2026.

The authors would also like to acknowledge Firozeh Darabi, Emma Kenagy, Jacqui Krawetz, Jami Hoffman, and Heather McConnell from the Center for Evidence-based Policy as well as our subject matter experts, Louis Libby, MD and Derek J. Lam, MD, MPH, for their contributions to this work.

APPENDIX A. GRADE TABLE ELEMENT DESCRIPTIONS

TABLE A1. GRADE TABLE ELEMENTS

ELEMENT	DESCRIPTION
Balance of benefits and harms	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. An estimate that is not statistically significant or has a confidence interval crossing a predetermined clinical decision threshold will be downgraded.
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted.
Resource allocation	The higher the costs of an intervention—that is, the greater the resources consumed in the absence of likely cost offsets—the lower the likelihood that a strong recommendation is warranted.
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted.
Other considerations	Other considerations include issues about the implementation and operationalization of the technology or intervention in health systems and practices within Oregon.

Abbreviation. GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach.

Confidence in Estimate Rating Across Studies for the Intervention and Outcome

Assessment of confidence in estimate includes factors such as risk of bias, precision, directness, consistency, and publication bias.

High: The subcommittee is very confident that the true effect lies close to that of the estimate of the effect. Typical sets of studies are randomized controlled trials (RCTs) with few or no limitations, and the estimate of effect is likely stable.

Moderate: The subcommittee is moderately confident in the estimate of effect: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Typical sets of studies are RCTs with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.

Low: The subcommittee's confidence in the estimate of effect is limited: The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.

Very low: The subcommittee has very little confidence in the estimate of effect: The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.

APPENDIX B. GRADE EVIDENCE PROFILES

TABLE B1. CERTAINTY ASSESSMENT (CONFIDENCE IN ESTIMATE OF EFFECT) FOR HGNS THERAPY IN ADULTS WITH MODERATE TO SEVERE OSA

NO. OF STUDIES SAMPLE SIZE	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER FACTORS	LEVEL OF CONFIDENCE
QUALITY OF LIFE						
3 studies (2 RCTs and 1 cohort study) N = 485	**Serious** Downgraded 1 level ■ All studies rated as high RoB ■ Industry funding and author COI ■ Limited randomization and blinding information ■ No control for confounding and in cohort study ■ Selection bias in RCTs ■ Data in crossover RCT analyzed for combined periods (subject to possible unit-of-analysis error)	**Not serious** ■ Consistent direction of effect across studies and timepoints (i.e., improved QoL favoring HGNS) ■ Reasonably consistent point estimates and magnitudes of effect	**Serious** Downgraded 1 level ■ Differences between studies in assessment timepoints ■ Study population concerns: 1) mismatch with current FDA indication [i.e., more limited by age, AHI, and BMI] 2) Participants mostly white and male (limited applicability to Medicaid) ■ No eligible studies assessed overall QoL	**Not serious** ■ Some wider confidence intervals, but reasonable samples sizes ■ Studies were sufficiently powered to detect differences in QoL	■ Short follow-up periods to assess a long-term intervention and outcome	**Low** ●●○○

NO. OF STUDIES SAMPLE SIZE	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER FACTORS	LEVEL OF CONFIDENCE
DEVICE-RELATED SAE						
13 studies (2 RCTs; 4 cohort studies; 6 registry studies; 1 SR)	**Serious** Downgraded 1 level ■ 10 studies rated high RoB; 2 studies rated moderate RoB ■ Industry funding and author COI ■ Reporting bias ■ Selection bias ■ Specific to the included systematic reviews, concerns over the transparency of methods used for risk of bias and integration of risk of bias evaluations into the synthesis	**Not serious** ■ Generally low rates of SAEs ■ Reasonably consistent rates of SAEs that could be compared (rates of participants with device explants or revisions)	**Not serious (device revisions and explants)** **Serious (other device-related SAEs)** Downgraded 1 level ■ Population mismatch [other device-related SAEs, not area of concern for device revisions or explants]: 1) mismatch with current FDA indication [i.e., more limited by age, AHI, and BMI] 2) Participants mostly white and male (limited applicability to Medicaid) ■ Variety of different outcomes reported under this broad category ■ Differences in classification of outcomes as an SAE or AE across the studies	**Not serious** ■ Few events are reported; studies have generally large sample sizes	■ Limited long-term data (the STAR NRS, at 5 years, is the longest available timepoint)	Moderate [device revisions and explants] ●●●○ **Low** (other device-related SAEs) ●●○○

NO. OF STUDIES SAMPLE SIZE	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER FACTORS	LEVEL OF CONFIDENCE
OSA SEVERITY (POLYSOMNOGRAPHY INDICES)						
5 studies (3 RCTs and 2 cohort studies) N = 673	**Serious** Downgraded 1 level ■ All studies rated as high RoB ■ Industry funding and author COI ■ Limited randomization and blinding information in RCTS ■ No control for confounding and in cohort study ■ Selection bias in RCTs ■ Data in crossover RCTs analyzed for combined periods (subject to possible unit-of-analysis error)	**Not serious** ■ Consistent direction and magnitude of effect, QOL severity measures, and timepoints across studies with inactive comparators (i.e., significantly lower OSA severity with HGNS) ■ No difference findings in study comparing HGNS and CPAP does not conflict with inactive comparator findings - both active conditions were significantly and clinically effective	**Serious** Downgraded 1 level ■ Differences between studies in terms of comparators and assessment timepoints ■ Study population concerns: 1) mismatch with current FDA indication [i.e., more limited by age, AHI, and BMI] 2) Participants mostly white and male (limited applicability to Medicaid)	**Not serious** ■ Some wider confidence intervals, but reasonable samples sizes ■ Studies were sufficiently powered to detect differences in AHI and ODI	■ Limited long-term data (12 months is longest follow-up) to assess an ongoing intervention	**Low** ●●○○

NO. OF STUDIES SAMPLE SIZE	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER FACTORS	LEVEL OF CONFIDENCE
DAYTIME SLEEPINESS						
4 studies (2 RCTs and 2 cohort studies) N = 611	**Serious** Downgraded 1 level ■ All studies rated as high RoB ■ Industry funding and author COI ■ Limited randomization and blinding information in RCTS ■ No control for confounding and in cohort study ■ Selection bias in RCTs ■ Data in crossover RCTs analyzed for combined periods (subject to possible unit-of-analysis error)	**Not serious** ■ Consistent direction and magnitude of effect across studies with inactive comparators (i.e., significantly lower daytime sleepiness with HGNS) ■ No difference findings in ESS means in study comparing HGNS and CPAP does not conflict with inactive comparator findings—values in both study groups indicated normal daytime sleepiness at 12 months	**Serious** Downgraded 1 level ■ Differences in assessment timepoints between studies ■ Study population concerns: 1) mismatch with current FDA indication [i.e., more limited by age, AHI, and BMI] 2) Participants mostly white and male (limited applicability to Medicaid)	**Not serious** ■ Some wider confidence intervals, but reasonable samples sizes ■ Studies were sufficiently powered to detect differences in ESS scores	■ Limited long-term data (12 months is longest follow-up) to assess an ongoing intervention	**Low** ●●○○
MAJOR ADVERSE CARDIAC EVENTS						
No eligible studies						

Notes. [a] These are all from the MAUDE database so there may be overlap in the number of reports.
Abbreviations. AHI: apnea-hypopnea index; BMI: body mass index; COI: conflict of interest; ESS: Epworth Sleepiness Scale; FDA: US Food and Drug Administration; HGNS: hypoglossal nerve stimulation; MAUDE: Manufacturer and User Facility Device Experience Database; NRS: nonrandomized study; OSA: obstructive sleep apnea; QoL: quality of life; RCT: randomized controlled trial; RoB: risk of bias; SAE: serious adverse event; SR: systematic review.

APPENDIX C. METHODS

Scope Statement

Populations

Adults aged 18 years and older with moderate to severe OSA (generally defined as having an AHI ≥ 15 events per hour)

Interventions

Upper airway nerve stimulation

- Hypoglossal nerve stimulation

Comparators

- No treatment
- Usual care (i.e., patient education)
- Sham surgery (i.e., placebo)
- Nonsurgical interventions for OSA
    - Noninvasive positive airway pressure therapy (i.e., CPAP, BiPAP)
    - Pharmacotherapy
    - Mandibular advancement devices

Outcomes

Critical:

- Procedure- or device-related serious adverse events
- Overall and sleep-related quality of life (as measured by validated assessment scales)

Important:

- Improvement in OSA severity as measured by polysomnography indices (i.e., apnea-hypopnea index, respiratory disturbance index, respiratory event index, oxygen desaturation index)
- Daytime sleepiness (as measured by validated assessment scales)
- Major adverse cardiac events

Considered, but not selected for GRADE table: All-cause mortality, change in A1c, remission of hypertension, fatigue-related accidents, other polysomnography-related outcomes

Study Designs*

Effectiveness:

- RCTs of any size
- Prospective comparative cohort studies (N > 100)

Harms:

- RCTs (as defined above)
- Prospective comparative cohort studies (as defined above)
- Systematic reviews (including any study design)
- Prospective single-arm cohort studies (N > 100)

- Registry studies (i.e., retrospective studies of data collected from a named centralized database with multisite inputs)

*Studies only eligible if conducted in the US or very-high Human Development Index (HDI) nations.

Follow-up

RCTS: 12 weeks or greater (including device implantation)
Cohort and registry studies: 6 months or greater

Publication Date

Primary studies: 2000 or later

Systematic reviews: 2014 or later

Key Questions

KQ1. What is the effectiveness of hypoglossal nerve stimulation versus nonsurgical treatments for OSA in adults?
KQ2. What are the harms of hypoglossal nerve stimulation for OSA?
KQ3. How does the effectiveness and harms of these interventions vary by:
  a. Intervention characteristics
  b. Patient characteristics
    i. Severity of OSA
    ii. Race, ethnicity, culture, or language
    iii. Gender or sex
    iv. Age
    v. Comorbidities
    vi. Response to prior interventions

Contextual Questions

CQ1. What is the evidence for effectiveness of hypoglossal nerve stimulation for OSA on outcomes (e.g., all-cause mortality, major adverse cardiac events, motor vehicle crashes) from systematic reviews that include observational and nonrandomized studies?
CQ2. What is the comparative effectiveness of hypoglossal nerve stimulation for OSA from randomized controlled trials?
CQ3. What is the cost-effectiveness of hypoglossal nerve stimulation for OSA?

Key Question Search Strategy

We searched bibliographic databases to identify randomized controlled trials (RCTs), systematic reviews (with and without meta-analyses), cohort studies, and clinical practice guidelines including the terms *obstructive sleep apnea, sleep disordered breathing, hypoglossal nerve, HGNS,* and *nerve stimulation*. We limited records retrieved to those studies focused on human subjects and published in the English language after 2000. No additional search limits were applied. Systematic reviews were used for reference list searching and not as evidence sources. Initial database searches were conducted on May 22, 2024. Updated database searches were conducted on July 1, 2025.

Bibliographic Databases

TABLE C1. BIBLIOGRAPHIC DATABASES SEARCHED FOR THIS REPORT

DATABASE	PLATFORM	ISSUE/VERSION	TOTAL NUMBER OF RECORDS RETRIEVED
Initial Database Search (May 2024)			
CENTRAL and CDSR	Wiley	Issue 5 of 12, May 2024	36 references
MEDLINE ALL	Ovid	1946 to May 22, 2024	432 references
Updated Database Search (July 2025)			
CENTRAL AND CDSR	WILEY	Issue 6 of 12, July 2025	50 references
MEDLINE ALL	Ovid	April 2024 to June 30, 2025	134 references

Abbreviations. CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials.

