Health Evidence Review Commission's Evidence-based Guideline Subcommittee

September 4, 2014

2:00 PM

Meridian Park Hospital
Community Health Education Center, Room 117
19300 SW 65th Avenue, Tualatin, OR 97062

Section 1.0

Call to Order

AGENDA

EVIDENCE-BASED GUIDELINES SUBCOMMITTEE (EbGS)
September 4, 2014
2:00pm - 5:00pm
Meridian Park Hospital
Community Health Education Center Room 117B&C

(All agenda items are subject to change and times listed are approximate)

#	Time	Item	Presenter
1	2:00 PM	Call to Order	Wiley Chan
2	2:05 PM	Review of August minutes	Wiley Chan
3	2:10 PM	Staff Report Evidence Review of Applied Behavioral Analysis for Autism Spectrum Disorder, Proposed Modifications	Cat Livingston
4	2:20 PM	Coverage Guidance Scanning	Alison Little
5	2:50 PM	New Draft Coverage Guidances 1. Home birth	Cat Livingston
6	3:50 PM	Review public comment and potentially finalize Coverage Guidances 1. Ablation for atrial fibrillation 2. Nuclear cardiac imaging	Alison Little Cat Livingston
7	4:45 PM	Public Comment	
8	4:55 PM	Confirmation of next meeting and next topics	Cat Livingston
9	5:00 PM	Adjournment	Wiley Chan

MINUTES

Evidence-based Guidelines Subcommittee
Meridian Park Community Health Education Center, Room 117B&C
19300 SW 65th Avenue, Tualatin, OR
June 5, 2014
2:00-5:00pm

Members Present: Wiley Chan, MD, Chair; Beth Westbrook, PsyD, MPH; Leda Garside, RN, MBA; Som Saha, MD, MPH; Bob Joondeph, JD; Eric Stecker, MD, MPH.

Members Absent: Steve Marks, MD, Vice-Chair; Vern Saboe, DC
Staff Present: Darren Coffman; Cat Livingston, MD, MPH; Jason Gingerich.

Also Attending: Alison Little, MD (CEBP); Shannon Vandergriff (CEBP);Erika Zoller, (CEBP), Barbara Morrow (Astellas), Bill Struyk (Johnson and Johnson), Sue Miller (Astellas), Stephen Heitner, MD (OHSU, appointed expert for Nuclear Cardiac Imaging).

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1. CALL TO ORDER

Wiley Chan called the meeting of the Evidence-based Guidelines Subcommittee (EbGS) to order at 2:09 pm.

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2. MINUTES REVIEW

No changes were made to the April 24, 2014 minutes.
Minutes approved 6-0.

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3. STAFF REPORT

Coffman reported that, prior to the May VbBS meeting, staff has discovered that putting intensity and duration limits on mental health services may conflict with Federal Mental Health parity regulations, which created concerns about the limits in the Evidence Evaluation on Applied Behavior Analysis for Autism Spectrum Disorder. Staff will present a revised recommendation to VbBS which summarizes the evidence on intensity and duration but does not create a hard limit. Staff believes it is allowable to have language requiring an evaluation to ensure that progress is being made. The Evidence Evaluation will eventually need to come back to EbGS to align the two documents. Chan asked about EIBI, as intensity is part of the definition of therapy. Coffman said that EIBI could be described but that the language on absolute limits would be removed. He acknowledged that the onus would be on the CCOs to interpret medical appropriateness in individual cases using a consistent methodology. The subcommittee discussed how parity really applies, and tried without success to identify similar services in the physical health field that are provided for many hours per week for long periods of time; however, there are certainly expensive medications that might be used for long periods of time. The group also discussed how cost effectiveness considerations might fit into parity.

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4. REVIEW OF PUBLIC COMMENTS

A) Ablation for atrial fibrillation

Alison Little reviewed the draft coverage guidance, including the evidence and clinical context. Livingston reviewed the GRADE table. Saha asked about the row on aventricular (AV) ablation versus rate control where indvidual pharmacotherapy was ineffective. This seems contradictory. Livingston said that she was hoping to get clear guidance on the best sequence of therapies based on the AHRQ report. There is no way to derive that kind of pathway from the evidence. In this case, if a patient fails to benefit rate control medication, the question is whether to try ablation or additional rate control. Stecker said that it would also be an option to tolerate inadequate heart rates, or to prescribe additional drugs. However, he said that for elderly patients, ablation is preferable to multiple drugs. Saha asked Stecker whether rhythm or additional rate control would be preferred for a patient who fails rate control. Stecker said some studies show you don't need to do rate control as aggressively as was done in the past—a rate of 100 to 110 may be ok. Depending on the heart rate, you may try rhythm or add a pacemaker and AV node ablation. For the elderly, he said quality of life is better with AV ablation. For younger patients you might try rhythm control before implanting a pacemaker for life. Saha asked what the threshold for rate control was and whether the studies in our report included the more relaxed rate control levels. Little said that in general a resting heart rate of 90, or 130 with exertion was considered as needing treatment for most of the studies. After discussion, the subcommittee modified the recommendation on ablation to allow coverage with patients who have inadequate rate control that makes them symptomatic or puts them at risk for left ventricular systolic dysfunction.

Chan observed that transcatheter pulmonary vein isolation would also be an option for patients who fail rate control. Westbrook asked whether the preference for this treatment differs from hospital to hospital. Stecker said the treatment is preference sensitive based on many factors, including, but not limited to, financial factors. There is not enough evidence to add additional nuance about the choice between these therapies. Chan asked what the purpose of the coverage guidance is. Stecker said one potential would be to address heterogeneity of care; another would be to identify treatments with an unfavorable balance of benefit and risk. There is not sufficient evidence to do either of these. Another possibility is to address when to choose rate versus rhythm control. There is data for elderly patients showing that the strategies are equal from a mortality standpoint, except that hospitalization rates vary.

Saha said the pulmonary vein isolation (PVI) recommendation reads as if a surgeon should not do PVI during another cardiac surgery but should complete the first procedure then do a transcatheter PVI procedure instead of doing it all at once. After discussion the subcommittee changed the language to clarify that PVI is recommended for certain patients undergoing other cardiac surgery, but transcatheter PVI could be done as a standalone procedure in patients not undergoing other cardiac surgery.

The subcommittee discussed whether to require failure of both rate and rhythm control medications before transcatheter PVI. Little said most studies required failure of both, though one trial did not include a trial of rhythm control. Stecker said the practice guidelines have recommended a trial of antiarrhythmics. After discussion the group decided to require a trial of antiarrhythmics.

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The subcommittee also decided to separate the recommendations about transcatheter PVI and PVI during other cardiac surgery since the populations are different. [CL1]
The subcommittee then discussed the Maze procedure. Members decided to remove the language about risk of mortality, as standard care would include weighing the risk of mortality during surgery. Stecker clarified that the historic Maze procedure is rarely done, with current practice being more like a PVI plus Maze. In addition, the subcommittee decided to recommend Maze only at the time of other cardiac surgery, due to risks of the procedure. Livingston asked Little to confirm that this aligns with the entry criteria for the trials.

The subcommittee made corresponding changes to the rationale section, working from a handout provided at the meeting. They also removed the last three rows of the GRADE table comparing rate versus rhythm control, along with related evidence, because the evidence to support detailed treatment approaches is lacking and can be left to the surgeon.

There was no public comment.

A motion was made to put the coverage guidance as modified out for public comment. **Motion approved 6-0.**

HERC COVERAGE GUIDANCE

AV node ablation is recommended for coverage only in persons with inadequate ventricular rate control resulting in symptoms, left ventricular systolic dysfunction or substantial risk of left ventricular systolic dysfunction. Coverage is recommended only when pharmacological therapy for rate control is ineffective or not tolerated *(weak recommendation).*

Transcatheter pulmonary vein isolation is recommended for coverage for those who are persistently symptomatic despite rate control medications and antiarrhythmic medications (*strong recommendation).*

Pulmonary vein isolation is recommended for coverage at the time of other cardiac surgery for patients who are persistently symptomatic despite rate control medications (*weak recommendation*).

The Maze procedure is recommended for coverage at the time of other cardiac surgery for patients with significant symptoms from atrial fibrillation *(weak recommendation).*

B) Nuclear Cardiac Imaging

Dr. Steve Heitner, the appointed expert for this topic, introduced himself and said that he has no conflicts of interest. Little presented the draft coverage guidance, based on the Washington Health Technology Assessment report on Nuclear Cardiac Imaging. Livingston reviewed the GRADE framework.

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There was discussion about ETT vs ECHO vs SPECT and it was determined that the indications for ETT vs ECHO were outside the scope of this coverage guidance. There were concerns that the cost analyses produced conflicting results, the potential harm of radiation is hard to quantify, and the risk of angiography (increased referrals due to false positives) may be inadequately accounted for.

Heitner clarified that in certain patients ECHO versus nuclear is not equivalent. For instance, in morbidly obese patients where acoustic windows are difficult to obtain, the accuracy of the stress ECHO goes way down and stress nuclear imaging would be preferred. He described several other cases where alternative tests might be preferred. Stecker shared that it is common for inappropriate testing modalities to be ordered (for example an exercise treadmill test on a wheelchair bound patient) and more appropriate tests may need to be done. Institutional expertise is also deemed to be a factor in preferred imaging testing. Using a nonpreferred test may result in risk to the patient and cost from additional testing and procedures.

The subcommittee chose to change the references to harm from radiation to "potential harm" as no evidence has been presented that the amounts of radiation used in these tests produces actual harms and an angiogram would include a higher dose of radiation.

The subcommittee chose to not recommend SPECT for screening. They chose to recommend against coverage for SPECT for diagnosis or risk stratification unless stress ECHO results would be suboptimal or would be contraindicated. Heitner provided a list of patient conditions for which ECHO would be suboptimal or contraindicated:

1) Preexisting cardiomyopathy or regional wall motion abnormalities
2) LBBB
3) Paced rhythm
4) Unsuitable acoustic window due to body habitus
5) Need for pharmacologic stress agent but contraindication to administration of dobutamine

The group decided to add these instances as appropriate for coverage of SPECT. Reference to a guideline was also recommended to assist clinicians and medical directors to justify when SPECT may be preferable to ECHO.

The subcomittee then moved to discussion of PET scanning. It was agreed that the evidence was insufficient at this time and recommended noncoverage.

A motion was made to approve the draft coverage guidance as modified and put it out for public comment. **Motion approved 6-0.**

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HERC COVERAGE GUIDANCE

PET is not recommended for coverage for screening or diagnosis of coronary artery disease (CAD) *(strong recommendation).*

Single photon emission computed tomography (SPECT) is not recommended for coverage for screening of CAD *(strong recommendation).*

SPECT is not recommended for coverage for diagnosis or risk stratification of CAD *(strong recommendation)*—except in patients for whom stress imaging is required and stress ECHO is contraindicated or would provide suboptimal imaging.*

**i.e. pre-existing cardiomyopathy, baseline regional wall motion abnormalities, left bundle branch block, paced rhythm, unsuitable acoustic windows due to body habitus, inability to utilize dobutamine in a setting where exercise is not possible or when the target workload is not achievable*

6. ADJOURNMENT

The meeting was adjourned at 5:00 pm. The next meeting is scheduled for September 4, 2014 from 2:00-5:00pm in Room 117B&C of the Meridian Park Hospital Community Health Education Center in Tualatin.

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Section 3.0

Staff Report

HEALTH EVIDENCE REVIEW COMMISSION (HERC)

EVALUATION OF EVIDENCE: APPLIED BEHAVIOR ANALYSIS FOR AUTISM SPECTRUM DISORDERS

Approved 8/14/2014

BACKGROUND

Oregon Senate Bill 365 was passed by the Oregon legislature in the 2013 regular session. That bill directs the Health Evidence Review Commission to evaluate applied behavior analysis (ABA) as a treatment for autism spectrum disorder (ASD) for the purposes of updating the prioritized list of health services. The bill also establishes requirements for state-regulated health plans to approve and manage autism treatment, including ABA therapy and any other medical or mental health services identified in an individualized treatment plan. The law applies to patients who seek care before age nine, covering up to 25 hours of ABA per week, and continuing as long as medically necessary. Health plans that provide coverage to OEBB and PEBB are required to begin coverage in 2015, and all other health plans are required to begin coverage in 2016. Applied behavior analysis is defined in the bill as the following:

The design, implementation and evaluation of environmental modifications, using behavioral stimuli and consequences, to produce significant improvement in human social behavior, including the use of direct observation, measurement and functional analysis of the relationship between environment and behavior and that is provided by:

> (i) A licensed health care professional registered under section 3 of this 2013 Act;
>
> (ii) A behavior analyst or an assistant behavior analyst licensed under section 3 of this 2013 Act; or
>
> (iii) A behavior analysis interventionist registered under section 3 of this 2013 Act.

“Applied behavior analysis” excludes psychological testing, neuropsychology, psychotherapy, cognitive therapy, sex therapy, psychoanalysis, hypnotherapy and long-term counseling as treatment modalities.

For details of the public process used to develop this evaluation of evidence, see http://www.oregon.gov/oha/herc/Pages/blog-ABA.aspx

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EVIDENCE SOURCES

Warren, Z., Veenstra-VanderWeele, J., Stone, W., Bruzek, J.L., Nahmias, A.S., Foss-Feig, J.H., et al. (2011). *Therapies for children with autism spectrum disorders. Comparative effectiveness review no. 26.* (Prepared by the Vanderbilt Evidence-based Practice Center under Contract No. 290-2007-10065-I). AHRQ Publication No. 11-EHC029-EF. Rockville, MD: Agency for Healthcare Research and Quality. April 2011. Retrieved from http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=651

Update of Warren 2011 in draft form:

Therapies for children with autism spectrum disorder – Behavioral interventions update. Draft Comparative Effectiveness Review. Rockville, MD: Agency for Healthcare Research and Quality. Retrieved January 27, 2014, from http://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayProduct&productID=1845

Lounds Taylor, J., Dove, D., Veenstra-VanderWeele, J., Sathe, N.A., McPheeters, M.L., Jerome, R.N., et al. (2012). *Interventions for adolescents and young adults with Autism Spectrum Disorders. Comparative Effectiveness Review No. 65.* (Prepared by the Vanderbilt Evidence-based Practice Center under Contract No. 290-2007-10065-I.) AHRQ Publication No. 12-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. Retrieved from http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=1197&pageaction=displayproduct

Maglione, M., Motala, A., Shanman, R., Newberry, S., Schneider Chafen, J., & Shekelle, P. (2012). *AHRQ Comparative Effectiveness Review Surveillance Program: Therapies for Children with Autism Spectrum Disorders, 2nd Assessment.* Rockville, MD: Agency for Healthcare Research and Quality. Retrieved from http://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=1536

Oono, I.P., Honey, E.J., & McConachie, H. (2013). Parent-mediated early intervention for young children with autism spectrum disorders (ASD). *Cochrane Database of Systematic Reviews*, Issue 4. Retrieved from http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD009774.pub2/abstract

- *List of included studies in Oono 2013 provided in Appendix D*

Glossary Sources

Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program. (n.d.). Glossary of terms. Retrieved from http://effectivehealthcare.ahrq.gov/index.cfm/glossary-of-terms/

National Cancer Institute (NCI) at the National Institutes of Health (NIH). (n.d.). NCI dictionary of cancer terms. Retrieved from http://www.cancer.gov/dictionary

The summary of evidence in this document is derived directly from these evidence sources, and portions are extracted verbatim.

SUMMARY OF EVIDENCE

Clinical Background

The following clinical background summary is extracted from the update to the Warren 2011 report (AHRQ draft, 2014).

> Autism spectrum disorder (ASD) is a neurodevelopmental disorder marked by impaired social communication and social interaction accompanied by atypical patterns of behavior and interest. ASD is differentiated from other developmental disorders by significant impairments in social interaction and communication, along with restrictive, repetitive, and stereotypical behaviors and activities. Social communication and social interaction features include deficits in social-emotional reciprocity (e.g., deficits in joint attention, atypical social approach and response, conversational challenges, reduced sharing of interest, emotions, and affect), deficits in nonverbal communication (e.g., atypical eye contact, reduced gesture use, limited use of facial expressions in social interactions, challenges understanding nonverbal communication), and deficits in forming and maintaining relationships (e.g., diminished peer interest, challenges joining in play, difficulties adjusting behavior to social context). ASD features of restricted, repetitive patterns of behavior, interests, or activities may include stereotyped motor mannerisms, use of objects, or speech (e.g., simple motor stereotypies, repetitive play, echolalia, and formal or idiosyncratic speech); insistence on sameness, inflexible adherence to routines, or ritualized patterns of behavior (e.g., distress at small changes, rigid patterns of thought and behavior, performance of everyday activities in ritualistic manner); intense preoccupation with specific interests (e.g., strong attachment to objects, circumscribed or perseverative topics of interest); and sensory sensitivities or interests (e.g., hyper- or hypo-reactivity to pain and sensory input, sensitivity to noise, visual fascination with objects or movement). These symptoms cause impairment across many areas of functioning and are present early in life. However, impairments may not be fully evident until environmental demands exceed children's capacity. They also may

> be masked by learned compensatory strategies later in life. Many children with ASD may also have intellectual impairment or language impairment, and the disorder may be associated with known medical, genetic, or environmental factors. (p. ES-1)
>
> The prevalence of ASD in the United States is 11.3 cases per 1,000 (or 1 in 88) children living in the communities surveyed, with rate estimates varying widely by region of the country, sex, and race/ethnicity. Considerably more males (1 in 54) than females (1 in 252) are affected. For some individuals, the core symptoms of ASD (impairments in communication and social interaction and restricted/repetitive behaviors and interests) may improve with intervention and maturation; however, core deficits typically translate into varying developmental presentations that remain throughout the lifespan. Longitudinal studies indicate that adults with ASD struggle to obtain adaptive independence. (p. 1)
>
> Treatments for ASD include behavioral, educational, medical, allied health, and complementary approaches. Individual goals for treatment vary for different children and may include combinations of therapies. For many individuals, core symptoms of ASD (impairments in communication and social interaction and restricted/repetitive behaviors and interests) may improve with intervention and over time5-8; however, deficits typically remain throughout the lifespan. Chronic management—often using multiple treatment approaches—may be required to maximize ultimate functional independence and quality of life. (p. ES-1)

This review of the evidence addresses only behavioral interventions for ASDs that utilize principles of applied behavior analysis (ABA).

> ABA is an umbrella term describing principles and techniques used in the assessment, treatment and prevention of challenging behaviors and the promotion of new desired behaviors. The goal of ABA is to teach new skills, promote generalization of these skills, and reduce challenging behaviors with systematic reinforcement. The principles and techniques of ABA existed for decades prior to specific application and study within ASDs. (AHRQ draft, 2014, p. 5)

Interventions that utilize the principles of ABA include comprehensive treatments referred to as Early Intensive Behavioral and Developmental Interventions (EIBI). Two of these intensive treatments have been manualized (i.e., have published treatment manuals to facilitate replication): the UCLA/Lovaas model and the Early Start Denver Model (ESDM). There are other treatment approaches that also incorporate ABA principles, and may be intensive in nature, but have not been manualized. A third particular set of interventions include those using the principles of ABA to focus on key

pivotal behaviors rather than global improvements. These approaches emphasize parent training as a modality for treatment delivery (e.g., Pivotal Response Training, Hanen More than Words, social pragmatic intervention, etc.) and may focus on specific behaviors such as initiating or organizing activity or on core social communication skills.

Play-/interaction-based interventions may employ ABA principles and are included in this review. These interventions use interactions between children and adults (either parents or researchers) to improve outcomes such as imitation or joint attention skills or the ability of the child to engage in symbolic play. They include teaching parents how to interact differently with their children within daily routines and interactions, often using standard behavior management strategies.

Evidence Review

Children Ages Two to Twelve

EIBI and Other ABA Interventions

Warren (2011)

The Warren (2011) AHRQ review included all study designs as long as there were at least 10 participants. A total of 30 discrete studies were included, with the largest study population being 78 participants. The longest duration of treatment in any included study was three years. The mean age of children at intake in the included studies ranged from 21 to 66 months for EIBI interventions and from 42 months to 10.8 years for other ABA interventions. Authors reach the following conclusions:

> The evidence suggests that early intensive behavioral and developmental intervention (EIBI) may improve core areas of deficit for individuals with ASDs; however, randomized controlled trials (RCTs) are few and include small numbers of participants. In addition, there are no direct comparison trials. "Within this category, studies of UCLA/Lovaas-based interventions report greater improvements in cognitive performance, language skills, and adaptive behavior skills than broadly defined eclectic treatments available in the community. However, strength of evidence is currently low" (Warren, 2011, p. ES-7). In addition, the consistency of benefit is lacking, in that "not all children demonstrate rapid gains, and many children continue to display substantial impairment" (Warren, 2011, p. ES-7). Although positive results are reported for the effects of intensive interventions that use a developmental framework, such as ESDM, evidence for this type of intervention is currently insufficient because few studies have been published to date.

Less intensive interventions focusing on providing parent training for bolstering social communication skills and managing challenging behaviors have also been studied. Some interventions have shown short-term gains in social communication and language use, but the current evidence base for such treatment remains insufficient. Strength of evidence is also considered insufficient for play- and interaction-based approaches.

Only one study was identified that directly addressed whether there are any modifiers of outcomes for different ABA-based behavioral approaches. It examined the impact of which provider (parent vs. professional) delivered the UCLA/Lovaas protocol-based interventions. There was no significant difference in outcomes for children receiving the intervention in a clinical setting vs. at home from highly trained parents.

Other potential correlates that warrant further study because of conflicting data include pretreatment IQ and language skills, and age of initiation of treatment (with earlier age potentially associated with better outcomes). "Social responsiveness and imitation skills have been suggested as skills that may correlate with improved treatment response in UCLA/Lovaas treatment, whereas 'aloof' subtypes of ASDs may be associated with less robust changes in IQ. Other studies have seen specific improvement in children with PDD-NOS vs. Autistic Disorder diagnoses, which may be indicative of baseline symptom differences. However, many other studies have failed to find a relationship between autism symptoms and treatment response" (Warren, 2011, p. ES-8).

"Research on very young children is preliminary, with four studies identified. One good-quality RCT suggested benefit from the use of ESDM in young children, with improvements in adaptive behavior, language, and cognitive outcomes. Diagnostic shifts within the autism spectrum were reported in close to 30 percent of children but were not associated with clinically significant improvements in Autism Diagnostic Observation Schedule severity scores or other measures" (Warren, 2011, p. ES-9).

There was no evidence identified in the Warren review that addressed treatment effectiveness in specific subgroups such as race, ethnicity, gender or socioeconomic status, other than age. Details of all comparative studies that reported comparative statistics are provided in the table below.

Table 1. Comparative Studies included in Warren 2011

Author	Study Design	Intervention Intensity	Intervention Duration	Summary of Outcome
Smith 2000	RCT, intensive vs. parent training	Intensive: 30 hrs/wk with therapist, 5	intensive: 2-3 yrs	Intensive group had improved IQ, developmental

Author	Study Design	Intervention Intensity	Intervention Duration	Summary of Outcome
		hrs/wk with parents X 3 months Parent: taught techniques from Lovaas manual 2 sessions/wk	parent: 3-9 mos	scores compared to parent training, as well as in 1 communication score, but not in 3 others, and no sig diff in adaptive function MIXED
Drew 2002	RCT, parent training vs. local services (ST, OT, ABA, home worker)	Parent: 6.3 hrs/wk Local: 3.5 hrs/wk	Not specified; follow up at 1 year	No sig diff between groups in cognitive[1] outcomes. parent group had some better communication outcomes MIXED
Aldred 2004	RCT, social communication intervention vs. routine care (not described)	Intervention: monthly treatment sessions X 6 months (time not specified), then less frequent for another 6 months Control: routine care	1 year	Intervention group had better language scores, parent synchrony. No diff in shared attention MIXED
Eikeseth 2002/ 2007	Non-randomized CT, Lovaas behavioral treatment vs. eclectic (TEACCH, sensory-motor therapies, ABA)	Lovaas: 28 hrs/wk Eclectic: 29 hrs/wk	Not specified; first follow up at 1 year	Lovaas group had sig more improvement than eclectic in IQ, communication, adaptive behavior at both 1 and 8 year follow up for most measures POSITIVE
Reed 2007	Non-randomized CT, high intensity ABA vs. low intensity ABA	High: mean 30 hrs/wk Low: mean 13 hrs/wk	Not specified	No diff in autism severity, adaptive behavior. Mixed result for cognitive, with high intensity scoring better on one measure but not another MIXED
Howard 2005	Prospective cohort, intensive ABA vs. intensive eclectic (delivered in school) vs. non-intensive public early intervention	ABA: 25-30 hrs/wk for age <3, 35-40 for age >3 plus parent training Intensive eclectic: not specified Public EI: not specified	Follow up at 14 mos	ABA group had sig higher scores than mean of the other two groups for all outcome measures except motor skills POSITIVE
Remington	Prospective cohort,	EI: mean 26 hrs/wk	2 years	EI group had sig higher

[1] Educational, cognitive, and academic outcomes are reported together and noted as "cognitive" unless specified otherwise.

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Author	Study Design	Intervention Intensity	Intervention Duration	Summary of Outcome
2007	home-based early intervention (parent delivered with tutors) vs. local education standard treatment	Control: not specified		scores for most outcomes, including social skills, communication, adaptive behavior, cognitive function POSITIVE
Cohen 2006	Prospective cohort, EIBI (Lovaas) vs. services from public school (parent choice)	Intervention: 35-40 hrs/wk, 47 wks/yr Control: not specified	3 years	Intervention group had higher IQ, were more likely in regular classroom and had higher adaptive scores; no sig diff in communication POSITIVE
Stahmer 2001	Prospective cohort, parent information support group and education course on PRT vs. education course only (control)	2 hrs/week for intervention group vs 1 hr/wk for control	12 weeks	Sig more parents in the intervention group correctly used PRT techniques, and their children had improved communication POSITIVE
Zachor 2007 (appears to be a subset of Itzchak 2009)	Prospective cohort, behavioral vs. eclectic	Behavioral: 1 to 1 35 hrs/wk Eclectic: special ed teacher, various therapists (OT, ST), parent training, at least 16 hrs/wk	Not specified	Sig improved overall severity, communication behavioral group compared to eclectic, no sig diff in social skills POSITIVE
Hayward 2009/ Eikeseth 2009	Prospective cohort, clinic based vs. parent managed	Clinic: 37 hrs/week Parent: 34 hrs/week (mean supervision hrs/mo = 5)	1 year	No differences between groups in communication, adaptive behavior, cognitive/academic NEGATIVE
Eldevik 2006	Retrospective cohort, low intensity behavioral (Lovaas) vs. eclectic (alternative communication, TEACCH, sensory-motor, ABA	Behavioral: 12 hrs/wk Eclectic: not specified	Behavioral: 20 mos Eclectic: 21 mos	Behavior group had mixed outcomes on cognitive measures (better on some measures, no diff on others), better communication scores, fewer problem behaviors. no diff in adaptive scores MIXED
Reed 2007	Retrospective cohort, ABA vs. special nursery vs. portage (parent training)	ABA: mean 30 hrs/wk Special nursery: mean 12 hrs/wk Portage: mean 8 hrs/wk	Not specified	27 diff outcomes measures reported on, no sig diffs on 18. ABA group had better scores than one or the other of the comparators for the following measures: 2 of 3 overall ratings, 4 of 8 communication scores, 3 of

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Author	Study Design	Intervention Intensity	Intervention Duration	Summary of Outcome
				7 behavior scores. There were no diffs in motor skills scores, cognitive scores, comorbidities MIXED

In summary, the intensity of experimental interventions ranged from less than two hours per week to 40 hours per week. For the control interventions, intensity was often not specified, but was as high as 34 hours per week. Of those studies showing a mostly positive outcome for the intervention, intensity ranged from 26 to 40 hours per week, with the exception of the Stahmer study, which was a very narrowly focused intervention aimed at teaching parents a specific skill.

With regard to duration, five studies did not specify the length of the intervention period. The shortest study was 12 weeks, while the longest was 3 years. Of those studies showing a mostly positive outcome for the intervention, duration ranged from no more than a year to three years, with the exception of the Stahmer study.

The following limitations of the evidence were noted by the report authors:

> A high proportion of studies in this review (36 percent) fail to use a comparison group, and while substantial strides have been made in the analysis of single-subject designs, these are not ideal for assessing effectiveness at a population level, nor are they appropriate for comparative effectiveness research. They are, however, used frequently in the behavioral literature, and so we address our decisions regarding them here. Because there is no separate comparison group in these studies they would be considered case reports (if only one child included) or case series (multiple children) under the rubric of the EPC study designs. Case reports and case series can have rigorous evaluation of pre- and post-measures, as well as strong characterization of the study participants.
>
> Studies using this design that included at least 10 children were included in the review. Studies of this type can be helpful in assessing response to treatment in very short time frames and under very tightly controlled circumstances, but they typically do not provide information on longer term or functional outcomes. They are useful in serving as demonstration projects, yielding initial evidence that an intervention merits further study, and, in the clinical environment, they can be useful in identifying whether a particular approach to treatment is likely to be helpful for a specific child. Our goal was to identify and review the best evidence for assessing the efficacy and effectiveness of therapies for children with ASD, with an eye toward their utility in the clinical setting, and for the larger population

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of children with ASD. By definition, “populations” in single-subject design studies are likely to be idiosyncratic and therefore not to provide information that is generalizable.

Nonetheless, even in studies with a comparison group, sample size is frequently insufficient to draw conclusions, and larger, multisite trials are needed across all treatment types. Furthermore, the choice of comparison groups in the studies that employed a group design was uneven. A number of studies used comparison groups that were inappropriate for observing group differences in treatment effect (e.g., comparing treatment in children with autism to the effects of the treatment in typically developing peers or to children with a different developmental disorder), and for those studies we could only use the pre-post case series data available in the group with autism, limiting the ability to comment on effectiveness.

We encourage investigators to provide adequate detail as they describe their interventions to allow for replicable research. In ideal circumstances, investigators publish and reference treatment manuals, but many studies made general references to their use of an underlying approach (e.g., ABA) without specifying the ways in which they used the technique or modifications they made to the original, published use of it. Lack of detail about the intervention makes it difficult to assess the applicability of individual studies, to synthesize groups of studies or to replicate studies.

Characterization of the study population was often inadequate, with 125 of 159 studies failing to use or report “gold standard” diagnostic measures (clinical DSM-IV-based diagnosis plus ADI-R and/or ADOS) for the participants. Because ASDs are spectrum disorders, it is difficult to assess the applicability of interventions when the population in which they were studied is poorly defined or described. Authors often do not consider diagnostic criteria in selecting participants for their studies; nor do they fully describe the children who do participate. We recommend that investigators fully describe participants in their study, both diagnostically and otherwise. In addition, because the myriad causes of ASDs are unknown, even children with the same diagnosis may have distinct genetic or other “causes” that could affect treatment effectiveness. Ideally, future research will better characterize participants genotypically and phenotypically.

We identified more than 100 distinct outcome measures used in this literature base, not accounting for subscales. The use of so many and such disparate outcome measures makes it nearly impossible to synthesize the effectiveness of the interventions, and we recommend a consistent set of rigorously evaluated outcome measures specific to each intended target of treatment to move

comparative effectiveness research forward and to provide a sense of expected outcomes of the interventions. At the same time, the means for assessing outcomes should include increased focus on use of observers or reporters masked to the intervention status of the participant, and where some outcomes are measured in a masked fashion but others not, more emphasis should be placed on those that are.

There also was a strong tendency for authors to present data on numerous outcomes without adjusting for multiple comparisons, and to fail to report the outcome that was the primary outcome of *a priori* interest and on which sample size calculations were based (when they were present). This may suggest a level of selective reporting bias in which results are published on a select group of outcomes that show the most effect. We attempted, but were unable, to identify a clear primary intended outcome in almost all of the papers.

Duration of treatment and follow up was generally short, with few studies providing data on long-term outcomes after cessation of treatment. Future studies should extend the follow up period and assess the degree to which outcomes are durable. Few studies adequately accounted for concomitant interventions that might confound observed effectiveness and this should be standardized in future research. (Warren, 2011, p. 124-125)

[Evidence Source]

Maglione (2012)

Surveillance of the literature pertaining to the Warren report was conducted by AHRQ in January 2012 and October 2012 (Maglione, 2012). Conclusions pertaining to ABA therapies that address the currency of the 2011 report are presented below:

- Original conclusions regarding low strength of evidence for Early Intensive Behavioral Interventions (EIBI) are possibly out of date due to new RCTs and long-term follow-up of previously included studies.
- Original conclusion regarding insufficient evidence for parent training is possibly out of date due to several new RCTs.
- For Key Question 2 [what are the modifiers of outcome for different treatments or approaches (frequency, duration or intensity of treatment, characteristics of child or family, training of therapy provider)], conclusions are still valid, with the exception of impact of provider type, which may possibly be out of date. (p. ii)

[Evidence Source]

AHRQ Draft Report Update (2014)

Given this evidence of additional research, AHRQ elected to update the Warren report, focusing only on behavioral interventions. They published their draft report in January 2014. A summary of the findings is below:

> We included 51 unique studies comprising 37 randomized trials and 14 nonrandomized, comparative studies (16 good, 31 fair, and 4 poor quality) published since the prior review. The quality of studies improved compared with that reported in the earlier review. Young children receiving high intensity applied behavior analysis-based early intervention over extended time frames commonly displayed substantial improvement in cognitive functioning and language skills relative to community controls. The magnitude of these effects varied across studies, potentially reflecting poorly understood modifying characteristics related to subgroups of children. Early intensive parent training programs modified parenting behaviors during interactions; however, data were more limited about their ability to improve developmental skills beyond language gains for some children. Social skills interventions varied in scope and intensity and showed some positive effects on social behaviors for older children in small studies. Evidence for play/interaction-based approaches suggested that joint attention interventions may be useful for young and preschool children with ASD when targeting joint attention skills; data on the effects of such interventions in other areas were limited. (AHRQ draft, 2014, p. v)

Of the 51 included studies, 25 addressed interventions included in this report (EIBI except when delivered as an educational intervention, symbolic play and joint attention interventions, parent training). Three studies addressed EIBI, 12 studies addressed parent training, nine studies addressed play and/or interaction based approaches and one evaluated the addition of parent training to individuals using risperidone. Some characteristics of the included studies are reported in the table below:

Table 2 Summary of new studies from AHRQ draft report update

Intervention Type	Intensity Range	Duration Range	Age Range
EIBI (excluding educational interventions)	15 to 26 hours/week[2]	24 months	15 to 54 months
Parent training	30 minutes sessions X 10 to 30	12 weeks to 2 years	18 to 66 months

[2] The study with 15 hours included an additional 16 hours of parent delivered treatment

Intervention Type	Intensity Range	Duration Range	Age Range
	hours/week home based ABA[3]		
Play/Interaction Based Interventions[4]	20 minutes 2X/day, 5 days/week to 3 hours/week[5]	6 to 12 weeks	21 to 82 months
Parent Training in addition to Risperidone	11 sessions + boosters, 1 home visit	16 weeks	4 to 14 years

With regard to the impact of intensity or duration on treatment effectiveness, the authors report the following:

- In a retrospective cohort study of EIBI, treatment duration was not determined to be a significant predictor of outcome after controlling for other variables.
- In one parent training RCT evaluating ESDM (12 one hour sessions plus treatment as usual), total intervention hours (range zero to 16 hours/week, mean 1.5 hours/week for intervention group vs. 3.7 hours/ week for control) were associated with improved developmental and vocabulary scores, as was younger child age.

With regard to strength of the evidence, the authors reach the following conclusions:

> A growing evidence base suggests that children receiving early intensive behavioral and developmental interventions (e.g., many hours of intervention a week over the course of 1-2 years) show substantial improvements in cognitive and language skills over time compared with children receiving low-intensity interventions, community controls, and eclectic non-ABA based intervention approaches. With this growing literature, our confidence (strength of evidence) in the effects of ABA-based early intensive approaches on cognitive and language outcomes is moderate, based on the need for additional research that identifies which groups of children benefit the most from specific high intensity approaches.

[3] The study that included 30 hours/week of home based ABA compared this group to three other interventions: special ed classroom (mean 13 hours/week), low-intensity, home based manualized intervention (mean 8 hours/week) and 1:1 behavioral intervention that included a 5 day parent training component (mean 13 hours/week). This study found no significant differences in cognitive or adaptive scores between groups, but did find differences in educational outcomes favoring the intensive ABA group.
[4] Typically delivered in addition to other treatment as usual
[5] Four of the studies did not report treatment intensity

> Our strength of evidence in these high intensity interventions to affect adaptive behavior skills, social skills, and core ASD symptom severity is low. At present it is challenging to understand which high intensity variants most robustly impact these domains for specific children and in general the impact of these skill domains is less consistent.
>
> A growing evidence base suggests that children receiving early joint attention-related intervention in combination with other interventions show substantial improvements in joint attention and language skills over time. Within this growing literature, our confidence (strength of evidence) in this effect is moderate, based on the need for additional research that identifies which groups of children benefit the most from this approach and how this intervention relates to other ongoing concurrent offered interventions. Results from a variety of play-based interventions also suggest that young children often display short-term improvements in early play, imitation, language, and social interaction skills. However, our confidence in these estimates is low, and substantial evidence that these short-term improvements are linked to broader indices of change over time is lacking (AHRQ draft, p. 75).
>
> The evidence base for parent training interventions is moderate for their impact on early language and communication skills and low for impact on ASD symptom severity and early cognition. There is not yet sufficient data from this literature base to understand impact on adaptive behavior skills. Available studies indicate variable responses, with modest improvement for some children in some approaches, but limited improvement in other parent training paradigms. (AHRQ draft, 2014, p. 67)

Parent-mediated Early Intervention

<u>Oono (2013)</u>

A review of parent-mediated early intervention in children less than seven was completed by the Cochrane Collaboration in April 2013 (Oono, 2013). It included 17 RCTs (one of which was identified in the AHRQ surveillance report, and eight of which were included in the original Warren report) and drew the following conclusions:

> Overall, we did not find statistical evidence of gains from parent-mediated approaches in most of the primary outcomes assessed (most aspects of language and communication - whether directly assessed or reported; frequency of child initiations in observed parent-child interaction; child adaptive behaviour; parents' stress), with findings largely inconclusive and inconsistent across studies. However, the evidence for positive change in patterns of parent-child interaction was strong and statistically significant (shared attention: standardized mean difference (SMD) 0.41; 95% confidence interval (CI) 0.14 to 0.68, P value <

> 0.05; parent synchrony: SMD 0.90; 95% CI 0.56 to 1.23, P value < 0.05). Furthermore, there is some evidence suggestive of improvement in child language comprehension, reported by parents (vocabulary comprehension: mean difference (MD 36.26; 95% CI 1.31 to 71.20, P value < 0.05). In addition, there was evidence suggesting a reduction in the severity of children's autism characteristics (SMD -0.30, 95% CI -0.52 to -0.08, P value < 0.05). However, this evidence of change in children's skills and difficulties as a consequence of parent-mediated intervention is uncertain, with small effect sizes and wide CIs, and the conclusions are likely to change with future publication of high-quality RCTs. (Oono, 2013, p. 2)

This conclusion differs from that of the AHRQ draft report, for unclear reasons. It may be because Oono 2013 limited their population to children less than seven, or it may be that the AHRQ draft included more recent studies, since there is nearly a year difference in the literature search end dates (July 2013 for the AHRQ draft and August 2012 for Oono 2013). It also may be variable interpretation of the strength of the evidence by different authors. Indeed, the Oono 2013 review does find a statistically significant benefit in language comprehension and autism severity, outcomes that the AHRQ draft authors assess as having moderate and low strength of evidence respectively. However, Oono 2013 downgrades these findings because they are based on parent self report, and have small effect sizes and wide confidence intervals.