Ovid MEDLINE ALL Search Strategy (May 2024)

1	exp sleep apnea, obstructive/	28415
2	((nocturnal or sleep*) adj3 (apn?e* or apn?ea-hypopne* or apn?eic-hypopne* or hypopn?e* or hypo-apn?e*)).ti,ab,kw.	48524
3	osa.ti,ab,kf.	20966
4	osahs.ti,ab,kf.	1752
5	sahs.ti,ab,kf.	625
6	shs.ti,ab,kf.	3915
7	or/1-6	58936
8	hypoglossal nerve/	3502
9	hypoglossal.ti,ab,kf.	6106
10	(cranial nerve* adj3 (twelve or twelfth or xii or 12*)).ti,ab,kw.	581
11	(cn xii or cn 12).ti,ab,kw.	119
12	or/8-11	7459
13	electric stimulation/	117188

14	electric stimulation therapy/	22246
15	implantable neurostimulators/	839
16	((electric* or neuro* or nerve* or upper airway) adj3 stimulat*).ti,ab,kw.	115931
17	electrotherap*.ti,ab,kf.	2590
18	(neurostimulat* or neuro-stimulat*).ti,ab,kf.	5113
19	hgns.ti,ab,kf.	160
20	or/13-19	205321
21	and/7,12,20	492
22	exp animals/ not humans/	5217727
23	21 not 22	468
24	limit 23 to (english language and yr="2000 -Current")	432

CDSR and CENTRAL via the Cochrane Library Search Strategy (May 2024)

Search Name: HERC - OSA hypoglossal nerve stimulators_05.22.24

Date Run: 22/05/2024 18:39:40

ID	Search	Hits
#1	[mh "sleep apnea, obstructive"]	3213
#2	((nocturnal:ti,ab OR sleep*:ti,ab) NEAR/3 (apn?e*:ti,ab OR apn?ea-hypopne*:ti,ab OR apn?eic-hypopne*:ti,ab OR hypopn?e*:ti,ab OR hypo-apn?e*:ti,ab)) ,kw.	42
#3	osa:ti,ab,kw	4450
#4	osahs:ti,ab,kw	250
#5	sahs:ti,ab,kw	97
#6	shs:ti,ab,kw	454
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	6409
#8	[mh ^"hypoglossal nerve"]	20
#9	hypoglossal:ti,ab,kw	94

#10 (("cranial" NEXT nerve*):ti,ab NEAR/3 (twelve:ti,ab OR twelfth:ti,ab OR xii:ti,ab OR 12*:ti,ab)) ,kw. 0

#11 ("cn xii":ti,ab OR "cn 12":ti,ab) ,kw. 0

#12 #8 OR #9 OR #10 OR #11 94

#13 [mh ^"electric stimulation"] 2438

#14 [mh ^"electric stimulation therapy"] 2541

#15 [mh ^"implantable neurostimulators"] 69

#16 ((electric*:ti,ab OR neuro*:ti,ab OR nerve*:ti,ab OR "upper airway":ti,ab) NEAR/3 stimulat*:ti,ab) ,kw. 55

#17 electrotherap*:ti,ab,kw 1188

#18 (neurostimulat*:ti,ab,kw OR neuro-stimulat*:ti,ab,kw) 1259

#19 hgns:ti,ab,kw 19

#20 #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 6969

#21 #7 AND #12 AND #20 36

#22 [mh "animals"] NOT [mh ^"humans"] 3664

#23 #21 NOT #22 with Cochrane Library publication date Between Jan 2000 and May 2024 36

Ovid MEDLINE ALL Search Strategy (July 2025)

1	exp sleep apnea, obstructive/	30420
2	((nocturnal or sleep*) adj3 (apn?e* or apn?ea-hypopne* or apn?eic-hypopne* or hypopn?e* or hypo-apn?e*)).ti,ab,kf.	54187
3	osa.ti,ab,kf.	23457
4	osahs.ti,ab,kf.	1856
5	sahs.ti,ab,kf.	656
6	shs.ti,ab,kf.	4264
7	or/1-6	64857
8	hypoglossal nerve/	3591
9	hypoglossal.ti,ab,kf.	6364
10	(cranial nerve* adj3 (twelve or twelfth or xii or 12*)).ti,ab,kf.	608
11	(cn xii or cn 12).ti,ab,kf.	125

12	or/8-11	7738
13	electric stimulation/	118073
14	electric stimulation therapy/	23027
15	implantable neurostimulators/	904
16	((electric* or neuro* or nerve* or upper airway) adj3 stimulat*).ti,ab,kf.	123665
17	electrotherap*.ti,ab,kf.	2705
18	(neurostimulat* or neuro-stimulat*).ti,ab,kf.	5757
19	hgns.ti,ab,kf.	209
20	or/13-19	212393
21	and/7,12,20	618
22	(baboon? or bovine? or canine? or cat? or chimpanzee? or chinchilla? or cow? or dog? or feline? or goat? or hens or macque? or mice or monkey? or (mouse adj2 model?) or murine? or ovine or pig? or porcine or (non-human adj2 primate?) or sheep or rabbit? or rat or rats or rattus or rhesus or rodent? or swine or zebrafish).ti.	2289173
23	21 not 22	596
24	(202404* or 202405* or 202406* or 202407* or 202408* or 202409* or 202410* or 202411* or 202412* or 202501* or 202502* or 202503* or 202504* or 202505* or 202506* or 202507* or 202508* or 202509* or 202510*).da,dt,ez.	2168261
25	and/23-24	138
26	limit 25 to english language	134

CDSR and CENTRAL via the Cochrane Library Search Strategy (July 2025)

#1	[mh "sleep apnea, obstructive"]	3140
#2	((nocturnal:ti,ab,kw OR sleep*:ti,ab,kw) NEAR/3 (apn?e*:ti,ab,kw OR apn?ea-hypopne*:ti,ab,kw OR apn?eic-hypopne*:ti,ab,kw OR hypopn?e*:ti,ab,kw OR hypo-apn?e*:ti,ab,kw))	9249
#3	osa:ti,ab,kw	4597
#4	osahs:ti,ab,kw	258
#5	sahs:ti,ab,kw	97
#6	shs:ti,ab,kw	478

#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	10348
#8	[mh "hypoglossal nerve"]	19
#9	hypoglossal:ti,ab,kw	94
#10	((cranial NEXT nerve*):ti,ab,kw NEAR/3 (twelve:ti,ab,kw OR twelfth:ti,ab,kw OR xii:ti,ab,kw OR 12*:ti,ab,kw))	6
#11	("cn xii":ti,ab,kw OR "cn 12":ti,ab,kw)	4
#12	#8 OR #9 OR #10 OR #11	102
#13	[mh ^"electric stimulation"]	2427
#14	[mh ^"electric stimulation therapy"]	2572
#15	[mh ^"implantable neurostimulators"]	68
#16	((electric*:ti,ab,kw OR neuro*:ti,ab,kw OR nerve*:ti,ab,kw OR "upper airway":ti,ab,kw) NEAR/3 stimulat*:ti,ab,kw)	22656
#17	electrotherap*:ti,ab,kw	1299
#18	(neurostimulat*:ti,ab,kw) OR (neuro NEXT stimulat*):ti,ab,kw	1397
#19	hgns:ti,ab,kw	22
#20	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	24019
#21	AND #7, #12, #20	62*

**12 results from clinical trial registries were manually removed*

Ongoing Studies Search Strategy

We searched Clinical Trials.gov in May 2024 and again in July 2025 for ongoing studies using the following search strategy:

- **Condition/Disease:** Obstructive Sleep Apnea \(OSA\) OR Sleep Apnea, Obstructive OR Sleep Apnea OR Sleep Disordered Breathing
- **Intervention/treatment:** Hypoglossal Nerve Stimulation (HGNS) OR Upper Airway Stimulation (UAS) OR Inspire® Upper Airway Stimulation \(UAS\) System
- **Status:** Not yet recruiting, Recruiting, Active, not recruiting, Completed, Enrolling by invitation, Unknown status studies
- **Age groups:** Adult (18–64), Older adult (65+)
- **Study type:** Interventional, Observational studies
- **Primary completion:** on or after 01/01/2020

Policy Landscape Methods

For the Policy Landscape section, we conducted targeted searches in Ovid MEDLINE, websites of relevant professional societies and guideline groups, UpToDate, and DuckDuckGo to identify relevant clinical practice guideline and key payer policies. Two reviewers independently assessed the quality of the included CPGs; disagreements were resolved through consensus or by a third reviewer.

We limited searches for CPGs to those issued by professional societies in the US or other very-high Human Development Index countries published since 2014. We conducted a search for relevant clinical practice guidelines using MEDLINE and the following sources:

- American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS)
- American Academy of Sleep Medicine (AASM)
- American College of Surgeons (ACS)
- American College of Physicians (ACP)
- American Medical Association
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Centers for Disease Control and Prevention (CDC)
- European Respiratory Society
- Health Quality Ontario
- The International Sleep Surgery Society (ISSS)
- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guidelines Network (SIGN)
- United States Preventive Services Task Force (USPSTF)
- Veterans Administration/Department of Defense (VA/DoD) Clinical Practice Guidelines

We additionally sought payer coverage policies from select public and commercial payers, including:

- Medicare
- Washington State Medicaid
- Aetna
- Cigna
- Moda
- Regence BlueCross BlueShield of Oregon

Risk of Bias of Included Studies

We assessed the risk of bias of the included systematic reviews, RCTs, cohort studies, and CPGs using standard instruments developed and adapted by the Center that are modifications of instruments used by several renowned, respected organizations.[112-115] Two experienced researchers independently rated all included studies. In cases in which there was disagreement about the risk of bias of a study, a third rater resolved the disagreement.

Systematic Reviews

If a meta-analysis or network meta-analysis was conducted, the risk of bias of the analyses was considered in the overall rating for the systematic review. In brief, low-risk-of-bias systematic reviews include a clearly focused question, a literature search sufficiently rigorous to identify all relevant studies,

criteria used to assess study quality and select studies for inclusion (e.g., randomized controlled trials), and assessment of similarities between studies to determine whether combining them is appropriate for evidence synthesis. Moderate-risk-of-bias systematic reviews have incomplete information about methods that might mask important limitations or a meaningful conflict of interest. High-risk-of-bias systematic reviews have clear flaws that could introduce significant bias.

Randomized Controlled Trials

Low-risk-of-bias randomized controlled trials include a clear description of the population, setting, intervention, and comparison groups; a random and concealed allocation of patients to study groups; low dropout rates; and intention-to-treat analyses. Low-risk-of-bias randomized controlled trials also have low potential for bias from conflicts of interest and funding source(s). Moderate-risk-of-bias randomized controlled trials have incomplete information about methods that might mask important limitations or a meaningful conflict of interest. High-risk-of-bias randomized controlled trials have clear flaws that could introduce significant bias.