[Evidence Source]

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Adolescents and Young Adults (Ages 13 to 30)

Lounds (2012)
Only one poor quality case series evaluated ABA-based intensive behavioral therapy, precluding conclusions regarding efficacy in this age group (Lounds, 2012).

[Evidence Source]

Evidence Summary

Based on the evidence presented in this document (Warren, 2011; AHRQ draft, 2014; Oono, 2013), there is moderate strength of evidence that EIBI improves cognitive and language skills, and low strength of evidence that EIBI improves adaptive behavior skills, social skills, and core symptoms of autism, although improvements are inconsistent. Parent-mediated early intervention improves early language and communication skills, including shared attention and parent synchrony (moderate strength of evidence), and may have some impact on autism symptom severity and early cognition (low strength of evidence). Play-/interaction-based interventions improve child joint attention and language skills (moderate strength of evidence) and play, imitation and social interaction skills (low strength of evidence). The evidence is insufficient to evaluate the effectiveness of ABA on children and adolescents older than twelve. The evidence is insufficient to determine whether there are any factors that modify the effectiveness of ABA therapy.

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GRADE-INFORMED FRAMEWORK

The HERC develops recommendations by using the concepts of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. GRADE is a transparent and structured process for developing and presenting evidence and for carrying out the steps involved in developing recommendations. There are four elements that determine the strength of a recommendation, as listed in the table below. The HERC reviews the evidence and makes an assessment of each element, which in turn is used to develop the recommendations. Balance between desirable and undesirable effects, and quality of evidence, are derived from the evidence presented in this document, while estimated relative costs, values and preferences are assessments of the HERC members.

Indication/Intervention	Balance between desirable and undesirable effects	Quality of evidence	Resource allocation	Values and preferences	Recommendation
Children aged 1 to 12 years at initiation					
Early Intensive Behavioral Interventions	Benefit on cognitive and language skills	Moderate	High	Low variability	Recommendation for coverage (strong recommendation)
	Benefit on adaptive behavior, social skills and overall autism severity	Low	High	Low variability	
Parent training interventions	Increased joint attention and parent synchrony, and improved early language and communication skills	Moderate	Moderate	Low variability	Recommendation for coverage (strong recommendation)
	Lessened overall severity of autism and improved early cognition	Low	Moderate	Low variability	
Play/interaction-based interventions (including joint attention interventions)	Improvements in joint attention and language skills	Moderate	Low	Low variability	Recommendation for coverage (strong recommendation)
	Short-term improvements in play, imitation, social skills	Low	Low	Low variability	
Adolescents and young adults					
ABA	Unknown	Insufficient	Moderate for focused, high	Low variability	Recommend noncoverage of

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Indication/Intervention	Balance between desirable and undesirable effects	Quality of evidence	Resource allocation	Values and preferences	Recommendation
			for more comprehensive		intensive ABA therapies *(weak recommendation)* Recommendation for coverage for specific problem behaviors with focused interventions *(weak recommendation)*

Note: GRADE framework elements are described in Appendix A

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SUMMARY CONCLUSIONS

Children ages 1 to 12

Applied behavior analysis (ABA), including early intensive behavioral intervention (EIBI), is recommended for coverage[6] for treatment of autism spectrum disorder[7] (*strong recommendation*).

> Rationale: This strength of recommendation was based on sufficient (moderate quality) evidence and expert input, including testimony on parent/caregiver values and preferences. The evidence does not lead to a direct determination of optimal intensity. Studies of EIBI ranged from 15-40 hours per week. Through Oregon's Senate Bill 365, other payers are mandated to cover a minimum of 25 hours per week of ABA. There is no evidence that increasing intensity of therapy yields improves outcomes. Studies for these interventions had a duration from less than one year up to 3 years.

~~Specifically, EIBI (for example, UCLA/Lovaas or ESDM), is recommended for coverage for up to 25 hours per week for a maximum of three years.~~

> ~~Rationale: The 25-hour limit would be similar to other payers in Oregon that were mandated through SB 365 and earlier Warren report had demonstrated 25 hours per week was effective. There is no evidence that increased intensity beyond this level yields improves outcomes. The duration limit is based on the fact that EIBI studies have a duration of 2-3 years.~~

Initial coverage of EIBI should be provided for up to six months. Ongoing coverage should be based on demonstrated progress towards meaningful predefined objectives (objectives should be achieved as a result of the EIBI, over and beyond gains that would be expected to arise from maturation alone) using standardized, multimodal assessments, no more frequently than every six months *(strong recommendation).* Examples of such assessments include Vineland, IQ tests (Mullen, WPPSI, WISC-R), language measures, behavioral checklists (CBCL, ABC), and autistic symptoms measures (SRS).

> Rationale: Ensuring that patients are making meaningful progress is important to ensure quality outcomes and effective use of resources. The six month assessment was chosen based on expert input and subcommittee deliberation to

[6] These conclusions apply to the Oregon Health Plan as governed by the Prioritized List of Health Services and to no other health plan.
[7] Autism spectrum disorder should be diagnosed by a qualified health care professional according to DSM-5 criteria.

allow for sufficient time for progress while not being burdensome to providers and plans.

Less intensive ABA-based interventions

If EIBI is not indicated, has been completed, or there is not sufficient progress toward multidimensional goals, then less intensive behavioral ABA-based interventions (such as parent training, play/interaction based interventions, and joint attention interventions) are recommended for coverage to address core symptoms of autism and/or specific problem areas *(strong recommendation*~~) for up to 8 hours per month. In extenuating circumstances (e.g severe aggressive behavior that is responding to interventions but requires increased intensity), an additional 8 hours per month is recommended for coverage.~~ Initial coverage should be provided for six months. Ongoing coverage should be based on demonstrated progress towards meaningful predefined objectives or emergence of new problem behaviors.

> Rationale: Not all autistic children require comprehensive therapy and less intensive interventions will be appropriate for many, or appropriate for those who have completed intensive intervention. Evidence supports these less intensive interventions in this age group. ~~Eight hours was chosen based on a wide range of intensity in the literature, expert input, and previous HERC Prioritized List guideline precedent.~~ Effective interventions from the research literature had lower intensity than EIBI, usually a few hours per week to a maximum of 16 hours per week, divided into daily, twice-daily or weekly sessions, over a period of several months.

Parent/caregiver involvement and training is recommended to be a component of treatment *(strong recommendation).*

> Rationale: Evidence and expert input indicated that parental involvement in ABA is a key part of effective treatment. Parent delivered therapy is effective.

Individuals ages 13 and older

Intensive ABA is not recommended for coverage for treatment of autism spectrum disorder in persons ages 13 and older (*weak recommendation*).

> Rationale: There is insufficient evidence to support intensive ABA treatment at older ages.

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For individuals age 13 and older, targeted behavioral interventions, including focused ABA*, are recommended for coverage for ~~up to 8 hours per month,~~ up to 6 months, only to address specific problem behaviors (*weak recommendation*). Behaviors eligible for coverage include those which place the member at risk for harm or create significant daily issues related to care, education, or other important functions. The interventions should involve predefined behavioral objectives that would result in socially important and sustainable outcomes for the individual. Ongoing coverage should be based on demonstrated progress towards meaningful predefined objectives with ongoing proof of medical appropriateness, or emergence of new problem behaviors.

> Rationale: According to the trusted evidence source, there is insufficient evidence to support ABA-based interventions in this age group. Public comment and some expert testimony involved submission of many single subject research design studies to support treatment in this age group, but the quality of this evidence did not meet predetermined criteria for inclusion. The subcommittee agreed that problem behaviors can be challenging to the individual, caregivers, and society and it is reasonable to consider targeted interventions for specific problem behaviors as long as there are clear objectives, progress toward meaningful predefined goals and ongoing proof of medical appropriateness. The net result was to recommend targeted interventions including ABA-based treatments for limited intensity to address problem behaviors. Very low quality evidence is available to illustrate needed intensity and duration of intervention. In the single-subject research design literature, frequency and duration of interventions were highly variable, with session duration ranging from 30 seconds to 3 hours, number of sessions ranging from a total of three to 8 times a day, and duration ranging from 1 to 20 weeks. These interventions were often conducted in inpatient or residential settings and studies often included patients with intellectual disabilities, some of which were not diagnosed with autism. Six months was chosen based on expert testimony and subcommittee discussion that more frequent assessments would potentially be burdensome to providers and plans.

Parent/caregiver involvement and training is encouraged *(weak recommendation)*

Note: The evidence for the treatment of conditions comorbid with autism spectrum disorder is beyond the scope of this evidence summary.

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POLICY LANDSCAPE

No quality measures were identified when searching the National Quality Measures Clearinghouse pertaining to autism and applied behavior analysis.

This report 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 (the Center). This document is intended to guide HERC in making informed decisions about the prioritization of health care services for the Oregon Health Plan.

The Center is not engaged in rendering any clinical, legal, business or other professional advice. The statements in this document do not represent official policy positions of the Center. Researchers involved in preparing this document have no affiliations or financial involvement that conflict with material presented in this document.

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Appendix A. GRADE Element Descriptions

Element	Description
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
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—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

Strong recommendation

In Favor: The subcommittee is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Against: The subcommittee is confident that the undesirable effects of adherence to a recommendation outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Weak recommendation

In Favor: the subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Against: the subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Quality of evidence across studies for the treatment/outcome

High = Further research is very unlikely to change our confidence in the estimate of effect.

Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low = Any estimate of effect is very uncertain.

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Appendix B. Potentially Applicable Codes

CODES	DESCRIPTION
ICD-9 Diagnosis Codes	
299.00	Autistic disorder, current or active state
299.01	Autistic disorder, residual state
299.10	Childhood disintegrative disorder, current or active state
299.11	Childhood disintegrative disorder, residual state
299.80	Other specified pervasive developmental disorders, current or active state
299.81	Other specified pervasive developmental disorders, residual state
299.90	Unspecified pervasive developmental disorder, current or active state
299.91	Unspecified pervasive developmental disorder, residual state
ICD-10 Diagnosis Codes	
F84.0	Autistic disorder
F84.2	Rett's syndrome
F84.3	Other childhood disintegrative disorder
F84.5	Asperger's syndrome
F84.8	Other pervasive developmental disorders
ICD-9 Volume 3 (Procedure Codes)	
None	
Procedure Codes	
Until July, 2014, no specific procedure codes exist for Applied Behavior Analysis. The list below provides examples of how various state Medicaid agencies covering ABA instruct providers to bill. Temporary codes shown in italics will be available starting July, 2014.	
90834	Psychotherapy, 45 min
90837	Psychotherapy, 60 min
0359T	*Behavior identification assessment, by the physician or other qualified health care professional, face-to-face with patient and caregiver(s), includes administration of standardized and non-standardized tests, detailed behavioral history, patient observation and caregiver interview, interpretation of test results, discussion of findings and recommendations with the primary guardian(s)/caregiver(s), and preparation of report*
0360T	*Observational behavioral follow-up assessment, includes physician or other qualified health care professional direction with interpretation and report, administered by one technician; first 30 minutes of technician time, face-to-face with the patient*
0361T	*…additional 30 minutes*
0362T	*Exposure behavioral follow-up assessment, includes physician or other qualified health care professional direction with interpretation and report, administered by physician or other qualified health care professional with the assistance of one or more technicians; first 30 minutes of technician(s) time, face-to-face with the patient*
0363T	*… additional 30 minutes*
0364T	*Adaptive behavior treatment by protocol, administered by technician, face-to-face with one patient; first 30 minutes of technician time*
0365T	*…additional 30 minutes*

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CODES	DESCRIPTION
0366T	*Group adaptive behavior treatment by protocol, administered by technician, face-to-face with two or more patients; first 30 minutes of technician time*
0367T	*….additional 30 minutes*
0368T	*Adaptive behavior treatment with protocol modification administered by physician or other qualified health care professional with one patient; first 30 minutes of patient face-to- face time*
0369T	*Adaptive behavior treatment with protocol modification, additional 30 minutes*
0370T	*Family adaptive behavior treatment guidance, administered by physician or other qualified health care professional (without the patient present)*
0371T	*Multiple-family group adaptive behavior treatment guidance, administered by physician or other qualified health care professional (without the patient present)*
0372T	*Adaptive behavior treatment social skills group, administered by physician or other qualified health care professional face-to-face with multiple patients*
0373T	*Exposure adaptive behavior treatment with protocol modification requiring two or more technicians for severe maladaptive behavior(s); first 60 minutes of technicians' time, face-to-face with patient*
0374T	*each additional 30 minutes of technicians' time face-to-face with patient (List separately in addition to code for primary procedure)*
G1076	Activity therapy, such as music, dance, art or play not for recreation, related to the care and treatment of patient's disabling mental health problems (45 min or more)
G1077	Training and educational services related to the care and treatment of patient's disabling mental health problems (45 min or more)
H0002	Behavioral health screening to determine eligibility for admission to treatment program
H0004	Behavioral health counseling and therapy, per 15 minutes
H0031	Mental health assessment by non-physician
H0032	Mental health service plan development by non-physician
H2000	Comprehensive multidisciplinary evaluation
H2010	Comprehensive medication services, per 15 minutes
H2019	Therapeutic behavioral service, per 15 minutes
H2020	Therapeutic behavioral service, per diem
H2027	Psychoeducational service, per 15 min
T1023	Screening to determine the appropriateness of consideration of an individual for participation in a specified program, project or treatment protocol, per encounter
T1024	Evaluation and treatment by an integrated, specialty team contracted to provide coordinated care to multiple or severely handicapped children, per encounter
T1027	Family training and counseling for child development, per 15 min
T2013	Habilitation, educational, waiver, per hour
T2026	Specialized childcare, waiver, per diem

Note: Inclusion on this list does not guarantee coverage

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Appendix C. HERC Guidance Development Framework

HERC Guidance Development Framework Principles

This framework was developed to assist with the decision making process for the Oregon policy-making body, the HERC and its subcommittees. It is a general guide, and must be used in the context of clinical judgment. It is not possible to include all possible scenarios and factors that may influence a policy decision in a graphic format. While this framework provides a general structure, factors that may influence decisions that are not captured on the framework include but are not limited to the following:

- Estimate of the level of risk associated with the treatment, or any alternatives;
- Which alternatives the treatment should most appropriately be compared to;
- Whether there is a discrete and clear diagnosis;
- The definition of clinical significance for a particular treatment, and the expected margin of benefit compared to alternatives;
- The relative balance of benefit compared to harm;
- The degree of benefit compared to cost; e.g., if the benefit is small and the cost is large, the committee may make a decision different than the algorithm suggests;
- Specific indications and contraindications that may determine appropriateness;
- Expected values and preferences of patients

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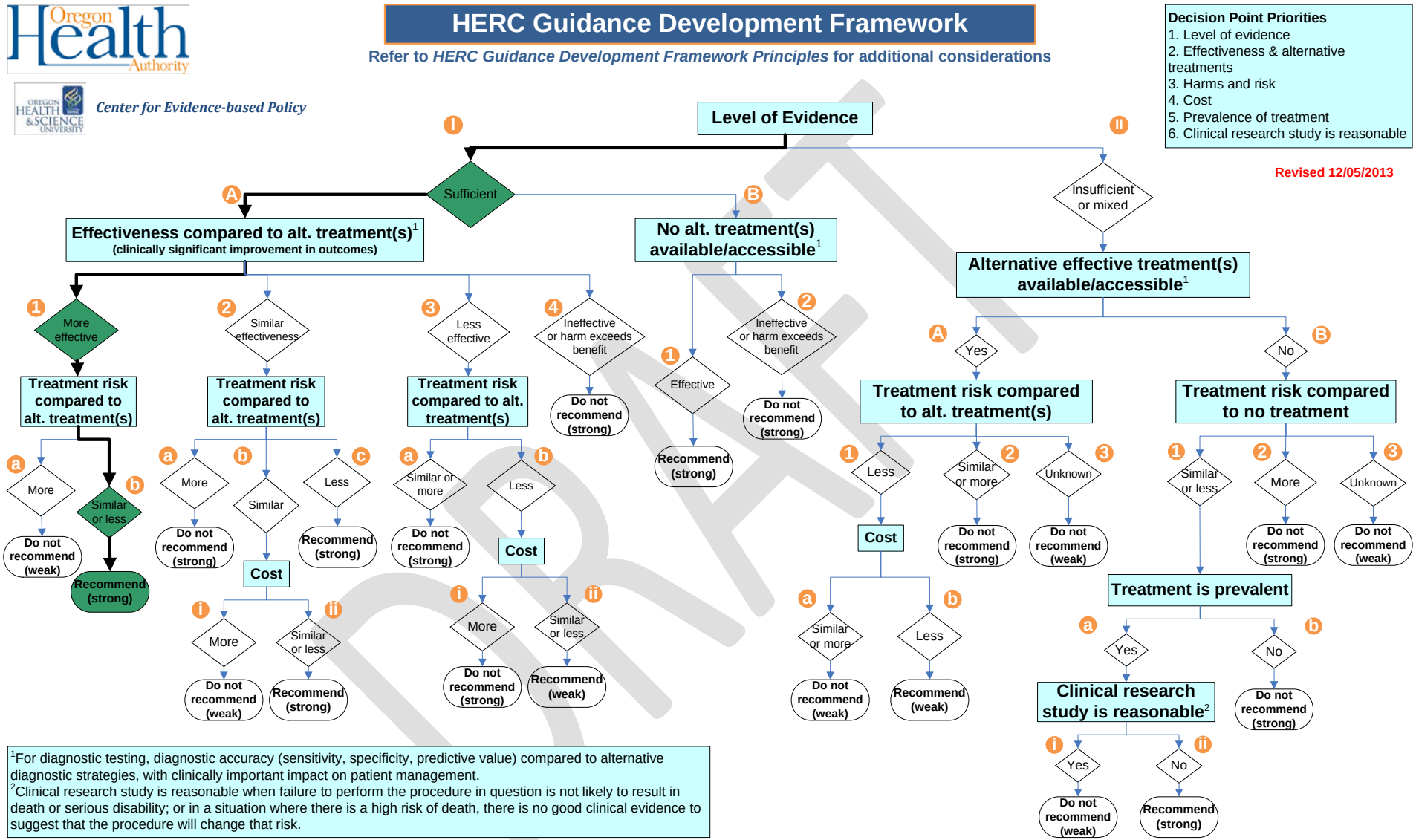
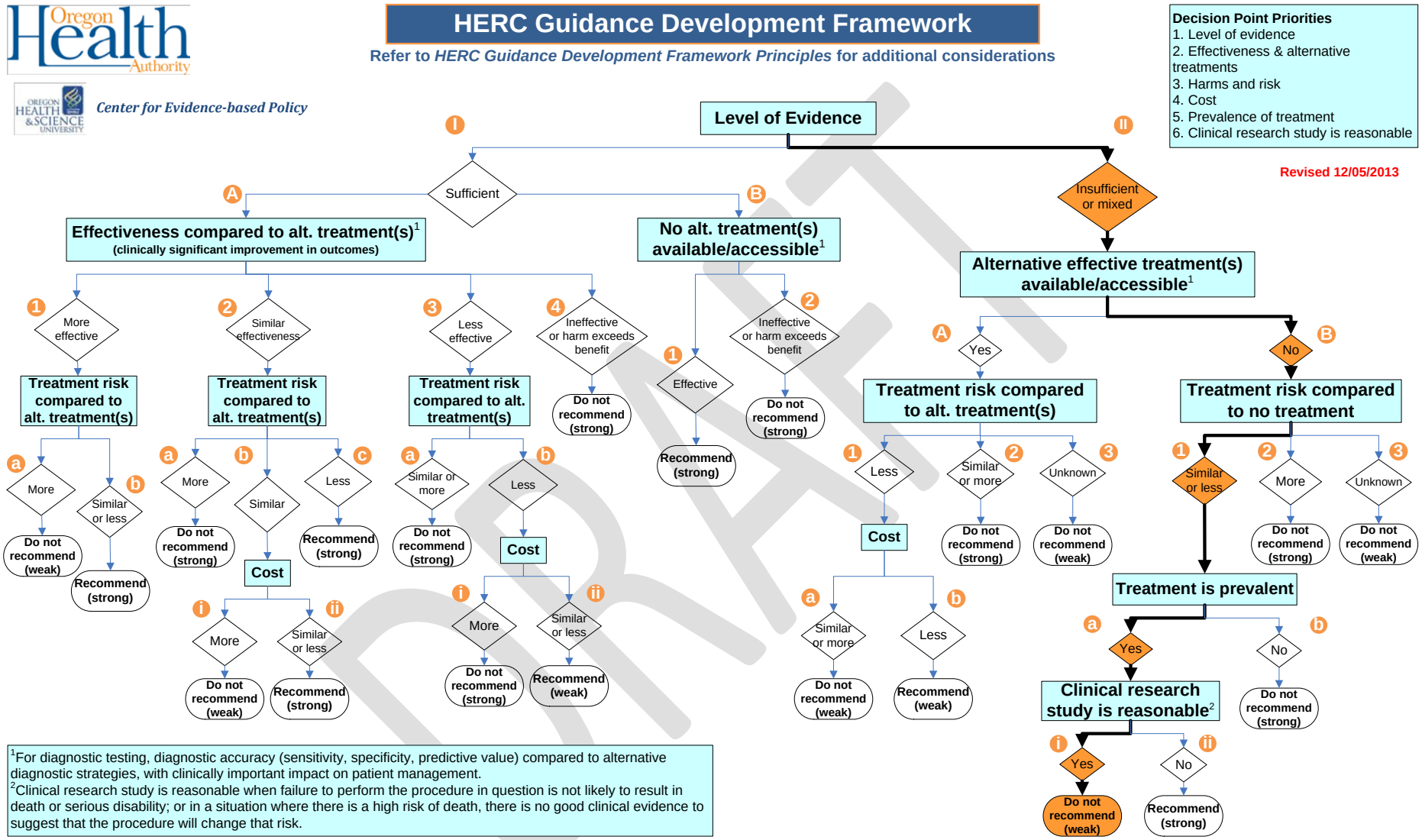
ABABA-based Treatments for Children Aged 1 to 12, including EIBI and Other Less Intensive Interventions





[1]For diagnostic testing, diagnostic accuracy (sensitivity, specificity, predictive value) compared to alternative diagnostic strategies, with clinically important impact on patient management.
[2]Clinical research study is reasonable when failure to perform the procedure in question is not likely to result in death or serious disability; or in a situation where there is a high risk of death, there is no good clinical evidence to suggest that the procedure will change that risk.

Appendix D. Key References from Evidence Sources

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Silva LTM, Schalock M, Ayres R, Bunse C, Budden S. Qigong massage treatment for sensory and self-regulation problems in young children with autism: a randomized controlled trial. *American Journal of Occupational Therapy* 2009;63(4):423-32. *{published data only}*

Smith T, Groen AD, Wynn JW. Randomized trial of intensive early intervention for children with pervasive developmental disorder. *American Journal on Mental Retardation* 2000;105(4):269–85. *{published data only}*

Tonge B, Brereton A, Kiomall M, Mackinnon A, King N, Rinehart N. Effects on parental mental health of an education and skills training program for parents of young children with autism: a randomised controlled trial. *American Academy of Child and Adolescent Psychiatry* 2006; 45(5):561–9. *{published data only}*

Wong VCN, Kwan QK. Randomized controlled trial for early intervention for autism: a pilot study of the Autism 1- 2-3 Project. *Journal of Autism and Developmental Disorders* 2010;40(6):677-88. *{published data only}*

DRAFT

Applied Behavior Analysis for Autism Spectrum Disorders

Question: How should applied behavior analysis (ABA) for autism spectrum disorder (ASD) be incorporated into the Prioritized List?

Question source: Oregon Legislative Assembly

Issue: See also ABA Overview and Update for details.

Senate Bill 365 (see attached for complete bill)
Oregon Senate Bill 365 was passed by the Oregon legislature in the 2013 regular session. That bill establishes requirements for state-regulated commercial health plans to approve and manage autism treatment, including ABA therapy and any other medical or mental health services identified in an individualized treatment plan. The law applies to patients who seek care before age nine, with a minimum coverage of up to 25 hours of ABA per week, and continuing as long as medically necessary. Health plans that provide coverage to OEBB and PEBB are required to begin coverage in 2015, and all other health plans are required to begin coverage in 2016. The bill required HERC to evaluate the evidence for ABA and make a coverage decision for OHP.

Applied behavior analysis is defined in the bill as the following:

> The design, implementation and evaluation of environmental modifications, using behavioral stimuli and consequences, to produce significant improvement in human social behavior, including the use of direct observation, measurement and functional analysis of the relationship between environment and behavior and that is provided by:
>
> > (i) A licensed health care professional registered under section 3 of this 2013 Act;
> > (ii) A behavior analyst or an assistant behavior analyst licensed under section 3 of this 2013 Act; or
> > (iii) A behavior analysis interventionist registered under section 3 of this 2013 Act.
>
> "Applied behavior analysis" excludes psychological testing, neuropsychology, psychotherapy, cognitive therapy, sex therapy, psychoanalysis, hypnotherapy and long-term counseling as treatment modalities.

EbGS has reviewed the evidence and adopted summary conclusions based on the evidence and a modified GRADE methodology. Expert input was solicited and reviewed. Public comment was solicited and reviewed. In addition to specific comments, a total of 336 unduplicated citations were provided by public commenters. Each citation was evaluated to determine study design or article type and population characteristics (number and ages of included individuals), the abstract was retrieved and a link to the article provided when available.

Given that the focus of most of the public comment pertained to requesting that ABA be recommended for coverage in individuals over age 12, detailed review of citations was limited to those studies. A random sample of 10% of SSRD study types (60 total) were reviewed in additional detail. In addition, all systematic reviews and meta-analyses of SSRDs were reviewed in more detail.

EbGS deliberations
EbGS met April 24, 2014, having reviewed the evidence, public written comment, in-person public comment, expert input and approved a modified Evidence Review Document to send to VbBS.

Staff additions
On further review of the requirements of the Medicaid Expansion and habilitative and mental health parity requirements of the ACA, staff suggested modifying the language to be more descriptive of studies and less directive of specific hour limits.

Current Prioritized List information:
Line: 313
Condition: AUTISM SPECTRUM DISORDERS (See Guideline Notes 64,65,75)
Treatment: CONSULTATION/MEDICATION MANAGEMENT/LIMITED BEHAVIORAL MODIFICATION
ICD-9: 299.00-299.91
CPT: 90785,90832-90840,90846-90849,90882,90887,96101,96118,98966-98969,99051,99060,99201-99215,99224-99226, 99366,99441-99444,99487-99496
HCPCS: G0176,G0177,G0406-G0408,G0425-G0427, H0023, H0032, H0034, H0038, H2010, H2011, H2014,H2027,H2032, S0270,S0272-S0274,S9484,T1016

Current guideline
GUIDELINE NOTE 75, AUTISM SPECTRUM DISORDERS
Line 334
There is limited evidence of the effectiveness of treatment (e.g., Applied Behavior Analysis) for Autism Spectrum Disorders (ASD). However, effective treatments may be available for co-morbid conditions such as mood disorders. When treating co-morbid conditions, that condition, not an ASD diagnosis, should be the primary diagnosis for billing purposes. The treatment of co-morbid mental health conditions should be consistent with the treatment methods, frequency, and duration normally applied to those diagnoses. Treatment of neurologic dysfunctions that may be seen in individuals with an ASD diagnosis are prioritized according to the four dysfunction lines found on the Prioritized List (Lines 78, 318, 375 and 407). Treatment for associated behaviors, such as agitation, that do not meet the criteria for co-morbid mental health diagnoses should be limited in frequency to a maximum of 8 hours of behavioral health

service per month, subject to utilization management review by the mental health organization (MHO) or other relevant payer.

New CPT codes for ABA therapy

1) New category III CPT codes have been published by the AMA effective July 1, 2014
    a. 0359T-0363T (adaptive behavior assessments)
    b. 0364T-374T (adaptive behavior treatments)
    c. See attached document submitted by Dr. Larsson for information on definition of these codes

Of note, DMAP has a rule that excludes the use of temporary codes. This rule would need to be deleted. As a result, there is a good likelihood of additional temporary codes being brought to VBBS/HERC for review in the future.

EbGS approved GRADE table

Indication/Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Values and preferences	Recommendation
Children aged 1 to 12 years at initiation					
Early Intensive Behavioral Interventions	Benefit on cognitive and language skills	Moderate	High	Low variability	Recommendation for coverage (strong recommendation)
	Benefit on adaptive behavior, social skills and overall autism severity	Low	High	Low variability	
Parent training interventions	Increased joint attention and parent synchrony, and improved early language and communication skills	Moderate	Moderate	Low variability	Recommendation for coverage (strong recommendation)

Indication/Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Values and preferences	Recommendation
Parent training interventions (cont'd)	Lessened overall severity of autism and improved early cognition	Low	Moderate	Low variability	
Play/interaction-based interventions (including joint attention interventions)	Improvements in joint attention and language skills	Moderate	Low	Low variability	Recommendation for coverage (strong recommendation)
	Short-term improvements in play, imitation, social skills	Low	Low	Low variability	
Adolescents and young adults					
ABA	Unknown	Insufficient	Moderate for focused, high for more comprehensive	Low variability	Recommend noncoverage of intensive ABA therapies *(weak recommendation)* Recommendation for coverage for specific problem behaviors with targeted interventions *(weak recommendation)*

EBGS APPROVED SUMMARY CONCLUSIONS

Children ages 1 to 12

Applied behavior analysis (ABA), including early intensive behavioral intervention (EIBI), is recommended for coverage[1] for treatment of autism spectrum disorder[2] (*strong recommendation*).

> Rationale: This strength of recommendation was based on sufficient (moderate quality) evidence and expert input, including testimony on parent/caregiver values and preferences.

Specifically, EIBI (for example, UCLA/Lovaas or ESDM), is recommended for coverage for up to 25 hours per week for a maximum of three years.

> Rationale: The 25-hour limit would be similar to other payers in Oregon that were mandated through SB 365 and earlier Warren report had demonstrated 25 hours per week was effective. There is no evidence that increased intensity beyond this level yields improves outcomes. The duration limit is based on the fact that EIBI studies have a duration of 2-3 years

Initial coverage of EIBI should be provided for up to six months. Ongoing coverage should be based on demonstrated progress towards meaningful predefined objectives (objectives should be achieved as a result of the EIBI, over and beyond gains that would be expected to arise from maturation alone) using standardized, multimodal assessments, no more frequently than every six months *(strong recommendation).* Examples of such assessments include Vineland, IQ tests (Mullen, WPPSI, WISC-R), language measures, behavior checklists (CBCL, ABC), and autistic symptoms measures (SRS).

> Rationale: Ensuring that patients are making meaningful progress is important to ensure quality outcomes and effective use of resources. The six month assessment was chosen based on expert input and subcommittee deliberation to allow for sufficient time for progress while not being burdensome to providers and plans.

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[1] These conclusions apply to the Oregon Health Plan as governed by the Prioritized List of Health Services and to no other health plan.

[2] Autism spectrum disorder should be diagnosed by a qualified health care professional according to DSM-5 criteria.

Less intensive ABA-based interventions

If EIBI is not indicated, has been completed, or there is not sufficient progress toward multidimensional goals, then less intensive ABA-based interventions (such as parent training, play/interaction based interventions, and joint attention interventions) are recommended for coverage to address core symptoms of autism and/or specific problem areas *(strong recommendation)* for up to 8 hours per month. In extenuating circumstances (e.g severe aggressive behavior that is responding to interventions but requires increased intensity), an additional 8 hours per month is recommended for coverage. Initial coverage should be provided for six months. Ongoing coverage should be based on demonstrated progress towards meaningful predefined objectives or emergence of new problem behaviors.

> Rationale: Not all autistic children require comprehensive therapy and less intensive interventions will be appropriate for many, or appropriate for those who have completed intensive intervention. Evidence supports these less intensive interventions in this age group. Eight hours was chosen based on a wide range of intensity in the literature, expert input, and previous HERC Prioritized List guideline precedent.

Parent/caregiver involvement and training is recommended to be a component of treatment *(strong recommendation).*

> Rationale: Evidence and expert input indicated that parental involvement in ABA is a key part of effective treatment. Parent delivered therapy is effective.

<u>Individuals ages 13 and older</u>

Intensive ABA is not recommended for coverage for treatment of autism spectrum disorder in persons ages 13 and older (*weak recommendation*).

> Rationale: There is insufficient evidence to support intensive ABA treatment at older ages.

For individuals age 13 and older, targeted behavioral interventions, including focused ABA*, are recommended for coverage for up to 8 hours per month, up to 6 months, only to address specific problem behaviors (*weak recommendation*). Behaviors eligible for coverage include those which place the member at risk for

harm or create significant daily issues related to care, education, or other important functions. The interventions should involve predefined behavioral objectives that would result in socially important and sustainable outcomes for the individual. Ongoing coverage should be based on demonstrated progress towards meaningful predefined objectives with ongoing proof of medical appropriateness, or emergence of new problem behaviors.

> Rationale: According to the trusted evidence source, there is insufficient evidence to support ABA-based interventions in this age group. Public comment and some expert testimony involved submission of many single subject research design studies to support treatment in this age group, but the quality of this evidence did not meet predetermined criteria for inclusion. The subcommittee agreed that problem behaviors can be challenging to the individual, caregivers, and society and it is reasonable to consider targeted interventions for specific problem behaviors as long as there are clear objectives, progress toward meaningful predefined goals and ongoing proof of medical appropriateness. The net result was to recommend targeted interventions including ABA-based treatments for limited intensity to address problem behaviors. Six months was chosen based on expert testimony and subcommittee discussion that more frequent assessments would potentially be burdensome to providers and plans.

Parent/caregiver involvement and training is encouraged *(weak recommendation)*

Note: The evidence for the treatment of conditions comorbid with autism spectrum disorder is beyond the scope of this evidence summary.

VbBS RECOMMENDATIONS:

1) Replace Guideline Note 75 with the following:

GUIDELINE NOTE 75 APPLIED BEHAVIOR ANALYSIS FOR AUTISM SPECTRUM DISORDER
Line 313

Applied behavior analysis (ABA), including early intensive behavioral intervention (EIBI), represented by CPT codes 0359T-0374T, is included on line 313 for the treatment of autism spectrum disorders.

ABA services are provided in addition to any rehabilitative services (e.g. physical therapy, occupational therapy, speech therapy) included in guideline note 6, REHABILITATIVE THERAPIES that are indicated for other acute qualifying conditions.

Individuals ages 1-12

Intensive interventions
Specifically, EIBI (for example, UCLA/Lovaas or Early Start Denver Model), is included on this line.

For a child initiating EIBI therapy, EIBI is included for up to six months. Ongoing coverage is based on demonstrated progress towards meaningful predefined objectives (objectives should be achieved as a result of the EIBI, over and beyond gains that would be expected to arise from maturation alone) using a standardized, multimodal assessment, no more frequently than every six months. Examples of such assessments include Vineland, IQ tests (Mullen, WPPSI, WISC-R), language measures, behavior checklists (CBCL, ABC), and autistic symptoms measures (SRS).

The evidence does not lead to a direct determination of optimal intensity. Studies of EIBI ranged from 15-40 hours per week. Through Oregon's Senate Bill 365, other payers are mandated to cover a minimum of 25 hours per week of ABA. There is no evidence that increasing intensity of therapy yields improves outcomes. Studies for these interventions had a duration from less than one year up to 3 years.

Less intensive ABA-based interventions

If EIBI is not indicated, has been completed, or there is not sufficient progress toward multidimensional goals, then less intensive ABA-based interventions (such as parent training, play/interaction based interventions,

and joint attention interventions) are included on this line to address core symptoms of autism and/or specific problem areas. Initial coverage is provided for six months. Ongoing coverage is based on demonstrated progress towards meaningful predefined objectives, with demonstration of medical appropriateness and/or emergence of new problem behaviors.

Effective interventions from the research literature had lower intensity than EIBI, usually a few hours per week to a maximum of 16 hours per week, divided into daily, twice-daily or weekly sessions, over a period of several months.

Parent/caregiver involvement

Parent/caregiver involvement and training is recommended as a component of treatment.

Individuals ages 13 and older

Intensive ABA is not included on this line.

Targeted ABA-based behavioral interventions to address problem behaviors, are included on this line. The quality of evidence is insufficient to support these interventions in this population. However, due to strong caregiver values and preferences and the potential for avoiding suffering and expense in dealing with unmanageable behaviors, targeted interventions may be reasonable. Behaviors eligible for coverage include those which place the member at risk for harm or create significant daily issues related to care, education, or other important functions. Ongoing coverage is based on demonstrated progress towards meaningful predefined objectives, with demonstration of medical appropriateness and/or emergence of new problem behaviors.

Very low quality evidence is available to illustrate needed intensity and duration of intervention. In the single-subject research design literature, frequency and duration of interventions were highly variable, with session duration ranging from 30 seconds to 3 hours, number of sessions ranging from a total of three to 8 times a day, and duration ranging from 1 to 20 weeks. These interventions were often conducted in inpatient or residential settings and studies often included patients with intellectual disabilities, some of which were not diagnosed with autism.

Parent/caregiver involvement and training is encouraged.

2) Add CPT 0359T-0374T (adaptive behavior assessments and treatments) to 1/1/15 line 313 AUTISM SPECTRUM DISORDERS
3) Recommend that EbGS view and revise their summary conclusions as time and meetings allows
4) Change treatment description of line: ~~CONSULTATION/MEDICATION MANAGEMENT/LIMITED BEHAVIORAL MODIFICATION~~ MEDICAL THERAPY/BEHAVIORAL MODIFICATION INCLUDING APPLIED BEHAVIOR ANALYSIS
5) Rescore and reprioritize the autism spectrum line on the 2016 Biennial List as shown below:

Scoring proposal (scoring for 1/1/15 line 313 in parentheses)
Category: 3 (3)
HL: 5 (5)
Suffering: 4 (4)
Population effects: 2 (1)
Vulnerable population: 0 (0)
Tertiary prevention: ()
Effectiveness: 3 (2)
Need for service: 0.7 (0.7)
Net cost: 1 (3)
Score: 1733 (1050)

Approximate new line placement: 199

Section 4.0

Coverage guidance rescan

Topic: Management of Chronic Otitis Media with Effusion in Children

Coverage Recommendation (Box Language):

Antibiotic and other medication therapy (including antihistamines, decongestants, and nasal steroids) should not be covered for children with children with otitis media with effusion (OME) (without another appropriate diagnosis).

There should be a 3 to 6 month watchful waiting period after diagnosis of otitis media with effusion, and if documented persistent hearing loss is greater than or equal to 25dB in the better hearing ear, referral for tympanstomy surgery may be covered, given short, but not long-term, improvement in hearing.

Formal audiometry should be covered for children with chronic OME present for 3 months or longer. Children with language delay, learning problems, or significant hearing loss should have hearing testing covered initially upon diagnosis. Children with chronic OME who are not at risk for language 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 should not be covered at the time of the first pressure equalization tube insertion.

Patients with craniofacial anomalies, Down's syndrome, cleft palate, and patients with speech and language delay along with hearing loss should have coverage based on an individualized treatment plan.

Source report:

Effros, R., & Little, A. (2010). *Pressure equalization tubes in children.* (Produced for the Medicaid Evidence-based Decision Project). Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University.

Key Sources Cited in MED Report:

American Academy of Family Physicians, American Academy of Otolaryngology – Head and Neck Surgery, & American Academy of Pediatrics (AAFP/AAOHNS/AAP) Subcommittee on Otitis Media with Effusion. (2004). Clinical Practice Guideline: Otitis Media with Effusion. *Pediatrics, 113*(5), 1412-1429.

Griffin, G., Flynn, C.A., Bailey, R.E., & Schultz, J.K. (2006). Antihistamines and/or decongestants for otitis media with effusion (OME) in children. *Cochrane Database of Systematic Reviews*, *4*(CD003423), 1-44.

Kay, D.J., Nelson, M., & Rosenfeld, R.M. (2001). Meta-analysis of tympanostomy tube sequelae. *Otolaryngology-Head and Neck Surgery*, *124*, 374-380.

Leach, A.J., & Morris, P.S. (2006). Antibiotics for the prevention of acute and chronic suppurative otitis media in children. *Cochrane Database of Systematic Reviews*, *4*(CD004401), 1-70.

Lous, J., Burton, M.J., Felding, J., Ovesen, T., Rovers, M., & Williamson, I. (2005). Grommets (ventilation tubes) for hearing loss associated with otitis media with effusion in children. *Cochrane Database of Systematic Reviews*, *1* (CD001801), 1-58.

Mandel, E.M., & Casselbrant, M.L. (2006). Recent developments in the treatment of otitis media with effusion. *Drug, 66*(12), 1545-1576.

McDonald, S., Langton Hewer, C.D., & Nunez, D.A. (2008). Grommets (ventilation tubes) for recurrent acute otitis media in children. *Cochrane Database of Systematic Reviews*, *4*(CD 004741), 1-14.

National Collaborating Centre for Women's and Children's Health. (2008). Surgical management of otitis media with effusion in children. London: National Institute for Health and Clinical Excellence (NICE). Retrieved July 6, 2012, from www.nice.org.uk/nicemedia/pdf/CG60NICEguideline.pdf

Perera, R., Haynes, J., Glasziou, P.P., & Heneghan, C.J. (2006). Autoinflation for hearing loss associated with otitis media with effusion. *Cochrane Database of Systematic Reviews, 4*(CD006285), 1-28.

Rovers, M.M., Black, N., Browning, G.G., Maw, R., Zielhuis, G.A., & Haggard, M.P. (2005). Grommets in otitis media with effusion: an individual patient data meta-analysis. *Archives of Diseases of Childhood*, *90*(5), 480-485.

Simpson, S.A., Thomas, C.L., van der Linden, M., MacMillan, H., van der Wouden, J.C., & Butler, C.C. (2007). Identification of children in the first four years of life for early treatment for otitis media with effusion. *Cochrane Database of Systemic Reviews*, *1*(CD004163), 1-24.

Thomas, C.L., Simson, S., Butler, C., & van der Voort, J. (2006). Oral or topical nasal steroids for hearling loss associated with otitis media with effusion in children. *Cochrane Database of Systemic Reviews*, *3*(CD001935), 1-26.

Scanning results:

Eight reviews were identified in the core sources that were published after the date of the MED report (some were updates of Cochrane reviews included in the guidance document). Summary results and/or conclusions are presented below:

Williamson, I. (2011). Otitis media with effusion in children. BMJ Clinical Evidence, 01(502), 1-30.

- Oral antibiotics, antihistamines plus oral decongestants, or mucolytics may be of no benefit in OME, and can cause adverse effects.
- Oral corticosteroids are unlikely to improve symptoms in OME, and can cause growth retardation.
- Intranasal corticosteroids are unlikely to be of benefit in children with bilateral otitis media with effusion.
- Ventilation tubes may improve short-term outcomes, but the clinical effect size is small. They may also increase the risk of tympanic membrane abnormalities. Ventilation tubes improve hearing for the first 2 years, but have no longer-term benefit, and may not improve cognition or language development.
- Adenoidectomy may improve hearing when performed with tympanostomy, but the clinical relevance of the improvements is unclear.
- Combination treatment with ventilation tubes plus adenoidectomy may be more effective than adenoidectomy alone.

van den Aardweg MTA, Schilder AGM, Herkert E, Boonacker CWB, Rovers MM. Adenoidectomy for otitis media in children. (2010). Cochrane Database of Systematic Reviews. Issue 1. Art. No.: CD007810. DOI: 10.1002/14651858.CD007810.pub2.

Main results:

Fourteen randomised controlled trials (2712 children) studying the effectiveness of adenoidectomy in children with otitis media were evaluated. Most of these trials were too heterogeneous to pool in a meta-analysis. Loss to follow up varied from 0% to 63% after two years.

Adenoidectomy in combination with a unilateral tympanostomy tube has a beneficial effect on the resolution of OME (risk difference (RD) 22% (95% CI 12% to 32%) and 29% (95% CI 19% to 39%) for the non-operated ear at six and 12 months, respectively (n = 3 trials)) and a very small (< 5 dB) effect on hearing, compared to a unilateral tympanostomy tube only. The results of studies of adenoidectomy with or without myringotomy versus non-surgical treatment or myringotomy only, and those of adenoidectomy in combination with bilateral tympanostomy tubes versus bilateral tympanostomy tubes only, also showed a small beneficial effect of adenoidectomy on the resolution of the effusion. The latter results could not be pooled due to large heterogeneity of the trials.

The effects of adenoidectomy on changes of the tympanic membrane or cholesteatoma have not been studied.

Authors' conclusions

Our review shows a significant benefit of adenoidectomy as far as the resolution of middle ear effusion in children with OME is concerned. However, the benefit to hearing is small and the effects on changes in the tympanic membrane are unknown. The risks of operating should be weighed against these potential benefits.

van Zon A, van der Heijden GJ, van Dongen TMA, Burton MJ, Schilder AGM. (2012). Antibiotics for otitis media with effusion in children. Cochrane Database of Systematic Reviews. Issue 9. Art. No.: CD009163. DOI: 10.1002/14651858.CD009163.pub2.

Main results:
We included 23 studies (3027 children) covering a range of antibiotics, participants, outcome measures and time points of evaluation. Overall, we assessed the studies as generally being at low risk of bias. Our primary outcome was complete resolution of OME at two to three months. The differences (improvement) in the proportion of children having such resolution (risk difference (RD)) in the five individual included studies ranged from 1% (RD 0.01, 95% CI -0.11 to 0.12; not significant) to 45% (RD 0.45, 95% CI 0.25 to 0.65). Results from these studies could not be pooled due to clinical and statistical heterogeneity. Pooled analysis of data for complete resolution at more than six months was possible, with an increase in resolution of 13% (RD 0.13, 95% CI 0.06 to 0.19). Pooled analysis was also possible for complete resolution at the end of treatment, with the following increases in resolution rates: 17% (RD 0.17, 95% CI 0.09 to 0.24) for treatment for 10 days to two weeks, 34% (RD 0.34, 95% CI 0.19 to 0.50) for treatment for four weeks, 32% (RD 0.32, 95% CI 0.17 to 0.47) for treatment for three months, and 14% (RD 0.14, 95% CI 0.03 to 0.24) for treatment continuously for at least six months.

We were unable to find evidence of a substantial improvement in hearing as a result of the use of antibiotics for otitis media with effusion; nor did we find an effect on the rate of ventilation tube insertion. We did not identify any trials that looked at speech, language and cognitive development or quality of life. Data on the adverse effects of antibiotic treatment reported in six studies could not be pooled due to high heterogeneity. Increases in the occurrence of adverse events varied from 3% (RD 0.03, 95% CI -0.01 to 0.07; not significant) to 33% (RD 0.33, 95% CI 0.22 to 0.44) in the individual studies.

Authors' conclusions:

The results of our review do not support the routine use of antibiotics for children up to 18 years with otitis media with effusion. The largest effects of antibiotics were seen in children treated continuously for four weeks and three months. Even when clear and relevant benefits of antibiotics have been demonstrated, these must be balanced against the potential adverse effects when making treatment decisions. Immediate adverse effects of antibiotics are common and the emergence of bacterial resistance has been causally linked to the widespread use of antibiotics for common conditions such as otitis media.

Griffin G, Flynn CA. Antihistamines and/or decongestants for otitis media with effusion (OME) in children. (2011). Cochrane Database of Systematic Reviews. Issue 9. Art. No.: CD003423. DOI: 10.1002/14651858.CD003423.pub3.

Main results:
Sixteen studies (1880 participants) were included in the review. No statistical or clinical benefit was found for any of the interventions or outcomes studied. However, treated study subjects experienced 11% more side effects than untreated subjects (number needed to treat to harm = 9).

Authors' conclusions:
The pooled data demonstrate no benefit and some harm from the use of antihistamines or decongestants alone or in combination in the management of OME, therefore we recommend against their use.

Perera R, Glasziou PP, Heneghan CJ, McLellan J, Williamson I. Autoinflation for hearing loss associated with otitis media with effusion. (2013). Cochrane Database of Systematic Reviews. Issue 5. Art. No.: CD006285. DOI: 10.1002/14651858.CD006285.pub2.

Main results:
Eight studies, with a total of 702 participants, met the inclusion criteria. Overall, the studies were predominantly assessed as being at low or unclear risk of bias; unclear risk was mainly due lack of information. There was no evidence of selective reporting. Pooled estimates favoured the intervention, but did not show a significant effect on tympanometry (type C2 and B) at less than one month, nor at more than one month. Similarly, there were no significant changes for discrete pure-tone audiometry and non-discrete audiometry. Pooled estimates favoured, but not significantly, the intervention for the composite measure of tympanogram or audiometry at less than one month; at more than one month the result became significant (RRI 1.74, 95% CI 1.22 to 2.50).

Subgroup analysis based on the type of intervention showed a significant effect using a Politzer device under one month (RRI 7.07, 95% CI 3.70 to 13.51) and over one month (RRI 2.25, 95% CI 1.67 to 3.04). None of the studies demonstrated a significant difference in the incidence of side effects between interventions.

Authors' conclusions:
All of the studies were small, of limited treatment duration and had short follow-up. However, because of the low cost and absence of adverse effects it is reasonable to consider autoinflation whilst awaiting natural resolution of otitis media with effusion. Primary care could prove a beneficial place to evaluate such interventions and there is ongoing research in this area. Further research should also consider the duration of treatment, the long-term impact on developmental outcomes in children and additional quality of life outcome measures for children and families.

Browning GG, Rovers MM, Williamson I, Lous J, Burton MJ. Grommets (ventilation tubes) for hearing loss associated with otitis media with effusion in children. (2010). Cochrane Database of Systematic Reviews. Issue 10. Art. No.: CD001801. DOI: 10.1002/14651858.CD001801.pub3.

Main results:
We included 10 trials (1728 participants). Some trials randomised children (grommets versus no grommets), others ears (grommet one ear only). The severity of OME in children varied between trials. Only one 'by child' study (MRC: TARGET) had particularly stringent audiometric entry criteria. No trial was identified that used long-term grommets.

Grommets were mainly beneficial in the first six months by which time natural resolution lead to improved hearing in the non-surgically treated children also. Only one high quality trial that randomised children (N = 211) reported results at three months; the mean hearing level was 12 dB better (95% CI 10 to 14 dB) in those treated with grommets as compared to the controls. Meta-analyses of three high quality trials (N = 523) showed a benefit of 4 dB (95% CI 2 to 6 dB) at six to nine months. At 12 and 18 months follow up no differences in mean hearing levels were found.

Data from three trials that randomised ears (N = 230 ears) showed similar effects to the trials that randomised children. At four to six months mean hearing level was 10 dB better in the grommet ear (95% CI 5 to 16 dB), and at 7 to 12 months and 18 to 24 months was 6 dB (95% CI 2 to 10 dB) and 5 dB (95% CI 3 to 8 dB) dB better. No effect was found on language or speech development or for behaviour, cognitive or quality of life outcomes.

Tympanosclerosis was seen in about a third of ears that received grommets. Otorrhoea was common in infants, but in older children (three to seven years) occurred in < 2% of grommet ears over two years of follow up.

Authors' conclusions:
In children with OME the effect of grommets on hearing, as measured by standard tests, appears small and diminishes after six to nine months by which time natural resolution also leads to improved hearing in the non-surgically treated children. No effect was found on other child outcomes but data on these were sparse. No study has been performed in children with established speech, language, learning or developmental problems so no conclusions can be made regarding treatment of such children.

Simpson SA, Lewis R, van der Voort J, Butler CC. Oral or topical nasal steroids for hearing loss associated with otitis media with effusion in children. (2011). Cochrane Database of Systematic Reviews. Issue 5. Art. No.: CD001935. DOI: 10.1002/14651858.CD001935.pub3.

Main results:
We included 12 medium to high-quality studies with a total of 945 participants. No study documented hearing loss associated with OME prior to randomisation. The follow-up period was generally limited, with only one study of intranasal steroid reporting outcome data beyond six months.

There was no evidence of benefit from steroid treatment (oral or topical) in terms of hearing loss associated with OME. Pooled data using a fixed-effect model for OME resolution at short-term follow up (< 1 month) showed a significant effect of oral steroids compared to control (RR 4.48; 95% CI 1.52 to 13.23; Chi^2 2.75, df = 2, P = 0.25; I^2 = 27%). Oral steroids plus antibiotic also resulted in an improvement in OME resolution compared to placebo plus antibiotic at less than one month follow up, using a random-effects model (RR 1.99; 95% CI 1.14 to 3.49; five trials, 409 children). However, there was significant heterogeneity between studies (P < 0.01, I^2 = 69%). There was no evidence of beneficial effect on OME resolution at greater than one month follow up with oral steroids (used alone or with antibiotics) or intranasal steroids (used alone or with antibiotics) at any follow-up period. There was also no evidence of benefit from steroid treatment (oral or topical) in terms of symptoms.

Authors' conclusions:
While oral steroids, especially when used in combination with an oral antibiotic, lead to a quicker resolution of OME in the short term, there is no evidence of longer-term

benefit and no evidence that they relieve symptoms of hearing loss. We found no evidence of benefit from treatment of OME with topical intranasal steroids, alone or in combination with an antibiotic, either at short or longer term follow up.

Berkman ND, Wallace IF, Steiner MJ, Harrison M, Greenblatt AM, Lohr KN, Kimple A, Yuen A. (2013). 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.

Results:
We identified 59 studies through the earlier reviews and our independent searches. Generally, studies examined interventions in otherwise healthy, non-infant children. We did not find any eligible studies covering complementary and alternative medicine. Findings are reported for clinical and functional outcomes, and harms. Variation in length of tympanostomy tube (TT) retention corresponded to whether TT were designed to be short versus long term, but variation in TT type was not related to improved OME and hearing outcomes. Tympanostomy tubes decreased OME for 2 years compared with watchful waiting (WW) or myringotomy, and improved hearing for 6 months compared with WW. OME resolution was more likely with adenoidectomy than no treatment at 12 months. Adenoidectomy and myringotomy were superior to myringotomy alone in relation to OME and hearing outcomes at 24 months. Adenoidectomy and TT were superior to WW for hearing outcomes at 24 months. Autoinflation was superior to standard treatment at improving OME at 1 month. We found no benefits from oral steroids at 2 months, or topical steroids at 9 months. In relation to functional outcomes, TT and WW did not differ in long-term language, cognitive or academic outcomes. Tympanosclerosis and otorrhea were more common in ears with TT. Adenoidectomy increased the risk of postsurgical hemorrhage. In one study of a subgroup, adults receiving autoinflation were more likely to recover from OME than those in the control group at one month. We found no studies examining the influence of any health care factors on treatment effectiveness.

Conclusions:
There is evidence that both TT and adenoidectomy reduce OME and improve hearing in the short term, but both treatments also have associated harms. Large, well-controlled studies could help resolve the risk-benefit ratio by measuring AOM recurrence, functional outcomes, quality of life measures, and long-term outcomes. Finally, additional research is needed to support treatment decisions in subpopulations,

particularly those with comorbidities and those who have received a pneumococcal vaccine inoculation.

Summary:

The recently published evidence does not contradict the current coverage guidance recommendations.

Topic: INDICATIONS FOR PLANNED CESAREAN SECTION

Coverage Recommendation (Box Language):

Planned cesarean section (CS) should be covered for:

- Breech presentation (if external cephalic version unsuccessful or contraindicated; and vaginal breech delivery is unavailable, undesired, or contraindicated)
- Partial or complete placenta previa
- Morbidly adherent placenta
- Human immunodeficiency virus (HIV) positive mothers who are not receiving anti-retroviral therapy, are receiving anti-retroviral therapy and have a viral load of 400 copies per ml or more, or who are co-infected with Hepatitis C
- Primary herpes simplex virus infection in the third trimester
- Twin pregnancy (if the presenting twin is not vertex)

Planned CS should not be covered for:

- Preterm birth
- Small for gestational age
- Suspected cephalopelvic disproportion
- Maternal Hepatitis B infection
- Maternal Hepatitis C infection
- Elective (without obstetrical or medical indication)

For prior cesarean delivery and other conditions for which there is insufficient evidence* of clear benefit over harms, coverage may be based on an individualized treatment plan.

Source reports:

Cunningham, F.G., Bangdiwala, S., Brown, S.S., Dean, T.M., Frederiksen, M., Rowland Hogue, C.J., et al. (2010). National Institutes of Health Consensus Development Conference Statement: Vaginal birth after cesarean: New insights. March 8-10, 2010. Obstetrics & Gynecology, 115(6), 1279–1295. Retrieved from http://consensus.nih.gov/2010/images/vbac/vbac_statement.pdf

Guise, J-M., Eden, K., Emeis, C., Denman, M.A., Marshall, N., Fu, R, et al. (2010). Vaginal birth after cesarean: New insights. Evidence Report/Technology Assessment No.191. (Prepared by the Oregon Health & Science University Evidence-based Practice Center under Contract No. 290-2007-10057-I). AHRQ Publication No. 10-E003. Rockville, MD: Agency for Healthcare Research and Quality. Retrieved from http://www.ncbi.nlm.nih.gov/books/NBK44571/

National Institute for Health and Clinical Excellence, & National Collaborating Centre for Women's and Children's Health. (2008). Diabetes in pregnancy: Management of diabetes and its complications from preconception to the postnatal period. London, UK: Royal College of Obstetricians and Gynaecologists Press. Retrieved from http://www.nice.org.uk/guidance/CG63

National Institute for Health and Clinical Excellence, & National Collaborating Centre for Women's and Children's Health. (2011). Caesarean section. (Clinical guideline 132). London, UK: Royal College of Obstetricians and Gynaecologists Press. Retrieved from http://guidance.nice.org.uk/CG132

NIH State-of-the-Science Conference Statement on Cesarean Delivery on Maternal Request. NIH Consens Sci Statements. 2006. Mar 27-29; 23(1) 1–29. Retrieved from http://consensus.nih.gov/2006/cesareanstatement.pdf

Risser, A., & King, V. (2010). Rapid review: Elective cesarean section. Portland: Center for Evidence-based Policy. Retrieved from http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/med/upload/Elective-Delivery-Elective-Cesarean_PUBLIC_Rapid-Review_Final_12_1_10.pdf

Scanning results:

Seven Cochrane reviews published or updated in 2010 or later were identified. Two were published prior to 2010 and assessed as up to date without changes after 2010. Of the remaining five, two identified no RCTs, and hence were empty reviews. The other three addressed cesarean section for a variety of conditions; main results and author's conclusions are reported below:

Dodd JM, Crowther CA, Huertas E, Guise JM, Horey D. Planned elective repeat caesarean section versus planned vaginal birth for women with a previous caesarean birth. (2013). Cochrane Database of Systematic Reviews. Issue 12. Art. No.: CD004224. DOI: 10.1002/14651858.CD004224.pub3.

> Main results:
> Two randomised trials involving 320 women and their infants were included. However, data for maternal and infant clinical outcomes were available from one trial with very low event rates, involving 22 women only. For the primary outcomes maternal death or serious morbidity (one study; 22 women; risk ratio (RR) not estimable), and infant death or serious morbidity (one study; 22 women; RR not estimable), there were no statistically significant differences between planned caesarean birth and planned vaginal birth identified.

Authors' conclusions:
Planned elective repeat caesarean section and planned VBAC for women with a prior caesarean birth are both associated with benefits and harms. Evidence for these care practices is largely drawn from non-randomised studies, associated with potential bias. Any results and conclusions must therefore be interpreted with caution. Randomised controlled trials are required to provide the most reliable evidence regarding the benefits and harms of both planned elective repeat caesarean section and planned vaginal birth for women with a previous caesarean birth.

Alfirevic Z, Milan SJ, Livio S. Caesarean section versus vaginal delivery for preterm birth in singletons. (2013). Cochrane Database of Systematic Reviews. Issue 9. Art. No.: CD000078. DOI: 10.1002/14651858.CD000078.pub3.

Main results:
We included six studies (involving 122 women) but only four studies (involving only 116 women) contributed data to the analyses.

Infant
There were very little data of relevance to the three main (primary) outcomes considered in this review: There was no significant difference between planned immediate caesarean section and planned vaginal delivery with respect to birth injury to infant (risk ratio (RR) 0.56, 95%, confidence interval (CI) 0.05 to 5.62; one trial, 38 women) or birth asphyxia (RR 1.63, 95% CI 0.84 to 3.14; one trial, 12 women). The only cases of birth trauma were a laceration of the buttock in a baby who was delivered by caesarean section and mild bruising in another allocated to the group delivered vaginally. The difference between the two groups with regard to perinatal deaths was not significant (0.29, 95% CI 0.07 to 1.14; three trials, 89 women) and there were no data specifically relating to neonatal admission to special care and/or intensive care unit. There was also no difference between the caesarean or vaginal delivery groups in terms of markers of possible birth asphyxia (RR 1.63, 95% CI 0.84 to 3.14; one trial, 12 women) or Apgar score less than seven at five minutes (RR 0.83, 95% CI 0.43 to 1.60; four trials, 115 women) and no difference in attempts at breastfeeding (RR 1.40, 95% 0.11 to 17.45; one trial, 12 women). There was also no difference in neonatal fitting/seizures (RR 0.22, 95% CI 0.01 to 4.32; three trials, 77 women), hypoxic ischaemic encephalopathy (RR 4.00, 95% CI 0.20 to 82.01; one trial, 12 women) or respiratory distress syndrome (RR 0.55, 95% CI 0.27 to 1.10; three trials, 103 women). There were no data reported in the trials specifically relating to meconium aspiration. There was

also no significant difference between the two groups for abnormal follow-up in childhood (RR 0.65, 95% CI 0.19 to 2.22; one trial, 38 women) or delivery less than seven days after entry (RR 0.95, 95% CI 0.73 to 1.24; two trials, 51 women).

Mother

There were no data reported on maternal admissions to intensive care. However, there were seven cases of major maternal postpartum complications in the group allocated to planned immediate caesarean section and none in the group randomised to vaginal delivery (RR 7.21, 95% CI 1.37 to 38.08; four trials, 116 women). There were no data reported in the trials specifically relating to maternal satisfaction (postnatal). There was no significant difference
between the two groups with regard to postpartum haemorrhage. A number of non-prespecified secondary outcomes were also considered in the analyses. There was a significant advantage for women in the vaginal delivery group with respect to maternal puerperal pyrexia
(RR 2.98, 95% CI 1.18 to 7.53; three trials, 89 women) and other maternal infection (RR 2.63, 95% CI 1.02 to 6.78; three trials, 103 women), but no significant differences in wound infection (RR 1.16, 95% CI 0.18 to 7.70; three trials, 103 women), maternal stay more than 10 days (RR 1.27, 95% CI 0.35 to 4.65; three trials, 78 women) or the need for blood transfusion (results not estimable).

Authors' conclusions:

There is not enough evidence to evaluate the use of a policy of planned immediate caesarean delivery for preterm babies. Further studies are needed in this area, but recruitment is proving difficult.

Hofmeyr GJ, Barrett JF, Crowther CA. Planned caesarean section for women with a twin pregnancy. Cochrane Database of Systematic Reviews. (2011). Issue 12. Art. No.: CD006553. DOI: 10.1002/14651858.CD006553.pub2

Main results:

One small trial with unconfirmed allocation concealment compared caesarean section with planned vaginal birth in 60 women with vertex/non-vertex twin pregnancies. There were no differences in perinatal outcome. The trial was too small to exclude the possibility of clinically meaningful benefits of either approach. There is one additional trial currently ongoing.

Authors' conclusions:

There is a lack of robust evidence to guide clinical advice regarding the method of birth for twin pregnancies. Women should be informed of possible benefits and risks of either approach, including short-term and long-term consequences for both mother and babies. Future research should aim to provide unbiased evidence, including long-term outcomes.

Summary:

The recently published evidence does not contradict the current coverage guidance recommendations.

Topic: Knee arthroscopy for osteoarthritis

Coverage Recommendation (Box Language):

In the absence of other appropriate indications, arthroscopic lavage and debridement of knee osteoarthritis (or osteoarthrosis) should not be covered.

Source report:

Washington State Health Care Authority Health Technology Assessment Program. (2008). HTA evidence report: Arthroscopic surgery of the knee for osteoarthritis. Retrieved from http://www.hta.hca.wa.gov/documents/ka_final.pdf

National Institute for Health and Clinical Excellence. (2007). Arthroscopic knee washout, with or without debridement, for the treatment of osteoarthritis: Guidance. London: NICE. Retrieved from http://guidance.nice.org.uk/IPG230/Guidance/pdf/English

Scanning results:

One review was identified in the core sources that was published after the date of the WA HTA report. Summary results and/or conclusions are presented below:

Reichenbach S, Rutjes AWS, Nüesch E, Trelle S, Jüni P. Joint lavage for osteoarthritis of the knee. (2010). Cochrane Database of Systematic Reviews. Issue 5. Art. No.: CD007320. DOI: 10.1002/14651858.CD007320.pub2.

> Main results:
> We included seven trials with 567 patients. Three trials examined arthroscopic joint lavage, two non-arthroscopic joint lavage and two tidal irrigation. The methodological quality and the quality of reporting was poor and we identified a moderate to large degree of heterogeneity among the trials (I2 = 65%). We found little evidence for a benefit of joint lavage in terms of pain relief at three months (SMD -0.11, 95% CI -0.42 to 0.21), corresponding to a difference in pain scores between joint lavage and control of 0.3 cm on a 10-cm visual analogue scale (VAS). Results for improvement in function at three months were similar (SMD -0.10, 95% CI -0.30 to 0.11), corresponding to a difference in function scores between joint lavage and control of 0.2 cm on a WOMAC disability sub-scale from 0 to 10. For pain, estimates of effect sizes varied to some degree depending on the type of lavage, but this variation was likely to be explained by differences in the credibility of control interventions: trials using sham interventions to closely mimic the process of joint lavage showed a null-effect. Reporting on adverse events and drop out rates was unsatisfactory, and we were unable to draw conclusions for these secondary outcomes.

Authors' conclusions:
Joint lavage does not result in a relevant benefit for patients with knee osteoarthritis in terms of pain relief or improvement of function.

Summary:
The recently published evidence does not contradict the current coverage guidance recommendations.

Topic: Neuroimaging in Dementia

Coverage Recommendation (Box Language):

Screening of asymptomatic patients for dementia with neuroimaging should not be covered.

Structural neuroimaging should be covered to rule out reversible causes of dementia.*

In patients with mild cognitive impairment, imaging should not be used to predict progression of the risk of developing dementia.

Functional neuroimaging (PET, SPECT or fMRI) should not be covered for screening, diagnosis, or monitoring of dementia.

Source report:

Clark, E.E., & Little, A., (2010). Imaging in dementia. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University.

Sources Cited in MED Report:

Boustani, M., Peterson, B., Harris, R., Lux, L.J., Krasnov, C., Sutton, S.F., et al. (2003). Screening for dementia: Systematic evidence review. Rockville, MD: Agency for Healthcare Research and Quality.

Chui, H. & Zhang, Q. (1997). Evaluation of dementia: A systematic study of the usefulness of the American Academy of Neurology's Practice Parameters. Neurology, 49, 925-935.

Dougall, N.J., Bruggink, S., & Ebmeier, K.P. (2004). Systematic review of the diagnostic accuracy of 99m Tc-HMPAO-SPECT in dementia. American J. Geriatric Psychiatry, 12, 554-570.

Foster, G.R., Scott, D.A., & Payne, S. (1999). The use of CT scanning in dementia: A systematic review. International Journal of Technology Assessment in Health Care, 15(2), 406-423

Gifford, D.R., Holloway, R.G., & Vickery, B.G. (2000). Systematic review of clinical prediction rules for neuroimaging in the evaluation of dementia. Archives of Internal Medicine, 160, 2855-2862.

Knopman, D.S., DeKosky, S.T., Cummings, J.L., Chui, H., Corey-Bloom, J., Relkin, N., et. al. (2006). Practice parameter: Diagnosis of dementia (an evidence-based review). American Academy of Neurology. Retrieved from http://www.neurology.org/cgi/reprint/56/9/1143.pdf

Matchar, D.B., Kulasingam, S.L., Huntington, A., Patwardhan, M., Mann, L.O. (2004). Positron emission tomography, single photon emission computed tomography, computed tomography,

functional magnetic resonance imaging and magnetic resonance spectroscopy for the diagnosis and management of Alzheimer's disease. Rockville, MD: Agency for Health Care Research and Quality. Retrieved from http://www.cms.gov/coverage/download /id104b.pdf

Matchar, D.B., Kulasingam, S.L., McCrory, D.C., Patwardhan, M.B., Rutschmann, O.T., Samsa, G.P., et al. (2001). Use of positron emission tomography and other neuroimaging techniques in the diagnosis and management of Alzheimer's disease and dementia. Rockville, MD: Agency for Healthcare Research and Quality. Retrieved from http://www.cms.gov/determination process /downloads/id9TA.pdf

National Collaborating Centre for Mental Health. (2006). Dementia: A NICE–SCIE guideline on supporting people with dementia and their carers in health and social care. Social Care Institute for Excellence. London: National Institute for Health and Clinical Excellence. Retrieved from http://www.nice.org.uk/nicemedia/live/10998/30318/30318.pdf

Scottish Intercollegiate Network of Guidelines (SIGN). (2006). Management of patients with dementia: update. Edinburg: Scottish Intercollegiate Network of Guidelines. Retrieved from http://www.sign.ac.uk/pdf/sign86.pdf

U.S. Preventive Services Task Force. (2003). Screening for Dementia, Topic Page. Retrieved from http://www.uspreventiveservicestaskforce.org/uspstf/uspsdeme.htm

Waldemar, G., Dubois, B., Emre, M., Georges, J., McKeith, I.G., Rossor, M., et al. (2007). Recommendations for the diagnosis and management of Alzheimer's disease and other disorders associated with dementia: EFNS guideline. Eur J Neurol, 14(1), e1-26.

Yuan, Y., Gu, Z.X., & Wei, W.S. (2009). FDG-positron emission tomography, single-photon emission tomography and structural imaging for prediction of rapid conversion to Alzheimer disease in patients with mild cognitive impairment: A meta-analysis. Am J Neuroradiology, 30, 404-410.

Scanning results:

Two reviews and two Cochrane protocols were identified in the core sources that were published after the date of the MED report. In addition, a WA HTA report is in progress and due for publication in December 2014. Summary results and/or conclusions of the two completed reviews are presented below:

<u>Zhang S, Smailagic N, Hyde C, Noel-Storr AH, Takwoingi Y, McShane R, Feng J. 11C-PIB-PET for the early diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). (2014) Cochrane Database of Systematic Reviews. Issue 7. Art. No.: CD010386. DOI: 10.1002/14651858.CD010386.pub2.</u>

Main results:
Conversion from MCI to Alzheimer's disease dementia was evaluated in nine studies. The quality of the evidence was limited. Of the 274 participants included in the meta-analysis, 112 developed Alzheimer's dementia. Based on the nine included studies, the median proportion converting was 34%. The studies varied markedly in how the PIB scans were done and interpreted.

The sensitivities were between 83% and 100% while the specificities were between 46% and 88%. Because of the variation in thresholds and measures of 11C-PIB amyloid retention, we did not calculate summary sensitivity and specificity. Although subject to considerable uncertainty, to illustrate the potential strengths and weaknesses of 11C-PIB-PET scans we estimated from the fitted summary ROC curve that the sensitivity was 96% (95% confidence interval (CI) 87 to 99) at the included study median specificity of 58%. This equated to a positive likelihood ratio of 2.3 and a negative likelihood ratio of 0.07. Assuming a typical conversion rate of MCI to Alzheimer's dementia of 34%, for every 100 PIB scans one person with a negative scan would progress and 28 with a positive scan would not actually progress to Alzheimer's dementia.

There were limited data for formal investigation of heterogeneity. We performed two sensitivity analyses to assess the influence of type of reference standard and the use of a pre-specified threshold. There was no effect on our findings.

Authors' conclusions:
Although the good sensitivity achieved in some included studies is promising for the value of 11C-PIB-PET, given the heterogeneity in the conduct and interpretation of the test and the lack of defined thresholds for determination of test positivity, we cannot recommend its routine use in clinical practice.11C-PIB-PET biomarker is a high cost investigation, therefore it is important to clearly demonstrate its accuracy and standardise the process of the 11C-PIB diagnostic modality prior to it being widely used.

<u>BCBS. (2013). Beta Amyloid Imaging with Positron Emission Tomography (PET) for Evaluation of Suspected Alzheimer's Disease or Other Causes of Cognitive Decline.</u>

"beta amyloid imaging with positron emission tomography (PET) to evaluate suspected Alzheimer's disease (AD) and other causes of cognitive decline does not meet the TEC criteria."

- Has regulatory approval

- Evidence is insufficient to support conclusions concerning the impact of beta amyloid PET imaging with florbetapir F18 on health outcomes. The evidence to date focuses solely on the correlation between the results of beta amyloid PET imaging and other indicators of cognitive decline, clinical diagnoses, and histopathologic results. Studies are needed to define the accuracy of beta amyloid imaging according to age (since beta amyloid deposition increases with age in cognitively normal individuals). Further evidence is also needed on the link between the test results and improving health outcomes.
- Because evidence is insufficient to permit conclusions on the effect of beta amyloid PET imaging on health outcomes, any improvement cannot be established.
- Comparative benefit cannot be established lacking sufficient evidence.
- Have not been evaluated outside the investigational setting.

Summary:
The recently published evidence does not contradict the current coverage guidance recommendations. Given three reviews currently in progress, it may be reasonable to consider updating this guidance once those reviews have been completed.

Topic: Routine Ultrasound in Pregnancy

Coverage Recommendation (Box Language):

Routine ultrasound for average risk pregnant women should be covered only: Once in the first trimester for the purpose of identifying fetal aneuploidy or anomaly (between 11 and 13 weeks of gestation) and/or dating confirmation. In some instances, if a patient's LMP is truly unknown, a dating ultrasound may be indicated prior to an aneuploidy screen.

Once for the purpose of anatomy screening after 18 weeks gestation

Only one type of routine prenatal ultrasound should be covered in a single day (i.e., transvaginal or abdominal).

Source report:

Washington State Health Care Authority Health Technology Assessment Program. (2010). Ultrasonography (ultrasound) in pregnancy: Health technology assessment. Retrieved from http://www.hta.hca.wa.gov/documents/final_report_ultrasound.pdf

Scanning results:

The only review identified in the core sources that was published after the date of the WA HTA report was a Hayes report, which was published just three months after the WA HTA report. Hayes was the author of the WA HTA report, and the document contains essentially the same information.

Summary:

No evidence has been published in the trusted sources since this guidance document was created. Therefore, it appears unlikely to need updating.

Topic: Non-pharmacologic Interventions for Treatment Resistant Depression

Coverage Recommendation (Box Language):

In patients with an episode of major depressive disorder who have failed an initial trial of antidepressants, psychotherapy should be covered.

In patients with an episode of major depressive disorder who have failed at least two or more pharmacologic treatments the following treatments should be covered:

1) Repetitive transcranial magnetic stimulation

2) Electroconvulsive therapy

Vagus nerve stimulation should not be covered.

Source report:

Gaynes, B.N., Lux, L., Lloyd, S., Hansen, R.A., Gartlehne, G., Thieda, P., et al. (2011). Nonpharmacologic interventions for treatment-resistant depression in adults. Comparative effectiveness review no. 33. (Prepared by RTI International-University of North Carolina [RTI-UNC] Evidence-Based Practice Center under Contract No. 290-02-0016I.) AHRQ Publication No. 11-EHC056-EF. Rockville, MD: Agency for Healthcare Research and Quality. Retrieved from www.effectivehealthcare.ahrq.gov/reports/final.cfm

Trivedi, R.B., Nieuwsma, J.A., Williams, J.W., & Baker, D. (2009). Evidence synthesis for determining the efficacy of psychotherapy for treatment resistant depression. Washington, DC: Department of Veterans Affairs Veterans Health Administration Health Services Research & Development Service. Retrieved from http://www.hsrd.research.va.gov/publications/esp/Depression-Q3.pdf

Scanning results:

Two reviews were identified in the core sources that were published after the date of the AHRQ report. Summary results and/or conclusions are presented below:

Nonpharmacological Treatments for Treatment Resistant Depression. (2014) http://www.hca.wa.gov/hta/Documents/TRD_final_report_022114.pdf

Summary:
Electroconvulsive therapy (ECT) has been in use for decades, but its efficacy has not been extensively investigated in recent decades. Only 2 small sham-controlled trials of ECT published in 1980 and 1981 and a comparison of ECT with new pharmacotherapy

published in 1997 were reviewed for this report. Trials published prior to 1980 were excluded from the 2011 AHRQ evidence report on Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults and hence were also excluded from the present report. Even the included RCTs of ECT may have limited generalizability to current practice because of differences in standard antidepressant (AD) medication regimens.

Some investigators have considered ECT the standard treatment for TRD against which to compare repetitive transcranial magnetic stimulation (rTMS) as an alternative more acceptable to patients. A large body of evidence has demonstrated the efficacy of rTMS compared with sham stimulation in patients with TRD. There is no evidence suggesting that rTMS is more effective than ECT, and the comparability of the 2 treatments has not been conclusively established. Although sham-controlled studies of rTMS showed no adverse effect on cognitive function, comparator trials did not prove rTMS to be safer than ECT in this regard. No serious safety issues were identified in trials of rTMS. Several variations are possible for the way ECT and rTMS are delivered, but optimal treatment parameters have not been identified. There is no evidence of at least moderate quality that establishes an association between the treatment effect of ECT or rTMS and the type of subgroup characteristics listed in Key Question #3.