Cohort Studies

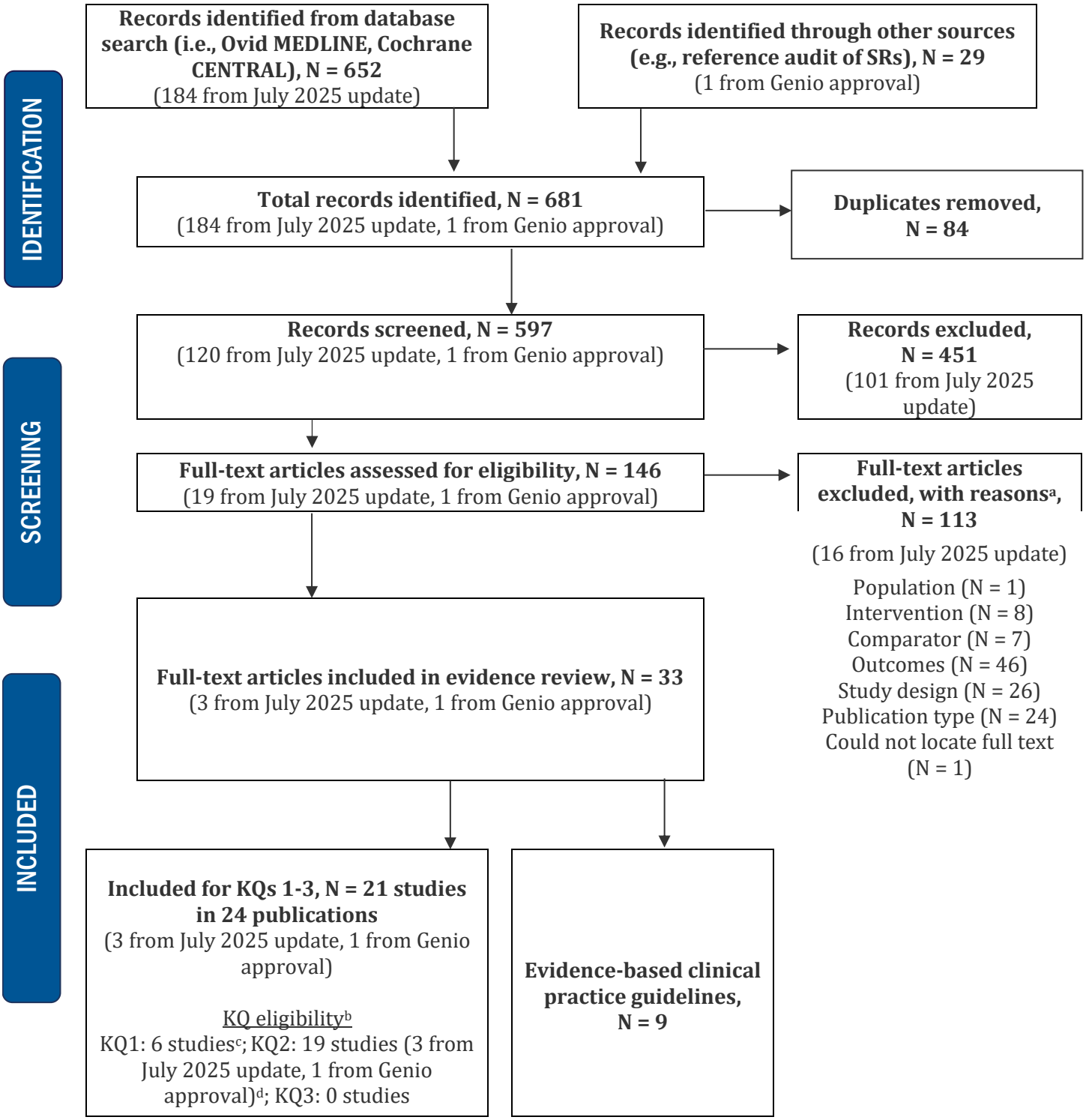
Low-risk-of-bias cohort studies include a sample that is representative of the source population, have low loss to follow-up, and measure and consider relevant confounding factors. Low-risk-of-bias cohort studies also list their funding source(s) and have a low potential of bias from conflicts of interest. Moderate-risk-of-bias cohort studies might not have measured all relevant confounding factors or adjusted for them in statistical analyses, have loss to follow-up that could bias findings, consist of a sample that is not representative of the source population, or have potential conflicts of interest that are not addressed. High-risk-of-bias cohort studies have a clear, high risk of bias that would affect findings.

Clinical Practice Guidelines

We assessed the methodological quality of the guidelines using an instrument adapted from the Appraisal of Guidelines Research and Evaluation (AGREE) Collaboration.[115-117] Each rater assigned the study a rating of good, fair, or poor based on its adherence to recommended methods and potential for biases. A good-quality guideline fulfills all or most of the criteria outlined in the instrument. A fair-quality guideline fulfills some of the criteria, and its unfulfilled criteria are not likely to alter the recommendations. A poor-quality guideline met few or none of the criteria.

APPENDIX D. ADDITIONAL FIGURE AND EVIDENCE TABLES

FIGURE D1. STUDY FLOW DIAGRAM



Notes. This diagram contains all references identified and reviewed in the initial search (May 2024) and the bridge search (July 2025). [a] No studies were excluded for study duration, study setting, publication date, or lack of availability in English. [b] There is overlap in the studies with data available for KQ1 and KQ2. [c] Five of these studies were eligible for GRADE as these evaluated the only currently FDA-approved device, Inspire UAS. [d] Twelve of these studies were eligible for GRADE as these evaluated the only currently FDA-approved device, Inspire UAS.
Abbreviations. FDA: US Food and Drug Administration; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations; KQ: key question; SRs: systematic reviews.

TABLE D1. OUTCOME MEASURES AND MINIMAL CLINICALLY IMPORTANT DIFFERENCES (MCIDS)

MEASUREMENT SCALE	ABBREVIATION	MEASURE	SCORE RANGE	SCORE INTERPRETATION	MCIDS
VALIDATED PATIENT-REPORTED OUTCOME SCALES					
Epworth Sleepiness Scale[81]	ESS	Daytime sleepiness	0–24 points	Higher scores indicate increased daytime sleepiness	■ ± 2 or 3 points
Functional Outcomes of Sleep Questionnaire[118]	FOSQ (long form) FOSQ10 (short form)	Functional status	5–20 points	Higher scores indicate improvement in functional status	■ ± 1 point
EuroQol-5d: Visual Acuity Scale[80]	EQ-5D VAS	Generic measure of health	0–100 points	Higher scores indicate higher self-rated overall health	Variability exists for this outcome measure.[119]
POLYSOMNOGRAPHY MEASURES					
Apnea-Hypopnea Index[118,120]	AHI	OSA severity	0–no upper limit	Higher scores indicate greater OSA severity	■ ± 5 events per hour ■ ± 10%
Oxygen Desaturation Index[118]	ODI	OSA severity	0–no upper limit	Higher scores indicate greater OSA severity	■ ± 5 events per hour
Respiratory Disturbance Index[118]	RDI	OSA severity	0–no upper limit	Higher scores indicate greater OSA severity	■ ±10%

Notes. The respiratory event index (REI) was not included in this table as it was not identified in any of the evidence eligible for inclusion in this report. The REI reports the number of apneas and hypopneas per hour of monitoring time and is commonly used in home sleep testing.
Abbreviations. MCIDs: minimal clinically important differences; OSA: obstructive sleep apnea.

TABLE D2. ADDITIONAL STUDY CHARACTERISTICS: PRIMARY STUDIES

AUTHOR, YEAR STUDY OR REGISTRY NAME RISK OF BIAS	POPULATION DESCRIPTION	STUDY SETTING	STUDY GROUP	BASELINE CHARACTERISTICS						
				MEAN AGE	MEAN BMI	MEAN NECK SIZE	MEAN AHI	MEAN ESS	% FEMALE	% RACE/ETHNICITY[a]
RCTs										
Dedhia, 2024[61,b] CARDIOSA-12 Moderate	N = 62 Adults with prior HGNS implantation	3 academic medical centers in the US	Total cohort (crossover RCT), n = 60[c]	67.3 years	28.7 kg/m²	NR	33.1 events/hr	NR	37%	■ Asian: 2% ■ Black: 5% ■ Hispanic: 2% ■ White: 92%
Heiser, 2021[60] EFFECT High	N = 89 Adults with prior HGNS implantation	3 clinical centers in Germany	Total cohort (crossover RCT), n = 89	57.5 years	29.2 kg/m²	NR	8.3 events/hr 32.3 events/hr (before implanta-tion)	7.0 10.6 (before implanta-tion)	19%	■ Caucasian: 100%
Schwartz, 2023[55,d] THN3 High	N = 138 CPAP intolerant adults	20 international clinical sites (Belgium, France, Germany, Israel, Portugal, US)	HGNS, n = 92	55.8 years	29.9 kg/m²	41.7 cm	39.2 events/hr	NR	18.5%	■ Hispanic or Latino: 10.9% ■ Non-Hispanic or Latino: 89.1% ■ Racial or ethnic minority group: 8.7% ■ White: 91.3%

AUTHOR, YEAR STUDY OR REGISTRY NAME RISK OF BIAS	POPULATION DESCRIPTION	STUDY SETTING	STUDY GROUP	BASELINE CHARACTERISTICS						
				MEAN AGE	MEAN BMI	MEAN NECK SIZE	MEAN AHI	MEAN ESS	% FEMALE	% RACE/ETHNICITY[a]
			Inactive device, n = 46	55.1 years	29.6 kg/m²	42.3 cm	35.4 events/hr	NR	4.3%	■ Hispanic or Latino: 19.6% ■ Non-Hispanic or Latino: 80.4% ■ Racial or ethnic minority group: 8.7% ■ White: 91.3%
Woodson, 2014[53] STAR RCT High	N = 46 CPAP intolerant adults	International sleep medicine and otolaryngology practices (Belgium, France, Germany, the Netherlands, US)	HGNS, n = 23	57.1 years	28.4 kg/m²	41.6 cm	7.2 events/hr 31.3 events/hr (before implanta-tion)	5.9 11.2 (before implanta-tion)	4.4%	NR
			Inactive device, n = 23	52.7 years	27.3 kg/m²	40.9 cm	7.6 events/hr 30.1 events/hr (before implanta-tion)	6.9 11.3 (before implanta-tion)	17.4%	NR

AUTHOR, YEAR STUDY OR REGISTRY NAME RISK OF BIAS	POPULATION DESCRIPTION	STUDY SETTING	STUDY GROUP	BASELINE CHARACTERISTICS						
				MEAN AGE	MEAN BMI	MEAN NECK SIZE	MEAN AHI	MEAN ESS	% FEMALE	% RACE/ETHNICITY[a]
COMPARATIVE COHORT STUDIES										
Heiser, 2023[59] Upper Airway Stimulation Versus Continuous Positive Airway Pressure High	N = 126[e] Adults with OSA	German university hospitals	HGNS, n = 63	57.3 years	29.2 kg/m²	NR	33.9 events/hr	15.4	11%	■ Blacks: 3% ■ Caucasians: 97%
			CPAP, n = 63	57.4 years	30.6 kg/m²	NR	36.8 events/hr	14.6	32%	■ Blacks: 3% ■ Caucasians: 97%
Mehra, 2020[66] ADHERE Comparative NRS High	N = 350 Individuals eligible for HGNS implantation	9 academic medical centers (Germany, US)	HGNS, n = 230	57.5 years	29.8 kg/m²	NR	33.7 events/hr	12.3	16%	■ White: 99%
			No treatment, n = 100	57.3 years	29.3 kg/m²	NR	34.9 events/hr	10.9	30%	■ White: 98%
NON-COMPARATIVE COHORT STUDIES										
Boon, 2018[67] ADHERE High	N = 1,849[f] CPAP intolerant adults	50 tertiary care hospitals[g] (Belgium, Germany, Switzerland, the Netherlands, US)	HGNS, n = 1,849	60.1 years	29.3 kg/m²	NR	36.0 events/hr	11.2	27%	■ Caucasian: 95% ■ Non-Caucasian: 5%
Strollo, 2014[54] STAR NRS High	N = 126 CPAP intolerant adults	International sleep medicine and otolaryngology practices (Belgium, France, Germany, the Netherlands, US)	HGNS, n = 126	54.5 years	28.4 kg/m²	41.2 cm	32.0 events/hr	11.6	17%	■ White race: 97%