These conclusions regarding ECT and rTMS are consistent with the conclusions of the 2011 Agency for Healthcare Research and Quality (AHRQ) evidence review, although the AHRQ conclusions were based only on studies in which patients had experienced ≥ 2 failed antidepressant (AD) trials. The authors of the AHRQ review noted that findings from the overall evidence base were consistent with findings specific to studies defining TRD as ≥ 2 AD failures but that the effect of combining patients meeting different definitions of TRD was unclear. The AHRQ review did not address treatment parameters and addressed only a limited number of patient characteristics (see Appendix V).

There is some positive evidence suggesting that transcranial direct current stimulation (tDCS) is efficacious as a treatment for TRD, but pooled estimates of response and remission were nonsignificant. Deep brain stimulation (DBS) has been studied only in very small case series with pretest/posttest (before-and-after) analyses; although mean improvement was demonstrated, no conclusion regarding causality may be made. DBS can result in serious complications.

The literature provides very little direct evidence of improvement in quality of life (QOL) or functional status attributable to the technologies of interest. However, there is some

evidence that lower symptom scores are associated with better function and QOL (this issue was not systematically investigated for this report). Thus, improvement in depression symptoms may also result in improvement in QOL and general function. Evidence of the durability of post-treatment benefits is sparse or missing for all of the technologies of interest.

One of the deficiencies of existing research evidence is the lack of a standard definition of TRD. The literature suggests a growing consensus that failure of 2 prior adequate trials of AD medication is an appropriate definition of TRD. The evidence reviewed for this report suggests that rTMS and ECT are effective even when TRD is defined as ≥ 1 failed AD trial. There was low-quality evidence suggesting that the effectiveness of ECT diminishes as medication resistance increases. The oft-cited STAR*D trial demonstrated that the effectiveness of new AD medication also diminishes with each round of failed treatment. No studies directly assessed the effectiveness of rTMS according to degree of medication resistance. Where reported in studies of tDCS, patients had generally failed ≥ 2 AD trials in their lifetime, but the evidence does not permit a conclusion regarding the effectiveness of tDCS by degree of medication. Studies of DBS required a failure of ≥ 3 prior AD trials.

Related to the lack of a standard definition of TRD is the need for greater standardization in the manner in which the adequacy of AD trials is defined and whether medication resistance should be demonstrated in the current episode. Regarding the duration of an adequate AD trial, ≥ 6 weeks was the most common threshold in studies that addressed this issue in inclusion criteria, American Psychiatric Association guidelines on the management of MDD advise that an AD trial should be continued 4 to 8 weeks, and other sources suggest 10 to 12 weeks for an adequate trial. No distinction was made in the studies reviewed for this report between patients who were and were not compliant in previous AD treatment. Very few studies clarified whether patients were enrolled on the basis of AD failure at any time in the past or on the basis of failure during the current episode.

No studies of any of the technologies of interest compared the technology with usual care or evaluated the technology as an add-on to usual care. Only 2 comparisons of nonpharmacologic treatment (ECT in 1 study, tDCS in the other) with a new AD medication as the control were identified. More studies providing a comparison with real-world alternatives are needed, ideally with a sham-controlled arm as well as a new pharmacotherapy or usual care arm.

BCBS. (2014). Transcranial Magnetic Stimulation for Depression.
http://www.bcbs.com/blueresources/tec/vols/28/28_09.pdf

- Has regulatory approval
- Three large, and many small, trials have compared TMS with sham for treatment-resistant depression. Two of the large trials employed a "duration adaptive design" that enforces dropout of patients failing to improve after 3 weeks. Effect estimates after the initial 3-week follow-ups are potentially biased and longer term follow-up of these trials is difficult to interpret. Limited data have been reported from the third trial because it is unpublished. No significant results were reported in the intention-to-treat analyses after 6 or 16 weeks of TMS. Results from other small trials, along with the 2 large published trials, have been included in meta-analyses. Although pooled effect estimates from the meta-analyses favor TMS, results from the later and potentially biased follow-up of the 2 large trials were used. Only one of the 7 meta-analyses reviewed evaluated study quality. A search of ClinicalTrials.gov identified unpublished completed studies. The available evidence does not permit conclusions regarding the effect of TMS on health outcomes.
- The available evidence does not permit conclusions on whether TMS improves the net health outcome.
- Lacking evidence to support conclusions about the effect of TMS on health outcomes, it is not possible to compare with established alternatives.
- Have not been evaluated outside the investigational setting.

Summary:
The recently published evidence is conflicting, with the WA HTA review supporting the current coverage guidance recommendations and the BCBS technology evaluation contradicting it. The primary discrepancy appears to be that BCBS believes that two of three large trials may be biased because of the trial design, and in addition, they are concerned about the existence of unpublished studies.

Topics: Advanced Imaging for Low Back Pain

Low back pain: Pharmacologic Interventions

Low back pain: Non-pharmacologic/ Non-invasive Interventions

Source report:

Chou, R., Qaseem, A., Snow, V., Casey, D., Cross, J.T., Jr., Shekelle, P., Owens, D.K.; Clinical Efficacy Assessment Subcommittee of the American College of Physicians; American College of Physicians; American Pain Society Low Back Pain Guidelines Panel. *Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society.* Annals of Internal Med. 2007; 147(7); 478-491. Retrieved from http://www.annals.org/content/147/7/478.long

Additional Information:

This report is in the process of being updated. The update process has just begun, and it is expected to be finalized next year or possibly 2016.

Topic: Percutaneous interventions for low back pain

Source report:

Chou, R., Loesser, J.D., Owens, D.K., Rosenquist, R.W., Atlas, S.J., Baisden, J., et al. (2009). Interventional therapies, surgery, and interdisciplinary rehabilitation for low back pain: An evidence-based clinical practice guideline from the American Pain Society. Spine, 34(10), 1066-1077. – Accompanied by:
Chou, R., Atlas, S.J., Stanos, S.P., & Rosenquist, R.W. (2009). Nonsurgical interventional therapies for low back pain: A review of the evidence for an American Pain Society clinical practice guideline. Spine, 34(10), 1078-1094.

Additional Information:

This report is in the process of being updated. It is in the final stages, and is expected to be finalized later this year or early 2015.

Section 5.0

Coverage Guidances

HEALTH EVIDENCE REVIEW COMMISSION (HERC)

COVERAGE GUIDANCE: PLANNED HOME BIRTH

DRAFT FOR EBGS MEETING MATERIALS 9/4/2014

HERC Coverage Guidance

Out-of-hospital birth for low risk pregnancies is recommended for coverage *(strong recommendation).*

Low risk pregnancies at a minimum are defined as:

- gestational age ≥ 36 weeks and ≤41 completed weeks of pregnancy
- singleton
- vertex position
- absence of significant preexisting or pregnancy-related maternal disease.

A more expansive definition of low risk based on several different sources excludes patients with:

Complications in a previous pregnancy:

- Unexplained stillbirth/neonatal death or previous death related to intrapartum difficulty
- Previous baby with neonatal encephalopathy
- Pre-eclampsia requiring preterm birth
- Placental abruption with adverse outcome
- Eclampsia
- Uterine rupture
- Primary postpartum hemorrhage requiring additional treatment or blood transfusion
- Retained placenta requiring manual removal in theatre Caesarean section
- Shoulder dystocia
- Cesarean section
- Blood group incompatibility
- Fetal growth retardation

Complications of current pregnancy

- Placenta previa
- Pre-eclampsia or pregnancy-induced hypertension
- Preterm labor or preterm prelabor rupture of membranes
- Placental abruption
- Anemia – hemoglobin less than 8.5 g/dl at onset of labor
- Confirmed intrauterine death
- Induction of labor
- Substance misuse
- Alcohol dependency requiring assessment or treatment
- Onset of gestational diabetes
- Body mass index at first prenatal visit of greater than 35 kg/m2

(continued on next page)

- Recurrent antepartum hemorrhage
- Small for gestational age fetus
- Abnormal fetal heart rate/Doppler studies
- Oligo or polyhydramnios
- Blood group incompatibility
- Prelabor rupture of membranes > 24 hours

Out-of-hospital birth in unselected pregnancies is not recommended for coverage *(strong recommendation).*

Women planning a home birth should be appropriately informed of the potential need for transfer and the potential risks associated with having a delay to emergency obstetric and neonatal care. There should be well defined system of transfer. Attendants of home birth should be licensed and certified, and appropriately trained in the identification and management of obstetric and neonatal emergencies.

Note: Definitions for strength of recommendation are provided in Appendix B GRADE Element Description

RATIONALE FOR GUIDANCE DEVELOPMENT

The HERC selects topics for guideline development or technology assessment based on the following principles:

- Represents a significant burden of disease
- Represents important uncertainty with regard to efficacy or harms
- Represents important variation or controversy in clinical care
- Represents high costs, significant economic impact
- Topic is of high public interest

Coverage guidance development follows to translate the evidence review to a policy decision. Coverage guidance may be based on an evidence-based guideline developed by the Evidence-based Guideline Subcommittee or a health technology assessment developed by the Heath Technology Assessment Subcommittee. In addition, coverage guidance may utilize an existing evidence report produced by one of HERC's trusted sources, generally within the last three years.

EVIDENCE SOURCES

Trusted sources

Olsen, O., & Clausen, J. A. (2012). Planned hospital birth versus planned home birth. Cochrane Database of Systematic Reviews, 9. Accessed August 9, 2014 from http://almenpraksis.ku.dk/nyheder/oleolsen/Hjemmef_dsel.pdf

National Institute for Clinical Excellence (2014). Intrapartum care: care of healthy women and their babies during childbirth Clinical Guideline 55, Draft for consultation, May 2014.

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Accessed August 12, 2014 from http://www.nice.org.uk/guidance/gid-cgwaver109/resources/intrapartum-care-update-nice-guideline2

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College of Midwives of British Columbia. (2014). Indications for discussion, consultation, and transfer of care. Accessed August 4, 2014 from http://www.cmbc.bc.ca/pdf.shtml?Registrants-Handbook-12-01-Indications-for-Discussion-Consultation-and-Transfer-of-Care

College of Midwives of Ontario (2000). Indications for mandatory discussion, consultation, and transfer of care. Accessed August 4, 2014 from http://www.cmo.on.ca/resources/STANDARDS-OF-PRACTICE/3.%20CLINICAL%20PRACTICE/05b.Indications%20for%20Mandatory%20Discussion%20Consultation%20and%20Transfer_June%202000.pdf

de Jonge, A., van der Goes, B. Y., Ravelli, A. C., Amelink-Verburg, M. P., Mol, B. W., Nijhuis, J. G., et al. (2009). Perinatal mortality and morbidity in a nationwide cohort of 529, 688 low-risk planned home and hospital births. BJOG: An International Journal of Obstetrics & Gynaecology, 116(9), 1177-1184.

Dowswell, T., Thornton, J. G., Hewison, J., Lilford, R. J., Raisler, J., MacFarlane, A., et al.(1996). Should there be a trial of home versus hospital delivery in the United Kingdom? BMJ: British Medical Journal,312(7033), 753.

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Hutton, E. K., Reitsma, A. H., & Kaufman, K. (2009). Outcomes Associated with Planned Home and Planned Hospital Births in Low-Risk Women Attended by Midwives in Ontario, Canada, 2003–2006: A Retrospective Cohort Study. Birth, 36(3), 180-189.

Janssen, P. A., Saxell, L., Page, L. A., Klein, M. C., Liston, R. M., & Lee, S. K. (2009). Outcomes of planned home birth with registered midwife versus planned hospital birth with midwife or physician. Canadian Medical Association Journal, 181(6-7), 377-383.

Netherlands Ministry of Health, Welfare, and Sport. (n.d). Final Report of the Obstetric Working Group of the National Health Insurance Board of the Netherlands (abridged version). The Hauge, NL: Government of the Netherlands. Accessed August 4, 2014 from http://blog.lib.umn.edu/kuli0015/studygroup/Dutch%20OB%20Indications.doc

Oregon Health Authority. (2013). Oregon Birth Outcomes by Planned Birth Place and Attendant. Accessed August 1, 2014 from https://public.health.oregon.gov/BirthDeathCertificates/VitalStatistics/birth/Documents/PlannedBirthPlaceandAttendant.pdf

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Wax, J. R., Lucas, F. L., Lamont, M., Pinette, M. G., Cartin, A., & Blackstone, J. (2010). Maternal and newborn outcomes in planned home birth vs planned hospital births: a metaanalysis. American journal of obstetrics and gynecology,203(3), 243-e1.

Zeitlin, J., Mohangoo, A., Alexander, S., Barros, H., Blondel, B., Bouvier-Colle, et al. (n.d). Health and Care of Pregnant Women and Babies in Europe in 2010. Accessed on August 1, 2014 from http://www.europeristat.com/images/doc/Peristat%202013%20V2.pdf

The summary of evidence in this document is derived directly from this evidence source, and portions are extracted verbatim.

TOPIC BACKGROUND

The Licensed Direct Entry Midwife (LDM) Staff Advisory Workgroup was convened in January 2014 by the Director of the Oregon Health Authority (OHA). The workgroup was established to provide recommendations regarding perinatal services provided to

Medicaid enrollees by LDMs. The workgroup was guided by the Triple Aim goals of improving population health, improving the individual's experience of care and reducing per capita costs. One of the recommendations of the final report of this workgroup to the OHA was the following:

Request that the Health Evidence Review Commission develop a Coverage Guidance related to home birth, including evidence regarding:

- The maternal and fetal/neonatal/child health outcomes of home birth compared with birth in other settings
- Appropriate candidates for home birth
- Criteria for optimizing safety with regard to provider training, equipment, standards, consultation, and other systems of care

EVIDENCE OVERVIEW

Clinical background

From Cochrane 2012

Medicalization of childbirth is a central feature in Western societies. The majority of women living in high and middle-income countries have given birth in hospitals since the middle of the 20th century. However, there are regions where home birth is considered part of normal practice. The most cited case is The Netherlands where planned home birth is supported by the official healthcare system. There, planned home birth is considered an appropriate choice for a woman of low risk and approximately 30% of all births take place at home. It is of historical interest to note that the transfer of low-risk births from home to hospital in the 1960s, despite lack of high-quality evidence, was one of the pivotal issues when Archie Cochrane laid out the ideological ground for The Cochrane Collaboration. Cochrane awarded 'the wooden spoon' to obstetrics, because "The specialty missed its first opportunity in the sixties, when it failed to randomize the confinement of low-risk pregnant women at home or hospital. Then, having filled

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the emptying beds by getting nearly all pregnant women into hospital, the obstetricians started to introduce a whole series of expensive innovations into the routines of pre- and postnatal care and delivery, without any rigorous evaluation. The list is long, but the most important were induction, ultrasound, foetal monitoring, and placental function tests" (Cochrane 1979). The relationship between hospitalization, childbirth, and intervention is still an important issue as "Concern about the iatrogenic effects of obstetric intervention in women who do not have a clinical need for it hasput "normal" birth firmly on the agenda for the 21st century." (EURO-PERISTAT 2008).

A range of interventions continue to be used routinely in relation to births at many hospitals despite the fact that for a long time they have been proven to have harmful effects, or only marginal or no beneficial effect, e.g. fetal monitoring, episiotomy and early cord clamping. Even though the use of a few specific interventions have been reduced (e.g. placental function tests), in general "Routine medical interventions have [...] increased steadily over time" (Hodnett 2010) despite the efforts of the Cochrane Pregnancy and Childbirth Group, its predecessors, and other researchers carrying out systematic reviews.

The Cochrane review is about healthy pregnant women at term for whom no serious complications have been identified prior to the spontaneous initiation of birth and for which the birth is expected to be medically uncomplicated. Generally, between 70% and 80% of all pregnant women may be considered as low risk at the start of labor.

Evidence review

Cochrane 2012

The inclusion criteria for the Cochrane 2012 review was limited to randomized controlled trials that compared planned hospital births to planned home births. Authors identified two RCTs, however one was only able to recruit one patient. This study (Hendrix 2009) was conducted in the Netherlands and recruited nulliparous women of low obstetric risk (n = 1). In this trial, 35 midwives in 14 primary care midwifery practices were involved in recruiting pregnant women in different parts of the Netherlands where 30% of all births are home births. However, the study author reported that only one of 116 women was willing to be randomized, the others having all decided where they wanted to deliver before being recruited into the study.

The second trial, Dowswell 1996, was conducted in the United Kingdom and recruited multiparous women judged to be at low obstetric risk by a consultant obstetrician and likely to have suitable home support and home circumstances (n = 71). Recruitment was carried out by one consultant obstetrician in an area where planned home birth was otherwise uncommon (0.5% to 1%). The midwives assisting the home births were community midwives who spent a few days each month in hospital; all UK midwives are trained to do home births, but the ones in the trial were probably not experienced with home birth. The hospital births were standard hospital care with intermittent auscultation at a university hospital with consultant obstetrician on call (but not called routinely) and full neonatal facilities. One midwife served one to two women in single rooms; she used intermittent auscultation and was not continuously present. This study was rated as having high methodologic quality, except for the small size.

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The fully assessed trial with reported outcomes was too small to draw reliable conclusions. Only 11 women agreed to randomization. Four of the primary outcomes in this review were available for inclusion: baby not breast fed, assisted vaginal birth, caesarean section, and other (non-epidural) medical pain relief. In addition, three other outcomes were reported and these are also included here: perineal sutures, mother disappointed about allocation, and father did not state that he was relieved. One difference seems statistically significant: the majority of mothers in the hospital group were disappointed about the allocation while none of the mothers in the home birth group were disappointed (Peto odds ratio 12.18, 95% confidence interval 1.05 to 141.17); however, the difference is non-significant using a Fisher's exact test P value = 0.07). There were no instances of assisted vaginal birth or cesarean section, and for the other outcomes, there were no statistically significant differences between groups.

The Cochrane authors report that these results to not "contradict the evidence from the largest observational studies (de Jonge 2009; Hutton 2009; Janssen 2009) identified in the most recent systematic review (Wax 2010)".

Because of the paucity of RCTs addressing this comparison, the systematic review and observational studies listed above are summarized below.

Wax 2010

This systematic review did not limit inclusion criteria by study design. The search was through November 2009, and included MEDLINE, EMBASE and Cochrane Database of Systematic Reviews. Inclusion criteria included performance in developed western countries, English language, peer reviewed and outcomes analyzed by planned delivery location. Twelve studies were included, including the three cohort studies described below and the single RCT described above, with a total of 342,056 planned home and 207,551 planned hospital deliveries.

Meta-analysis of maternal outcomes found that planned home births experienced significantly fewer medical interventions including epidural analgesia, electronic fetal heart rate monitoring, episiotomy, and operative vaginal and cesarean deliveries. Likewise, women intending home deliveries had fewer infections, third degree lacerations, perineal and vaginal lacerations, hemorrhages, and retained placentas. There was no significant difference in the rate of umbilical cord prolapse.

Meta-analysis of neonatal outcomes found that women planning home births were less likely to have preterm deliveries or babies who were low birth weight. Planned home births more often progressed to at least 42 weeks. While there was no overall pooled difference in the rate of assisted ventilation, one large study found more frequent ventilation among planned home births, while two smaller studies noted lower rates in this group. Perinatal mortality was similar by intended delivery location (OR 0.95 95% CI 0.77 to 1.18), as well as just among nonanomalous offspring (OR 0.95, 95% CI 0.76 to 1.18). In contrast, neonatal mortality was almost twice as high in planned home versus planned hospital births (OR 1.98, 95% CI 1.19 to 3.28, absolute number 32 out of 16,500 planned home births [0.20%] compared to 32 out of 33,302 planned hospital births [0.09%]), and almost tripled among nonanomalous neonates (OR 2.87, 95% CI 1.32 to 6.25, absolute number 23 out of 15,633 planned home births [0.15%]

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compared to 14 out of 31,999 planned hospital births [0.04%]). While the reason for the difference between neonatal and perinatal mortality rates is unclear from this analysis, the authors speculate that it may be due to the lower obstetric risk associated with patients planning home births. If this is the case, planned home births may face a higher perinatal mortality rate than similar risk planned hospital births.

The results of the sensitivity analyses excluding studies that included home births attended by other than certified midwives or certified nurse midwives had findings similar to the original analysis, except that the ORs for neonatal deaths among all (OR, 1.57; 95% CI, 0.62–3.98) and nonanomalous (OR, 3.00; 95% CI, 0.61–14.88) newborns were not statistically significant.

De Jonge

This is a nationwide cohort study conducted in the Netherlands that included a total of 529 688 low-risk women who were in primary midwife-led care at the onset of labor. In the Netherlands, the indications for referral to an obstetrician have been agreed upon by the professional groups involved and are laid out in the "Obstetric Indication List" (see Appendix A). Of these, 321 307 (60.7%) intended to give birth at home, 163 261 (30.8%) planned to give birth in hospital and for 45 120 (8.5%), the intended place of birth was unknown. Authors adjusted for a number of maternal characteristics (parity, gestational age, maternal age, ethnic background and socioeconomic status).

No significant differences were found between planned home and planned hospital birth in neonatal outcomes reported. Adjusted relative risks and 95% confidence intervals were as follows: intrapartum death 0.97 (0.69 to 1.37), intrapartum death and neonatal death during the first 24 hours 1.02 (0.77 to 1.36), intrapartum death and neonatal death up to 7 days 1.00 (0.78 to 1.27), admission to neonatal intensive care unit 1.00 (0.86 to 1.16).

Hutton 2009

Midwives in Ontario, Canada, provide care in the home and hospital and are required to submit data for all births to the Ontario Ministry of Health database. The purpose of this study was to compare maternal and perinatal/neonatal mortality and morbidity and intrapartum intervention rates for women attended by Ontario midwives who planned a home birth compared with similar low-risk women who planned a hospital birth between 2003 and 2006. The following types of pregnancies are not eligible for home birth in Ontario:

- Twins
- Breech
- Medical complications in the mother
- More than one prior cesarean section
- Gestational age less than 37 or more than 42 weeks

The database provided outcomes for all women planning a home birth at the onset of labor (n = 6, 692) and for a cohort, stratified by parity, of similar low-risk women planning a hospital birth. The rate of perinatal and neonatal mortality was very low (1/1,000) for both groups, and no difference was shown between groups in a composite measure of perinatal and neonatal

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mortality or serious morbidity (RR 2.4% vs 2.8%; 95% CI: 0.84 [0.68–1.03]). No maternal deaths were reported. All measures of maternal morbidity were lower in the planned home birth group, including augmentation (RR 0.76, 95% CI 0.72 to 0.80), pharmaceutical pain relief (RR 0.37, 95% CI 0.35 to 0.39), episiotomy (RR 0.73, 95% CI 0.63 to 0.84) , assisted delivery (RR 0.67, 95% CI 0.56 to 0.80), perineal trauma (RR 0.87, 95% CI 0.83 to 0.90) and blood loss greater than 1,000 ml (RR 0.68, 95% CI 0.49 to 0.96). In addition, the rates for cesarean section were lower in the planned home birth group (5.2% vs 8.1%; RR 0.64, 95% CI 0.56 to 0.73). When stratified by parity, nulliparas were less likely to deliver at home, and had higher rates of ambulance transport from home to hospital than multiparas planning home birth. However, nulliparas planning home birth still had rates of intervention and outcomes that were similar to, or lower than, nulliparas planning hospital births.

Janssen 2009

This study was also a retrospective cohort study utilizing a database of all births in the province of British Columbia that occurred between 2000 and 2004. Eligibility for home birth by the College of Midwives of British Columbia includes the following:

- Absence of significant pre-existing disease in the mother
- Absence of significant disease arising during pregnancy (pregnancy-induced hypertension, hemorrhage, diabetes, herpes, placenta previa, abruption)
- Singleton fetus
- Cephalic presentation
- Gestation age between 36 and 41 weeks
- No more than one prior cesarean section
- Spontaneous labor (or induced as an outpatient)
- No transfer from a referring hospital

Planned home births were compared to midwife attended planned hospital births and physician attended planned hospital births, both limited to patients who meet the criteria for home birth and matched by age, parity, single parent status, maternal age and hospital location. There were 2899 women in the planned home birth group, 4752 in the planned hospital birth group attended by midwives, and 5331 in the planned hospital group attended by physicians.

The perinatal mortality rate was 0.35 per 1000 births in the home birth group, 0.57 per 1000 in the hospital midwife group and 0.64 in the hospital physician group, with no statistically significant differences between groups (RR for home midwife vs. hospital midwife 0.61, 95% CI 0.06 to 5.88; RR for home midwife vs. hospital physician 0.55, 95% CI 0.06 to 5.25). Infants in the planned home birth group were significantly less likely to have an Apgar score less than seven at one minute, to suffer birth trauma, or to require resuscitation or oxygen therapy for more than 24 hours when compared to either hospital group.

Compared to planned home birth, the frequency of obstetric interventions was higher in the planned hospital group (either physician or midwife), including fetal monitoring (RR 0.32, 95% CI 0.29 to 0.36 for midwife, RR 0.17, 95% CI 0.16 to 0.19 for physician), augmentation of labor (RR 0.59, 95% CI 0.55 to 0.69 for midwife, RR 0.47, 95% CI 0.44 to 0.51 for physician),

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assisted vaginal delivery (RR 0.41, 95% CI 0.33 to 0.52 for midwife, RR 0.22, 95% CI 0.18 to 0.27 for physician), cesarean section (RR 0.76, 95% CI 0.64 to 0.91 for midwife, RR 0.65, 95% CI 0.56 to 0.76 for physician)and episiotomy (RR 0.49, 95% CI 0.38 to 0.63 for midwife, RR 0.19, 95% CI 0.15 to 0.23 for physician). They were also more likely to have third or fourth degree perineal tears (RR 0.43, 95% CI 0.29 to 0.63 for midwife, RR 0.34, 95% CI 0.24 to 0.49 for physician).

Guidelines

The NICE guideline on intrapartum care in healthy women was last published in 2007. However, it is in the process of being updated, with a draft being released for comment in May 2014. The guideline recommends the following regarding place of birth:

> "Women at low risk of complications
>
> 1.1.1 Explain to women who are at low risk of complications that giving birth is generally very safe for both the woman and her baby. [2014]
>
> 1.1.2 Explain to the woman that she may choose any birth setting (home, freestanding midwifery unit, alongside midwifery unit or obstetric unit), and support her in her choice of setting wherever she chooses to give birth. [new 2014]
>
> 1.1.3 Advise low-risk multiparous women to plan to give birth at home or in a midwifery-led unit (freestanding or alongside). Explain that this is because the rate of interventions is lower and the outcome for the baby is no different compared with an obstetric unit. [new 2014]
>
> 1.1.4 Advise low-risk nulliparous women to plan to give birth in a midwifery-led unit (freestanding or alongside). Explain that this is because the rate of interventions is lower and the outcome for the baby is no different compared with an obstetric unit, but if they plan birth at home there is a small increase in the risk of an adverse outcome for the baby. [new 2014]
>
> 1.1.5 Using tables 1 and 2, explain to low-risk multiparous women that:
>
> - planning birth at home or in a freestanding midwifery unit is associated with a higher rate of spontaneous vaginal birth than planning birth in an alongside midwifery unit, and these 3 settings are associated with higher rates of spontaneous vaginal birth than planning birth in an obstetric unit
> - planning birth in an obstetric unit is associated with a higher rate of interventions, such as instrumental vaginal birth, caesarean section and episiotomy, compared with planning birth in other settings
> - there are no differences in outcomes for the baby associated with planning birth in any setting. [new 2014]

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Table 1 (Rates of spontaneous vaginal birth, transfer to an obstetric unit and obstetric interventions for each planned place of birth: low-risk multiparous women)

	Number of incidences per 1000 multiparous women giving birth			
	Home	Freestanding midwifery unit	Alongside midwifery unit	Obstetric unit
Spontaneous vaginal birth	980	975	965	925
Transfer to an obstetric unit	86	94	125	10
Epidural	28	40	60	121
Episiotomy	15	23	35	56
Cesarean birth	7	8	10	35
Forceps birth	4	8	11	20
Ventouse (vacuum) birth	5	4	12	37
Blood transfusion	4	4	5	8

Table 2 (Outcomes for the baby for each planned place of birth: low-risk multiparous women)

	Number of babies per 1000 births			
	Home	Freestanding midwifery unit	Alongside midwifery unit	Obstetric unit
Babies without serious medical problems	980	975	965	925
Babies with serious medical problems	86	94	125	10

Using tables 3 and 4, explain to low-risk nulliparous women that:

- planning birth at home or in a freestanding midwifery unit is associated with a higher rate of spontaneous vaginal birth than planning birth in an alongside midwifery unit, and these 3 settings are associated with higher rates of spontaneous vaginal birth than planning birth in an obstetric unit
- planning birth in an obstetric unit is associated with a higher rate of interventions, such as instrumental vaginal birth, caesarean section and episiotomy, compared with planning birth in other settings

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- there are no differences in outcomes for the baby associated with planning birth in an alongside midwifery unit, a freestanding midwifery unit or an obstetric unit
- planning birth at home is associated with an overall small increase (about 4 more per 1000 births) in the risk of a baby having a serious medical problem compared with planning birth in other settings.

Table 3 (Rates of spontaneous vaginal birth, transfer to an obstetric unit and obstetric interventions for each planned place of birth: low-risk nulliparous women)

	Number of incidences per 1000 nulliparous women giving birth			
	Home	Freestanding midwifery unit	Alongside midwifery unit	Obstetric unit
Spontaneous vaginal birth	792	810	765	686
Transfer to an obstetric unit	440	363	402	10
Epidural	218	200	240	349
Episiotomy	165	165	216	242
Cesarean birth	80	69	76	121
Forceps birth	70	61	81	106
Ventouse (vacuum) birth	62	57	78	113
Blood transfusion	12	8	11	16

Table 4 (Outcomes for the baby for each planned place of birth: low-risk nulliparous women)

	Number of babies per 1000 births			
	Home	Freestanding midwifery unit	Alongside midwifery unit	Obstetric unit
Babies without serious medical problems	991	995	995	995
Babies with serious medical problems	9	5	5	5

Medical conditions and other factors that may affect planned place of birth

1.1.11 Use tables 6, 7, 8 and 9 as part of an assessment for a woman choosing her planned place of birth:

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- Tables 6 and 7 show medical conditions or situations in which there is increased risk for the woman or baby during or shortly after labour, where care in an obstetric unit would be expected to reduce this risk.
- The factors listed in tables 8 and 9 are not reasons in themselves for advising birth within an obstetric unit, but indicate that further consideration of birth setting may be required.
- Discuss these risks and the additional care that can be provided in the obstetric unit with the woman so that she can make an informed choice about planned place of birth. [2007, amended 2014]

Table 6 Medical conditions indicating increased risk suggesting planned birth at an obstetric unit

Disease area	Medical condition
Cardiovascular	Confirmed cardiac disease Hypertensive disorders
Respiratory	Asthma requiring an increase in treatment or hospital treatment Cystic fibrosis
Haematological	Haemoglobinopathies – sickle-cell disease, beta-thalassaemia major History of thromboembolic disorders Immune thrombocytopenia purpura or other platelet disorder or platelet count below 100,000 Von Willebrand's disease Bleeding disorder in the woman or unborn baby Atypical antibodies which carry a risk of haemolytic disease of the newborn
Infective	Risk factors associated with group B streptococcus whereby antibiotics in labour would be recommended Hepatitis B/C with abnormal liver function tests Carrier of/infected with HIV Toxoplasmosis – women receiving treatment Current active infection of chicken pox/rubella/genital herpes in the woman or baby Tuberculosis under treatment
Immune	Systemic lupus erythematosus Scleroderma
Renal	Abnormal renal function Renal disease requiring supervision by a renal specialist
Neurological	Epilepsy Myasthenia gravis Previous cerebrovascular accident
Gastrointestinal	Liver disease associated with current abnormal liver function

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	tests
Psychiatric	Psychiatric disorder requiring current inpatient care

Table 7 Other factors indicating increased risk suggesting planned birth at an obstetric unit

Factor	Additional Information
Previous complications	Unexplained stillbirth/neonatal death or previous death related to intrapartum difficulty Previous baby with neonatal encephalopathy Pre-eclampsia requiring preterm birth Placental abruption with adverse outcome Eclampsia Uterine rupture Primary postpartum haemorrhage requiring additional treatment or blood transfusion Retained placenta requiring manual removal in theatre Caesarean section Shoulder dystocia
Current pregnancy	Multiple birth Placenta praevia Pre-eclampsia or pregnancy-induced hypertension Preterm labour or preterm prelabour rupture of membranes Placental abruption Anaemia – haemoglobin less than 8.5 g/dl at onset of labour Confirmed intrauterine death Induction of labour Substance misuse Alcohol dependency requiring assessment or treatment Onset of gestational diabetes Malpresentation – breech or transverse lie Body mass index at booking of greater than 35 kg/m2 Recurrent antepartum haemorrhage Small for gestational age in this pregnancy (less than fifth centile or reduced growth velocity on ultrasound) Abnormal fetal heart rate/Doppler studies Ultrasound diagnosis of oligo-/polyhydramnios
Previous gynaecological history	Myomectomy Hysterotomy

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Table 8 Medical conditions indicating individual assessment when planning place of birth

Disease area	Medical condition
Cardiovascular	Cardiac disease without intrapartum implications
Haematological	Sickle-cell trait, Thalassaemia trait Atypical antibodies not putting the baby at risk of haemolytic disease Anemia – haemoglobin 8.5-10.5 g/dl at onset of labor
Infective	Hepatitis B/C with normal liver function tests
Immune	Nonspecific connective tissue disorders
Endocrine	Unstable hypothyroidism such that a change in treatment is required
Skeletal/Neurological	Spinal abnormalities Previous fractured pelvis Neurologic deficits
Gastrointestinal	Liver disease without current abnormal liver function Crohn's disease Ulcerative colitis

Table 9 Other factors indicating individual assessment when planning place of birth

Factor	Additional Information
Previous complications	Stillbirth/neonatal death with a known non-recurrent cause Pre-eclampsia developing at term Placental abruption with good outcome History of previous baby more than 4.5 kg Extensive vaginal, cervical, or third- or fourth-degree perineal trauma Previous term baby with jaundice requiring exchange transfusion
Current pregnancy	Antepartum bleeding of unknown origin (single episode after 24 weeks of gestation) Body mass index at booking of 30–34 kg/m2 Blood pressure of 140 mmHg systolic or 90 mmHg diastolic on two occasions Clinical or ultrasound suspicion of macrosomia Para 4 or more Recreational drug use Under current outpatient psychiatric care Age over 35 at booking
Fetal indications	Fetal abnormality
Previous gynaecological history	Major gynaecological surgery Cone biopsy or large loop excision of the transformation zone Fibroids

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Service organisation and clinical governance

1.1.17 Ensure that all women giving birth have prompt access to an obstetric unit in case they need transfer of care for medical reasons or because they request epidural analgesia. [new 2014]

1.1.18 Ensure that there are robust protocols in place for transfer of care between settings (see also section 1.6). [new 2014]

1.1.19 Ensure that there are clear local pathways for the continued care of women who are transferred from one setting to another, including where this involves crossing provider boundaries. These pathways should include arrangements for occasions when the nearest obstetric or neonatal unit is closed to admissions or when the local midwifery-led unit is full. [new 2014]"

Other Evidence

In 2013 the Oregon Public Health Division published its first report on birth outcomes by planned birth place and attendant. Because this report specifically addresses home birth outcomes in the state of Oregon, a summary is presented here.

In 2011, the Oregon Legislature passed House Bill 2380, which required the Oregon Public Health Division to add two questions to the Oregon Birth Certificate to determine planned place of birth and birth attendant, and to report annually on birth outcomes, including death, by location and attendant type. The specific questions were: "Did you go into labor planning to deliver at home or at a freestanding birthing center? If yes, what was the planned primary attendant type at the onset of labor?" In addition, for 2012, the Oregon Public Health Division conducted a special study of deaths in term infants (≥ 37 weeks' gestation) intended to deliver out-of-hospital. The perinatal fatality analysis includes fetal and early neonatal deaths ≥ 37 weeks' estimated gestational age through the first 6 days of life.

During 2012, 42,011 live term births occurred in Oregon. Of these 2,021 (4.8%) planned an out-of-hospital birth (home birth or freestanding birthing center).

Key findings of term fetal and early neonatal deaths by planned place of birth and planned birth attendant include the following:

- 62 term (≥ 37 weeks' gestation) fetal deaths occurred in Oregon during 2012; 4 (6.5%) of these occurred among planned out-of-hospital births.
- 30 term early neonatal deaths (during the first 6 days of life) occurred in Oregon during 2012; 4 (13.3%) of these occurred among planned out-of-hospital births.
- In total, 92 term fetal and early neonatal deaths occurred in Oregon during 2012; 8 (8.7%) occurred among planned out-of-hospital births. These 8 deaths underwent a fetal and neonatal mortality case review per published national guidelines.

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Key findings of the perinatal fatality case review of term births planned to occur out-of-hospital include the following:

- 4 term fetal and 4 early neonatal deaths occurred during 2012 among women who planned to deliver out-of-hospital.
- Planned birth attendants: Certified Nurse Midwife (1), Licensed Direct-Entry Midwives (4), Unlicensed Midwife (1), Undetermined Licensure Midwife (1), and Naturopathic Physician (1).
- Median birth weight: 3515 grams
- Maternal characteristics were similar to the larger group of planned out-of-hospital births.
- Two pregnancies had inadequate or no prenatal care.
- Chart review noted that, among perinatal deaths:
    - 2 pregnancies were twin gestations
    - 4 mothers declined prenatal ultrasound (to confirm gestation and identify pathology.)
    - 5 mothers declined Group B streptococcal testing (to identify women who are carriers of GBS; treatment during labor is recommended to decrease the risk of early GBS neonatal sepsis.)
    - 2 mothers declined prophylaxis during labor for Group B streptococcal positive tests.
- 6 of 8 transferred to the hospital during labor:
    - Indications for transfer to a hospital from home or birthing center included (multiple causes may apply): loss of fetal heart tones (3), prolonged labor (2), decreased fetal movement (2), and malpresentation (2).
    - One mother initially declined transfer during labor despite recommendation by birth attendant.
- 6 of 8 pregnancies did not meet published low-risk criteria for out-of-hospital birth*:
    - More than 41 weeks gestation (4)
    - Twin gestation (2)
    - Morbid obesity (> 40 BMI) (1)
    - Planned attendants among these 6: Certified Nurse Midwife (1), Licensed Direct-Entry Midwives (3), Unlicensed Midwife (1), and Naturopathic Physician (1).
- Causes of death and major contributing factors (more than one may apply):
    - Hypoxic ischemic encephalopathy or cardiorespiratory failure (lack of blood flow) (3)
    - Chorioamnionitis (infection in the womb) (3)
    - Pre-existing, or pregnancy-related maternal disease (2)
    - Respiratory failure (1)
    - Undetermined, umbilical cord wrapped around neck, large baby (1)
    - Undetermined, twin gestation, small baby (2)

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The term perinatal mortality rate for planned out-of-hospital births (4.0/1,000 pregnancies) was nearly twice that of in-hospital births (2.1/1,000). When excluding those pregnancies that did not meet published criteria for being low risk, the perinatal mortality rate for planned out-of-hospital births is 1.0/1000.

Risk Criteria for Planned Home Birth

The 2014 NICE draft guideline for antepartum care clearly outlines conditions which make a woman high risk. In addition, the Oregon Public Health Division referenced a report from the American College of Obstetrics and Gynecology (ACOG) on Planned Home Birth[1] as their published criteria for being low risk. This includes the following requirements:

- gestational age ≥ 36 weeks and ≤41 completed weeks of pregnancy
- singleton
- vertex position
- absence of preexisting or pregnancy-related maternal disease.

The ACOG committee opinion references Hutton 2006 and Janssen 2009 as a source for these criteria. They also note that the low risk criteria utilized in these two observational studies did not exclude women with a prior cesarean section; however, because of potential risks they state that ACOG "considers a prior cesarean delivery to be an absolute contraindication to planned home birth". They also note that studies showing favorable perinatal outcomes (Hutton 2006, Janssen 2009, de Jonge 2009) were conducted in settings that have "highly integrated health care systems with established criteria and provisions for emergency intrapartum transport". Therefore, ACOG "believes that the availability of timely transfer and an existing arrangement with a hospital for such transfers is a requirement for consideration of a home birth".

The final report of the Licensed Direct Entry Midwife (LDM) Staff Advisory Workgroup also recommends that planned home birth be limited to patients who are low risk, defined as pregnancies that do not have any of the following characteristics:

- presentation other than cephalic
- previous cesarean delivery
- gestational age < 36 or > 43 weeks
- multiple gestations
- diabetes/uncontrolled gestational diabetes or gestational diabetes controlled with medication
- pre-eclampsia

All three observational studies included in this document were based on registries in countries or provinces that strictly control the practice of midwifery and adhere to established criteria for planned home birth. All three lists of criteria are provided in Appendix A.

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[1] Planned home birth. Committee Opinion No. 476. American College of Obstetricians and Gynecologists. Obstet Gynecol 2011;117:425–428.

Midwifery Certification

Training and certification requirements for midwives vary among the countries referenced in this document. A summary is presented below:

The Netherlands[2]

"The midwifery training is a four year fulltime direct entry education which eventually leads to a bachelors degree. The total study load is 240 ECTS and equals nearly 6800 hours of education. Altogether, there are two years of theory, one year of primary care internships and one year of secondary and tertiary care internships. The internships are

spread equally over these four years. Students are primarily trained to become

independent primary care midwives. 190 Students enroll each year nationwide. They have had an extensive assessment which selects the best candidates. Around three times more candidates apply for the course than places are available."

British Columbia[3]

"All current CMBC approved programs are Canadian four -year direct-entry education programs leading to a university degree, or bridging programs leading to equivalency."

Ontario[4]

"1. The applicant must have at least one of the following,

i. A baccalaureate degree in health sciences (midwifery) from a university in Ontario.
ii. A degree, diploma or certificate from a program listed in Schedule 1.
iii. Qualifications that are equivalent to the degree referred to in subparagraph i, as determined by the Council or by a body or bodies designated by the Council.

2. The applicant must,

i. have current clinical experience consisting of active practice for at least two years out of the four years immediately before the date of the application, and
ii. have attended at least 60 births, of which at least,
A. 40 were attended as primary midwife,
B. 30 were attended as part of the care provided to a woman in accordance with the principles of continuity of care,
C. 10 were attended in hospital, of which at least five were attended as primary midwife, and
D. 10 were attended in a residence or remote clinic or remote birth centre, of which at least five were attended as primary midwife.

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[2] http://www.nurse.or.jp/nursing/international/icm/report/data/2012/icm-dutch.pdf
[3] http://www.cmbc.bc.ca/pdf.shtml?Exploring-Midwifery-as-a-Career
[4] http://www.e-laws.gov.on.ca/html/source/regs/english/2011/elaws_src_regs_r11168_e.htm

3. The applicant must have successfully completed the qualifying examination that was set or approved by the Registration Committee at the time the applicant took the examination."

United Kingdom[5]

Midwifery degree

- Students are awarded both an academic and a professional qualification, through integrated study of theory and supervised midwifery practice.
- Supervised midwifery practice is 50% of the program and takes place in both community and hospital settings, including antenatal clinics and wards, labour wards, postnatal wards and neonatal care.
- The programs are normally three years in length and studied on a full-time basis.

Oregon[6]

Mandatory licensure of direct entry midwives in Oregon was established in 2013 with passage of House Bill 2997, which requires any direct entry midwife practicing after January 1, 2015 to hold a license. The Oregon Board of Direct Entry Midwifery already requires that LDMs hold a certified professional midwife (CPM) credential from the North American Registry of Midwives, complete an examination, be certified in infant and adult cardiopulmonary resuscitation, have a written plan for transport of the patient, hold a high school diploma (or equivalent), and attend and participate in, at a minimum:

- 25 assisted deliveries;
- 25 deliveries for which the LDM applicant was the primary care provider;
- 100 prenatal care visits;
- 25 newborn examinations; and
- 40 postnatal examinations

North American Registry of Midwives (NARM)[7]

There are multiple routes to certification by the NARM, but in general they include a written test, a skills assessment test and the following experience requirements:

Phase 1: Births as an Observer

- 10 births in any setting, in any capacity

Phase 2: Clinicals as Assistant Under Supervision

- 20 births, 25 prenatal exams, 20 newborn exams, 10 postpartum visits

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[5] http://www.nhscareers.nhs.uk/explore-by-career/midwifery/training-to-be-a-midwife/
[6] http://www.oregon.gov/OHLA/DEM/Pages/Midwifery_How_to_Get_Licensed.aspx
[7] http://narm.org/entry-level-applicants/

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Phase 3: Clinicals as Primary Under Supervision

- 20 births, 75 prenatal visits, 20 newborn exams, and 40 postpartum exams

It is also required that the applicant have a preceptor(s) that attests to the applicant's proficiency on "Skills, Knowledge, and Abilities Essential for Competent Practice" and that the applicant be certified in Adult CPR and Neonatal Resuscitation Certification.

[Evidence Source]

Evidence summary

The evidence pertaining to home birth from randomized trials is extremely sparse, limited to just 11 participants, and hence insufficient to draw conclusions from. The largest observational studies suggest that home birth results in fewer obstetrical interventions and maternal adverse outcomes. The evidence pertaining to neonatal outcomes is less clear; while one meta-analysis found an elevated risk of neonatal death, this was no longer true when the analysis was limited to studies in which the attendant was either a certified midwife or certified nurse midwife. Observational studies conducted in settings where there are clear criteria for appropriateness of home birth (Canada, the Netherlands) do not find an elevated neonatal death rate.

In their first year of reporting, evidence from the State of Oregon Public Health Department identified an elevated risk of perinatal death in pregnancies with a planned home delivery. However, when excluding those pregnancies that did not meet published criteria for being low risk, the rate is not elevated compared to planned hospital births.

Criteria for low risk have been established by national or provincial governments as well as by US national and state provider organizations. These criteria have varying levels of detail, but at a minimum include the following:

- gestational age ≥ 36 weeks and ≤41 completed weeks of pregnancy
- singleton
- vertex position
- absence of preexisting or pregnancy-related maternal disease.

Additional criteria adopted by some or all of the entities discussed in this document include the following :

Complications in a previous pregnancy:

- Unexplained stillbirth/neonatal death or previous death related to intrapartum difficulty
- Previous baby with neonatal encephalopathy
- Pre-eclampsia requiring preterm birth
- Placental abruption with adverse outcome
- Eclampsia
- Uterine rupture
- Primary postpartum hemorrhage requiring additional treatment or blood transfusion

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- Retained placenta requiring manual removal in theatre Caesarean section
- Shoulder dystocia
- Cesarean section
- Blood group incompatibility
- Fetal growth retardation

Complications of current pregnancy

- Placenta previa
- Pre-eclampsia or pregnancy-induced hypertension
- Preterm labor or preterm prelabor rupture of membranes
- Placental abruption
- Anemia – hemoglobin less than 8.5 g/dl at onset of labor
- Confirmed intrauterine death
- Induction of labor
- Substance misuse
- Alcohol dependency requiring assessment or treatment
- Onset of gestational diabetes
- Body mass index at first prenatal visit of greater than 35 kg/m2
- Recurrent antepartum hemorrhage
- Small for gestational age fetus
- Abnormal fetal heart rate/Doppler studies
- Oligo or polyhydramnios
- Blood group incompatibility
- Prelabor rupture of membranes > 24 hours

Certification requirements for the practice of midwifery vary significantly between the US and other countries, with US requirements being less rigorous with regard to both years of formal education and experience.

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GRADE-INFORMED FRAMEWORK

The HERC develops recommendations by using the concepts of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. GRADE is a transparent and structured process for developing and presenting evidence and for carrying out the steps involved in developing recommendations. There are four elements that determine the strength of a recommendation, as listed in the table below. The HERC reviews the evidence and makes an assessment of each element, which in turn is used to develop the recommendations presented in the coverage guidance box. Balance between desirable and undesirable effects, and quality of evidence, are derived from the evidence presented in this document, while estimated relative costs, values and preferences are assessments of the HERC members.

Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Variability in values and preferences	Coverage recommendation	Rationale
Out of hospital birth for low risk pregnancies	Decreased maternal morbidity, possible improved neonatal outcomes	Moderate	Low	High	Recommended for coverage (strong recommendation)	CG Framework 1a1b
Out-of-hospital birth – unselected pregnancies	Lower maternal morbidity, increased neonatal mortality	Moderate	Moderate	High	Not recommended for coverage (strong recommendation)	CG Framework 1a3a

*The Quality of Evidence rating was assigned by the primary evidence source, not the HERC Subcommittee

Note: GRADE framework elements are described in Appendix B

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POLICY LANDSCAPE

Quality measures

No pertinent quality measures were identified when searching the National Quality Measures Clearinghouse.

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 (the Center). This document is intended to guide public and private purchasers in Oregon in making informed decisions about health care services.

The Center is not engaged in rendering any clinical, legal, business or other professional advice. The statements in this document do not represent official policy positions of the Center. Researchers involved in preparing this document have no affiliations or financial involvement that conflict with material presented in this document.

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APPENDIX A. RISK CRITERIA FOR PLANNED HOME BIRTH

Dutch List of Obstetric Indications

OBSTETRIC MANUAL

Final report of the Obstetric Working Group of the National Health Insurance Board of the Netherlands (abridged version)

The List of Obstetric Indications

What follows is the list of specific obstetric indications, including an explanation of the description of the obstetrical care provider and guidelines on how to deal with the consultative situation.

The obstetric indication list is divided into six main groups, within which reference is made to the various obstetric and medical disorders and diseases. Where necessary, an explanation is provided about the obstetric policy related to specific indications and upon what the referral policy is based. The right-hand column shows for each indication who is the most suitable care provider.

The main purpose of the indication list is to provide a guide for risk-selection. The primary obstetric care provider, midwife or GP is primarily responsible for this risk-selection. The Manuel is a consensus document showing the agreement reached by the professional groups on their decision-making structure.

Explanation of the codes used for the care providers

Code	Description	Care provider
A Primary obstetric care	The responsibility for obstetric care in the situation described is with the primary obstetric care provider.	midwife/G.P.
B Consultation situation	This is a case of evaluation involving both primary and secondary care. Under the item concerned, the individual situation of the pregnant woman will be evaluated and agreements will be made about the responsibility for obstetric care (see Section 4.5).	depending on agreements
C Secondary obstetric care	This is a situation requiring obstetric care by an obstetrician at secondary level for as long as the disorder continues to exist.	obstetrician
D Transferred primary obstetric care	Obstetric responsibility remains with the primary care provider, but in this situation it is necessary that birth takes place in a hospital in order to avoid possible transport risk during birth.	midwife/G.P.

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List of specific obstetric indications

1. Pre-existing disorders – non-gynaecological

In cases of pre-existing disorders that are relevant to obstetrics, other care providers other than the midwife are regularly involved with care of the pregnant woman. In cases requiring consultation, it is necessary to involve the other care providers in the consultation.

For this reason, in disorders given code B in this section, attention should be given to collaboration with others outside the field of obstetrics. Attention should be paid to the counselling of women who are considering the possibility of becoming pregnant.

1.1	Epilepsy, without medication	A
1.2	Epilepsy, with medication Prenatal diagnostics are recommended in connection with the disorder and its medication. Optimal care requires consultation between all care providers concerned (midwife, G.P, obstetrician, neurologist).	B
1.3	Subarachnoid haemorrhage, aneurysms Care during puerperium can be at primary level.	C
1.4	Multiple sclerosis Depending upon the neurological condition, a complicated delivery and the possibility of urine retention should be taken into account. For optimal care, consultation between all care providers concerned is indicated.	B
1.5	Hernia nuclei pulposi This represents a C-situation in cases of a recently suffered HNP or where there are still neurogenic symptoms. It is an A-situation after treated hernia, especially if a previous pregnancy was normal. Both the medical history and the current clinical condition are relevant.	A/ C
1.6	Lung function disorder The opinion of the lung specialist should be taken into account during evaluation.	B
1.7	Asthma Care during pregnancy, birth and puerperium can only take place at a primary level when the asthma involves lengthy symptom-free intervals, whether or not use is made	A/ C

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	of inhalation therapy. Consultation with the GP/specialist involved is recommended.	
1.8	Tuberculosis, active Tuberculosis, non-active In cases of an active tuberculoses process and subsequent treatment, consultation should take place with the physician involved and the obstetrician regarding the clinical condition and care during pregnancy and birth. In cases of non-active tuberculosis, care during pregnancy and birth can take place at a primary level.	C A
1.9	HIV-infection As a result of the current possibilities of medical therapy for preventing vertical transmission, these patients should be cared for during pregnancy and birth in a hospital equipped for the treatment of HIV and AIDS.	C
1.10	Hepatitis B with positive serology (Hbs-AG+) Since 1988 it is important that a screening programme for this serology is carried out on pregnant women.	A
1.11	Hepatitis C Consultation with the obstetrician and follow-up by the pediatrician is recommended.	B
1.12	A heart condition with haemodynamic consequences Pregnancy and birth will have an effect on the pre-existing haemodynamic relationships. A cardiac evaluation is important.	C
1.13	Thrombo-embolic process Of importance are the underlying pathology and the presence of a positive family medical history. Pre-conceptual counselling is important.	B
1.14	Coagulation disorders	C
1.15	Renal function disorders When there is a disorder in renal function, with or without dialysis, referral to secondary care is recommended.	C
1.16	Hypertension Pre-existing hypertension, with or without medication therapy, will require referral to	A/ C

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	secondary care. Hypertension has been defined by the ISSHP as: A single event of diastolic blood pressure of 110 mm Hg or more (Korotkoff IV). Diastolic blood pressure of 90 mm Hg or more at two subsequent blood pressure measurements with an interval of at least 4 hours between the two measurements. A distinction should be drawn between a diastolic blood pressure under 95 mm and a pressure of 95 mm and higher. Extra attention should be paid to a pregnant woman with a diastolic pressure between 90 and 95 mm; from 95 mm, referral to secondary care should take place.	
1.17	Diabetes mellitus	C
1.18	Hyperthyroidism	C
1.19	Hypothyroidism In cases of biochemical euthyroid, without antibodies and without medication, or stable on levothyroxine medication, care can take place at a primary level. Where levothyroxine medication is given, specific tests are recommended due to the frequent increase in medication required during pregnancy.	B
1.20	Anemia, due to a lack of iron Anemia is defined as Hb<6.0 mmol that has existed for some time.	B
1.21	Anemia, other This includes the haemoglobinopathies.	B
1.22	Inflammatory Bowel Disease This includes ulcerative colitis and Crohn's disease.	C
1.23	System diseases and rare diseases These include rare maternal disorders such as Addison's disease and Cushing's disease. Also included are systemic lupus erythematosus (SLE), anti-phospholipid syndrome (APS), scleroderma, rheumatoid arthritis, periarteritis nodosa, Marfan's syndrome, Raynaud's disease and other systemic and rare disorders.	C
1.24	Use of hard drugs (heroin, methadone, cocaine, XTC, etc.) Attention should be paid to actual use. A urine test can be useful even in cases of past use in the medical history. The involvement of the pediatrician is indicated during the follow-up postpartum.	C

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1.25	Alcohol abuse The fetal alcohol syndrome is important. The involvement of the pediatrician is indicated during the follow-up postpartum.	C
1.26	Psychiatric disorders Care during pregnancy and birth will depend on the severity and extent of the psychiatric disorder. Consultation with the physician in charge is indicated.	B

2. Pre-existing gynaecological disorders

2.1	Pelvic floor reconstruction This refers to colpo-suspension following prolaps , fistula and previous rupture. Depending on the cause, the operation technique used and the results achieved, the obstetrician will determine policy regarding the birth. A primary caesarean section or an early primary episiotomy can be considered, to be repaired by the obstetrician. If the chosen policy requires no special measures and no specific operating skill, then care during birth can be at primary level.	C
2.2	Cervical amputation	C
	Cervical cone biopsy	B
	Cryo- and lis-treatment The practical application of obstetric policy in this field can be worked out in local mutual agreements. If an uncomplicated pregnancy and birth have taken place following cone biopsy then a subsequent pregnancy and birth can take place at primary level.	A
2.3	Myomectomy (serous,mucous) Depending on the anatomical relationship, the possibility of a disturbance in the progress of the pregnancy or birth should be taken into account.	B
2.4	Abnormalities in cervix cytology (diagnostics, follow-up) There should be differentiation according to obstetric versus gynaecological policy. Gynaecological consultation can be indicated even without obstetric consequences. Participation in national cervical cancer screenings program is not provided pregnant women. The gynaecological follow-up is not an impediment to obstetric care at primary level.	B/A

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2.5	DES-daughter (untreated and under supervision) There should be a differentiation according to obstetric versus gynecological policy. Gynaecological care related to the problems surrounding DES may be necessary, while obstetric care can take place at primary level.	B
2.6	IUD in situ	B
	Status following removal of the IUD	A
2.7	Status following infertility treatment In practice, the wish of the patient to be cared for at secondary level plays a role here, even though the pregnancy and birth are otherwise normal. There is no question of an increased obstetric risk.	A
2.8	Pelvic deformities (trauma, symphysis rupture, rachitis) Consultation should take place at the start of the last trimester. It should be pointed out that care at secondary level has not been shown to have any added value in cases of pelvic instability and symphysis pubis dysfunction.	B
2.9	Female circumcision/Female genital mutilation Circumcision as such can require extra psychosocial care. Where there are serious anatomical deformities, consultation should take place in the third trimester.	A/B

3. Obstetric medical history

3.1	Active blood group incompatibility (Rh, Kell, Duffy, Kidd)	C
	ABO-incompatibility Pregnancy and birth can take place at primary care level in cases of ABO-antagonism, but one should be on the alert for neonatal problems. Consultation is indicated.	B
3.2	Pregnancy induced hypertension in the previous pregnancy	A
	Pre-eclampsia in the previous pregnancy	B
	HELLP-syndrome in the previous pregnancy	C
3.3	Habitual abortion (□3 times) If an abortion should occur again, the need to carry out pathological study of fetal	A

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	material should be discussed. Genetic counselling prior to pregnancy is also advised.	
3.4	Pre-term birth (<37 weeks) in a previous pregnancy If a normal pregnancy has taken place subsequent to the premature birth, then a further pregnancy can be conducted at primary care level.	B
3.5	Cervix insufficiency (and/or Shirodkar-procedure) Secondary level care during pregnancy is indicated up to 37 weeks; with a full term pregnancy, home birth is allowed. If a subsequent pregnancy was normal, then future pregnancies and deliveries can be conducted at primary care level.	C/A
3.6	Placental abruption	C
3.7	Forceps or vacuum extraction Evaluation of information from the obstetrical history is important. Documentation showing a case of an uncomplicated assisted birth will lead to the management of the present pregnancy and birth at primary care level. Consultation should take place when no documentation is available or when there are signs of a complicated assisted birth.	A/B
3.8	Caesarean section	C
3.9	Fetal growth retardation (Light for date) A birth weight of P<2.3 or obvious neonatal hypoglycemia related to fetal growth retardation.	C
3.10	Asphyxia Defined as an APGAR score of <7 at 5 minutes. It is important to know whether a pediatrician was consulted because of asphyxia at a previous birth.	B
3.11	Perinatal death Such an obstetrical history requires consultation. It is also important to know whether there was a normal pregnancy following the perinatal death. Pregnancy and birth can then be conducted at primary care level.	B
3.12	Prior child with congenital and/or hereditary disorder It is important to know the nature of the disorder and what diagnostics were carried out at the time. If no disorders can currently be discerned, then further care can be at primary care level.	B

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3.13	Postpartum haemorrhage as a result of episiotomy	A
3.14	Postpartum haemorrhage as a result of cervix rupture (clinically demonstrated) The assumption is that there is a chance of a recurrence; the pregnancy and birth can be conducted at primary care level. The decision can be taken to allow birth to take place in the hospital.	D
3.15	Postpartum haemorrhage, other causes (>1000 cc) In view of the chance of a recurrence, although the pregnancy and birth can be conducted at primary care level, the decision can be taken to allow birth to take place in the hospital.	D
3.16	Manual placenta removal in a previous pregnancy In view of the increased recurrence risk, the next following pregnancy and birth can be cared for at primary care level, with the birth taking place in hospital. When the birth following one in which the manual placenta removal has taken place has had a normal course, a subsequent pregnancy and birth can be cared for at primary level. When in the previous birth a placenta accreta is diagnosed, obstetrical care at secondary level is indicated.	D
3.17	4th degree perineal laceration (functional recovery/no functional recovery) If satisfactory functional recovery has been achieved following the 4th degree tear, then pregnancy and birth can be managed at primary care level. The possibility of performing a primary episiotomy during birth should be considered. If secondary repair surgery was necessary, then referral to secondary care is indicated (similarly to that which is stated for pelvic floor reconstruction). If no functional repair has been achieved following a 4th degree tear , then birth should be managed at secondary care level.	A/C
3.18	Symphysis pubis dysfunction There is no added value to managing pregnancy or birth at secondary care level in cases with a symphysis pubis dysfunction in the history or with pelvic instability.	A
3.19	Postpartum depression There is no added value to managing pregnancy or birth at secondary care level in cases with a p.p.d. in the history. Postpartum depression occurs at such a time postpartum that even the puerperium can be cared for at primary care level.	A
3.20	Postpartum psychosis	A

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	It is necessary to distinguish whether there is a case of long-term medicine use. It is important to have a psychiatric evaluation of the severity of the psychosis and the risk of recurrence.	
3.21	Grand multiparty Defined as parity >5. There is no added value to managing a pregnancy and birth at secondary care level.	A
3.22	Post-term pregnancy Post-term pregnancy in the obstetrical history has no predictive value for the course of the current pregnancy and birth.	A

4. Developed/discovered during pregnancy

In this section it is the case that supervision at secondary level care is necessary in situations given the code C, as long as the problem described still exists. If it no longer exists, then the patient can be referred back to primary level care.

4.1	Uncertain duration of pregnancy by amenorrhoea >20 weeks Consultation is required when the duration of pregnancy is uncertain after 20 weeks amenorrhoea. The primary care provider has access to sufficient additional diagnostic tools in the first 20 weeks.	B
4.2	Anemia (Hb<6.0 mmol/l) It is important that the nature and the severity of the anemia are analysed during consultation.	B
4.3	Recurrent urinary tract infections One can speak of recurrent urinary tract infection when an infection has occurred more than twice. Further analysis of the infection is required. The risk of renal function disorders and the risk of pre-term birth are important. The course of further diagnostics can take place within the local mutual agreements made between the three professional groups.	B
4.4	Pyelitis Hospital admission is required for the treatment of pyelitis, so that care will have to be at secondary level. After successful treatment of the pyelitis, further care during	C

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	pregnancy and birth can be at primary level.	
4.5	Toxoplasmosis, diagnostics and therapy Referral to secondary level is required both for diagnostics and for therapeutic policy.	C
4.6	Rubella An increased risk of fetal growth retardation, pre-term birth and visual and hearing disorders should be taken into account in a case of primary infection with rubella during pregnancy.	C
4.7	Cytomegalovirus An increased risk of perinatal death and subsequent morbidity should be taken into account.	C
4.8	Herpes genitalis (primary infection) Herpes genitalis (recurrent) During a primary infection there is a (slight) risk of transplacental fetal infection. In the first year after the primary infection, there is a higher frequency of recurrences and asymptotic virus excretion. If a primary infection occurs shortly before or during birth, there is an increased risk of neonatal herpes. Due to the possibility of treatment with antiviral drugs, referral to secondary care is indicated for primary infections. For recurrences and where herpes genitalis is in the medical history, it is advisable to carry out a virus culture from the oropharynx of the neonate. If there are frequent recurrences (>1/month) or where there is a recurrence during birth, referral is indicated due to the increased risk of infection of the neonate. It is as yet not clear whether the presence of antibodies are sufficient protection for the child.	C A
4.9	Parvo virus infection This infection can lead to fetal anemia and hydrops. Possibilities exist for treating these problems.	C
4.10	Varicella/Zoster virus infection This refers to a maternal infection. Primary infection with varicella/zoster virus (chicken pox) during the pregnancy might require treatment of the pregnant woman with VZV-immunoglobulin due to the risk of fetal varicella syndrome. If varicella occurs shortly before birth or early during the puerperium, there is a risk of neonatal infection. Treatment of the mother and child with an antiviral drug is sometimes indicated. If there is a case of manifest herpes zoster (shingles), then there is no risk of	B

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	fetal varicella syndrome.	
4.11	Hepatitis B (Hbs-Ag+)	A
4.12	Hepatitis C This is an indication for referral to secondary care for consultation. Attention must be given to follow-up by the pediatrician.	B
4.13	Tuberculosis This refers to an active tuberculous process.	C
4.14	HIV-infection In connection with the present possibilities of medical therapy for preventing vertical transmission, care for these patients during pregnancy and birth should take place in a hospital/center equipped to deal with HIV and AIDS.	C
4.15	Syphilis Positive serology and treated	A
	Positive serology and not yet treated	B
	Primary infection Attention should be paid to collaboration between the primary and secondary care providers involved during referral. It is important to ensure perfect information exchange between the midwife, the GP, the obstetrician and the venereologist. Structural agreements can be worked out in local collaboration.	C
4.16	Hernia nuclei pulposi, (slipped disk) occurring during pregnancy Policy should be determined according to complaints and clinical symptoms. Where there are no complaints, (further) care can take place at primary level.	B
4.17	Laparotomy during pregnancy As soon as wound healing has occurred and if the nature of the operation involves no further obstetric risks, care for the pregnant woman can return to primary level. During hospitalisation the obstetrician will be involved in the care. If there are no further obstetric consequences then care for the pregnant woman can return to primary level.	C
4.18	Cervix cytology PAP III or higher	B

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	What is important here is that further gynaecological policy (for the purpose of subsequent diagnostics) may be necessary, while the pregnancy and birth can be conducted at primary level.	
4.19	Medicine use What is obviously important here is the effect of drugs on the pregnant woman and the unborn child. Attention should also be paid to the effect on lactation and the effects in the neonatal period. In cases of doubt, consultation should take place. Note: information is available from the NIAD (030-2971100) and from the teratology center of the RIVM (030-2742017).	A/ B
4.20	Use of hard drugs (heroin, methadone, cocaine, XTC etc.) The severity of the addiction to hard drugs is important here and their effects during pregnancy and birth and in the puerperium, particularly for the neonate.	C
4.21	Alcohol abuse This involves the fetal alcohol syndrome. Obviously the long-term involvement of the pediatrician can be necessary during follow up.	C
4.22	Psychiatric disorders (neuroses/psychoses) The severity of the psychiatric problems and the opinion of the physician in charge of treatment are important.	A/ C
4.24	Hyperemesis gravidarum Referral to secondary care is necessary for treatment of this condition. After recovery the pregnancy and birth can take place at primary care level.	C
4.24	Ectopic pregnancy	C
4.25	Antenatal diagnostics Attention should be given to the presence of a risk for congenital deformities. If no deformities can be found, then further care can take place at primary level. In cases of an age-related indication, direct referral from primary care level to a genetic center can take place.	C
4.26	(Suspected) fetal deformities	B
4.27	Pre-term rupture of membranes (<37 weeks amenorrhoea)	C

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4.28	Diabetes Mellitus (incl. pregnancy diabetes)	C
4.29	Pregnancy induced hypertension This refers to hypertension (according to the ISSHP definition, see 1.16) in the second half of pregnancy in a previously normotensive woman. Distinction is drawn between diastolic blood pressure up to 95 mm and blood pressure starting at 95 mm. At a diastolic pressure between 90 and 95 mm, a pregnant woman should receive extra care, from 95 mm upwards, she should be referred to secondary level care.	A/ C
4.30	Pre-eclampsia, super-imposed pre-eclampsia, HELLP-syndrome Pre-eclampsia is a combination of pregnancy induced hypertension and proteinuria. The latter is defined by an albustix ++ in a urine sample or by a total protein excretion of 30 mg or more during a period of 24 hours. A super-imposed pre-eclampsia exists when there is 'de novo' proteinuria during a pregnancy in a patient with pre-existing hypertension. The HELLP-syndrome is characterised by the combination of haemolysis, liver function disorder and a decrease in the number of platelets.	C
4.31	Blood group incompatibility	C
4.32	Thrombosis	C
4.33	Coagulation disorders	C
4.34	Recurring blood loss prior to 16 weeks	B
4.35	Blood loss after 16 weeks After the blood loss has stopped, care can take place at primary care level if no incriminating causes were found.	C
4.36	Placental abruption	C
4.37	(Evaluation of) negative size-date discrepancy A negative size-date discrepancy exists if the growth of the uterus remains 2 to 4 weeks behind the normal size for the duration of the pregnancy.	B
4.38	(Evaluation of) positive size-date discrepancy	B
4.39	Post-term pregnancy	C

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	This refers to amenorrhoea lasting longer than 294 days.	
4.40	Threat of or actual pre-term birth As soon as there is no longer a threat of pre-term birth, care during the pregnancy and birth can be continued at primary care level.	B
4.41	Insufficient cervix Once the pregnancy has lasted 37 weeks, further care can take place at primary care level.	C
4.42	Symphysis pubis dysfunction (pelvic instability) This refers to complaints that started during the present pregnancy	A
4.43	Multiple pregnancy	C
4.44	Abnormal presentation at full term (including breech presentation)	C
4.45	Failure of head to engage at full term If at full term there is a suspected cephalo-pelvic disproportion, placenta praevia or comparable pathology, consultation is indicated.	B
4.46	No prior prenatal care (□full term) Attention should be paid to the home situation. The lack of prenatal care can suggest psychosocial problems. This can lead to further consultation and a hospital delivery.	A
4.47	Baby up for adoption The prospective adoption often goes hand-in-hand with psychosocial problems. This can lead to further consultation and a hospital delivery.	A
4.48	Dead fetus If the mother prefers to give birth at home, the care she receives should be the same as if the birth were to take place in a hospital. Attention should be paid to postmortem examination study and evaluation according to protocol.	C
4.49	Obstetrically relevant fibroids (myoma) Depending on the anatomical proportions, the possibility of a disturbance in the progress of pregnancy or birth should be taken into account.	B

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5. Occurring during birth

For the C-category in this section, when one of the items mentioned below occurs, an attempt should still be made to achieve an optimal condition for further intrapartum care, whilst referral to secondary care level may be urgent ,depending on the situation. When referring from the home situation, the risk of transporting the woman also needs to be included in the considerations.

5.1	Abnormal presentation of the child What counts here is abnormal presentation and not abnormal position.	B
5.2	Signs of fetal distress It is important that fetal distress can be expressed in various ways (fetal heart rate, meconium staining in the amniotic fluid).	C
5.3	Intrapartum fetal death Attention should be paid to post-mortem examinations	C
5.4	Pre-labour rupture of membranes Referral should take place the morning after the membranes have been broken for 24 hours.	C
5.5	Failure to progress in the first stage of labour If the contractions are good, both regarding strength and frequency, but there is no change in the cervix or progress in dilation after the latent phase for a duration of 4 hours, one can speak of a failure to progress in labour. Consultation is necessary to be able to determine further treatment based on an analysis of the possible cause.	B
5.6	Failure to progress in second stage of labour This exists where there is a lack of progress, after a maximum of one hour, in cases with full dilation, ruptured membranes, strong contractions and sufficient maternal effort.	C
5.7	Excessive bleeding during birth The degree of bleeding during birth cannot be objectively measured, but needs to be estimated. Excessive loss of blood can be a sign of a serious pathology.	C
5.8	Placental abruption	C
5.9	Umbilical cord prolaps	C

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5.10	(Partial) retained placenta It is not always possible to be sure of the retention of part of the placenta. If there is reasonable cause to doubt, then referral to secondary care should take place	C
5.11	Fourth degree perineal laceration	C
5.12	Meconium stained amniotic fluid	C
5.13	Fever It is obviously important to find out the cause of the fever. In particular, the possibility of an intrauterine infection should be taken into account and the administration of antibiotics intrapartum should be considered.	C
5.14	Analgesia It is important to be aware of the effects on dilatation and respiratory depression. The use of painkillers during birth is a subject that can be covered during local discussions with the aid of guidelines. One should attempt to achieve well-founded consensus.	B
5.15	Vulva haematoma Treatment policy is determined according to the complaints intrapartum and in the early puerperium.	C
5.16	Symphyiolysis This refers to rupturing of the symphyseal rupture. It should be distinguished from pelvic instability. The added value of consultation in cases of pelvic instability has not been proven.	B
5.17	Birth with no prior prenatal care A lack of prenatal care can be a sign of psychosocial problems and in particular addiction. Intrapartum monitoring, serological screening and immunisation are of utmost importance.	C

6. Occurring during the puerperium

6.1	Puerperal fever It is important to know the underlying cause. In cases of reasonable doubt, referral should be considered.	A/C

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6.2	(Threat of) eclampsia, (suspected) HELLP-syndrome	C
6.3	Thrombosis	C
6.4	Psychosis It is important to involve (non-obstetrically) the GP and the psychiatrist in treating the psychiatric disorder.	B
6.5	Postpartum haemorrhage	C
6.6	Hospitalisation of child It is obviously important here to involve (non-obstetrically) the GP and the pediatrician. The bonding between mother and child are important in the period following birth.	C

<u>Ontario College of Midwives Indications for Mandatory Discussion, Consultation and Transfer of Care</u>

"As a primary caregiver, the midwife together with the client is fully responsible for decision-making. The midwife is responsible for writing orders and carrying them out or delegating them in accordance with the standards of the College of Midwives.

The midwife discusses care of a client, consults, or transfers primary care responsibility according to the Indications for Mandatory Discussion, Consultation and Transfer of Care.1 The responsibility to consult with a family physician/general practitioner, obstetrician and/or specialist physician lies with the midwife. It is also the midwife's responsibility to initiate a consultation within an appropriate time after detection of an indication for consultation. The severity of the condition and the availability of a physician(s) will influence these decisions.

The informed choice agreement between the midwife and client should outline the extent of midwifery care, in order to make clients aware of the scope and limitations of midwifery care. The midwife should review the Indications for Mandatory Discussion, Consultation and Transfer of Care with the client.

DEFINITIONS

Category 1: Discuss with another midwife or with a physician

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It is the midwife's responsibility to initiate a discussion with or provide information to another midwife or physician, with whom the care is shared, in order to plan care appropriately.

Category 2: Consult with a physician

It is the midwife's responsibility to initiate a consultation and to clearly communicate to the consultant that she is seeking a consultation. A consultation refers to the situation where a midwife, in light of her professional knowledge of the client and in accord with the standards of practice of the College of Midwives, or where another opinion is requested by the client, requests the opinion of a physician competent to give advice in this field. The midwife should expect that:

The consultation involves addressing the problem that led to the referral, an in-person assessment of the patient, and the prompt communication of the findings and recommendations to the patient and the referring professional.

Following the assessment of the patient by the consultant(s), discussion can occur between the health professional and consultant regarding future patient care.

The consultation can involve the physician providing advice and information and/or providing therapy to the woman/newborn or prescribing therapy to the midwife for the woman/newborn.

Consultation must be documented by the midwife in her records in accord with the regulations of the College of Midwives.

After consultation with a physician, primary care of the client and responsibility for decision-making together with the client either:

a) continues with the midwife, or b) is transferred to a physician.

Once a consultation has taken place and the consultant's findings, opinions and recommendations are communicated to the client and the midwife, the midwife must discuss the consultant's recommendations with the client and ensure the client understands which health professional will have responsibility for primary care.

Where urgency, distance or climatic conditions make an in-person consultation with a physician not possible, the midwife should seek advice from the physician by phone or other similar means. The midwife should document this request for advice, in her records, in accord with the requirement of the College of Midwives and discuss with the client the advice received.

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The consultant may be involved in, and responsible for, a discrete area of the client's care, with the midwife maintaining overall responsibility within her scope of practice. Areas of involvement in client care must be clearly agreed upon and documented by the midwife and the consultant.

The College of Midwives has agreed that:

One health professional has overall responsibility for a patient at any one time and the patient's care should be co-ordinated by that health professional whose identity should be clearly known to all of those involved and documented in the records of the referring health professional and consultant. Responsibility could be transferred temporarily to another health professional, or be shared between health professionals according to the patient's best interests and optimal care; however, transfer or sharing of care should only occur after discussion and agreement among patients, referring health professionals, and consultants.3

Category 3: Transfer to a physician for primary care

When primary care is transferred, permanently or temporarily, from the midwife to a physician, the physician, together with the client, assumes full responsibility for subsequent decision-making. When primary care is transferred to a physician, the midwife may provide supportive care4 within her scope of practice, in collaboration with the physician and the client.