AUTHOR, YEAR STUDY OR REGISTRY NAME RISK OF BIAS	POPULATION DESCRIPTION	STUDY SETTING	STUDY GROUP	BASELINE CHARACTERISTICS						
				MEAN AGE	MEAN BMI	MEAN NECK SIZE	MEAN AHI	MEAN ESS	% FEMALE	% RACE/ETHNICITY[a]
Woodson, 2025[75,76] DREAM High	N = 115 CPAP intolerant adults	International academic and community sleep centers (Australia, Belgium, Germany, US)	HGNS, N = 115	56.8 years	28.5 kg/m^2	NR	28.0 events/hr	9.7	29.6%	■ Caucasian race: 93.9%
REGISTRIES										
Bellamkonda, 2021[65] MAUDE database High	N = 132 Reports on AEs filed under the manufacturer Inspire	US-based registry	HGNS, n = 132	NA	NA	NA	NA	NA	NA	NA
Bentan and Nord, 2024[74] MAUDE database High	N = 1,178 Reports on AEs using the code for HGNS	US-based registry	HGNS, n = 1,178	NA	NA	NA	NA	NA	NA	NA
Bestourous, 2020[64] MAUDE database High	N= 204 Reports on AEs filed under the HGNS Inspire	US-based registry	HGNS, n = 180[h]	NA	NA	NA	NA	NA	NA	NA
Commesso, 2025[72] MAUDE database High	N = 765 Reports on AEs using the code for HGNS	US-based registry	HGNS, n = 765	NA	NA	NA	NA	NA	NA	NA

AUTHOR, YEAR STUDY OR REGISTRY NAME RISK OF BIAS	POPULATION DESCRIPTION	STUDY SETTING	STUDY GROUP	BASELINE CHARACTERISTICS						
				MEAN AGE	MEAN BMI	MEAN NECK SIZE	MEAN AHI	MEAN ESS	% FEMALE	% RACE/ETHNICITY[a]
Lorenz, 2023[57] TriNetX Research Network High	N = 1,813 Participants with OSA who were implanted with HGNS	25 health care organizations in the US	HGNS, n = 1,813	59.9 years	NR	NR	NR	NR	32%	Race: ■ Black or African American: 5% ■ Other: 1% ■ White: 94% Ethnicity: ■ Hispanic or Latino: 4% ■ Not Hispanic or Latino: 96%
Moroco, 2024[56] Post market surveillance data High	N = 20,881 Implanted HGNS	476 reporting centers (Austria, Belgium, Finland, Germany, Spain, Switzerland, the Netherlands, US)	HGNS, n = 20,881	NA	NA	NA	NA	NA	NA	NA

Notes. [a] Terminology used is directly from study publications. [b] Missing baseline characteristics for this study were extrapolated from FDA criteria for implantation of the Inspire UAS system given the US population. [c] Modified intention to treat cohort. [d] This study includes non-FDA-approved device(s) and is not included in GRADE. [e] Sample size after propensity matching; N = 227. [f] As of March 2020. The most recent publication contains N = 2,755 participants as this is an ongoing trial that has not yet published final results. [g] Data from 2021 indicates there are now 53 tertiary care hospitals. [h] Reports suitable for analysis according to study authors.
Abbreviations. AEs: adverse events; AHI: apnea hypopnea index; BMI: body mass index; CPAP: continuous positive air pressure; ESS: Epworth Sleepiness Scale; FDA: US Food and Drug Administration; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations; HGNS: hypoglossal nerve stimulation; MAUDE: Manufacturer and User Facility Device Experience; NA: not applicable; NCT: national clinical trial; NR: not reported; NRS: nonrandomized study; OSA: obstructive sleep apnea; RCT: randomized controlled trial; UAS: upper airway stimulation; US: United States.

TABLE D3. ADDITIONAL STUDY CHARACTERISTICS: COMORBIDITIES AND CONCOMITANT MEDICATION USE IN PRIMARY STUDIES

AUTHOR, YEAR STUDY NAME	STUDY GROUP, N	COMORBIDITIES, N (%)	CONCOMITANT MEDICATION USE, N (%)
RCTs			
Dedhia, 2024[61] CARDIOSA-12	Total cohort (crossover RCT), n = 60	■ Diabetes: 15 (25) ■ Hypertension: 35 (58)	■ Receiving hypertension medications: 36 (60) ■ Smoking status: current: 6 (10); former: 27 (45)
Schwartz, 2023[55,a] THN3	HGNS, n = 92	■ Asthma: 4 (4) ■ Congestive heart failure: 0 ■ Diabetes: 5 (5) ■ Hypertension: 43 (46.7)	■ Antidepressants: 31 (34) ■ Current smoker: 9 (10) ■ Sedatives/hypnotics: 54 (59)
	Inactive device, n = 46	■ Asthma: 3 (7) ■ Congestive heart failure: 0 ■ Diabetes: 5 (11) ■ Hypertension: 23 (50)	■ Antidepressants: 14 (30) ■ Current smoker: 7 (15) ■ Sedatives/hypnotics: 21 (46)
COMPARATIVE COHORT STUDIES			
Heiser, 2023[59] Upper Airway Stimulation Versus Continuous Positive Airway Pressure	HGNS, n =63	■ Arterial hypertension: 23 (37) ■ Coronary heart disease:2 (3) ■ Diabetes mellitus: 7 (11)	NR
	CPAP, n = 63	■ Arterial hypertension: 22 (35) ■ Coronary heart disease: 4 (6) ■ Diabetes mellitus: 6 (10)	NR

AUTHOR, YEAR STUDY NAME	STUDY GROUP, N	COMORBIDITIES, N (%)	CONCOMITANT MEDICATION USE, N (%)
NONCOMPARATIVE COHORT STUDIES			
Boon, 2018[67] ADHERE	HGNS, n = 1,849	■ Anxiety: 106 (5.7) ■ Atrial fibrillation: 111 (6.0) ■ Depression: 426 (23.0) ■ Diabetes: 250 (13.5) ■ Hypertension: 866 (46.8) ■ Myocardial infarction: 68 (3.7) ■ Stroke: 79 (4.3)	NR
Strollo, 2014[54] STAR NRS	HGNS, n = 126	■ Asthma: 6 (5) ■ Congestive heart failure: 2 (2) ■ Diabetes: 11 (9) ■ Hypertension: 48 (38)	NR
None of the other included primary studies reported on comorbidities or concomitant medication use.			

Note. [a] This study includes non-FDA-approved device(s) and is not included in GRADE.
Abbreviations. CPAP: continuous positive airway pressure; FDA: US Food and Drug Administration; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations; HGNS: hypoglossal nerve stimulation; NR: not reported; NRS: nonrandomized study; RCT; randomized controlled trial.

TABLE D4. ADDITIONAL STUDY CHARACTERISTICS: SYSTEMATIC REVIEWS

AUTHOR, YEAR	REVIEW OBJECTIVE	PUBLICATION DATE RANGE	STUDY INCLUSION CRITERIA	STUDY EXCLUSION CRITERIA	TOTAL INCLUDED STUDIES STUDY DESIGNS	TOTAL PARTICIPANTS
Certal, 2015[63,a] Moderate	Systematically review the evidence regarding the key clinical questions of efficacy and safety of HGNS in the treatment of OSA	2010 to 2014	■ Studies with a primary objective of evaluating the efficacy of HGNS to treat OSA in adults ■ Studies that provided quantitative outcomes pre- and post-implantation of a HGNS device for AHI, ODI, and ESS	■ Studies that didn't include quantitative outcomes pre- and post-implantation of a HGNS device for AHI, ODI, and ESS ■ Studies focused on pediatric populations ■ Studies with less than 2 participants were excluded from the meta-analysis	N = 6 studies ■ Case report ■ Prospective case series	200 participants
Chu, 2024[73,a] Moderate	Explore reasons for HGNS device explantation and associated complications	2014 to 2023	■ Case series, case reports, cohort studies ■ Studies on HGNS for OSA on implantation and explantation ■ Adults ■ English only	■ Commentaries, meta-analyses, systematic reviews, book chapters, conference abstracts, study protocols, animal studies, letters to the editor ■ Non-English papers	N = 14 studies ■ Case report ■ Case series ■ Prospective cohort studies ■ Retrospective cohort studies	1,040 participants

AUTHOR, YEAR	REVIEW OBJECTIVE	PUBLICATION DATE RANGE	STUDY INCLUSION CRITERIA	STUDY EXCLUSION CRITERIA	TOTAL INCLUDED STUDIES STUDY DESIGNS	TOTAL PARTICIPANTS
Costantino, 2020[62,a] Moderate	Quantify long-term clinical outcomes for HGNS with a larger patient cohort through a systematic review and meta-analysis	2011 to 2018	■ Studies including adults with OSA ■ Studies on HGNS ■ Pre (baseline) and post-implantation data on AHI, ODI, ESS (at minimum) ■ Prospective studies ■ No language, publication date, follow-up, or publication status restrictions ■ Articles had to be published in a peer-reviewed journal	■ Animal study ■ Intervention other than HGNS ■ Children ■ Retrospective design ■ Insufficient data ■ Redundant cohort ■ Unrelated study ■ Non-original study	N = 12 studies ■ Prospective cohort studies	350 participants
Kompelli, 2019[58,a] High	Meta-analyze objective and subjective outcomes and side effects of HGNS for OSA	2001 to 2018	■ Studies with the primary objective of assessing HGNS to treat sleep apnea in adults	■ Case reports, review articles, and nonhuman studies ■ Articles without primary endpoints of AHI, ODI, and ESS	N = 16 studies ■ NR	NR
Wollny, 2024[68,a] Moderate	Synthesize the best-available information on HGNS safety and AEs for OSA	2012 to 2023	■ Studies with at least 10 participants ■ Studies published between 2000 to 2023 ■ Studies written in English	■ Case reports, review articles, editorials, abstracts ■ Nonhuman and in vitro studies ■ Pediatric populations	N = 17 studies ■ Cohort studies ■ RCTs	1,962 participants

AUTHOR, YEAR	REVIEW OBJECTIVE	PUBLICATION DATE RANGE	STUDY INCLUSION CRITERIA	STUDY EXCLUSION CRITERIA	TOTAL INCLUDED STUDIES STUDY DESIGNS	TOTAL PARTICIPANTS
			■ Studies with a follow-up at least 6 months post implant ■ Studies that reported on adverse events and complications related to HGNS	■ Language other than English		
Zhou, 2022[52] Moderate	Evaluate and compare the efficacy of MMA and HGNS for moderate-to-severe OSA through the assessment of AHI and ESS as well as assess postoperative complications	1997 to 2021 (all studies) 2012 to 2021 (HGNS studies only)	■ Studies on adult patients with moderate-to-severe OSA who underwent MMA or HGNS ■ Studies that reported pre- and post-operative PSG data ■ Studies with a follow-up ≥ 6 months ■ Study designs: RCTS, quasi-experimental studies, and cohort studies ■ English language	■ Sample size < 10 patients ■ Patients who underwent other adjunctive surgical procedures at the time of MMA or HGNS ■ Preliminary studies in which the findings had been nested in other studies with larger sample size and/or longer follow-up	N = 30 (studies on MMA or HGNS) ■ Prospective cohort studies ■ Retrospective cohort studies	N = 1,029 (in the 9 studies on HGNS)

Note. [a] This study includes non-FDA-approved device(s) and is not included in GRADE.
Abbreviations. AEs: adverse events; AHI: apnea hypopnea index; ESS: Epworth Sleepiness Scale; FDA: US Food and Drug Administration; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations; HGNS: hypoglossal nerve stimulation; MMA: maxillomandibular advancement; NR: not reported; ODI: oxygen desaturation index; OSA: obstructive sleep apnea; PSG: polysomnogram; RCT: randomized controlled trial.