INDICATIONS: Initial History and Physical Examination

Category 1:

• adverse socio-economic conditions

• age less than 17 years or over 35 years

• cigarette smoking

• grand multipara (para 5)

• history of infant over 4500 g

• history of one late miscarriage (after 14 completed weeks) or preterm birth

• history of one low birth weight infant

• history of serious psychological problems

• less than 12 months from last delivery to present due date

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• obesity

• poor nutrition

• previous antepartum hemorrhage

• previous postpartum hemorrhage

• one documented previous low segment cesarean section

• history of essential or gestational hypertension

• known uterine malformations or fibroids

Category 2:

• current medical conditions for example: cardiovascular disease, pulmonary disease, endocrine disorders, hepatic disease, neurologic disorders

• family history of genetic disorders

• family history of significant congenital anomalies

• history of cervical cerclage

• history of repeated spontaneous abortions

• history of more than one late miscarriage or preterm birth

• history of more than one low birth weight infant

• history of gestational hypertension with proteinuria and adverse sequelae

• history of significant medical illness

• previous myomectomy, hysterotomy or cesarean section other than one documented previous low segment cesarean section

• previous neonatal mortality or stillbirth

• rubella during first trimester of pregnancy

• significant use of drugs or alcohol

• age less than 14 years

Category 3:

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• any serious medical condition, for example: cardiac or renal disease with failure or insulin dependent diabetes mellitus

INDICATIONS: Prenatal Care

Category 1:

• presentation other than cephalic at 36 completed weeks

• no prenatal care before 28 completed weeks

• uncertain expected date of delivery

• uncomplicated spontaneous abortion less than 12 completed weeks

Category 2:

• anemia (unresponsive to therapy)

• documented post term pregnancy (42 completed weeks)

• fetal anomaly

• inappropriate uterine growth

• medical conditions arising during prenatal care, for example: endocrine disorders, hypertension, renal disease, suspected significant infection, hyperemesis

• placenta previa without bleeding

• polyhydramnios or oligohydramnios

• gestational hypertension

• isoimmunization

• serious psychological problems

• sexually transmitted disease

• twins

• vaginal bleeding other than transient spotting

• presentation other than cephalic, unresponsive to therapy, at 38 completed weeks

Category 3:

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• cardiac or renal disease with failure

• insulin dependent diabetes

• multiple pregnancy (other than twins)

• gestational hypertension with proteinuria and/or adverse sequelae

• symptomatic placental abruption

• vaginal bleeding, continuing or repeated

• placenta previa after 28 completed weeks

INDICATIONS: During Labour and Birth

Category 1:

• no prenatal care

• non-particulate meconium

Category 2:

• breech presentation

• preterm labour (34 - 37 completed weeks)

• prolonged active phase

• prolonged rupture of membranes

• prolonged second stage

• retained placenta

• suspected placenta abruption and/or previa

• third or fourth degree tear

• twins

• unengaged head in active labour in primipara

• preterm prelabour rupture of membranes (PPROM) between 34 and 37 completed weeks

• particulate meconium

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• gestational hypertension

Category 3:

• active genital herpes at time of labour

• preterm labour (less than 34 completed weeks)

• abnormal presentation (other than breech)

• multiple pregnancy (other than twins)

• gestational hypertension with proteinuria and/or adverse sequelae

• prolapsed cord or cord presentation

• placenta abruption and/or previa

• severe hypertension

• confirmed non-reassuring fetal heart patterns, unresponsive to therapy

• uterine rupture

• uterine inversion

• hemorrhage unresponsive to therapy

• obstetric shock

• vasa previa

INDICATIONS: Post Partum (Maternal)

Category 2:

• suspected maternal infection e.g. breast, abdomen, wound, uterine, urinary tract, perineum

• temperature over 38° C (100.4° F) on more than one occasion

• persistent hypertension

• serious psychological problems

Category 3:

• hemorrhage unresponsive to therapy

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• postpartum eclampsia

• thrombophlebitis or thromboembolism

• uterine prolapse

INDICATIONS: Post Partum (Infant)

Category 1:

• feeding problems

• failure to pass urine or meconium within 24 hours of birth

Category 2:

• 34 to 37 weeks gestational age

• infant less than 2,500 g

• less than 3 vessels in umbilical cord

• excessive moulding and cephalohematoma

• abnormal findings on physical exam

• excessive bruising, abrasions, unusual pigmentation and/or lesions

• birth injury requiring investigation

• congenital abnormalities, for example: cleft lip or palate, congenital dislocation of hip, ambiguous genitalia

• abnormal heart rate or pattern

• abnormal cry

• persistent abnormal respiratory rate and/or pattern

• persistent cyanosis or pallor

• jaundice in first 24 hours

• suspected pathological jaundice after 24 hours

• temperature less than 36° C, unresponsive to therapy

• temperature more than 37.4° C, axillary, unresponsive to non-pharmaceutical therapy

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• vomiting or diarrhea

• infection of umbilical stump site

• significant weight loss (more than 10% of body weight)

• failure to regain birth weight in three weeks

• failure to thrive

• failure to pass urine or meconium within 36 hours of birth

• suspected clinical dehydration

Category 3:

• APGAR lower than 7 at 5 minutes

• suspected seizure activity

• major congenital anomaly requiring immediate intervention, for example: omphalocele, myelomeningocele

• temperature instability"

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College of Midwives of British Columbia: Indications for Mandatory Discussion, Consultation and Transfer of Care

The introduction and definition sections of this document are similar, though not identical, in format and content to the Ontario Indications. The list of indications is also very similar; variations from the Ontario list are presented below:

INDICATIONS: Initial History and Physical Examination

Category 1 (Discussion):

- British Columbia includes age less than 17 years or over 40 years (Ontario upper age limit is 35)
- Ontario includes history of essential hypertension
- British Columbia includes history of trauma or sexual abuse

Category 2 (Consultation):

- British Columbia includes a history of eclampsia
- British Columbia includes a history of post-partum hemorrhage requiring transfusion

INDICATIONS: Prenatal Care

Category 1 (Discussion):

- Ontario includes uncomplicated spontaneous abortion at less than 12 weeks gestation

Category 2 (Consultation):

- British Columbia includes hemaglobinopathies and blood dyscrasias
- British Columbia includes presentation other than cephalic at 37 weeks (Ontario specifies 38 weeks and “unresponsive to therapy”)
- British Columbia includes insulin-dependent diabetes (this is a category 3 condition in Ontario)

Category 3 (Transfer):

- Ontario includes continued vaginal bleeding
- Ontario includes placenta previa after 28 weeks gestation

INDICATIONS: During Labour and Birth

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Category 1 (Discussion):

- Ontario includes preterm premature rupture of membranes between 34 and 37 weeks of gestation
- British Columbia includes temperature of 38° or greater more than once

Category 2 (Consultation):

- Ontario includes vasa previa

INDICATIONS: Post Partum (Infant)

Category 1 (Discussion):

- British Columbia includes excessive molding and cephalohematoma (Ontario lists these indications as Category 2, requiring consultation)
- Ontario includes failure to pass urine or meconium within 24 hours of birth

Category 2 (Consultation):

- British Columbia includes suspicion of or significant risk of infection
- British Columbia includes poor suck, hypotonia and jitteriness
- British Columbia includes temperature of 38° or greater unresponsive to therapy (Ontario uses 37.4° as the criteria)
- Ontario includes failure to pass urine or meconium within 36 hours of birth

Category 3 (Transfer):

- British Columbia includes an Apgar score lower than 7 at 10 minutes (Ontario uses 5 minutes for their criteria)

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APPENDIX A. GRADE ELEMENT DESCRIPTIONS

Element	Description
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
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—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

Strong recommendation

In Favor: The subcommittee is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Against: The subcommittee is confident that the undesirable effects of adherence to a recommendation outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Weak recommendation

In Favor: The subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Against: The subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Quality or strength of evidence rating across studies for the treatment/outcome[8]

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 RCTs with few or no limitations and the estimate of effect is likely stable.

Moderate: The subcommittee is moderately confident in the effect estimate: 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 effect estimate 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 effect estimate: 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.

[8] Includes risk of bias, precision, directness, consistency and publication bias

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APPENDIX C. APPLICABLE CODES

CODES	DESCRIPTION
ICD-9 Diagnosis Codes	
V22	Normal pregnancy
V23	Supervision of high-risk pregnancy
V24	Post-partum care and examination
ICD-10 Diagnosis Codes	
Z34	Encounter for supervision of normal first pregnancy, unspecified trimester
O09	Supervision of high-risk pregnancy
Z39	Encounter for care and examination of mother immediately after delivery
ICD-9 Volume 3 (Procedure Codes)	
72	Forceps, vacuum and breech delivery
73	Other procedures inducing or assisting delivery
74	Cesarean section and removal of the fetus
75	Other obstetric operations
CPT Codes	
59400-10	Vaginal delivery
59412	External cephalic version, with or without tocolysis
59414	Delivery of placenta (separate procedure)
59425-6	Antepartum care only
59430	Postpartum care only (separate procedure)
59510-15	Cesarean delivery
59610-22	Delivery after previous cesarean
HCPCS Level II Codes	
H1000-5	Prenatal care, at risk assessment

Note: Inclusion on this list does not guarantee coverage

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APPENDIX D. HERC GUIDANCE DEVELOPMENT FRAMEWORK

HERC Guidance Development Framework Principles

This framework was developed to assist with the decision making process for the Oregon policy-making body, the HERC and its subcommittees. It is a general guide, and must be used in the context of clinical judgment. It is not possible to include all possible scenarios and factors that may influence a policy decision in a graphic format. While this framework provides a general structure, factors that may influence decisions that are not captured on the framework include but are not limited to the following:

- Estimate of the level of risk associated with the treatment, or any alternatives;
- Which alternatives the treatment should most appropriately be compared to;
- Whether there is a discrete and clear diagnosis;
- The definition of clinical significance for a particular treatment, and the expected margin of benefit compared to alternatives;
- The relative balance of benefit compared to harm;
- The degree of benefit compared to cost; e.g., if the benefit is small and the cost is large, the committee may make a decision different than the algorithm suggests;
- Specific indications and contraindications that may determine appropriateness;
- Expected values and preferences of patients.

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Out-of-hospital births in low risk pregnancies

Oregon Health Authority

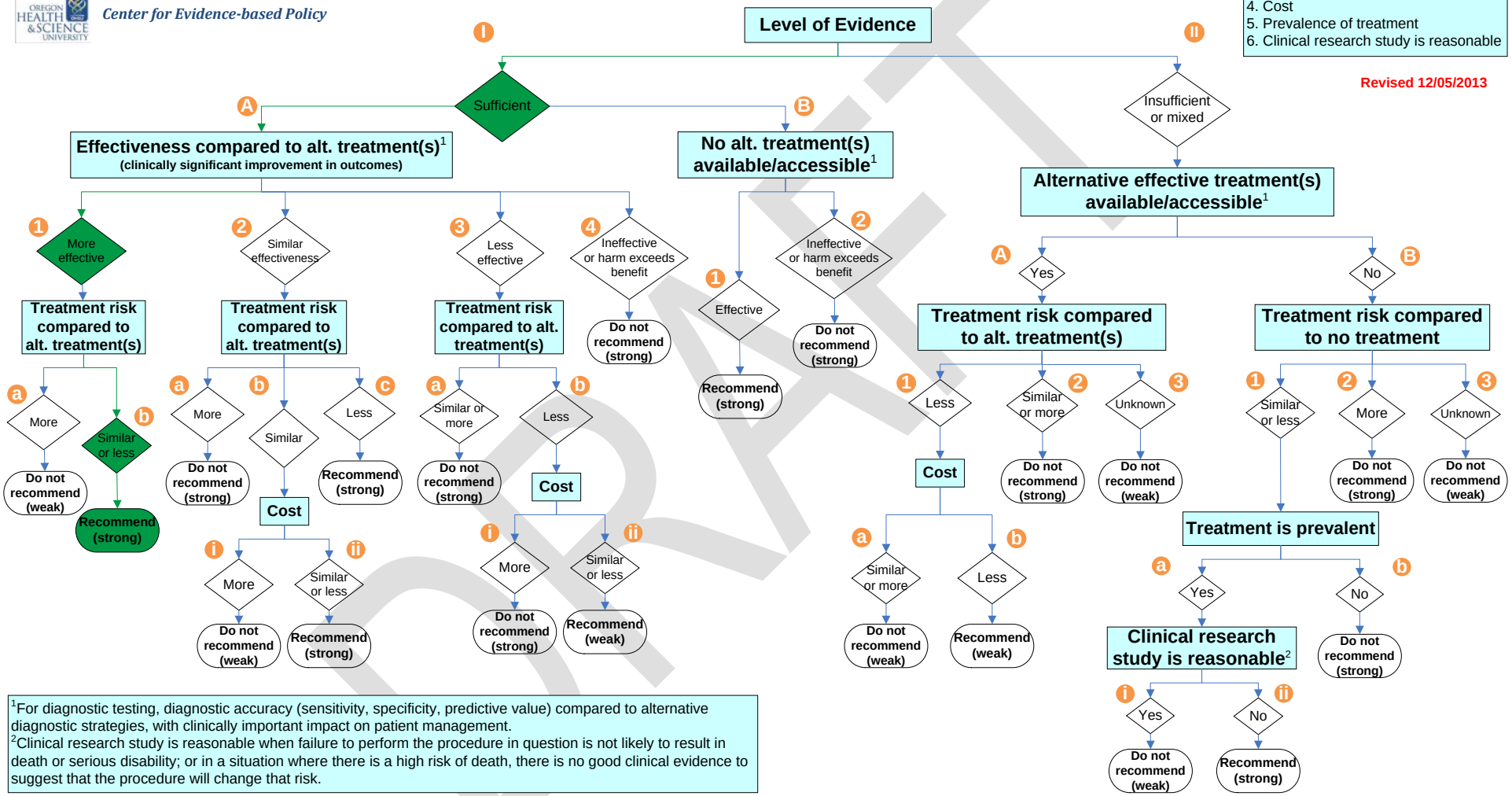
Oregon Health & Science University — *Center for Evidence-based Policy*

HERC Guidance Development Framework

Refer to *HERC Guidance Development Framework Principles* for additional considerations

Decision Point Priorities
1. Level of evidence
2. Effectiveness & alternative treatments
3. Harms and risk
4. Cost
5. Prevalence of treatment
6. Clinical research study is reasonable

Revised 12/05/2013



[1]For diagnostic testing, diagnostic accuracy (sensitivity, specificity, predictive value) compared to alternative diagnostic strategies, with clinically important impact on patient management.
[2]Clinical research study is reasonable when failure to perform the procedure in question is not likely to result in death or serious disability; or in a situation where there is a high risk of death, there is no good clinical evidence to suggest that the procedure will change that risk.

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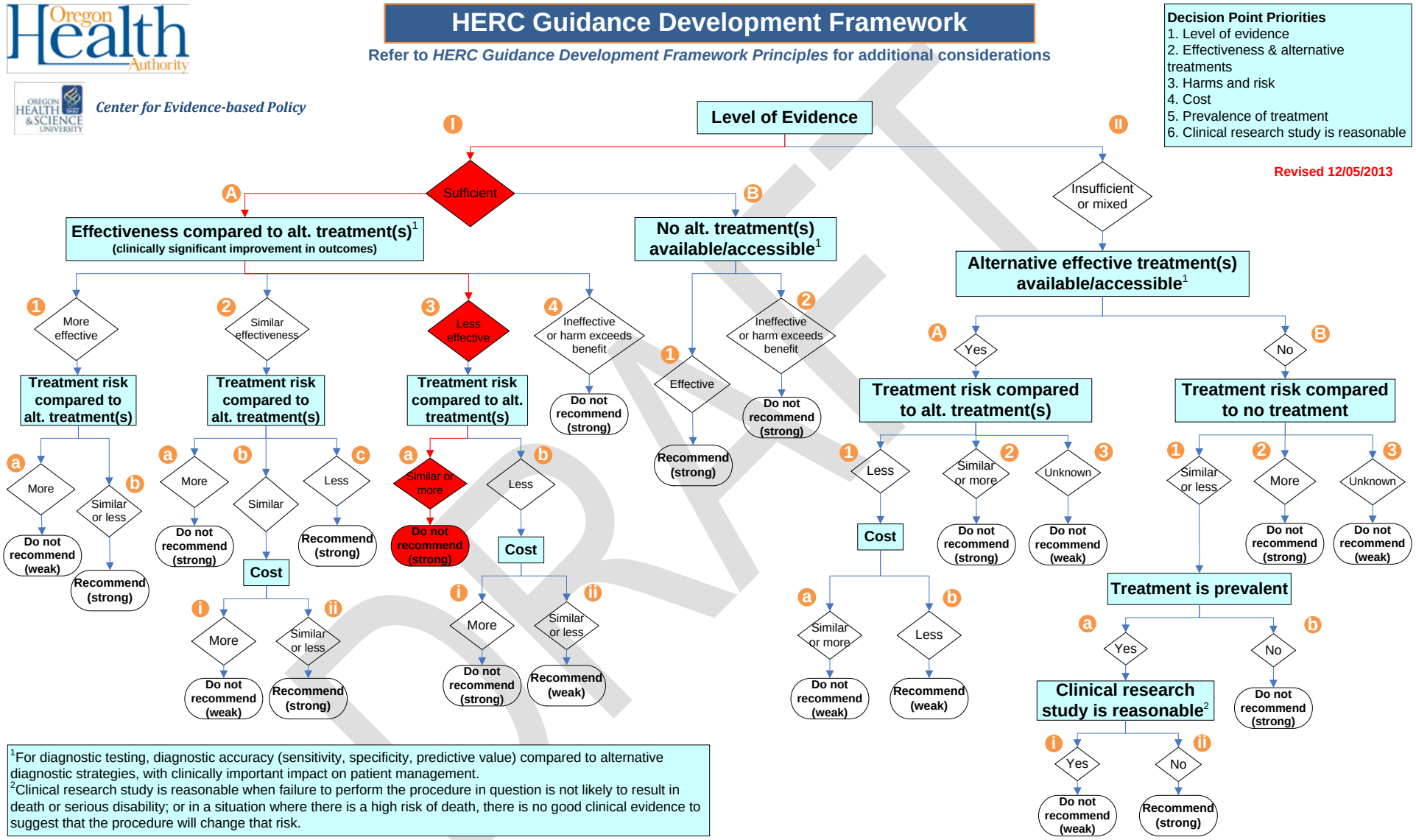
Out of hospital births in unselected pregnancies



[1]For diagnostic testing, diagnostic accuracy (sensitivity, specificity, predictive value) compared to alternative diagnostic strategies, with clinically important impact on patient management.
[2]Clinical research study is reasonable when failure to perform the procedure in question is not likely to result in death or serious disability; or in a situation where there is a high risk of death, there is no good clinical evidence to suggest that the procedure will change that risk.

Final Report to the Director

The Licensed Direct Entry Midwife (LDM) Staff Advisory Workgroup was convened in January 2014 by the Director of the Oregon Health Authority (OHA). The workgroup was established to provide recommendations regarding perinatal services provided to Medicaid enrollees by licensed, direct entry midwives. The workgroup was guided by the Triple Aim goals of improving population health, improving the individual's experience of care and reducing per capita costs. The final recommendations in this report aim to ensure maternal and infant health as well as to provide women with choice in prenatal care and birthing options.

Background: Historical and Policy Context

Direct Entry Midwifery in Oregon

Direct entry midwives (DEMs) typically enter the profession following an apprenticeship and training through self-study, a midwifery school, or a college- or university-based program. Education, experience, and training vary, but all DEMs practice independently in the state of Oregon. DEMs supervise labor and childbirth and provide prenatal, intrapartum and postpartum care to the mother and infant.

In 1993, voluntary licensure for DEMs in Oregon was first established through legislation that additionally enabled licensed direct entry midwives (LDMs) to receive reimbursement through medical assistance programs. The 1993 legislation also created the Board of Direct Entry Midwifery, which establishes and ensures compliance with regulatory standards.[1]

House Bill 2380, passed during the 2011 regular legislative session, added two questions to the Oregon Birth Certificate in order to capture data on the intended location of the birth (e.g., home birth, hospital, etc.) and the intended birth attendant (e.g., direct entry midwife, MD, DO, etc.). With this information the Center for Health Statistics can now provide data to better understand birth outcomes in Oregon. The first report on out-of-hospital births in Oregon was published in October 2013.[2]

HB 2380 also added limited liability language to protect hospitals and physicians against risk following a patient transfer. It states that a person may not bring a cause of action against a licensed physician or hospital for injury to a patient that occurred as a result of care from a DEM, provided that the physician or hospital does not contribute to the injury or is otherwise negligent.

Mandatory licensure of direct entry midwives in Oregon was established in 2013 with passage of House Bill 2997, which requires any direct entry midwife practicing after January 1, 2015 to hold a license. Final licensure conditions will be established by a Rules Advisory Committee. However, the Board of Direct Entry Midwifery already requires that LDMs hold a certified professional midwife (CPM) credential from the North American Registry of Midwives, complete an examination, be certified in infant and adult cardiopulmonary resuscitation, have a written plan for transport of the patient, hold a

[1] Licensure rules, standards, and requirements for direct entry midwives can be found in ORS 687.405.
[2] CD Summary, October 1, 2013,Public Health Division. Accessible at: http://public.health.oregon.gov/DiseasesConditions/CommunicableDisease/CDSummaryNewsletter/Documents/2013/ohd6220.pdf

high school diploma (or equivalent), and attend and participate in, at a minimum: 25 assisted deliveries; 25 deliveries for which the LDM applicant was the primary care provider; 100 prenatal care visits; 25 newborn examinations; and 40 postnatal examinations for licensure.

Additionally, HB 2997 delegated authority to the Board of Direct Entry Midwives for any investigations following complaints, reviews, or other issues related to DEMs

Oregon Births

In 2013 the Oregon Public Health Division published its first report on birth outcomes by planned birth place and attendant.[3] Nearly five percent of women who had a live, term birth in Oregon in 2012 (2,021 out of 42,011 or 4.8%) intended to deliver outside of the hospital (either at home or at a free-standing birthing center). Ultimately, 18% of those planned OOH births occurred in a hospital following transfer of care. As a result, 3.9% of all live term births in Oregon in 2012 were delivered outside of the hospital setting. Licensed direct-entry midwives were the planned birth attendant for 59.1% of the planned OOH births; unlicensed direct entry midwives were the intended birth attendant for an additional 9.7% of planned OOH births. Ultimately, 2.9% of total births in Oregon were attended by LDMs or DEMs in 2012. Women who planned an OOH birth tended to be older, white, married, college-educated, self-pay, less overweight or obese pre-pregnancy, and less likely to smoke.

The Oregon Health Plan (Medicaid) paid for 466 planned OOH births in 2012 (23.3% of all planned OOH births in the state). Currently there are 78 LDMs licensed in the state of Oregon. The vast majority of OOH births delivered by LDMs occur in counties with an urban hub, such as Deschutes County, as well as counties throughout the Willamette Valley (e.g. Washington, Clackamas, Yamhill, Multnomah, Linn, and Lane Counties).

Health System Transformation

Oregon's Coordinated Care Model began implementation in 2011. A foundation of this model, Coordinated Care Organizations (CCOs) serve as umbrella organizations that govern and administer care for Medicaid/Oregon Health Plan (OHP) members in the local community. Health care providers, hospitals, community members, and other stakeholders in the health system participate in the governance of each CCO. Nearly all OHP members are enrolled in a CCO for their medical, behavioral and dental services.

CCOs operate under a flexible global budget. Each CCO is accountable for health outcomes of the population they serve and can use the budget in a manner appropriate to the community and its needs.

To date, CCOs have not credentialed or contracted with LDMs. Leading reasons for this include, but may not be limited to, lack of LDM liability insurance coverage and uncertainty regarding safety and

[3] https://public.health.oregon.gov/BirthDeathCertificates/VitalStatistics/birth/Pages/planned-birth-place.aspx

outcomes for home delivery. Without LDM reimbursement by CCOs, women enrolled in Medicaid are greatly constrained in their ability to choose delivery by a LDM.

Since 2012, the Oregon Health Policy Board (OHPB) and the OHA have received substantial public input requesting access to midwifery care as part of Oregon's Coordinated Care Model, including 137 comments submitted during a public forum (summary of comments available at link below).[4] Currently, the only opportunity for women with Medicaid coverage to obtain covered services by an LDM is through a CCO exemption called the "third trimester rule." This rule allows women who enroll in Medicaid during their third trimester of pregnancy to continue with their established prenatal provider on a fee-for-service basis. This rule will sunset on June 30, 2014. Recommendations put forth by this staff advisory committee will be considered by OHA when addressing the future of this policy.

The LDM Staff Advisory Workgroup

All members of the LDM Staff Advisory Workgroup were appointed by the Director of the OHA based on their experience and perspectives regarding maternity services in Oregon. The ten members of the workgroup are listed below:

Name	Affiliation/Region
Duncan Neilson, MD *Chairperson*	Obstetrician-Gynecologist, Chief of Women's Health Services, Legacy Health
Silke Akerson, LDM, CPM	President, Oregon Midwifery Council; Two Rivers Midwifery
Melissa Cheyney, PhD, LDM, CPM	Chair, Board of Direct Entry Midwifery; Associate Professor, Anthropology, OSU
Shafia Monroe, MPH, DEM, DT	President and CEO, International Center for Traditional Childbearing (ICTC); President and CEO, Shafia Monroe, Consulting
Kelley Kaiser, MPH	CEO, InterCommunity Health Network CCO
Doug Flow, PhD	CEO, All Care Health Plan
John Sattenspiel, MD	Senior Medical Director, Trillium Community Health Plan
Dominique Greco, MD	Family Physician, Providence Seaside Hospital
Kate Pelosi, CNM	Women's Healthcare Associates
Monica Arce, CNM	OB Lead Clinician, Virginia Garcia Memorial Health Center

Additional workgroup participants include: Holly Mercer (Executive Director, Oregon Health Licensing Agency), Wally Shaffer (Medical Director, Division of Medical Assistance Programs, OHA), Chris Barber (Quality and Clinical Services Director, OHA), Dana Hargunani (Child Health Director, OHA; lead workgroup staff), Stephanie Jarem (OHA; workgroup staff). The workgroup met a total of five times between January and April 2014. This report provides a summary of the workgroup recommendations.

[4] http://www.oregon.gov/oha/OHPB/2013MeetingMaterials/December%2011,%202012%20Summary%20of%20Public%20Input.pdf

Final Report to the Director

Issue Identification

Through a facilitated process, the workgroup identified the following priority issues for consideration regarding direct entry midwifery: safety, liability insurance, access, systems of care (care coordination/team-based care), reimbursement, cost containment/cost effectiveness, credentialing, cultural competency, and choice. During the course of their meetings, the workgroup reviewed existing research and other state and national policies regarding DEM services, and heard multiple presentations to guide their work.

Consensus-based Recommendations

The LDM staff advisory workgroup recommends the following set of consensus-based recommendations to integrate LDMs into Oregon's Coordinated Care Model. The recommendations are interconnected and often address multiple overlapping priority issues. The first recommendations are directly related to the Oregon Health Authority. The remaining recommendations will require participation or direction by entities beyond the Oregon Health Authority but are necessary for moving this work forward:

Recommendations for the Oregon Health Authority:

1. **Identify a phased-in approach for including LDMs in Oregon's Coordinated Care Model and CCOs.**

   The workgroup agreed that the incorporation of LDMs into the CCO model is a strategy consistent with the Triple Aim. However, the absence of affordable liability insurance for LDMs is the predominant barrier to CCO credentialing for these practitioners. A phased approach over time is therefore necessary to achieve integration of LDMs into Oregon's Coordinated Care Model. See Diagram 1 for a high-level timeline depicting a phased-in approach towards integration.

2. **When LDM care is not available through a CCO, OHA should establish a Medicaid fee-for-service ("open card") option for women who choose to receive services from LDMs (for duration of pregnancy through 6 weeks post-partum).**

   With acknowledgement that the ultimate goal is to incorporate LDMs into Oregon's coordinated care system, this recommendation aims to provide an interim solution that protects a woman's choice in birthing options. CCOs would not be required to contract with or credential LDMs, but LDMs could still provide maternity care to Medicaid enrollees and receive reimbursement for services in low risk situations (see recommendation #3 below).

   This recommendation enables Medicaid enrollees to choose the fee-for-service "open card" option at the onset of pregnancy in low-risk situations, and ensures that the woman is receiving consistent care throughout the entire pregnancy which can increase safety and quality of care.

   The workgroup acknowledges that a fee-for service option would likely include all aspects of a women's care during this perinatal time period (e.g. not just maternity services). Further work will

be needed to ensure that care is coordinated during any transition between "open card" and prior/future CCO coverage for Medicaid enrollees.

3. **For high risk births, require in-hospital delivery for Medicaid reimbursement. Exclude payment for planned out-of-hospital births when high-risk criteria exist. High-risk criteria should include, at minimum:**
    - **presentation other than cephalic (e.g. breech),**
    - **previous caesarian delivery,**
    - **gestational age < 36 or > 43 weeks,**
    - **multiple gestations,**
    - **diabetes/uncontrolled gestational diabetes or gestational diabetes controlled with medication,**
    - **pre-eclampsia,**
    - **additional criteria included in the applicable provider or facility OARs**

The safety of a mother and fetus throughout the pregnancy and birth is central to this workgroup's efforts. In addition to examining the Public Health Division's 2013 report on planned OOH births, the workgroup discussed additional research on safety and outcomes. The workgroup gave particular attention to two recently published articles from the Journal of Midwifery & Women's Health, both of which explored the Midwives' Alliance of North America's National Data Registry for midwife-led births (see Appendix A).

The workgroup agreed that OOH birth can be safe in the right, low-risk situations. The workgroup recommends that OHA apply high-risk criteria to determine whether a Medicaid enrollee is eligible to have an OOH birth attended by an LDM. These criteria were informed by existing rules for LDM licensure and free-standing birthing centers, in addition to existing evidence relating to OOH outcomes. Ultimately, those deemed low risk would be eligible to choose the "open card" option listed in Recommendation #3.

4. **Provide information to Medicaid members regarding covered options for maternity care (including midwifery care).**

Improving access to care and empowering women in choosing a care provider begins with education and outreach. The workgroup recommends that OHA provide information to Medicaid enrollees regarding all of the covered options for maternity care services.

5. **Request that the Health Evidence Review Commission (HERC) develop a Coverage Guidance related to home birth, including evidence regarding:**
    - **The maternal and fetal/neonatal/child health outcomes of home birth compared with birth in other settings**
    - **Appropriate candidates for home birth**

- **Criteria for optimizing safety with regard to provider training, equipment, standards, consultation, and other systems of care**

The HERC reviews medical evidence, promotes evidence-based medical practices and establishes coverage guidance for high priority issues. With newly published articles and a clearer set of data on Oregon home births, a fresh review of the evidence would be timely and useful to consumers, practitioners, CCOs and the state.

6. **Analyze birth-related costs in Oregon by intended place of birth and provider. Comparative analyses should include immediate and long-term costs of care for women, infants and children.**

A better understanding of the immediate and long-term costs of births (by intended place of birth and provider) would help decipher the true costs and benefits related to midwifery care. The workgroup recognizes that some effects are difficult to quantify (e.g. the costs savings associated with higher rates of breastfeeding).

The State of Washington Department of Health conducted a review on the economic costs and benefits of the midwifery licensure and discipline program in the state. This workgroup recommends that a similar study and analysis be conducted for the state of Oregon.

7. **Work with CCO and hospital partners to explore payment methodologies that support optimum intrapartum care and appropriate and timely transfer.**

The workgroup acknowledges that bundled payments for maternity services may represent an unintended deterrent to timely and safe transfer of care to a hospital when indicated. Exploring new payment methodologies or other opportunities to unbundle reimbursement could further incentivize timely and appropriate transfer of care by out-of-hospital providers including LDMs.

8. **Reconvene the LDM Staff Advisory Workgroup at periodic intervals to assess progress on these recommendations and evaluate new evidence and opportunities for continued integration of LDM services within Coordinated Care Organizations (CCOs).**

Because full integration of LDM services in the Coordinated Care Model will take time, this group recommends that this staff advisory workgroup be periodically reconvened to evaluate progress on these recommendations and consider emerging best practices and data to support an integrated system of maternity care.

Recommendations the Oregon Health Authority could support:

9. **Study options for affordable liability insurance for licensed, direct-entry midwifes (LDMs), including state options such as a joint underwriting association.**

   Malpractice insurance, a prerequisite for providers interested in contracting with CCOs, continues to be unaffordable for the majority of LDMs practicing in the state. Estimates obtained from the leading LDM liability insurance carrier indicated the premium cost for the $1,000,000/$3,000,000 coverage limit commonly required for healthcare providers would likely exceed 25% of an LDM's total annual income. Facing similar barriers, a number of other states have explored options to increase affordability, such as the Washington Joint Underwriting Association.

   This workgroup addressed the issue of liability insurance from a variety of perspectives. Another option that was considered was to implement a liability affidavit/document, modeled after documents from New Mexico, intended to hold the state (and CCOs, if/when applicable) harmless from any claims, demands and actions resulting from services provided to a client by a LDM. Ultimately, the workgroup determined that more information and input from legal experts would be necessary to understand whether this approach offers the intended protections.

10. **Convene a multi-disciplinary workgroup consisting of a variety of stakeholders and experts including LDMs, CNMs, MDs, DOs, and the insurance division, to offer recommendations on overall maternity-related liability reform in the state of Oregon.**

    Access to affordable liability insurance is not limited to DEMs, and can be particularly difficult for any maternity care provider in the state of Oregon. It is recommended that a subsequent workgroup be formed to address access to affordable liability insurance for all Oregon maternity providers.

11. **Support a coordinated system of maternity care. Convene local learning collaboratives across the state to consider and implement best practices for CCO and hospital coordination and collaboration with LDMs, including an emphasis on timely transfer of care.**

    In 2012, 18.8% of the planned OOH births in Oregon were delivered in a hospital. The need for transfer arises regularly, and a smooth transition of care from one provider (LDM) to another will have a positive impact on safety and the experience of the patient and care team. While LDMs are currently required to have a written transport plan for their patients, additional opportunities for improvement exist including more collaborative relationships with hospitals.

    The workgroup heard many examples of collaborative, innovative partnerships and positive relationships that have been established in the state between LDMs and hospitals, Certified Nurse Midwives (CNMs), or other providers who are invested in improving transfer of care. Locally-driven learning collaboratives would provide support and structure for sharing these experiences and

building a coordinated system that encourages safe, high-quality births in all communities across the state.

12. **Support statewide efforts to reduce demand for high-risk out-of-hospital births by improving access to vaginal delivery options for breeches, twins, and vaginal births after caesarian section (VBACs).**

    This workgroup acknowledges that improved access to vaginal delivery within hospital settings (e.g., for breech, twin, and previous caesarian deliveries) may prevent women from attempting to deliver these higher-risk births outside of the hospital. The workgroup recommends that OHA support statewide efforts to improve access to vaginal delivery.

The LDM Staff Advisory Workgroup respectfully submits the above, consensus-based recommendations for consideration by the Oregon Health Authority.

Oregon Birth Outcomes, by Planned Birth Place and Attendant

Pursuant to: HB 2380 (2011)

In 2011, the Oregon Legislature passed House Bill 2380, which required the Oregon Public Health Division to add two questions to the Oregon Birth Certificate to determine planned place of birth and birth attendant, and to report annually on birth outcomes, including death, by location and attendant type. The specific questions were: "Did you go into labor planning to deliver at home or at a freestanding birthing center? If yes, what was the planned primary attendant type at the onset of labor?" In addition, for 2012, the Oregon Public Health Division conducted a special study of deaths in term infants (≥ 37 weeks' gestation) intended to deliver out-of-hospital. The perinatal fatality analysis includes fetal and early neonatal deaths ≥ 37 weeks' estimated gestational age through the first 6 days of life.

Key findings of ***live term births by planned place of birth and planned birth attendant*** (Table 1):

- During 2012, 42,011 live term births[1] occurred in Oregon. Of these 2,021 (4.8%) planned an out-of-hospital birth (home birth or freestanding birthing center).
- Among all live term births, planned birth attendants[2] included: MDs & DOs (78.6%), Certified Nurse Midwives (17.4%), Direct-Entry Midwives (Total 3.0%, Licensed 2.5%, Unlicensed 0.5%), and Naturopathic Physicians (0.5%).
- Among live term births to women who planned out-of-hospital births, planned birth attendants included: Certified Nurse Midwives (24.7%), Direct-Entry Midwives (Total 61.8%, Licensed 52.1%, Unlicensed 9.7%), and Naturopathic Physicians (10.8%).
- 379 of 2,021 (18.8 %) planned out-of-hospital births ultimately delivered in-hospital.

Table 1. Live term births by planned place of birth and planned birth attendant, Oregon occurrence, 2012

Planned Birth Attendant	Term Births				
	Total	Planned Hospital	Planned Out-of-Hospital		
			Total	Intrapartum Transfer to Hospital	Neonatal Transfer
State Total	42,011	39,990	2,021	379	24
MDs and DOs	33,030	33,030	0	0	0
Certified Nurse Midwives	7,319	6,819	500	202	3
All Direct-Entry Midwives	1,249	0	1,249	147	17
(Licensed)	*1,052*	*0*	*1,052*	*85*	*16*
(Unlicensed)	*197*	*0*	*197*	*62*	*1*
Naturopathic Physicians	219	0	219	22	1
Other	194	141	53	8	3

1. Total excludes 79 term births that occurred en route, were unplanned home births, or other out-of-hospital births not otherwise characterized.
2. For planned hospital births, actual attendant is used. For planned out-of-hospital births with intrapartum transfer to hospitals, planned attendant type is reported by mother and not verified.

Oregon Health Authority

Key findings of ***term fetal and early neonatal deaths by planned place of birth and planned birth attendant*** (Table 2):

- 62 term (≥ 37 weeks' gestation) fetal deaths occurred in Oregon during 2012; 4 (6.5%) of these occurred among planned out-of-hospital births.
- 30 term early neonatal deaths (during the first 6 days of life) occurred in Oregon during 2012; 4 (13.3%) of these occurred among planned out-of-hospital births.
- In total, 92 term fetal and early neonatal deaths occurred in Oregon during 2012; 8 (8.7%) occurred among planned out-of-hospital births. These 8 deaths underwent a fetal and neonatal mortality case review per published national guidelines. (See www.nfmir.org.)

Table 2. Term fetal deaths and early neonatal deaths by planned place of birth and planned birth attendant, Oregon occurrence, 2012*

Planned Birth Attendant	Term Fetal Deaths			Term Early Neonatal Deaths			Term Fetal + Early Neonatal Deaths		
	Total	Planned Hospital	Planned Out-of-Hospital	Total	Planned Hospital	Planned Out-of-Hospital	Total	Planned Hospital	Planned Out-of-Hospital
State Total	62	58	4	30	26	4	92	84	8
MDs and DOs	49	49	0	22	22	0	71	71	0
Certified Nurse Midwives	8	8	0	5	4	1	13	12	1
All Direct-Entry Midwives	3	0	3	3	0	3	6	0	6
(Licensed)	*2*	*0*	*2*	*2*	*0*	*2*	*4*	*0*	*4*
(Unlicensed)	*1*	*0*	*1*	*1*	*0*	*1*	*2*	*0*	*2*
Naturopathic Physicians	1	0	1	0	0	0	1	0	1
Other	1	1	0	0	0	0	1	1	0

* 2012 Oregon birth and death certificate data; final data will be available in Winter 2013. March 2013 report included an additional neonatal death that upon review did not meet case definition and was therefore excluded from this report.

Key findings of ***maternal characteristics of term births by planned place of birth*** (Table 3):

- 2,021 (4.8%) mothers planned an out-of-hospital birth.
- Women who planned out-of-hospital births compared to women who planned in-hospital births tended to be:
  - ◊ Older (57.2% vs. 42.5% aged 30 years and older)
  - ◊ White, non-Hispanic (87.7% vs. 67.7%)
  - ◊ Married (82.1% vs. 64.3%)
  - ◊ College-educated (45.9% vs. 29.0%)
  - ◊ Self-pay delivery (28.2 % vs. 1.0%)
  - ◊ Less overweight or obese pre-pregnancy (32.3% vs. 49.1%)
  - ◊ Less likely to smoke (2.1% vs. 10.6%).
- Women who planned out-of-hospital births compared to women who planned in-hospital births were more likely to have no prenatal care (2.8% vs. 0.4%) or inadequate prenatal care (9.8% vs. 4.8%), and less likely to begin prenatal care in the first trimester (63.6% vs. 76.6%).