TABLE D5. CLINICAL RESEARCH POPULATION OVERLAP WITH KEY FDA CRITERIA AND WARNINGS FOR HGNS

	Woodson, 2014[51]	Mehra, 2020[64]	Heiser, 2021[58]	Heiser, 2023[57]	Dedhia, 2024[59]
	STAR RCT	ADHERE Comparative	EFFECT		CARDIOSA-12
STUDY PARTICIPANT SELECTION CRITERIA RELEVANT TO INSPIRE UAS SYSTEM FDA LABELS					
AHI, events per hour (pre-implant)					
15–65 (FDA Inspire UAS 2014 and Genio System 2025 approval)	✓[a]	✓	✓[b]	✓	✓[b]
15–100 (FDA Inspire UAS 2023 expansion)					
Upper limit of BMI warning (kg/m^2)					
32 (FDA Inspire UAS 2014 and Genio System 2025 approval)	✓	✓[c]	✓[b]	✓[d]	✓[b]
40 (FDA Inspire UAS 2023 expansion)					
PAP Failure or Intolerance	✓	✓	✓	✓	✓
DISE Findings Consistent with Absence of Concentric Collapse	✓	✓	✓	✓	✓

Table Key. A check indicates the criterion was used as part of research participant selection criteria. Blank cells indicate the criterion did not apply to the study or falls into a different category (for AHI and BMI demographics).

Notes. [a] AHI enrollment criteria for the STAR study was 20–50 events per hour. [b] No upper AHI or BMI limits were defined for participants in the EFFECT and CARDIOSA-12 trials; however, participants were implanted with the Inspire UAS system in community settings before enrollment and were subject to the pre-2023 FDA criteria. [c] No defined BMI enrollment criteria, but mean baseline BMI was < 32. [d] BMI enrollment threshold ≤ 35, but mean baseline BMI was < 32.

Abbreviations. AHI: apnea hypopnea index; BMI: body mass index; DISE: drug-induced sleep endoscopy; FDA: United States Food and Drug Administration; HGNS: hypoglossal nerve stimulation; PAP: positive airway pressure.

TABLE D6. QUALITY OF LIFE OUTCOMES

STUDY INFO	STUDY DESIGN	TIME POINT	MEASURE	HGNS		CONTROL		BETWEEN-GROUP ESTIMATE	*P* VALUE
				N	MEAN (SD)	N	MEAN (SD)		
FUNCTIONAL OUTCOMES OF SLEEP QUESTIONNAIRE (FOSQ)[a]									
Heiser, 2021[60] EFFECT N = 89 High RoB	Crossover RCT ■ Inspire UAS ■ Subtherapeutic stimulation	2 wk	Mean	86	17.0 (3.2)	86	14.9 (3.6)	NR	*P* < .001
			CFB	86	+0.2 (95% CI, −0.5 to 0.9)	86	−1.9 (95% CI, −2.6 to −1.2)	MD, 2.1 (95% CI, 1.4 to 2.8)	*P* < .001
Mehra, 2020[66] ADHERE Comp. N = 350 High RoB	Cohort study ■ Inspire UAS ■ No therapy	6 mo	Mean	221	17.1 (3.2)	75	12.4 (3.7)	NR	*P* < .001
Schwartz, 2023[55] THN3 N = 138 High RoB	RCT ■ aura6000 ■ Inactive device	4 mo	CFB	92	+5.3 (13.4)	46	+0.6 (8.4)	MD, 4.7 (95% CI, 0.9 to 8.6)	NR
Woodson, 2014[53] STAR RCT N = 46 High RoB	RCT ■ Inspire UAS ■ Inactive device	1 mo	Mean	23	17.9 (2.9)	23	15.0 (4.0)	MD, 2.9 (95% CI, 0.8 to 5.0)	*P* = .008
			CFB	23	0.0 (1.0)	23	−2.3 (3.0)	MD, −2.3 (95% CI, −3.8 to −0.9)	*P* = .001
EUROQOL 5D VISUAL ANALOGUE SCALE (EQ-5D VAS)[b]									
Schwartz, 2023[55] THN3 N = 138 High RoB	RCT ■ aura6000 ■ Inactive device	4 mo	CFB	92	+2.5 (3.0)	46	+1.1 (3.2)	MD, 1.5 (95% CI, 0.3 to 2.6)	NR

Notes. [a] FOSQ score range, 5–20 points; higher scores are better; MCID ≥ 1 point.[78,79] [b] EQ-5D VAS score range, 0–100 points; higher scores are better; MCID not established.
Abbreviations. CFB: change from baseline; CI: confidence interval; HGNS: hypoglossal nerve stimulation; MCID: minimal clinically important difference; MD: mean difference; mo; month; NR: not reported; RCT: randomized controlled trial; RoB: risk of bias; SD: standard deviation; UAS: upper airway stimulation, wk: week.

TABLE D7. REPORTED DEVICE-RELATED SERIOUS ADVERSE EVENTS IN ≥2 ELIGIBLE STUDIES

AUTHOR, YEAR STUDY OR REGISTRY NAME HGNS DEVICE	STUDY DESIGN	TIMEPOINT	DEVICE-RELATED SAEs FOR HGNS[a]
DEVICE REVISIONS			
Schwartz, 2023[55,b,c] THN3 aura6000	RCT	12 mos	▪ 10 events ▪ 9 out of 138 participants (6.5%) **Revision reasons NR**
Mehra, 2020[66] ADHERE comparative Inspire UAS	Comparative cohort	6 mos	▪ 2 events ▪ 1 out of 230 participants (0.4%) **Reported revision reasons:** uncomfortable stimulation lead position
Boon, 2018[67,69] ADHERE Inspire UAS	Noncomparative cohort	12 mos	▪ 13 out of 1,849 participants (0.7%) (sensor lead revision)[d] ▪ 12 out of 1,849 participants (0.7%) (stimulation lead revision)[d] ▪ 2 out of 1,849 participants (0.1%) (IPG pocket revision)[d] ▪ 3 out of 1,849 participants (0.2%) (system revision, 2 or more components)[d] **Revision reasons NR**
Strollo, 2014[54,71] STAR NRS Inspire UAS	Noncomparative cohort	5 yrs	▪ 9 events ▪ 8 out of 126 participants (6.3%) **Reported revision reasons:** resolution of discomfort, unfavorable tongue placement, to improve response, insulation failure, and stimulation lead cut
Woodson, 2025[75] DREAM Genio System	Noncomparative cohort	12 mos	▪ 2 out of 115 participants (1.7%) **Reported revision reasons:** device malfunction resulting in replacement

AUTHOR, YEAR STUDY OR REGISTRY NAME HGNS DEVICE	STUDY DESIGN	TIMEPOINT	DEVICE-RELATED SAEs FOR HGNS[a]
Chu, 2024[73,b,c,e] Apnex Medical HGNS Inspire UAS NR	SR	NR	■ 13 out of 1,040 participants (1.3%) ■ **Reported revision reasons:** device malfunction, infection, device migration, discomfort, improper placement, ineffective device, post-implantation complications, need for MRI, traction, elective removal, nerve palsy, poor cosmesis, mixed tongue activity, unrelated systematic septic arthritis, overstimulation, need for unrelated surgery
Zhou, 2022[52e] Inspire UAS	SR	NA	■ In 4 out of 5 studies reporting on patient complications there were 50 serious device-related AEs that required surgical repositioning or replacement of the neurostimulator or implanted leads **Reported revision reasons:** serious device-related AEs
Wollny, 2024[68,c,e] Inspire UAS Apnex HGNS System aura6000 Genio System	SR	NR	■ Pooled rate: 0.08% (95% CI, 0.0 to 0.2%) **Reported revision reasons:** hematoma or seroma, scar corrections, or repositioning of device components due to discomfort or technical dysfunction
Commesso, 2025[72,f, g] MAUDE database Inspire UAS	Registry	NR	■ 7 out of 12 reports on adverse events related to whole respiratory lead migration (58.3%) ■ **Reported revision reasons:** pain, pneumothorax, lump, dehiscence, dyspnea
Bestourous, 2020[64,f,g] MAUDE database Inspire UAS	Registry	NR	■ 83 out of 196 adverse events (42.3%) **Reported revision reasons:** pain, allergic reaction, infection, hematoma/seroma, neck swelling, neuropraxia, overstimulation, muscle tethering/traction, device expulsion through skin, postoperative complications, IPG, sensing lead, stimulation lead, device placement

AUTHOR, YEAR STUDY OR REGISTRY NAME HGNS DEVICE	STUDY DESIGN	TIMEPOINT	DEVICE-RELATED SAEs FOR HGNS[a]
Lorenz, 2023[57] TriNetX Research Network Inspire UAS	Registry	NR	■ 25 out of 1,813 participants (1.4%)[h] **Revision reasons NR**
Morocco, 2024[56] Post market surveillance data Inspire UAS	Registry	12 mos	■ 322 out of 20,881 devices (1.5%) **Reported revision reasons:** surgical correction, device correction, device defect, twiddler syndrome, cardioversion, other causes
		12 mos to 3 yrs	■ 207 out of 5,820 devices (3.6%) **Reported revision reasons:** surgical correction, device defect, device correction, twiddler syndrome, cardioversion, other indications
DEVICE EXPLANTS			
Schwartz, 2023[55,b,c] THN3 aura6000	RCT	12 mos	■ 10 events ■ 9 out of 138 participants (6.5%) **Explant reasons NR**
Boon, 2018[67,69] ADHERE Inspire UAS	Noncomparative cohort	12 mos	■ 1 out of 1,849 participants (0.05%)[c] **Explant reasons NR (elective explant)**
Strollo, 2014[54,71] STAR NRS Inspire UAS	Noncomparative cohort	5 yrs	■ 3 events ■ 3 out of 126 participants (2.4%) **Reported explant reasons:** implantable pulse generator removal in a nonresponder, system removal in a nonresponder, nonelective removal in a nonresponder due to septic arthritis

AUTHOR, YEAR STUDY OR REGISTRY NAME HGNS DEVICE	STUDY DESIGN	TIMEPOINT	DEVICE-RELATED SAEs FOR HGNS[a]
Woodson, 2025[75] DREAM Genio System	Noncomparative cohort	12 mos	■ 3 out of 115 participants with an SAE-related explant (2.6%) ■ 3 out of 115 participants with a non-SAE-related explant (2.6%) ■ 6 out of 115 participants with any device explant (5.2%) **Reported explant reasons:** failure of hypoglossal nerve activation due to postoperative device migration (scar tissue prevented reimplantation), device extrusion during a dental procedure, device malfunction, loss of stimulation due to undetermined cause
Certal, 2014[63, c] Apnex HGNS System aura6000 Inspire UAS	SR	NA	■ 9 out of 200 participants (4.5%) **Reported explant reasons:** serious-device related AEs
Chu, 2024[73,b,c,e] Apnex Medical HGNS Inspire UAS NR	SR	NR	■ 13 out of 1,040 participants (1.3%) ■ **Reported explant reasons:** device malfunction, infection, device migration, discomfort, improper placement, ineffective device, post-implantation complications, need for MRI, traction, elective removal, nerve palsy, poor cosmesis, mixed tongue activity, unrelated systematic septic arthritis, overstimulation, need for unrelated surgery
Wollny, 2024[68,c,e] Inspire UAS Apnex HGNS System aura6000 Genio System	SR	12 mos (median)	■ System survival probability: 0.99 (95% CI, 0.98 to 0.99)
		5 yrs (maximum)	■ System survival probability: 0.98 (95% CI, 0.98 to 0.99) **Reported explant reasons**: most common reasons were infection in the implant area and patient request for various reasons
Bellamkonda, 2021[65,f,g] MAUDE database Inspire UAS	Registry	5 yrs	■ 17 out of 134 reports (12.7%) **Reported explant reasons:** infection, vocal cord weakness, CN VII palsy, hematoma, twiddler's syndrome, lead erosion, lead wire protrusion from wound

AUTHOR, YEAR STUDY OR REGISTRY NAME HGNS DEVICE	STUDY DESIGN	TIMEPOINT	DEVICE-RELATED SAEs FOR HGNS[a]
Bentan and Nord, 2024[74,g] MAUDE database Inspire UAS	Registry	NR	■ 253 out of 1,025 procedure-related adverse events (24.7%) ■ 85 out of 287 device-related adverse events (29.6%) ■ **Reported explant reasons:** pain, infection, hematoma or seroma, edema or swelling, neuropraxia, pneumothorax, allergic reaction, stimulation discomfort, lead tethering or traction, device erosion or skin extrusion, device migration, twiddler syndrome
Commesso, 2025[72,f,g] MAUDE database Inspire UAS	Registry	NR	■ 3 out of 12 reports on adverse events related to whole respiratory lead migration (25%) ■ **Reported explant reasons:** malfunction, infection, dehiscence, pain, pneumothorax
Lorenz, 2023[57] TriNetX Research Network Inspire UAS	Registry	NR	■ 22 out of 1,813 participants (1.2%) **Explant reasons NR**
Morocco, 2024[56] Post market surveillance data Inspire UAS	Registry	12 mos	■ 151 out of 20,881 devices (0.7%) **Reported explant reasons:** infection, elective removal, lack of symptom relief, inadequate effectiveness, pain, discomfort, MRI, twiddler syndrome, other reasons or indications
		12 mos to 3 yrs	■ 156 out of 5,820 devices (2.7%) **Reported explant reasons:** no symptom relief, pain, removal due to MRI, infection, twiddler syndrome, other reasons or indications
INFECTIONS			
Boon, 2018[67,69] ADHERE Inspire UAS	Noncomparative cohort	12 mos	■ 1 out of 1,849 participants (0.05%)[i]

AUTHOR, YEAR STUDY OR REGISTRY NAME HGNS DEVICE	STUDY DESIGN	TIMEPOINT	DEVICE-RELATED SAEs FOR HGNS[a]
Lorenz, 2023[57] TriNetX Research Network Inspire UAS	Registry	NR	■ 17 out of 1,813 participants (0.9%)[j]
PNEUMOTHORAX			
Boon, 2018[67,69] ADHERE Inspire UAS	Noncomparative cohort	12 mos	■ 1 out of 1,849 participants (0.05%)[i]
Bentan and Nord, 2024[74,f,g] MAUDE database Inspire UAS	Registry	NR	■ 50 out of 1,025 procedure-related adverse events (4.9%)
Commesso, 2025[72,f,g] MAUDE database Inspire UAS	Registry	NR	■ 2 out of 12 reports on adverse events related to whole respiratory lead migration (16.7%)
Lorenz, 2023[57] TriNetX Research Network Inspire UAS	Registry	NR	■ 44 out of 1,813 participants (2.4%)
TOTAL SAEs			
Boon, 2018[67,69] ADHERE Inspire UAS	Noncomparative cohort	12 mos	■ 426 out of 1,849 participants (2.3%) [total SAEs][k] ■ 8 out of 1,849 participants (0.4%) [total intraoperative SAEs] ■ 35 out of 1,849 participants (1.9%) [total follow-up period SAEs]
Strollo, 2014[54] STAR NRS Inspire UAS	Noncomparative cohort	21 mos	■ 35 events ■ 27 out of 126 participants (21.4%)

AUTHOR, YEAR STUDY OR REGISTRY NAME HGNS DEVICE	STUDY DESIGN	TIMEPOINT	DEVICE-RELATED SAEs FOR HGNS[a]
Woodson, 2025[75] DREAM Genio System	Noncomparative cohort	12 mos	■ 11 events ■ 8 device- or procedure-related events ■ 10 out of 115 participants (8.7%)
Constantino, 2020[62,c] Apnex HGNS System aura6000 Inspire UAS	SR	NA	■ 14 events ■ 12 out of 195 participants (6.2%)
Bestourous, 2020[64,f,g] MAUDE database Inspire UAS	Registry	NR	■ 1 out of 146 patient-related adverse events (0.7%)

Notes. [a] This is referring to the intervention group (active HGNS) unless otherwise specified. [b] These are reported as combined device explants, revisions, and replacements in the study publication so are reported in both sections of this table. [c] This study includes non-FDA-approved device(s) and is therefore not included in GRADE. [d] Reported as a follow-up period SAE. [e] This SR includes primary studies that have also been included in this review, due to this there is some suspected overlap in the data. [f] This study is only collecting reports on AEs for the FDA-approved HGNS device, the Inspire UAS system. [g] There is likely overlap across all the MAUDE data. [h] Reported as combined "revision/replacement" in the study publication. [i] Reported as an intraoperative SAE. [j] It is unclear if any of these events were serious. [k] Unclear if all events are treatment related.

Abbreviations. AEs: adverse events; CN: cranial nerve; FDA: US Food and Drug Administration; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations; HGNS: hypoglossal nerve stimulation; IPG: implanted pulse generator; MAUDE: Manufacturer and User Facility Device Experience; mos: months; MRI: magnetic resonance imaging; NA: not applicable: NR: not reported; NRS: nonrandomized study; RCTs: randomized controlled trials; SAEs: serious adverse events; SR: systematic review; UAS: upper airway stimulation. wks: weeks; yrs: years.

TABLE D8. OSA SEVERITY OUTCOMES

STUDY INFO	STUDY DESIGN	TIME POINT	MEASURE	HGNS		CONTROL		BETWEEN-GROUP ESTIMATE	*P* VALUE
				N	MEAN (SD)	N	MEAN (SD)		
APNEA-HYPOPNEA INDEX (AHI)[a,b]									
Dedhia, 2024[61] CARDIOSA-12 N = 62 Moderate RoB	Crossover RCT ■ Inspire UAS ■ Subtherapeutic stimulation	10 wk	Mean	60	18.1 (14.8)	60	23.0 (15.6)	MD, –4.9 (95% CI, –8.8, to –1.0)	NR
Heiser, 2021[60] EFFECT N = 89 High	Crossover RCT ■ Inspire UAS ■ Subtherapeutic stimulation	2 wk	CFB	86	+0.6 (95% CI, –1.8 to 2.9)	86	+16.1 (95% CI, 13.7, 18.4)	MD, –15.5 (95% CI, –18.3 to –12.8)	*P* < .001
			AHI < 15	45	33 (73.3%)	44	13 (29.5%)	MD, 43.8% (95% CI, 25.1 to 62.5)	*P* < .001
			AHI < 10	45	23 (51.1%)	44	7 (15.9%)	NR	NR
			AHI < 5	45	16 (35.6%)	44	0 (0%)	NR	NR
Heiser, 2023[59] N = 126 High RoB	Cohort study ■ Inspire UAS ■ CPAP	12 mo	Mean	63	8.1 (6.3)	63	6.6 (8.0)	NR	NR
			CFB	63	–23.0 (13.0)	63	–30.9 (NR)	NR	*P* = .08
			AHI < 15	63	53 (84.0%)	63	55 (87.0%)	NR	*P* = .63
			AHI < 10	63	47 (74.0%)	63	51 (81.0%)	NR	*P* = .27
			AHI < 5	63	32 (51.0%)	63	37 (59.0%)	NR	*P* = .27
Mehra, 2020[66] ADHERE Comp. N = 350 High RoB	Cohort study ■ Inspire UAS ■ No therapy	6 mo	Mean	228	14.7 (13.8)	100	26.8 (17.6)	NR	*P* < .001
			CFB	228	–19.1 (15.8)	100	–8.1 (20.9)	NR	*P* < .001
Schwartz, 2023[55] THN3 N = 138	RCT ■ aura6000 ■ Inactive device	4 mo	Mean	88	24.1 (NR)	46	32.0 (NR)	NR	*P* < .002
			≥ 50% reduction	88	46 (52.3%)	46	9 (19.6%)	RR, 32.7 (95% CI, 15.2 to 49.0)	NR

STUDY INFO	STUDY DESIGN	TIME POINT	MEASURE	HGNS		CONTROL		BETWEEN-GROUP ESTIMATE	*P* VALUE
				N	MEAN (SD)	N	MEAN (SD)		
High RoB			*and* < 20 events/hr						
Woodson, 2014[53] STAR RCT N = 46 High RoB	RCT ■ Inspire UAS ■ Inactive device	1 mo	Mean	23	8.9 (9.1)	23	25.8 (16.2)	MD, −16.9 (95% CI, −24.7 to −9.0)	*P* < .001
			CFB	23	+1.7 (6.4)	23	+18.2 (15.6)	MDIC, 16.4 (95% CI, 9.2 to 23.7)	*P* < .001
OXYGEN DESATURATION INDEX (ODI) [a,c]									
Heiser, 2021[60] EFFECT N = 89 High RoB	Crossover RCT ■ Inspire UAS ■ Subthera-peutic stimulation	2 wk	CFB	86	+0.6 (95% CI, −1.9 to 3.0)	86	+12.7 (95% CI, 10.3 to 15.2)	MD, −12.2 (95% CI, −14.8 to −9.6)	*P* < .001
Mehra, 2020[66] ADHERE Comp. N = 350 High RoB	Cohort study ■ Inspire UAS ■ No therapy	6 mo	Mean	219	14.1 (14.1)	96	25.5 (17.9)	NR	*P* < .001
Schwartz, 2023[55] THN3 N = 138 High RoB	RCT ■ aura6000 ■ Inactive device	4 mo	Mean	85	26.3 (NR)	46	33.8 (NR)	NR	*P* < .002
			≥ 25% reduction	85	55 (62.5%)	46	19 (41.3%)	RR, 21.2 (95% CI, 3.3 to 38.1)	NR
Woodson, 2014[53] STAR RCT N = 46 High RoB	RCT ■ Inspire UAS ■ Inactive device	1 mo	Mean	23	8.0 (8.9)	23	23.0 (15.6)	MD, −15.1 (95% CI, −22.7 to −7.5)	*P* < .001
			CFB	23	+1.6 (5.8)	23	+17.0 (14.5)	MD, −15.4 (95% CI, −22.1 to −8.7)	*P* < .001

Notes. [a] AHI and ODI are measured as events per hour of sleep; lower scores are better; MCID ≥ 5 events per hour.[79] [b] All studies assessed AHI4, meaning that hypopneas were defined as a reduction in airflow ≥ 30% for at least 10 sections with a blood oxygen desaturation of ≥ 4%. [c] All studies applied an oxygen desaturation threshold of ≥ 4%.
Abbreviations. AHI: apnea-hypopnea index; CFB: change from baseline; CI: confidence interval; CPAP: continuous positive airway pressure; HGNS: hypoglossal nerve stimulation; hr: hour; MCID: minimal clinicallyimportant difference; MD: mean difference; mo; month; NR: not reported; ODI: oxygen desaturation index; RCT: randomized controlled trial; RoB: risk of bias; SD: standard deviation; UAS: upper airway stimulation, wk: week.