Table 3: Maternal characteristics of term births by planned place of birth, Oregon occurrence, 2012

Selected Maternal Characteristics	Total Births	Planned Hospital Birth		Planned Out-of-Hospital Birth	
		No.	Pct.	No.	Pct.
Total Term Births	42,011	39,990	N/A	2,021	N/A
Mother's Age (years)					
< 20	2,682	2,655	6.6	27	1.3
20-24	9,027	8,801	22.0	226	11.2
25-29	12,207	11,594	29.0	613	30.3
30-34	11,346	10,619	26.6	727	36.0
35-39	5,530	5,181	13.0	349	17.3
40+	1,219	1,140	2.9	79	3.9
Single Mention Race/Ethnicity					
White	28,838	27,065	67.7	1,773	87.7
African American	815	806	2.0	9	0.4
American Indian	460	439	1.1	21	1.0
Asian/Hawaiian/Pacific Islander	2,311	2,271	5.7	40	2.0
Other/Multiple Races	1,406	1,354	3.4	52	2.6
Hispanic	7,979	7,867	19.7	112	5.5
Marital Status					
Married	27,385	25,726	64.3	1,659	82.1
Unmarried	14,618	14,257	35.7	361	17.9
Mother's Education					
8th grade or less	1,741	1,731	4.3	10	0.5
Some high school	4,949	4,887	12.2	62	3.1
High school graduate/GED	9,391	9,048	22.6	343	17.0
Some college	10,232	9,692	24.2	540	26.7
Associate's Degree	3,193	3,055	7.6	138	6.8
Bachelor's Degree	7,781	7,190	18.0	591	29.2
Postbaccalaureate	4,724	4,387	11.0	337	16.7
Source of Payment					
Medicaid/Oregon Health Plan	18,588	18,122	45.5	466	23.3
Private Insurance	21,621	20,710	52.0	911	45.6
Self-Pay	956	392	1.0	564	28.2
Other Coverage	634	575	1.4	59	3.0
Initiation of Care					
1st Trimester	31,450	30,169	76.6	1,281	63.6
2nd Trimester	8,197	7,638	19.4	559	27.7
3rd Trimester	1,565	1,446	3.7	119	5.9
No Care	213	157	0.4	56	2.8
Prenatal Care*					
Adequate	38,295	36,490	95.2	1,805	90.2
Inadequate	2,046	1,850	4.8	196	9.8
Pre-pregnancy Body Mass Index					
Underweight (< 18.5)	1,376	1,305	3.3	71	3.6
Normal (18.5 - 24.9)	19,799	18,532	47.5	1,267	64.1
Overweight (25.0 - 29.9)	10,246	9,842	25.2	404	20.4
Obese (> 30.0)	9,545	9,309	23.9	236	11.9
Maternal Tobacco Use					
Tobacco Use During Pregnancy	4,264	4,221	10.6	43	2.1

* Adequate care: Care that began in the first or second trimester and included at least five visits.
Inadequate care: No care, or care that began in the third trimester or fewer than five visits.

Key findings of ***characteristics of labor & delivery, and maternal & infant health characteristics of term births by planned place of birth*** (Table 4):

- Women who planned out-of-hospital births compared to women who planned in-hospital births tended to have lower rates of medical intervention including:
- Epidural/Spinal Anesthesia (11.4% vs. 70.4%)
- Vacuum-assisted delivery (0.8% vs. 2.7%)
- Primary Cesarean delivery (5.9% vs. 16.1%)
- Women who planned out-of-hospital births were less likely to be tested for Group B streptococcal during pregnancy compared to women who planned in-hospital births (81.5% vs. 97.2%).

Table 4: Characteristics of labor & delivery, and maternal & infant health characteristics of term births by planned place of birth, Oregon occurrence, 2012

Selected Medical and Health Characteristics	Total Births	Planned Hospital Birth		Planned Out-of-Hospital Birth	
		No.	Pct.	No.	Pct.
Total Term Births	**42,011**	**39,990**	**N/A**	**2,021**	**N/A**
Characteristics of Labor and Delivery					
Premature Rupture of Membrane (≥12 hours)	2,241	2,068	5.2	173	8.6
Precipitous Labor (<3 hours)	2,248	2,062	5.2	186	9.2
Prolonged Labor (≥ 20 hours)	1,235	1,074	2.7	161	8.0
Induction/Augmentation of Labor	19,205	18,956	47.4	249	12.3
Epidural/Spinal Anesthesia	28,388	28,157	70.4	231	11.4
Non-vertex Presentation	1,539	1,512	3.8	27	1.3
Moderate/Heavy Meconium Staining	2,039	1,938	4.8	101	5.0
Fetal Intolerance of Labor	1,477	1,433	3.6	44	2.2
Chorioamnionitis	843	823	2.1	20	1.0
Neonatal Transfer	274	250	0.6	24	1.2
Method of Delivery					
Vaginal	28,558	26,790	67.0	1,768	87.5
Forceps	224	216	0.5	8	0.4
Vacuum	1,089	1,072	2.7	17	0.8
VBAC (Vaginal birth after Cesarean section)	904	817	2.0	87	4.3
Primary Cesarean section	6,555	6,436	16.1	119	5.9
Repeat Cesarean section	4,681	4,659	11.7	22	1.1

continued on next page

Table 4: Characteristics of labor & delivery, and maternal & infant health characteristics of term births by planned place of birth, Oregon occurrence, 2012 (continued)

Selected Medical and Health Characteristics	Total Births	Planned Hospital Birth		Planned Out-of-Hospital Birth	
		No.	Pct.	No.	Pct.
Maternal Conditions					
Multiples	677	664	1.7	13	0.6
Diabetes-Gestational	2,899	2,864	7.2	35	1.7
Diabetes-Chronic	295	293	0.7	2	*
Hypertension-Chronic	566	559	1.4	7	0.3
Hypertension-Gestational	2,210	2,186	5.5	24	1.2
Eclampsia	207	203	0.5	4	*
Group B Streptococcal Test	39,263	38,123	97.2	1,140	81.5
Maternal Transfusion	192	180	0.5	12	0.6
Perineal Laceration	506	482	1.2	24	1.2
Ruptured Uterus	13	12	*	1	*
Admission to Intensive Care	46	44	0.1	2	*
Unplanned Operating Room Procedure	208	191	0.5	17	0.8
Characteristics of Infant					
Immediate Assisted Ventilation	1,328	1,254	3.1	74	3.7
Assisted Ventilation 6+ hours	193	179	0.4	14	0.7
Admission to NICU	1,375	1,332	3.3	43	2.1
Surfactant Therapy	15	15	*	3	*
Antibiotics	666	639	1.6	27	1.3
Seizure	20	18	*	2	*

* Percentages based on a small number of events may be unreliable and are suppressed.

Key findings of ***perinatal fatality case review of term births planned to occur out-of-hospital:***

- 4 term fetal and 4 early neonatal deaths occurred during 2012 among women who planned to deliver out-of-hospital (Table 2).
- Planned birth attendants: Certified Nurse Midwife (1), Licensed Direct-Entry Midwives (4), Unlicensed Midwife (1), Undetermined Licensure Midwife (1), and Naturopathic Physician (1).
- Median birth weight: 3515 grams
- Maternal characteristics were similar to the larger group of planned out-of-hospital births (Table 3).
- Two pregnancies had inadequate or no prenatal care.
- Chart review noted that, among perinatal deaths:
  - ◊ 2 pregnancies were twin gestations
  - ◊ 4 mothers declined prenatal ultrasound (to confirm gestation and identify pathology.)
  - ◊ 5 mothers declined Group B streptococcal testing (to identify women who are carriers of GBS; treatment during labor is recommended to decrease the risk of early GBS neonatal sepsis.)
  - ◊ 2 mothers declined prophylaxis during labor for Group B streptococcal positive tests.
- 6 of 8 transferred to the hospital during labor:
  - ◊ Indications for transfer to a hospital from home or birthing center included (multiple causes may apply): loss of fetal heart tones (3), prolonged labor (2), decreased fetal movement (2), and malpresentation (2).
  - ◊ One mother initially declined transfer during labor despite recommendation by birth attendant.
- 6 of 8 pregnancies did not meet published low-risk criteria for out-of-hospital birth*:
  - ◊ More than 41 weeks gestation (4)
  - ◊ Twin gestation (2)
  - ◊ Morbid obesity (> 40 BMI) (1)
  - ◊ Planned attendants among these 6: Certified Nurse Midwife (1), Licensed Direct-Entry Midwives (3), Unlicensed Midwife (1), and Naturopathic Physician (1).
- Causes of death and major contributing factors (more than one may apply):
  - ◊ Hypoxic ischemic encephalopathy or cardiorespiratory failure (lack of blood flow) (3)
  - ◊ Chorioamnionitis (infection in the womb) (3)
  - ◊ Pre-existing, or pregnancy-related maternal disease (2)
  - ◊ Respiratory failure (1)
  - ◊ Undetermined, umbilical cord wrapped around neck, large baby (1)
  - ◊ Undetermined, twin gestation, small baby (2)
- The term perinatal mortality rate for planned out-of-hospital births (4.0/1,000 pregnancies) was nearly twice that of in-hospital births (2.1/1,000).

* Planned home birth. Committee Opinion No. 476. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2011;117:425–428. Low-risk criteria: gestational age ≥ 36 weeks and ≤41 completed weeks of pregnancy, singleton, vertex position, and absence of preexisting or pregnancy-related maternal disease. See also College of Midwives of British Columbia, Canada; Australian College of Midwives; Obstetric Working Group of the National Health Insurance Board of the Netherlands (2009).

Birth attendant definitions:

- Certified Nurse Midwives (CNMs) are registered nurses who have graduated from a nurse-midwifery education program and have passed a national certification examination to receive the professional designation of certified nurse-midwife. They are licensed with the Oregon Board of Nursing.
- Direct-Entry Midwives (DEM) are independent practitioners educated in the discipline of midwifery through self-study, apprenticeship, a midwifery school, or a college- or university-based program distinct from the discipline of nursing.
  - ◊ A Licensed Direct Entry Midwife (LDM) is licensed to practice in a particular jurisdiction (usually a state or province).
- Birth Attendants also include: Medical Doctors (MDs), Doctors of Osteopathic Medicine (DOs), and Naturopathic Doctors (NDs).
- Other Midwife may include the uncertified or unlicensed midwife who was educated through informal routes such as self-study or apprenticeship rather than through a formal program. Other similar terms are traditional midwife, traditional birth attendant, granny midwife and independent midwife.

Prepared by Oregon Public Health Division, 8/30/2013

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HEALTH EVIDENCE REVIEW COMMISSION (HERC)

COVERAGE GUIDANCE: NUCLEAR CARDIAC IMAGING

DRAFT for EbGS meeting materials 9/4/2014

HERC COVERAGE GUIDANCE

PET is not recommended for coverage for screening or diagnosis of coronary artery disease (CAD) *(strong recommendation).*

Single photon emission computed tomography (SPECT) is not recommended for coverage for screening ~~of~~ for CAD in asymptomatic patients *(strong recommendation).*

SPECT is not recommended for coverage for diagnosis or risk stratification of CAD *(strong recommendation)*—except in patients for whom stress imaging is required and stress ECHO is contraindicated or would provide suboptimal imaging*)

**i.e. pre-existing cardiomyopathy, baseline regional wall motion abnormalities, left bundle branch block, paced rhythm, unsuitable acoustic windows due to body habitus, inability to utilize dobutamine in a setting where exercise is not possible or when the target workload is not achievable*

Note: Definitions for strength of recommendation are provided in Appendix A GRADE Element Description

RATIONALE FOR GUIDANCE DEVELOPMENT

The HERC selects topics for guideline development or technology assessment based on the following principles:

- Represents a significant burden of disease
- Represents important uncertainty with regard to efficacy or harms
- Represents important variation or controversy in clinical care
- Represents high costs, significant economic impact
- Topic is of high public interest

Coverage guidance development follows to translate the evidence review to a policy decision. Coverage guidance may be based on an evidence-based guideline developed by the Evidence-based Guideline Subcommittee or a health technology assessment developed by the Heath Technology Assessment Subcommittee. In addition, coverage guidance may utilize an existing evidence report produced by one of HERC's trusted sources, generally within the last three years.

DRAFT

EVIDENCE SOURCE

Washington State Health Care Authority Health Technology Assessment Program. (2013). *Cardiac Nuclear Imaging.* Olympia, WA: Health Technology Assessment Program. Retrieved December 2, 2013, from http://www.hca.wa.gov/hta/Pages/nuclear.aspx

The summary of evidence in this document is derived directly from this evidence source, and portions are extracted verbatim.

SUMMARY OF EVIDENCE

Clinical Background

Coronary artery disease (CAD) is among the most common chronic conditions in the U.S., affecting over 16 million adults. Due to its prevalence, and because several options (e.g., surgery, medication) exist to reduce CAD-related morbidity and mortality, accurate diagnosis and/or risk stratification of CAD is critical. Currently the definitive standard for diagnosis is invasive coronary angiography. Because angiography primarily documents the anatomic presence of significant stenosis rather than identifying the "culprit" lesions likely to cause an adverse cardiovascular event, a growing number of non-invasive tests have been developed to identify CAD lesions significant enough to affect the flow of blood to the heart (i.e., myocardial perfusion). These functional tests are typically performed under exercise- or pharmacologically induced stress to determine whether blood flow deteriorates when the stressor is introduced.

The most common tests of cardiac function include the stress-electrocardiogram (ECG), or treadmill test (ETT), which measures cardiac activity via electrical signals, and the echocardiogram (ECHO), which uses ultrasound to measure abnormalities in heart wall motion using 2-dimensional imagery. ETT has fallen out of favor for use in patients at higher risk of CAD, however, as it has relatively low sensitivity in these patients, while stress-ECHO has been found to lack precision in detecting single-vessel versus multi-vessel disease and may produce suboptimal imagery in obese patients, those with chronic respiratory conditions, and patients with chest deformities or pre-existing myocardial damage.

To address some of these concerns, "nuclear imaging tests" have been developed to provide perfusion data in a broader spectrum of patients. The most longstanding of these is single photon emission computed tomography (SPECT), which uses a radioactive tracer and gamma camera to obtain 3-dimensional images of tracer uptake; areas of poor uptake are associated with abnormal levels of perfusion. Positron emission tomography (PET) scanners are also used with a radiotracer, and are felt by some to provide better image resolution in heavier patients and those with dense breast

tissue. So-called “hybrid” modalities have also been introduced to visualize both perfusion abnormalities and anatomic lesions using CT or MRI imagery in addition to nuclear testing.

There are trends in the use of cardiac nuclear imaging tests that are currently points of controversy, however. For one, the use of nuclear imaging for cardiovascular testing has grown substantially in recent years. In addition, questions have been raised about the appropriateness of nuclear imaging in certain populations. A substantial decrease in the prevalence of abnormal findings on such tests has been observed over time, due in part to greater recognition and treatment of cardiac risk factors but also to possible changes in referral patterns. This combination of substantial growth in utilization of cardiac nuclear imaging and declining rates of “positive” test results raises questions about the populations and indications for which such testing is appropriate.

Evidence Review

In the Washington HTA report, “symptomatic” means a patient with symptoms suggestive of myocardial ischemia (symptoms not specified). Risk categories of low, moderate and high were defined by the authors based on the Diamond-Forrester model of pretest probability, which incorporates age, gender and type of chest pain. These categories equate to probability ranges of <10%, 10-90% and >90% respectively. However, when other risk classification systems were used in the included studies, that information was utilized and reported by the authors.

Comparative Clinical Effectiveness

Asymptomatic Patients at High Risk of CAD

The one available study assessing the impact of cardiac nuclear imaging in asymptomatic, high-risk patients found no difference between SPECT screening and no screening in mortality or cardiovascular events, although many patients in both groups received subsequent stress testing for clinical reasons over approximately 5 years of follow-up. SPECT screening did increase the short-term rates of referral for angiography and revascularization vs. no screening.

Symptomatic Patients at Low-to-Intermediate Risk of CAD

Correlation of Imaging Study Findings with Mortality and Cardiovascular Events
Rates of mortality and major cardiac adverse events (MACE) did not generally differ between imaging modalities in available studies. Patients in the WOMEN study, an RCT of 772 women randomized to SPECT or ETT-based testing strategies were at very low CAD risk. The rates of all major adverse cardiovascular events at 2 years were 1.7% and 2.3% for ETT and rest/stress SPECT respectively, but this difference was not

significant (Hazard Ratio [HR]: 1.3; 95% CI: 0.5, 3.5; p=.59). The rate of revascularization also did not statistically differ between groups.

The long-term prognostic value of exercise SPECT, exercise ECHO, ETT, and clinical parameters was measured in a single cohort of 248 patients who were followed for a mean of 3.7 years. A total of 64 MACE occurred during follow-up. In multivariate analyses examining the incremental impact of (1) clinical + ETT data; (2) data in (1) + rest ECHO data; (3) data in (1) + exercise ECHO data; and (4) data in (1) + exercise SPECT data on predicting MACE events, the area under the curve[1] did not statistically differ between the SPECT and ECHO models (0.78 and 0.77 respectively), but was significantly (p<.05) higher than the base model (0.68) or the rest ECHO model (0.72).

One study evaluated the impact on all-cause mortality of normal findings on stress-only vs. stress/rest SPECT protocols in nearly 17,000 low-to-intermediate risk patients followed for a median of 4.5 years. Annualized unadjusted mortality rates were statistically-significantly greater in the stress/rest group (2.92% vs. 2.57% for stress-only, p=.02); however, this difference was no longer apparent after multivariate adjustment for differences in baseline characteristics. The authors conclude that a stress/rest protocol may be unnecessary in lower-risk individuals.

Downstream Testing and Clinical Decision-Making

The impact of testing on downstream resource utilization and clinical decisions was evaluated only in the WOMEN study. Over 2 years of follow-up, repeat testing with the same modality was more frequent in the SPECT group vs. ETT (9% vs. 3%), although this difference was not statistically tested. However, 18% of women randomized to ETT crossed over to SPECT during follow-up. The overall rate of referral to angiography was higher in the ETT group (9.0% vs. 5.5% for SPECT, p<.0001). Changes in the use of nitrates, beta-blockers, and antidepressant therapies during follow-up did not differ between the two arms in the study.

Health-related Quality of Life

The impact of testing on health-related quality of life (HrQOL) also was examined only in the WOMEN study. Similar proportions of women in each treatment group reported “excellent” or “very good” QoL as well as “best” or “average” life satisfaction, with no statistical differences between groups. There were also no statistically-significant differences between ETT and SPECT groups in relation to changes in any of the subscales.

[1] This measure refers to the receiver operating characteristic (ROC) curve, a figure depicting the power of a diagnostic test. It includes both test sensitivity and specificity. A ROC curve for a perfect test has an area under the ROC curve of 1.0, while a test that performs no better than chance has an area under the curve of 0.5.

Symptomatic Patients at High Risk of CAD

Correlation of Imaging Study Findings with Mortality and Cardiovascular Events
In high risk populations, some differences in event rates by modality were apparent. An RCT of ETT vs. SPECT in 457 intermediate-to-high risk patients focused primarily on the period between testing and diagnosis, but did report on the rate of revascularization, which occurred more frequently in the ETT group (18% vs. 11% for SPECT, not statistically tested). In the "SPARC" registry, a study comparing short-term outcomes of PET, SPECT and coronary CT angiography (CCTA), revascularization rates at 90 days did not materially differ between PET and SPECT, regardless of whether findings were mildly or moderately-severely abnormal. Neither of these studies evaluated longer term outcomes such as mortality or cardiovascular events.

Another study assessed the prognostic value of both dobutamine ECHO and dobutamine SPECT in 301 patients who were unable to exercise and were at intermediate-to-high risk of CAD; patients were followed for a mean of 7.3 years. Event-free survival was significantly better for patients with normal vs. abnormal findings on both tests, and did not differ statistically between tests. In multivariate models based on clinical data, stress testing, and imaging results, abnormal findings on either SPECT or ECHO were the strongest predictors of both cardiac death (HR [95% CI]: 4.4 [1.2, 21.0] and 3.4 [1.2, 12.0] for SPECT and ECHO respectively) and cardiac events (3.1 [1.1, 8.9] and 2.6 [1.1-6.2] respectively).

Downstream Testing and Clinical Decision-Making
Two studies reported on the effects of testing on downstream resource use and/or clinical decisions. Of the 207 patients randomized to ETT in one RCT, a total of 146 (71%) were referred for further testing (47% to angiography and 23% to stress ECHO). In contrast, further testing was requested in only 16% of patients randomized to SPECT, all of which were angiography procedures ($p<.0001$ for the comparison). ETT also appeared to generate more false-positives for significant CAD. Only 38% of ETT patients referred to angiography were revascularized, vs. 66% of SPECT patients so referred ($p<.05$).

In a registry study, referral for angiography occurred in a greater percentage of PET patients (11.1% vs. 4.3% for SPECT; $p<.001$). In multivariate analyses controlling for patient characteristics, comorbidities, and testing location, imaging modality was significantly and positively correlated with referral to angiography for PET (OR: 5.0; 95% CI: 1.0, 24.4) in comparison to SPECT. Neither PET nor SPECT were associated with significant medication changes.

Health-Related Quality of Life
There were no studies in symptomatic, high-risk individuals that reported on the impact of cardiac nuclear imaging tests on HrQoL.

Known CAD

Correlation of Imaging Study Results with Mortality and Cardiovascular Events
One comparative cohort study compared the rate of revascularization in 2,951 patients with known CAD and left ventricular dysfunction and (1) who had been tested with SPECT before referral for angiography; (2) were tested with SPECT only after a positive angiography; or (3) had no SPECT before or after angiography. The rate of revascularization differed significantly (p=.001) among groups, with the lowest rate of 35.8% seen in postangiography SPECT patients, 45.6% in patients who had SPECT pre-angiography, and 53.2% among patients undergoing angiography with SPECT neither before nor afterward.

Downstream Testing and Clinical Decision-Making
In one study, 100 consecutive patients, 79% of whom had known CAD, underwent rest-stress PET perfusion testing. Physicians were first queried on proposed patient management strategies without PET perfusion data; actual patient management was measured 4 weeks after PET. Proposed patient management was altered in 78% of patients. Most prominently, conservative medical management was initially proposed in 28% of patients; after PET testing, 76% were managed this way in actuality. In addition, use of angiography to guide treatment via PTCA was proposed in 6%, but was performed in 20% after PET testing.

Health-Related Quality of Life
There were no studies in patients with known CAD that reported on the impact of cardiac nuclear imaging tests on HrQoL.

No comparative studies evaluating the impact of serial nuclear imaging in asymptomatic patients with known CAD were identified.

Mixed Populations

The largest number of studies was available for populations that did not fit neatly into the categories described above. They represented a true “mix” of patients based on relatively uniform distributions by risk or pretest probability, presence or absence of symptoms, and/or inclusion of patients with known vs. suspected CAD. A total of 10 studies were identified.

Correlation of Imaging Study Results with Mortality and Cardiovascular Events
Data on mortality and cardiovascular events were available in 8 studies. The Cost-Effectiveness of Functional Cardiac Testing (CeCAT) Trial was an RCT comparing multiple diagnostic strategies—rest-adenosine stress SPECT, ECHO (dobutamine stress), adenosine stress cardiac magnetic resonance imaging (cardiac MR), and direct referral to angiography—among 898 primarily high-risk patients with known or suspected CAD and stable symptoms of ischemia who were referred to a tertiary center

in the UK for angiography and were followed for 18 months. In this study, the number of total, cardiac, and noncardiac deaths did not statistically differ by imaging modality. When compared with the referent angiography group, the number of nonfatal adverse cardiac *events* did not differ for SPECT or cardiac MR, but was statistically-significantly higher for ECHO (relative risk [RR]: 1.95; 95% CI: 1.23, 3.08; p=.012), primarily because of more admissions for chest pain. When the number of *patients* reporting adverse cardiac events was compared, however, no significant differences were observed (one patient in the ECHO group was responsible for seven hospital admissions).

Findings from a study comparing PET and SPECT were somewhat mixed. No differences in cardiovascular mortality or the rate of MI were observed between groups. However, the rates of CABG (3.4% vs. 7.8%, p<.01) and any revascularization (6.0% vs. 11.4%, p<.01) were statistically-significantly lower for PET vs. the internal (identified by report authors) SPECT control group. The rate of any revascularization was also significantly lower in comparison to the external (using results from another published trial) SPECT control group (6.0% vs. 13.0%, p<.0001).

Three cohort studies comparing the prognostic ability of SPECT and ECHO generally showed comparable results for both tests. No statistical differences between imaging modalities in event rates or event-free survival were observed in 2 studies. In the third, an evaluation of exercise stress ECHO vs. exercise stress SPECT in 206 symptomatic veterans who received both tests and were followed for up to 10 years, moderate-to-large ischemia on ECHO was the strongest independent predictor of overall mortality (RR: 6.2; p<.0001), cardiovascular death (RR: 17.6; p=.01), congestive heart failure (RR: 17.4; p=.0005), or sudden death (RR: 26.8; p=.003). The presence of moderate-to-large fixed defects on SPECT was the strongest independent predictor of nonfatal MI (RR: 8.1; p=.0002) and unstable angina (RR: 3.0; p=.005).

One study assessed the predictive capability of functional data from ETT, exercise stress SPECT, and the “Gensini score” from angiography evaluation in 732 patients who were followed for a mean of 3.5 years. Abnormal results on SPECT and the Gensini score were significantly (p≤.01) associated with poorer event-free survival, while ETT data were not. Analyses of the receiver operator curve (ROC) for events indicated that SPECT was the strongest independent predictor of events (0.67 vs. 0.61 and 0.46 for Gensini score and ETT, p<.05).

Downstream Testing and Clinical Decision-Making

A total of three studies examined the impact of cardiac nuclear imaging on further testing and clinical decision-making. In the CeCAT trial, the proportions of patients in the SPECT, ECHO, and cardiac MR groups who were referred to angiography ranged between 75-80% and did not statistically differ between groups; in addition, decisions on

further invasive or medical management were also similar. The rate of referral to angiography in the study comparing PET and SPECT was statistically-significantly lower for PET (13%) in comparison to both the internal (identified by report authors) and external (using results from another published trial) SPECT groups (31% and 34% respectively, p<.0001). The rate of angiography negative results was also significantly lower for PET vs. internal SPECT controls (5.2% vs. 15.6%, p<.0001).

Finally, a hypothetical referral rate to angiography was assessed in 955 patients undergoing ETT and rest-exercise stress SPECT. Algorithms using ETT data alone, SPECT data alone, and a combination of the 2 tests were applied. An estimated 27% of patients would have been referred to angiography based on ETT results alone, vs. 13% for SPECT data alone and 12% using both ETT and SPECT data (p<.01 for both comparisons to ETT alone). Findings were similar when compared among patients without known CAD.

Health-Related Quality of Life
HrQoL was assessed in the CeCAT trial. While some statistically-significant differences were noted in certain subscales at particular time points, improvements in HrQoL were clinically comparable across testing groups for all measures.

Diagnostic Accuracy

A total of 8 studies were available that examined the accuracy of cardiac nuclear imaging tests in relation to a functional reference standard. This is currently believed to be a more accurate method to determine whether a defect noted on non-invasive imaging relates to CAD that is functionally-significant—that is, likely to be the cause of an adverse cardiovascular event if not treated. Recent research has raised questions about the use of anatomic data on angiography to confirm findings of functional tests such as ECHO, SPECT, and PET. There is nevertheless a large body of evidence evaluating the accuracy of noninvasive functional tests using visualization of coronary arteries as the reference standard.

One of the most widely-cited meta-analyses compared the diagnostic accuracy of exercise ECHO and exercise SPECT based on 44 studies. Pooled sensitivity of the 2 tests was similar (85% and 87% for ECHO and SPECT respectively), but pooled specificity was rated higher for ECHO (77% vs. 64% for SPECT, p<.05). However, substantial heterogeneity in study populations, imaging protocols, and SPECT radiotracers was noted for this sample; subsequent reanalysis with controls for heterogeneity found no statistical differences between the tests.

Methods to assess diagnostic accuracy have also evolved, and feature newer techniques designed to capture the natural correlation between sensitivity and specificity. A recent meta-analysis using newer bivariate methods found that ECHO was

slightly more sensitive than SPECT (87% vs. 83% respectively), while SPECT was somewhat more specific (77% vs. 72% for ECHO). An additional bivariate meta-analysis using a much larger set of 113 SPECT studies found greater sensitivity (88%) and similar specificity (76%), although other commentators have noted that the older SPECT studies included in this review were subject to “verification bias” (i.e., use of the reference standard only in test-positive or other selected individuals), which tends to inflate sensitivity and may also reduce specificity. This meta-analysis also included estimates of diagnostic accuracy from 9 PET studies (pooled estimates of 93% and 81% for sensitivity and specificity respectively).

Finally, a third recent meta-analysis estimated diagnostic performance from 114 SPECT and 15 PET studies. SPECT sensitivity was similar to that reported elsewhere (88%), but specificity was somewhat lower (61%). Sensitivity and specificity for PET was estimated to be 84% and 81% respectively.

Other Outcomes

Extracardiac Findings

With the enhanced imagery available for many noninvasive tests, incidental findings outside of the area of interest can be problematic given the additional resources required for investigation. The reported rate of incidental extracardiac findings is very low with nuclear imaging tests given the limited field of detection, however; most available studies are limited to case reports of mediastinal masses. One recent study compared the rate of such findings between CCTA and SPECT in 479 patients; extracardiac findings requiring further investigation were detected in 7% of CCTA patients but in no SPECT patients (p=.0001). Another analysis examined images of 2,155 patients undergoing SPECT studies, 6 (0.3%) of whom had extracardiac findings requiring follow-up. Four of the 6 patients had malignancies requiring further treatment. No PET studies reported on extracardiac findings.

While SPECT itself is associated with a low rate of extracardiac findings, the increasing use of CT for attenuation correction may result in increased detection of these findings. In a cohort study assessing prevalence of extracardiac findings from 582 SPECT/CT studies, a total of 400 (68.7%) included noncardiac findings, 196 (33.7%) of which were felt to be potentially relevant.

Equivocal/Indeterminate Results

While equivocal or indeterminate findings are possible with any diagnostic test, these results are rarely published. A recent systematic review of nearly 1,200 diagnostic accuracy studies found that 35% reported the presence of inconclusive results. Inconclusive results were reported in only one of the studies in this report. In the CeCAT

trial comparing SPECT with ECHO, cardiac MR, and angiography, rates of equivocal findings were 4.0%, 6.6%, 6.6% and 2.0% respectively.

Risks of Testing

Patients appear to be at minimal immediate risk from cardiac nuclear imaging tests in and of themselves, although harms data are reported in only a small number of comparative studies. The risks that are reported are related primarily to the stressor employed (i.e., exercise or pharmacologic stress).

Comparative Data on Testing Risks

Only 2 studies compared adverse effects of multiple testing modalities. In the WOMEN study that randomized patients to ETT or exercise SPECT, no statistically significant differences between groups were noted in rates of chest pain, dyspnea, or fatigue after testing. In the CeCAT trial comparing SPECT, ECHO, cardiac MR, and angiography, specific reasons for failed tests were recorded. Failure to complete the test due to adverse effects occurred in 4 ECHO patients (1.8%), due to vasovagal reactions, blood pressure changes and dyspnea; no patient failed to complete SPECT due to adverse effects.

Adverse Effects by Stressor

Information on adverse effects attributed to specific stressors was obtained from 15 studies. Regardless of the comparisons made, events were typically described as non-serious and resolved once the stressor infusion ended. Reported ranges of adverse effects were similar across pharmacologic agents. Limited data suggest lower rates of adverse effects for exercise vs. pharmacologic stress in the 2 studies making this comparison, although statistical comparisons were not available for all event types.

Radiation Exposure

Potential adverse health effects associated with radiation exposure are important factors to consider in the evaluation of cardiac nuclear imaging tests, particularly because patients may already be exposed to radiation at other points along the diagnostic pathway (e.g., CCTA, angiography), cumulative radiation dose may be substantial in patients receiving serial imaging studies, and imaging alternatives such as ECHO and cardiac MR exist that do not involve radiation. Radiation dose is a measure of ionizing energy absorbed per unit of mass, expressed as units of Gy (Gray) or mGy; it often is quoted as an equivalent “effective” dose to major organs in the scanned area, in units of Sv (Sievert) or mSv. For x-rays, the radiation type produced by CT scanners, 1 mSv = 1 mGy. Average total effective dosages for SPECT range from 7 to 30 mSv, while for PET and CCTA the range is 2 to 14 mSv, and for invasive coronary angiography the range for is 5 to 7. While exposure to ionizing radiation at these levels

is associated with potential increase in cancer risk, the latency period for the development of such cancers may range from 10 to 40 years for solid tumors depending on the age and sex of the patient being tested. The intended use of cardiac imaging tests then becomes a critical consideration.

Differential Effectiveness/Safety for Key Patient Subgroups

The *comparative* impact of cardiac nuclear imaging tests vs. alternative testing strategies in certain subgroups is presented below.

Patient Age, Sex, Race or Ethnicity, and Comorbidities

A single comparative cohort study was available that assessed all-cause mortality for stress only vs. stress-rest SPECT (n=16,854) in specific subgroups over a mean of 4.5 years of follow-up. On a univariate basis, stress-rest protocols were associated with a statistically-significantly higher mortality rate in older (age >65) individuals, men, patients with a BMI <30 kg/m2, and patients with diabetes. However, after multivariate adjustment for baseline characteristics, no statistically-significant differences remained. Several large cohort studies and meta-analyses have assessed the performance of SPECT in certain patient subgroups. For example, several studies have found that SPECT's diagnostic and prognostic performance is similar for women and men. Comparable results have also been found in several large ECHO studies. A meta-analysis of risk-stratification studies in over 13,000 patients age >65 years found that both stress SPECT and stress ECHO accurately risk-stratified patients vs. ETT. A multicenter cohort study of approximately 1,100 patients found that SPECT results were predictive of cardiac events in both Caucasian and African-American patients.

Analyses comparing patients with and without diabetes suggest that, while diabetes is a predictor of mortality for any nuclear imaging result, SPECT testing provides incremental prognostic information in patients with and without diabetes alike. Multiple studies have found that SPECT is feasible and has comparable diagnostic and prognostic performance in normal-weight, overweight, and obese patients. Finally, a meta-analysis of SPECT and ECHO studies in hypertensive patients showed diagnostic accuracy similar to that observed in all patients with suspicion of CAD.

Clinical Setting

In a comparison of stress-only vs. stress-rest SPECT, mortality was initially statistically-significantly higher in stress-rest patients in an inpatient setting. After multivariate adjustment, however, no significant differences remained. Limited additional data are available explicitly comparing the performance of SPECT by setting. One study evaluating the potential benefit of an emergency department chest pain clinic estimated that unnecessary hospitalizations would be reduced in 30% of patients and inappropriate discharges avoided in 6% through the use of a selective SPECT protocol.

Selection of Test by Primary Care vs. Specialty Physician

No study assessed the impact of ordering specialty on patient outcomes, clinical decision-making, or costs. There are, however, several studies that have assessed the impact of specialty on whether ordered cardiac SPECT studies meet published appropriate use criteria (AUC). In a multicenter assessment of an online SPECT appropriateness classification system, one study found that the rate of inappropriate studies was statistically-significantly higher among non-cardiologists (19.5% vs. 13.2% for cardiologists, p<.0001). Similar findings have been observed in several single center studies. Of note, most inappropriate ordering of SPECT perfusion studies appears to have occurred in women, younger patients, and/or those without symptoms.

Scan Vendor, Type of Assessment, Type of Radioisotope, and Type of Stressor

No study assessed the impact of scan vendor or qualitative vs. quantitative assessment on patient outcomes, clinical decision-making, or costs. Most of the studies evaluating differences according to stressor type focused on rates of adverse effects of pharmacologic testing. The study that evaluated stress-only vs. stress-rest SPECT found no statistically-significant effects on mortality with subgroups defined by exercise vs. pharmacologic stress.

Two studies examined the impact of different SPECT radiotracers on outcomes. In one, a total of 1,818 patients underwent exercise or pharmacologic stress SPECT with Tc-99m sestamibi or Tc-99m tetrofosmin. Patients were followed for a mean of 1.5 years, during which no statistically-significant differences were observed between groups in the rates of overall mortality, cardiovascular mortality, or the composite endpoint of cardiovascular mortality or nonfatal MI.

The other study compared mortality outcomes among 2,147 patients with known CAD undergoing pharmacologic stress SPECT with either Tc-99m sestamibi or Tc99m tetrofosmin who were followed for a median of 4 years. During follow-up, a total of 704 all-cause deaths (493 cardiovascular-related) were reported. There was no significant difference in either overall or cardiovascular mortality between radiotracer groups on both an unadjusted and multivariate-adjusted basis.

Analysis of Comparative Value

Limited evidence is available that directly measured and compared the economic impact of non-invasive testing strategies for CAD. Three RCTs compared costs of SPECT to other imaging. In the only economic study performed in the US, an RCT of ETT vs. SPECT in 772 women at low-to-intermediate risk of CAD in 43 cardiology practices across the U.S., total mean costs of testing over 2 years were higher in the SPECT arm ($643 vs. $338, p<.001), as the higher costs of initial SPECT testing outweighed the increased costs of downstream testing in the ETT arm. In another 2-year RCT

conducted in 457 primarily intermediate-risk patients in the UK, however, downstream testing costs were substantially higher in the ETT arm, leading to significantly higher total costs from randomization to diagnosis using National Health Service (NHS) estimates ($1,244 v $743 for SPECT, p<.001). The final UK RCT compared costs of initial and repeat testing, treatment, and adverse events over 18 months of follow-up for mixed-risk patients randomized to SPECT, ECHO, cardiac MR, or direct referral to angiography. Direct referral to angiography was the lowest-cost strategy. Incremental costs (relative to angiography) were similar for the SPECT and cardiac MR strategies (~$650), but were twice as high for patients in the ECHO group (~$1,250) due to a higher rate of hospital readmissions.

Economic evidence for PET was limited to 2 studies. In one, an evaluation of planned vs. actual management before and after PET perfusion testing in 100 patients with known CAD, savings from reduced need for angiography were greater than the incremental costs of PET testing and revascularization, leading to overall savings of $240 per patient. In the other, a matched comparative cohort analysis of PET and SPECT, mean costs of all diagnostic testing were approximately $2,500 in both groups, but greater requirements for revascularization at 1 year led to higher total costs in the SPECT group ($5,937 vs. $4,110 for PET).