TABLE D9. DAYTIME SLEEPINESS OUTCOMES

STUDY INFO	STUDY DESIGN	TIME POINT	MEASURE	HGNS		CONTROL		BETWEEN-GROUP ESTIMATE	*P* VALUE
				N	MEAN (SD)	N	MEAN (SD)		
EPWORTH SLEEPINESS SCALE (ESS)[a]									
Heiser, 2021[60] EFFECT N = 89 High RoB	Crossover RCT ■ Inspire UAS ■ Subtherapeutic stimulation	1 wk	CFB	45	+0.4 (2.3)	44	+5.0 (4.6)	MD, −4.6 (95% CI, −6.1 to −3.1)	*P* < .001
		2 wk	CFB	86	+0.2 (95% CI,0.7 to 1.1)	86	+3.5 (95% CI, 2.6 to 4.4)	MD, −3.3 (95% CI, −4.4 to −2.2)	*P* < .001
Heiser, 2023[59] N = 126 High RoB	Cohort study ■ Inspire UAS ■ CPAP therapy	12 mo	Mean	63	7.5 (4.7)	63	10.8 (5.6)	NR	*P* = .27
			CFB	63	−8.0 (5.1)	63	−3.9 (6.8)	NR	*P* = .04
Mehra, 2020[66] ADHERE Comp. N = 350 High RoB	Cohort study ■ Inspire UAS ■ No therapy	6 mo	Mean	226	7.2 (4.8)	90	12.8 (5.2)	NR	*P* < .001
			CFB	222	-5.1 (5.5)	75	+1.8 (3.7)	NR	*P* < .001
Schwartz, 2023[55] THN3 N = 138 High RoB	RCT ■ aura6000 ■ Inactive device	4 mo	CFB	92	−4.4 (4.2)	46	−1.1 (3.5)	SMD, −0.86 (95% CI, −1.29 to −0.50)	NR
Woodson, 2014[53] STAR RCT N = 46 High RoB	RCT ■ Inspire UAS ■ Inactive device	1 mo	Mean	23	5.6 (3.9)	23	10.0 (6.0)	MD, −4.5 (95% CI, −7.5 to −1.4)	*P* = .005
		1 mo	CFB	23	+0.3 (1.8)	23	+3.1 (4.6)	MD, 4.2 (95% CI, 2.0 to 6.4)	*P* < .001

Notes. [a] ESS score range, 0–24 points; lower scores are better; MCID ≥ 2 points.[79,81]
Abbreviations. CFB: change from baseline; CI: confidence interval; CPAP: continuous positive airway pressure; ESS: Epworth Sleepiness Scale; HGNS: hypoglossal nerve stimulation; MCID: minimal clinically important difference; MD: mean difference; mo; month; NR: not reported; RCT: randomized controlled trial; RoB: risk of bias; SD: standard deviation; SMD: standardized mean difference; UAS: upper airway stimulation, wk: week.

TABLE D10. ONGOING STUDIES OF HGNS FOR ADULTS WITH OSA

REGISTRY NUMBER STUDY TITLE	STUDY DESIGN	SAMPLE SIZE FOLLOW-UP LOCATION(S)	KEY ENROLLMENT CRITERIA	INTERVENTION CONTROL GROUP(S)	RELEVANT OUTCOMES	PRIMARY COMPLETION DATE
NCT04031040[83] A Post-Market Clinical Follow up of the Genio System for the Treatment of Obstructive Sleep Apnea in Adults (EliSA)	NRS (single-arm study)	N = 110 12 months Belgium, France, Germany, Netherlands, Switzerland	AHI 15-65 events/hr BMI < 35 kg/m^2	Genio System No control group	■ Quality of life ■ SAE[a] ■ OSA severity[b]	September 2022
NCT04950894[87] Treating Obstructive Sleep Apnea Using Targeted Hypoglossal Neurostimulation (OSPREY)	Crossover RCT	N = 150 13 months[c] US	Moderate to severe OSA diagnosis BMI < 35 kg/m^2	aura6000 Inactive device	■ Quality of life ■ SAE ■ OSA severity ■ Daytime sleepiness	October 2023
NCT03868618[90] Dual-Sided Hypoglossal Nerve Stimulation for the Treatment of Obstructive Sleep Apnea (DREAM)	NRS (single-arm study)	N = 115 12 months (primary) 5 years (extension) US, Australia, Belgium, Germany	Likely diagnosis of moderate to severe OSA	Genio System No control group	■ SAE ■ OSA severity	February 2024 (primary) February 2028 (extension)
NCT02413970[91] Inspire Upper Airway Stimulation System: Post-Approval Study	NRS (single-arm study)	N = 127 Up to 5 years US	AHI ≥ 15 events/hr	Inspire UAS No control group	■ SAE ■ OSA severity ■ Daytime sleepiness	March 2025

REGISTRY NUMBER STUDY TITLE	STUDY DESIGN	SAMPLE SIZE FOLLOW-UP LOCATION(S)	KEY ENROLLMENT CRITERIA	INTERVENTION CONTROL GROUP(S)	RELEVANT OUTCOMES	PRIMARY COMPLETION DATE
NCT02907398[88] Adherence and Outcome of Upper Airway Stimulation for OSA International Registry (ADHERE)	Registry	N = 5000 12 months US, Belgium, Germany, Netherlands, Switzerland	Implanted with Inspire UAS	Inspire UAS Control group	■ Quality of life ■ OSA severity ■ Daytime sleepiness	September 2025
NCT05592002[92] Safety and Effectiveness of the Genio Bilateral Stimulation for Treatment of Complete Concentric Collapse and OSA (ACCCESS)	NRS (single-arm study)	N = 124 4.5 years US	AHI 15-65 events/hr BMI ≤ 32 kg/m^2 Complete concentric collapse of soft palate	Genio System No control group	■ OSA severity	January 2026
NCT07331285[93] Bi-lateral HGN Therapy in Real-World Patients - Post Approval Research Investigation (BREATHE)	NRS (single-arm study)	N = 229 5 years US	Adults 22 years and older AHI 15–65 events/hr BMI ≤ 32 kg/m^2 Complete concentric collapse of soft palate	Genio System No control group	■ OSA severity ■ Daytime sleepiness ■ SAE	October 2028 (overall completion October 2032)
NCT06332404[89] Hypoglossal Nerve Stimulation Therapy in Patients With Obstructive Sleep Apnea: Belgian Registry (B-HNS)	Registry (single-arm study)	N = 225 5 years Belgium	Implanted with Inspire UAS AHI 15-65 events/hr BMI ≤ 32 kg/m^2	Inspire UAS No control group	■ Quality of life ■ OSA severity ■ Daytime sleepiness	April 2034

Notes. Table reflects studies registered on ClinicalTrials.gov as of May 2024. [a] SAE includes both procedure- and device-related SAEs. [b] OSA severity refers to polysomnography outcomes. [c] This study has a total duration of 13 months, but AHI outcomes between the treatment and control groups are assessed at 7 months.
Abbreviations. AHI: apnea-hypopnea index; BMI: body mass index; HGNS: hypoglossal nerve stimulation; NRS: nonrandomized study; OSA: obstructive sleep apnea; RCT: randomized controlled trial; SAE: serious adverse events; UAS: upper airway stimulation.

TABLE D11. FDA SUPPLEMENTAL ANALYSIS OF ADHERE REGISTRY STUDY PARTICIPANTS THROUGH 2022

	ORIGINAL INSPIRE APPROVAL (2014)	SUPPLEMENTAL INSPIRE APPROVAL (2023)
AHI		
AHI Limit	≥ 20 and ≤ 65	≥ 15 and ≤ 100
Type of Supportive Evidence	Data from 1 multi-center, prospective trial with a 12-month single arm study and a responder-only withdrawal RCT at 13 months (STAR Trial)[a] ▪ Patients with AHI > 50 were excluded ▪ Mean AHI in withdrawal RCT: 30.7 (11.9)	Stratified outcomes data from 1 prospective, single-arm, observational registry study (ADHERE) analyzed by FDA[b] ▪ AHI ≤ 65: N = 1,483 ▪ AHI > 65 to ≤ 100: N = 57
Relevant Findings	**Study outcomes not evaluated by AHI subgroup** Cohort study: AHI responder rate[c] at 12 months ▪ 66% (81 of 126 participants); *P* = .0002 RCT: Significant improvement in outcomes for active treatment group (vs. inactive device) at 1 month: ▪ Final AHI: 8.9 vs. 25.8; *P* < .001 ▪ Final ESS: 5.6 vs. 10.0; *P* = .005	**No statistically significant difference between the groups (AHI ≤ 65 vs. AHI > 65 to ≤ 100):** ▪ Final AHI: 15.6 vs. 18.8; *P* = .66 ▪ AHI responder rate[c]: 64.3% vs. 66.7%; *P* = .87 ▪ Final ESS: 6.9 vs. 6.4; *P* = .31 ▪ Change in ESS: -4.5 vs, -4.0; *P* = .47 Similar profile of device-related adverse events ▪ Participants with AE: 3.7% vs. 2.4% (*P* value NR) ▪ Participants with SAE: 0.7% vs. 0% (*P* value NR)
BMI		
Upper Limit of BMI Warning	32 kg/m^2	40 kg/m^2
Type of Supportive Evidence	Data from 1 multi-center, prospective trial with a 12-month single arm study and a responder-only withdrawal RCT at 13 months (STAR Trial)[a] ▪ Patients with BMI > 32 were excluded ▪ Mean BMI in withdrawal RCT: 28.4 (2.6)	Stratified outcomes data from 1 prospective, single-arm, observational registry study (ADHERE) analyzed by FDA[b] ▪ BMI ≤ 32: N = 1,218 (mean: 27.8 [2.8]) ▪ BMI >32 to ≤ 40: N = 279 (mean: 34.0 [1.6])
Relevant Findings	**Study outcomes not evaluated by BMI subgroup** Cohort study: AHI responder rate[c] at 12 months	**No statistically significant difference between the groups (BMI ≤ 32 vs. BMI >32 to ≤ 40):** ▪ Final AHI: 15 vs. 17; *P* = .09

ORIGINAL INSPIRE APPROVAL (2014)	SUPPLEMENTAL INSPIRE APPROVAL (2023)
■ 66% (81 of 126 participants); *P* = .0002 RCT: Significant improvement in outcomes for active treatment group (vs. inactive device) at 1 month: ■ Final AHI: 8.9 vs. 25.8; *P* < .001 ■ Final ESS: 5.6 vs. 10.0; *P* = .005	■ Change in AHI: -20 vs. -21; *P* =.74 ■ AHI responder rate[c,d]: 65% vs. 61%; *P* = .24 ■ Final ESS: 6.9 vs. 6.8; *P* = .79 ■ Change in ESS: -4.6 vs, -4.3; *P* = .47 Similar profile of device-related adverse events ■ Participants with AE: 3.7% vs. 3.2% (*P* value NR) ■ Participants with SAE: 0.7% vs. 0.7% (*P* value NR)

Notes. [a] Inspire UAS 2014 Premarket Approval (P130008) data: https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130008B.pdf. [b] Inspire UAS 2023 supplemental approval (P130008/S090) data: https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130008S090B.pdf. [c] Based on Sher criteria: reduction in AHI of at least 50% and a final AHI of less than 20 events per hour.[d] Additional BMI subgroup analysis (specific outcomes data not reported): "When the data on the BMI groups was further analyzed using groups of BMI≤32, 32<BMI≤35, 35<BMI≤40, it was noted that the Sher responder rate was not statistically different across the three groups."

Abbreviations. AE: adverse events; AHI: apnea-hypopnea index; BMI: body mass index; ESS: Epworth Sleepiness Scale; FDA: US Food and Drug Administration; NR: not reported; RCT: randomized controlled trial; SAE: serious adverse events.

APPENDIX E. APPLICABLE CODES

TABLE E1. APPLICABLE CODES FOR HYPOGLOSSAL NERVE STIMULATION

CODE	DESCRIPTION
ICD-10-CM CODES	
G47.33	Obstructive sleep apnea (adult) (pediatric)
CPT CODES	
64568	Incision for implantation of cranial nerve (e.g.: vagus nerve) neurostimulator electrode array and pulse generator
64582	Open implantation of hypoglossal nerve neurostimulator array, pulse generator and distal respiratory sensor electrode or electrode array.
64583	Revision or replacement of hypoglossal nerve neurostimulator array and distal respiratory sensor electrode or electrode array, including connection to existing pulse generator.
64584	Removal of hypoglossal nerve neurostimulator array, pulse generator, and distal respiratory sensor electrode or electrode array.
0466T	Insertion of chest wall respiratory sensor electrode or electrode array, including connection to pulse generator (list separately in addition to code for primary procedure)
0467T	Revision or replacement of chest wall respiratory sensor electrode or electrode array, including connection to existing pulse generator
0468T	Removal of chest wall respiratory sensor electrode or electrode array
HCPCS CODES	
	None reported

Abbreviations. CPT: Current Procedural Terminology; HCPCS: Healthcare Common Procedure Coding System; ICD-10-CM: International Classification of Diseases, Tenth Revision, Clinical Modification.

HERC Coverage Guidance: Hypoglossal Nerve Stimulation for Obstructive Sleep Apnea
Disposition of Public Comments

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Overview

The official 30-day public comment period for this coverage guidance began at 8am on September 12, 2025, and closed at 8am on October 16, 2025. No public comments were received during the open comment period.

Commenters

Identification	Stakeholder
None received	

Public Comments

ID/#	Comment	Disposition
None received		

References Provided by Commenters

ID	References
None received	

DRAFT

Public Comment Disposition: Hypoglossal Nerve Stimulation for Obstructive Sleep Apnea

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Commenters

Identification	Commenter
A	Paul Sabin – Regional Vice President of Norco Inc. *[Submitted February 11, 2026]*
B	Jennifer March, MD, MS – Assistant Professor, Department of Otolaryngology-Head and Neck Surgery, Oregon Health & Science University *[Submitted February 24, 2026]*

Public Comments

ID/#	Comment	Disposition
A1	I glanced at your coverage criteria and my only suggestion is to avoid re-defining the criteria that constitutes successful usage of a CPAP. The industries well established language of 4-Hours per night, 70% of nights in a 30-day period should be used instead of the current language in your proposed policy. Although your proposed language ; "Inability to use CPAP greater than 5 nights per week of at least 4 hours per night;" seems like a simplistic way of saying something similar it isn't the same. The databases relied upon to measure PAP adherence are designed around the 70% usage language, not a 5-day (71%) usage. The industry appreciates consistency. Please consider.	Thank you for your comment. The criteria in the coverage recommendation align with those in the FDA approval letter for Inspire UAS and the Genio system. These criteria are also used by the Medicare LCD (L38310) that covers Oregon.[1] For Inspire UAS (from FDA approval dated June 8, 2023), the threshold for "inability to use PAP" is defined as "greater than 5 nights per week of usage; usage defined as greater than 4 hours of use per night)" For the Genio system, the same definition is provided in the FDA approval letter dated August 8, 2025.
B1	I am writing in support of coverage for the Inspire hypoglossal nerve stimulator (HGNS) for treatment of moderate-severe obstructive sleep apnea (OSA) in patients who cannot tolerate positive pressure therapy. I am a head and neck surgeon who primarily treats patients with OSA, both with soft tissue reconstructive procedures as well as with implantation of the Inspire HGNS device.	Thank you for your comment and for your involvement in caring for OHP members.

ID/#	Comment	Disposition
B2	Inspire HGNS therapy has demonstrated efficacy for management of moderate-severe OSA in 2 separate clinical cohort studies. The STAR trial (first published in 2014 with 5 year follow up outcomes published in 2018) demonstrated a significant reduction in AHI and improvement in subjective measures via the Epworth Sleepiness Score with hypoglossal nerve stimulator therapy. The original patient cohort in the STAR trial included those with pre-treatment AHI between 15-65 and BMI 32 or less. Given the encouraging results from therapy in this population, the patient cohort was subsequently expanded to include AHI 15-100 and BMI 40 or less with the ADHERE study. These data demonstrated sustained efficacy of therapy with expanded AHI and BMI parameters with no statistical differences in response to therapy between patients who satisfied the original criteria (AHI 15-65, BMI < 32) compared to those in the expanded criteria group (AHI 65-100, BMI 32-40). The findings from the ADHERE study allowed for expanded FDA approval for Inspire HGNS therapy to include patients with a BMI 40 or less and AHI 15-100.	Thank you for providing this additional information. The referenced study by Thaler et al., was a retrospective registry study of 1,017 individuals who received the Inspire UAS from October 2016 to February 2019. The mean BMI of study participants was 29.3 kg/m^2. Investigators found that a lower BMI was a predictor of success, and that "[e]ach unit decrease of BMI is associated with 8.5% increased odds of having a more favorable [apnea-hypopnea index] response." In the discussion, the authors noted that, "[a]lthough surgical success has been reported at higher BMIs, the BMI cutoff of 32 by STAR criteria remains a useful guide for surgical decision-making until there are better preoperative assessment tools available to screen out those patients who would not succeed with UAS therapy." The FDA has since expanded the Inspire UAS approval to increase the upper limit BMI warning to 40 kg/m^2; however, the comparative prospective cohort studies and randomized trials we identified that reported on efficacy did not include subgroup analyses by BMI. Further, the mean baseline BMI of participants ranged from 27.3 kg/m^2 to 30.6 kg/m^2. In other words, we did not find comparative prospective cohort study or randomized trial evidence to support similar efficacy of the Inspire UAS at higher BMIs. Consequently, the initial HERC staff recommendation was

ID/#	Comment	Disposition
		coverage up to a BMI of 32 kg/m^2. The Coverage Guidance has been updated to include additional information on this topic.
B3	While there are differences between insurance company coverage for the device, the vast majority have now expanded their approval criteria at least up to 35, if not all the way to 40. The Centers for Medicare/Medicaid Services (CMS) currently uses the BMI criteria up to 35 in their approval for the device in patients covered by Medicare.	In the Coverage Guidance, we found that the upper limit of BMI for coverage was 32 kg/m^2 for Cigna and Moda, 35 kg/m^2 for Medicare (LCD 38312 which covers Oregon) and Regence, and 40 kg/m^2 for Aetna. In response to this comment, we performed another search on March 16, 2026, and found several policy changes: the upper limit of BMI changed to 40 kg/m^2 for Cigna,[2] Moda,[3] and Regence,[4] with the Medicare LCD (35 kg/m^2) and Aetna (40 kg/m^2) policy remaining unchanged. We will provide the subcommittee with this information for their discussion. The Coverage Guidance has been updated to reflect current payer policies.
B4	I encourage the review team to consider coverage of the Inspire HGNS device for treatment of patients with moderate-severe OSA (AHI 15-100) and at least BMI of 35 or less, in line with current standard set by CMS and many other commercial insurance providers (Aetna, Regents Blue Cross, United Healthcare, Cigna, and Providence).	We thank you for your comment and will provide it to the subcommittee for discussion.

References Provided by Commenters

ID	References
A	None submitted
B	• B.T. Woodson, K.P. Strohl, R.J. Soose, et al. Upper airway stimulation for obstructive sleep apnea: 5-year outcomes. Otolaryngol Head Neck Surg, 159 (1) (2018), pp. 194-202 • Thaler E, Schwab R, Maurer J, et al. Results of the ADHERE upper airway stimulation registry and predictors of therapy efficacy. Laryngoscope. 2020 May;130(5):1333-1338. doi: 10.1002/lary.28286. Epub 2019 Sep 14. PMID: 31520484; PMCID: PMC7217178.
Staff Response in B3	• (1) Medicare LCD L38310: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?LCDId=38310 • (2) Cigna 2026: https://static.cigna.com/assets/chcp/pdf/coveragePolicies/medical/mm_0158_coveragepositioncriteria_obstructive_sleep_apnea_diag_trtment_svc.pdf • (3) Moda 2025: https://www.modahealth.com/-/media/modahealth/shared/medical-necessity-criteria/ObstructiveSleepApnea_SurgicalMgmt.pdf • (4) Regence 2025: https://beonbrand.getbynder.com/m/3c203411c688b63e/

Section 9.0

HERC

Reproductive Health Equity Act (RHEA) – 2026 Review

Plain Language Summary:

Every 2 years the Health Evidence Review Commission reviews clinical practice recommendations related to providing preventive care and ensures that these services remain covered per Oregon law.

Staff Analysis Summary:

No significant change to current coverage or statute are recommended.

Background:

House Bill 3391 was passed in 2017 to ensure coverage of reproductive health services in Oregon. It requires health plan coverage (including commercial plans and coverage for those who would be eligible for Medicaid but for their immigration status) for screening and other services without a deductible, coinsurance, copayment, or any other cost-sharing requirement.

ORS 414.694 states:

> The Health Evidence Review Commission shall review the coverage described in ORS 743A.067 (2) and, no later than November 1 of each even-numbered year, report to the interim committees of the Legislative Assembly related to health any recommended changes to the coverage described in ORS 743A.067 (2) based upon the latest clinical research.

Previous HSC/HERC reviews:

Previous HERC reviews were completed in 2018, 2020, 2022 and 2024.

Current HERC review:

HERC staff reviewed relevant evidence-based clinical guidelines which are new since January 1, 2024. These included review of US Preventive Service Task Force (USPSTF) A and B recommendations, as well as the Health Resources and Services Administration (HRSA) Women's Preventive Services Guidelines.

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HERC staff recommendation:

HERC staff have reviewed the statute and do not recommend any changes because existing statute generally meets the reproductive health needs of Oregonians.

To further reinforce its commitment to providing updated and inclusive reproductive health and preventive services, the legislature could consider the following minor changes:

1) Update the date referencing USPSTF and HRSA to January 1, 2026.
2) Clarify that listed preventive services should be covered in accordance with national evidence-based standards (i.e., USPSTF, HRSA), when applicable.

See attached draft report.

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Dear Legislative Leaders,

This report was approved by the Health Evidence Review Commission (HERC), in fulfillment of ORS 414.694, which requires HERC to report to the interim committees related to recommended changes to the coverage described in ORS 743A.067. HERC does not recommend any changes to this statute because existing law supports coverage of the relevant health services.

Rationale

ORS 743A.067, enacted under House Bill 3391 (2017), includes a list of preventive reproductive health and other services to be provided without cost sharing to people insured under state-regulated health plans. This statute lists a comprehensive set of reproductive and reproduction-related health services, including services related to pregnancy, family planning, prevention of intimate partner violence, and prevention of sexually transmitted infections. In addition, it includes "Any additional preventive services for women that must be covered without cost sharing under 42 U.S.C. 300gg-13, as identified by the United States Preventive Services Task Force or the Health Resources and Services Administration of the United States Department of Health and Human Services as of January 1, 2017." A separate law (ORS 743A.262) also references the services required to be covered in 42 U.S.C. 300gg-13 as of January 1, 2023, and requires that they be covered by state-regulated health plans without cost sharing except as allowed by federal law.

In addition, ORS 414.432 (House Bill 3391) created a program covering the services listed in ORS 743A.067(2) for individuals who can become pregnant and who would otherwise be eligible for medical assistance if not for federal law excluding certain immigrants from medical assistance programs (8 U.S.C. 1611 and 1612).

Before November 1 of each even numbered year, ORS 414.694 requires the Health Evidence Review Commission (HERC) to report to the legislature on recommended changes to the coverage listed in ORS 743A.067(2).

After review of statute and recent federal guidance, the most important preventive services for women are currently required to be covered by Oregon state-regulated insurance plans without cost sharing by ORS 743A.067(2) and ORS 743A.262. Thus, HERC recommends no changes to statute.