Because evidence is limited comparing the short-term clinical consequences and costs for all relevant non-invasive strategies for CAD diagnosis, the authors of this report developed a decision-analytic model to provide additional information. The target population involved men and women with suspected or known CAD who had stable symptoms of myocardial ischemia (i.e., atypical or typical chest pain or other symptoms such as dyspnea). Model outcomes and costs were estimated over a 90-day period. The authors of the Washington HTA report developed 7 different strategies, alone and in combination, to capture a wide range of management approaches:

1. ECHO, followed by invasive coronary angiography if ECHO is positive or inconclusive
2. ETT, followed by angiography if ETT is positive or inconclusive
3. SPECT, followed by angiography if ETT is positive or inconclusive
4. PET, followed by angiography if ETT is positive or inconclusive
5. ETT, followed by ECHO if ETT is positive or inconclusive, followed by angiography if the ECHO is positive or inconclusive
6. ETT, followed by SPECT if ETT is positive or inconclusive, followed by angiography if the SPECT is positive or inconclusive
7. ETT, followed by PET if ETT is positive or inconclusive, followed by angiography if the PET is positive or inconclusive

Because the underlying CAD prevalence varies in different patient populations, the authors calculate results of the identical testing strategies for a population with 10%, 30%, 50% and 70% CAD prevalence. Comparing these results demonstrates the importance of the underlying prevalence on the relative balance of false negatives, false positives, rates of referral to angiography, and costs. For example, among a patient population with a CAD prevalence of 10%, the difference in false negatives between SPECT and ECHO almost vanishes (4 per 1,000). In contrast, the difference in false positives between SPECT and ECHO in a population with 50% CAD prevalence was 33 per 1,000 but is increased to 60 per 1,000 when the underlying prevalence of CAD is only 10%. The relative differences in angiography referral, patients exposed to radiation, and costs also shift.

The authors of this report have devised their own evidence rating system, and reach the following conclusions for specific populations:

- Asymptomatic, high-risk individuals
    - SPECT vs. no screening – high certainty of a comparable net health benefit, low value
    - SPECT vs. ETT or ECHO – insufficient evidence
    - PET vs. any alternative – insufficient evidence
- Symptomatic individuals at low-to-intermediate CAD risk
    - SPECT vs. ETT – moderate certainty of a comparable net health benefit, low value
    - SPECT vs. ECHO – high certainty of a comparable net health benefit, reasonable/comparable value
    - PET vs. any alternative – insufficient evidence
- Symptomatic individuals at high CAD risk
    - SPECT vs. ETT – moderate certainty of a small net health benefit, reasonable/comparable value
    - SPECT vs. ECHO – high certainty of a comparable net health benefit, comparable/reasonable value
    - PET vs. any alternative – insufficient evidence
- Known CAD
    - SPECT vs. ETT – insufficient evidence
    - SPECT vs. ECHO – high certainty of a comparable net health benefit, comparable/reasonable value

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- PET vs. any alternative – insufficient evidence

[Evidence Source]

Evidence Summary

In **asymptomatic individuals** at high risk of CAD, there is no evidence of benefit for SPECT screening compared to no screening. In **symptomatic patients at low to intermediate risk of CAD**, evidence is conflicting with regard to ability to predict mortality and cardiovascular events, with one study finding no difference between ETT and SPECT, and another finding that stress SPECT and stress ECHO were better predictors than ETT and rest ECHO. In **symptomatic patients at high risk of CAD**, evidence is conflicting regarding rates of revascularization in those who undergo ETT compared to SPECT. Prognostic value does not differ between stress ECHO and stress SPECT. In **populations with mixed risk of CAD**, stress SPECT, stress ECHO, stress CMR and angiography do not differ in subsequent death or patient reported adverse cardiac events. SPECT and ECHO have similar prognostic abilities, and those tests as well as cardiac MR result in similar proportions of referrals to angiography or change in medical management.

With regard to diagnostic accuracy, SPECT and ECHO have similar sensitivity (83% to 87%) and specificity (64% to 77%), although some analyses suggest that ECHO may be slightly more sensitive and SPECT may be slightly more specific. Extracardiac findings (which may require additional evaluation) are identified rarely with SPECT, and significantly less frequently than CCTA.

Comparative evidence on the risks of various testing strategies is very limited, with the only apparent difference being that exercise stress has lower rates of adverse events than pharmacologic stress. SPECT has the highest radiation exposure of any testing strategy at a range of 7 to 30 mSv. SPECT appears to perform similarly in men and women, Caucasians and African-Americans, normal weight and obese patients, those with and without diabetes and those with and without hypertension.

Evidence is conflicting regarding the value of ETT compared to SPECT. One study suggests that direct referral to angiography is the most cost effective strategy, with SPECT and cardiac MR being of moderate cost, and ECHO being the most costly. Another analysis finds that SPECT has low value compared to no screening in an asymptomatic population and compared to ETT in a low-to-intermediate risk population, and has comparable value compared to ECHO in all other populations.

The evidence pertaining to PET is insufficient to draw conclusions for any outcome.

GRADE-INFORMED FRAMEWORK

The HERC develops recommendations by using the concepts of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. GRADE is a transparent and structured process for developing and presenting evidence and for carrying out the steps involved in developing recommendations. There are four elements that determine the strength of a recommendation, as listed in the table below. The HERC reviews the evidence and makes an assessment of each element, which in turn is used to develop the recommendations presented in the coverage guidance box. Balance between desirable and undesirable effects, and quality of evidence, are derived from the evidence presented in this document, while estimated relative costs, values and preferences are assessments of the HERC members.

Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Variation in values and preferences	Coverage recommendation	Rationale
SPECT in asymptomatic at high risk of CAD	No net benefit, potential harm of radiation	High	Moderate	Low variability	Not recommended for coverage (strong recommendation)	Sufficient evidence of no net benefit, potential harms due to radiation, and higher cost.
SPECT in symptomatic with low/mod risk of CAD	Comparable to ETT and ECHO; potential harms from radiation	Moderate (ETT) High (ECHO)	Moderate	Moderate variability	Not recommended for coverage (strong recommendation)	Sufficient evidence of no net benefit, potential harms due to radiation. **
SPECT in symptomatic with high risk of CAD	Small health benefit compared to ETT, comparable to ECHO but potential harms from radiation	Moderate (ETT) High (ECHO)	Moderate	Moderate variability	*SPECT vs. ETT* Not recommended for coverage (weak recommendation) *SPECT vs. ECHO* Not recommended for coverage (strong recommendation)	*SPECT vs. ETT* Sufficient evidence of small net benefit over ETT, may outweigh potential harms due to radiation, upgrading algorithmic derived recommendation against from “strong” to “weak”. *SPECT vs. ECHO*** Sufficient evidence of no net benefit, potential harms due to radiation.

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Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Variation in values and preferences	Coverage recommendation	Rationale
SPECT in known CAD	Unknown compared to ETT Comparable to ECHO but potential harms from radiation	Insufficient (ETT) High (ECHO)	Moderate	Moderate variability	Not recommended for coverage (strong recommendation)	*SPECT vs. ETT* Insufficient evidence, but has potential risks of radiation exposure, unlike alternatives, and is higher cost. *SPECT vs. ECHO*** Sufficient evidence of no net benefit, potential harms due to radiation.
PET in all populations	Unknown compared to all interventions	Insufficient	High	Low variability	Not recommended for coverage (strong recommendation)	Insufficient evidence; also has potential risks of radiation exposure, unlike alternatives and is higher cost.

*The Quality of Evidence rating was assigned by the primary evidence source, not the HERC Subcommittee

**Expert input let to the decision to recommend coverage for SPECT when stress echo may be contraindicated or provide suboptimal imaging, in the following circumstances: pre-existing cardiomyopathy, baseline regional wall motion abnormalities, left bundle branch block, paced rhythm, unsuitable acoustic windows due to body habitus, inability to utilize dobutamine in a setting where exercise is not possible or when the target workload is not achievable

Note: GRADE framework elements are described in Appendix A

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POLICY LANDSCAPE

There were no quality measures that pertained to this topic identified when searching the National Quality Measures Clearinghouse.

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 (the Center). This document is intended to guide public and private purchasers in Oregon in making informed decisions about health care services.

The Center is not engaged in rendering any clinical, legal, business or other professional advice. The statements in this document do not represent official policy positions of the Center. Researchers involved in preparing this document have no affiliations or financial involvement that conflict with material presented in this document.

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Appendix A. GRADE Element Descriptions

Element	Description
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
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—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

Strong recommendation

In Favor: The subcommittee is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Against: The subcommittee is confident that the undesirable effects of adherence to a recommendation outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Weak recommendation

In Favor: The subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Against: The subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Quality or strength of evidence rating across studies for the treatment/outcome[2]

***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 RCTs with few or no limitations and the estimate of effect is likely stable.

***Moderate*:** The subcommittee is moderately confident in the effect estimate: 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 effect estimate 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 effect estimate: 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.

[2] Includes risk of bias, precision, directness, consistency and publication bias

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Appendix B. Applicable Codes

CODES	DESCRIPTION
ICD-9 Diagnosis Codes	
402.0-402.9	Hypertensive heart disease
411.0	Postmyocardial infarction syndrome
411.1	Intermediate coronary syndrome (impending infarction, preinfarction angina, preinfarction syndrome, unstable angina
411.8	Other acute and subacute forms of ischemic heart disease
411.81	Acute coronary occlusion without myocardial infarction
411.89	Other acute and subacute forms of ischemic heart disease, other
413.0	Angina decubitus (nocturnal angina)
413.1	Prinzmetal angina (variant angina pectoris)
413.9	Other and unspecified angina pectoris (NOS, cardiac, equivalent, of effort, angina syndrome, status anginosus, stenocardia, syncope anginosa)
428.0	Congestive heart failure, unspecified
428.1	Left heart failure
428.20	Systolic heart failure, unspecified
428.21	Acute systolic heart failure
428.22	Chronic systolic heart failure
428.23	Acute on chronic systolic heart failure
428.30	Diastolic heart failure, unspecified
428.31	Acute diastolic heart failure
428.32	Chronic diastolic heart failure
428.33	Acute on chronic diastolic heart failure
428.40	Combined systolic and diastolic heart failure, unspecified
428.41	Acute combined systolic and diastolic heart failure
428.42	Chronic combined systolic and diastolic heart failure
428.43	Acute on chronic combined systolic and diastolic heart failure
428.9	Heart failure, unspecified (cardiac failure, NOS, heart failure NOS, myocardial failure NOS, weak heart
429.2	Cardiovascular disease, unspecified
429.3	Cardiomegaly
429.4	Functional disturbances following cardiac surgery
429.7	Certain sequelae of myocardial infarction not elsewhere classified
429.79	Certain sequelae of myocardial infarction not elsewhere classified, other
429.83	Takotsubo syndrome
429.9	Heart disease, unspecified
786.50	Chest pain, unspecified
ICD-9 Volume 3 (Procedure Codes)	
92.05	Cardiovascular scan and radioisotope function study
CPT Codes	
75557	Cardiac magnetic resonance imaging for morphology and function without

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CODES	DESCRIPTION
	contrast material
75559	with stress imaging
75561	Cardiac magnetic resonance imaging for morphology and function without contrast material(s), followed by contrast material(s) and further sequences
75563	with stress imaging
75565	Cardiac magnetic resonance imaging for velocity flow mapping (List separately in addition to code for primary procedure)
75571	Computed tomography, heart, without contrast material, with quantitative evaluation of coronary calcium
75572	Computed tomography, heart, with contrast material, for evaluation of cardiac structure and morphology (including 3D image postprocessing, assessment of cardiac function, and evaluation of venous structures, if performed)
75573	Computed tomography, heart, with contrast material, for evaluation of cardiac structure and morphology in the setting of congenital heart disease (including 3D image postprocessing, assessment of LV cardiac function, RV structure and function and evaluation of venous structures, if performed)
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)
78452	multiple studies, at rest and/or stress (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)
78454	multiple studies, at rest and/or stress (exercise or pharmacologic) and/or redistribution and/or rest reinjection
78459	Myocardial imaging, positron emission tomography (PET), metabolic evaluation
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
78473	multiple studies, wall motion study plus ejection fraction, at rest and stress (exercise and/or pharmacologic), with or without additional quantification
78481/3	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)
78491	Myocardial imaging, positron emission tomography (PET), perfusion; single study at rest or stress
78492	multiple studies at rest and/or stress
78499	Unlisted cardiovascular procedure, diagnostic nuclear medicine

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CODES	DESCRIPTION
93000	Electrocardiogram, routine ECG with at least 12 leads; with interpretation and report
93005	tracing only, without interpretation and report
93010	interpretation and report only
93015	Cardiovascular stress test using maximal or submaximal treadmill or bicycle exercise, continuous electrocardiographic monitoring, and/or pharmacological stress; with supervision, interpretation and report
93016	supervision only, without interpretation and report
93017	tracing only, without interpretation and report
93018	interpretation and report only
93350	Echocardiography, transthoracic, real-time with image documentation (2D), includes M-mode recording, when performed, during rest and cardiovascular stress test using treadmill, bicycle exercise and/or pharmacologically induced stress, with interpretation and report
93351	including performance of continuous electrocardiographic monitoring, with supervision by a physician or other qualified health care professional
93454	Catheter placement in coronary arter(s) for coronary angiography, including intraprocedural injection(s) for coronary angiography, imaging supervision and interpretation
93455	with catheter placement(s) in bypass graft(s) (internal mammary, free arterial, venous grafts) including intraprocedural injection(s) for bypass graft angiography
93456	with right heart catheterization
HCPCS Level II Codes	
A9500	Technetium tc-99m sestamibi, diagnostic, per study dose
A9502	Technetium tc-99m tetrofosmin, diagnostic, per study dose
A9505	Thallium tl-201 thallous chloride, diagnostic, per millicurie
A9526	Nitrogen n-13 ammonia, diagnostic, per study dose, up to 40 millicuries
A9555	Rubidium rb-82, diagnostic, per study dose, up to 60 millicuries
A9560	Technetium tc-99m labeled red blood cells, diagnostic, per study dose, up to 30 millicuries
J0280	Injection, aminophyllin, up to 250 mg
J0461	Injection, atropine sulfate, 0.01 mg
J0151	Injection, adenosine for diagnostic use, 1 mg
J1245	Injection, dipyridamole, per 10 mg
J1250	Injection, dobutamine hydrochloride, per 250 mg
J2785	Injection, regadenoson, 0.1 mg

Note: Inclusion on this list does not guarantee coverage

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Appendix C. HERC Guidance Development Framework

HERC Guidance Development Framework Principles

This framework was developed to assist with the decision making process for the Oregon policy-making body, the HERC and its subcommittees. It is a general guide, and must be used in the context of clinical judgment. It is not possible to include all possible scenarios and factors that may influence a policy decision in a graphic format. While this framework provides a general structure, factors that may influence decisions that are not captured on the framework include but are not limited to the following:

- Estimate of the level of risk associated with the treatment, or any alternatives;
- Which alternatives the treatment should most appropriately be compared to;
- Whether there is a discrete and clear diagnosis;
- The definition of clinical significance for a particular treatment, and the expected margin of benefit compared to alternatives;
- The relative balance of benefit compared to harm;
- The degree of benefit compared to cost; e.g., if the benefit is small and the cost is large, the committee may make a decision different than the algorithm suggests;
- Specific indications and contraindications that may determine appropriateness;
- Expected values and preferences of patients.

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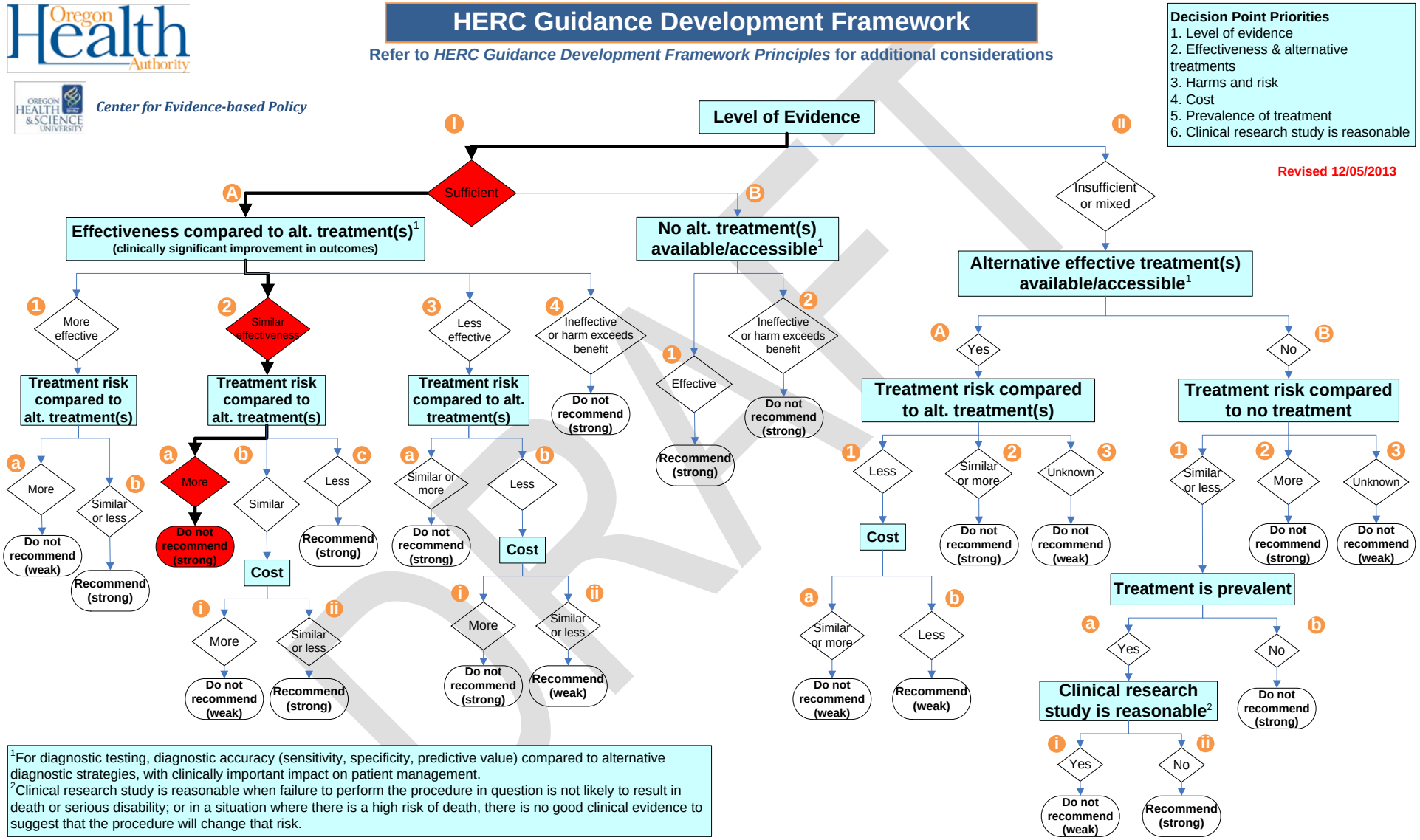
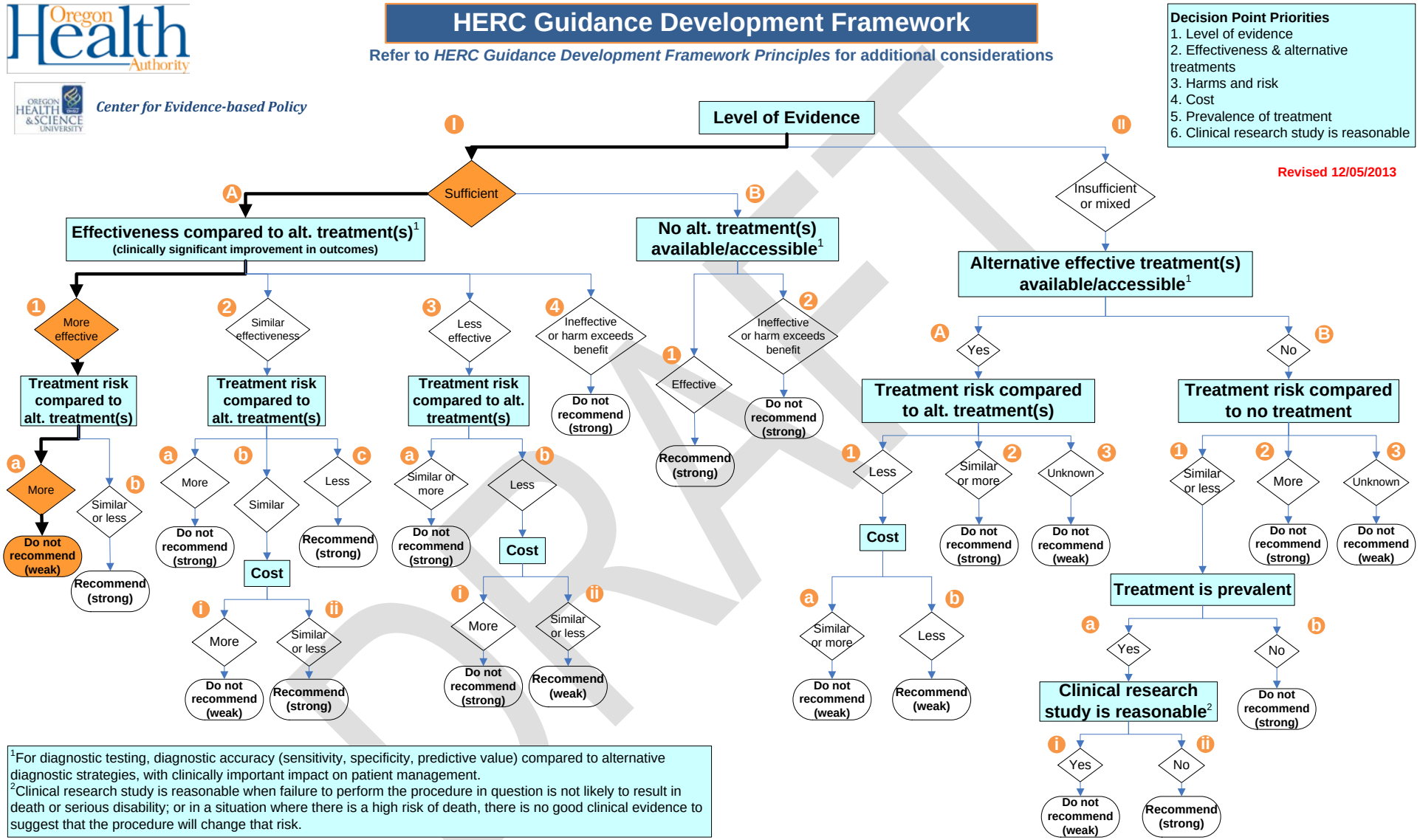
SPECT in: Asymptomatic at high risk of CAD; Symptomatic with low/mod risk of CAD (compared to ETT and ECHO); Symptomatic with high risk of CAD (compared to ECHO); Known CAD (compared to ECHO)

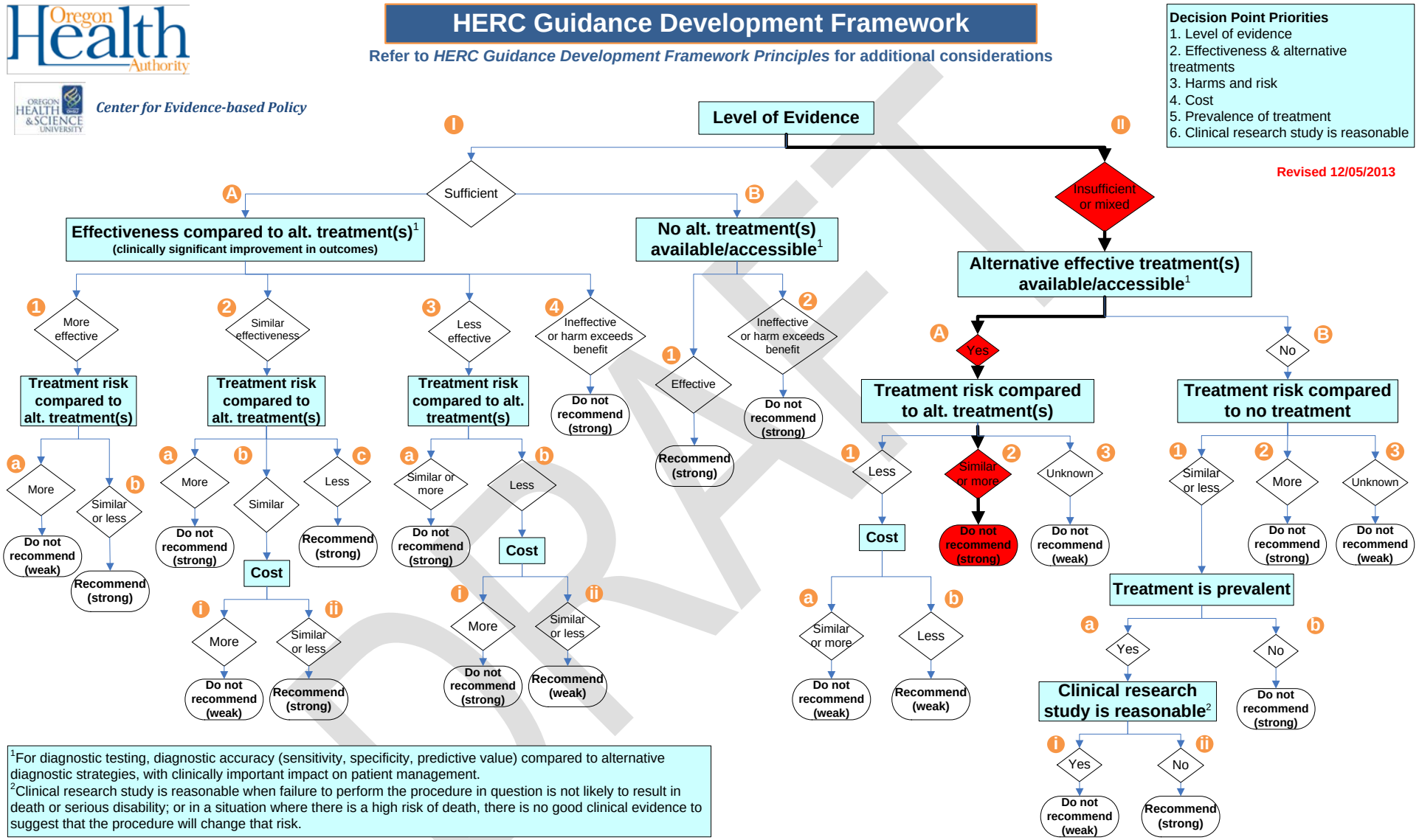


[1]For diagnostic testing, diagnostic accuracy (sensitivity, specificity, predictive value) compared to alternative diagnostic strategies, with clinically important impact on patient management.
[2]Clinical research study is reasonable when failure to perform the procedure in question is not likely to result in death or serious disability; or in a situation where there is a high risk of death, there is no good clinical evidence to suggest that the procedure will change that risk.

SPECT in symptomatic with high risk of CAD (compared to ETT)



SPECT in known CAD (compared to ETT); PET in all populations



[1]For diagnostic testing, diagnostic accuracy (sensitivity, specificity, predictive value) compared to alternative diagnostic strategies, with clinically important impact on patient management.
[2]Clinical research study is reasonable when failure to perform the procedure in question is not likely to result in death or serious disability; or in a situation where there is a high risk of death, there is no good clinical evidence to suggest that the procedure will change that risk.

HERC Coverage Guidance – Nuclear Cardiac Imaging
Disposition of Public Comments

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Commenters

Identification	Stakeholder
A	Medical Imaging and Technology Alliance, Arlington, VA [*Submitted July 23, 2014*]
B	Oregon Chapter of the American College of Cardiology, the American College of Cardiology, the American Society of Nuclear Cardiology, the Society of Nuclear Medicine and Molecular Imaging, and the Society of Cardiovascular Computed Tomography [*Submitted July 24, 2014*]

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Public Comments

Ident.	#	Comment	Disposition
A	1	The Medical Imaging and Technology Alliance (MITA) is pleased to submit comments on the Oregon Health Evidence Review Commission (HERC) draft guidance for Nuclear Cardiac Imaging posted on June 25, 2014. As the leading trade association representing medical imaging, radiotherapy, and radiopharmaceutical manufacturers, MITA has in-depth knowledge of the significant benefits to the health of Americans that medical imaging and radiotherapy provide.	Thank you for taking the time to comment and providing this background.
A	2	Myocardial perfusion imaging is an important and established technology which has provided great benefit to patients suffering from coronary artery disease (CAD) for decades. By using a radiopharmaceutical to pinpoint perfusion defects, cardiologists/doctors are able to identify areas of blockages in the coronary arteries and to determine severity of disease.	EbGS is aware of the value of myocardial perfusion imaging (MPI).
A	3	Because the value of myocardial perfusion imaging is widely acknowledged, we are concerned that the limitations introduced by the draft guidance would negatively affect access to this timely and important modality for your beneficiaries. Instead, we urge you to adopt the established Appropriate Use Criteria (AUC) for Cardiac Radionuclide Imaging (attachment 1). This document represents years of extensive and careful consideration of numerous studies representing thousands of patients and the cumulative experience of experts in cardiology. To wit, the AUC Task Force comprises expertise from the American Society of Nuclear Cardiology, the American College of 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, the Society of Nuclear Medicine and has been endorsed by the American College of Emergency Physicians.	Methodology of appropriate use criteria is a combination of literature review and expert opinion. Neither aspect meets HERC standards as an appropriate data source to override 'trusted source' systematic reviews such as those provided by AHRQ or WA HTA. Panel members were "asked to refer to the relevant guidelines for a summary of the relevant literature". Relationships to industry were reported (and extensive) but not managed in any stated way. Indications for MPI are rated by panel members as "appropriate", "uncertain", or "inappropriate". A total of eight clinical scenarios were rated. The following received "appropriate" scores: • Detection of CAD: symptomatic; evaluation of ischemic equivalent (nonacute) if ECG uninterpretable or unable to exercise, or intermediate or high probability of CAD; • Detection of CAD: symptomatic; acute chest pain (5 different scenarios for possible ACS); • Detection of CAD/risk assessment: without ischemic equivalent; asymptomatic if high risk OR new onset heart failure with LV systolic

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Ident.	#	Comment	Disposition
			dysfunction OR ventricular tachycardia OR syncope OR elevated troponin; • Risk assessment with prior test results and/or known chronic stable angina; prior non-invasive evaluation inconclusive OR new/worsening symptoms OR angiography with coronary stenosis of uncertain significance OR asymptomatic with coronary calcium score 100 to 400 and high risk, or >400 OR duke treadmill score intermediate or high risk; • Risk assessment: Preoperative evaluation for vascular surgery; • Risk assessment: within 3 months of an ACS; • Risk assessment: postrevascularization; • Assessment of viability/ischemia in ischemic cardiomyopathy; and • Evaluation of ventricular function. The following comment is made pertaining to other imaging modalities: "technical panel members were asked to rate indications for cardiac RNI in a manner independent and irrespective of the prior published ACCF ratings for SPECT MPI (1) as well as the prior ACCF ratings for similar diagnostic stress imaging modalities, such as stress echocardiography (2), cardiac computed tomography, or cardiac magnetic resonance (3). Given the iterative nature of the process, readers are counseled not to compare too closely individual appropriate use ratings among modalities rated at different times over the past 2 years."
A	4	Finally, each patient is unique and, by following the AUC instead of more rigid criteria, decision-making would rightly take place between the physician and the patient to determine the best path for the individual patient's care, which may or may not include nuclear cardiac imaging at a particular decision point.	EbGS is aware of the uniqueness of patients, but that does not obviate the need for development of coverage policy.

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Ident.	#	Comment	Disposition
A	5	In consideration of the established Appropriate Use Criteria for nuclear cardiac imaging, we strongly recommend that you reconsider your draft guidance and instead follow the AUC as developed by medical professional societies.	*For EbGS discussion*
B	1	The Oregon Chapter of the American College of Cardiology, the American College of Cardiology, the American Society of Nuclear Cardiology, the Society of Nuclear Medicine and Molecular Imaging and the Society of Cardiovascular Computed Tomography appreciate the opportunity to provide comments on the Health Evidence Review Commission's (HERC) Coverage Guidance on Nuclear Cardiac Imaging (NCI).	Thank you for taking the time to comment.
B	2	We strongly disagree with the HERC's draft coverage recommendations for NCI as well its attempting to define a selection algorithm between two appropriate and indicated tests. We do not feel that the algorithm will improve upon the judgment of the ordering physician, lower costs or improve outcomes.	The algorithm (Guidance Development Framework) is a tool to assist the HERC with development of coverage recommendations. It does not apply to individual patients or specific clinical situations.
B	3	We strongly urge the HERC to adopt the recommendations finalized last year by the Washington State Health Care Authority Health Technology Assessment Program on this matter.	The WA HTA decision is as follows: Cardiac Nuclear Imaging is a covered benefit with conditions including: - SPECT - Covered for patients with symptoms of myocardial ischemia (symptomatic) who are: • At high risk of coronary artery disease (CAD), or • At low to intermediate risk of CAD, and o Have abnormal/indeterminate exercise treadmill test (ETT), or o Unable to perform ETT, or o ECG abnormality that prevents accurate interpretation of ETT - For patients with known CAD, monitoring: • Changes in symptoms - PET - Covered under the same conditions as SPECT when: • SPECT is not technically feasible; or • SPECT is inconclusive

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Ident.	#	Comment	Disposition
			Non-Covered Indicators - Cardiac Nuclear Imaging is not a covered benefit for: • Asymptomatic patients* • Patients with known CAD and no changes in symptoms *Does not apply to pre-operative evaluation of patients undergoing high-risk non-cardiac surgery or patients who have undergone cardiac transplant.
B	4	First, we would like to highlight the paper, Appropriate Use Criteria for Cardiac Radionuclide Imaging, published in JACC Vol. 53, No 23, 2009 (June 9, 2009, pages 2201-29), a copy of which is enclosed. The paper covers SPECT myocardial perfusion imaging (MPI) and cardiac PET, and reviews appropriate use of imaging, defined by specific clinical indication (Tables 1-8, Pages 2207-2210). The appropriate use criteria (AUC) describe a rigorous process of literature review and decision making, are endorsed by eight different specialty societies, and have become widely accepted by the medical community and third-party payers. This paper should answer the majority of the commission's concerns and questions about imaging selection for patients. Of note, the terms Appropriate, Uncertain, and Inappropriate have been replaced in new guidelines with the terms Appropriate Care, May be Appropriate Care, and Rarely Appropriate Care (Hendel 2013).	See comment #A3
B	5	<u>Sensitivity and Specificity</u> • There are a large number of papers which look at MPI accuracy, and the "gold standard" for comparison is most commonly invasive coronary angiography. Generally, the sensitivity and specificity of MPI is in the range of 80-90%. Predictive value, of course, is based upon the pretest prevalence of the disease in the population studied. Though comparative "head to head" studies against stress echo are few, most indicate a superior sensitivity and specificity for MPI, although not all comparisons reach statistical significance. Since sensitivity and specificity of both echo and MPI technologies are quite good, relative differences (favoring MPI) tend to be modest. Subsets where MPI compares particularly favorably to stress echo include patients with single vessel coronary disease, patients who are obese, patients who are unable to exercise or achieve target heart rate, patients with pacemakers or implantable defibrillators or left bundle branch block, patients with prior myocardial infarction or other known coronary or other heart disease, patients with resting ECG abnormalities, and patients with otherwise poor echo image quality. Many patients in these subsets cannot be identified prospectively.	EbGS agrees that sensitivity and specificity of both ECHO and MPI technologies are good, and that relative differences are modest. However, ECHO is not associated with harms of radiation and is substantially less expensive. EbGS agrees that there are certain subpopulations in which MPI compares favorably to ECHO, and these are accounted for in the coverage guidance recommendation: "patients for whom stress imaging is required and stress ECHO is contraindicated or would provide suboptimal imaging* *i.e. pre-existing cardiomyopathy or regional wall motion abnormalities, left bundle branch block, paced rhythm, unsuitable acoustic windows due to body habitus, inability to utilize dobutamine in a setting where exercise is not

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Ident.	#	Comment	Disposition
			possible or when the target workload is not achievable."
B	6	• Head-to-head comparisons of MPI versus stress echo in the literature tend to include only patients who have a clinical indication to undergo invasive coronary angiography. In these studies, invasive angiography determines which of the noninvasive tests is "correct". This approach has several limitations. o First, patients already selected for invasive angiography on clinical grounds have a much higher likelihood of obstructive coronary disease than those undergoing testing in an office setting. Patients with a negative study most often are reassured in practice, and are then seldom referred for angiography. A better outcome measure for patients with a negative test might be "percent event free survival at 3 years," though this is an exceedingly difficult assessment to make in patients who will not be having regular cardiac follow up.	EbGS agrees that a better outcome measure is event-free survival. Indeed, one study included in the WA HTA review compared the ability of SPECT and stress ECHO to predict major adverse coronary events (MACE) after 3.7 years, and found no significant difference between the two when evaluating the area under the ROC curve. Another study assessed the prognostic value of stress ECHO and SPECT in patients who were followed for 7.3 years and found no statistical differences between the tests. Three additional cohort studies also did not find significant differences in the prognostic ability of SPECT and ECHO.
	7	o Second, invasive angiography is an anatomic test, whereas MPI and stress echo are physiologic tests. Angiography will often identify a stenosis in the range of 50-70%, which is considered equivocal on anatomic grounds. Multiple studies have shown that MPI is more likely to demonstrate ischemia in such territories, as compared to stress echo. Though fractional flow reserve assessment can be done at the time of angiography, and does provide a functional assessment of whether such lesions are flow limiting, currently we are not aware of any studies which have utilized this technology in comparison to the results obtained with stress echo or MPI.	Citations not provided. Ability to demonstrate ischemia in an area of known stenosis was not specifically addressed in the WA HTA report. *For EbGS discussion*
	8	Frequency of incidental findings (outside the heart) • Research indicates that the incidence of noncardiac findings on nuclear MPI is about 2.5% (Williams 2003). Detection of breast cancer, lung cancer, and abnormalities in the thyroid are not uncommon and may result in early detection of disease and subsequent life-saving treatment.	Studies reported in the WA HTA report cite a very low rate of extracardiac findings (0-0.3%) for SPECT. While incidental findings can occasionally result in early detection of disease, more often they result in unnecessary additional testing, increased anxiety and potential harms.
	9	Relevant Outcome Data • First, research shows that major adverse cardiac events are better predicted by SPECT than by visually-analyzed coronary angiograms. In addition, there is no incremental prognostic value from visually-analyzed coronary angiograms over SPECT perfusion data (Iskandrian 1993). • Second, in 2002 a study demonstrated that "ischemia guided angiography" using SPECT was	The WA HTA report does not address the comparison of SPECT with invasive angiography, or the additional value that SPECT may provide. Iskandrian 1993 is a case series of 316 medically treated patients with CAD who had undergone both angiography

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Ident.	#	Comment	Disposition
		more cost effective than routine angiography in patients with stable chest pain (Shaw 2002). • Further, Hachamovitch et al. (2003) published research that showed patients with a lesser degree of reversible ischemia on SPECT perfusion imaging had higher survival rates with medical therapy than with revascularization. However, those with a greater degree of ischemia were likely to benefit from invasive procedures. A subsequent study demonstrated that women who had a "false positive" noninvasive study and thus had coronary angiography showing "no significant" stenosis often had endothelial dysfunction documented in the catheterization lab. • Finally, the FAME trial affirmed the prognostic value of physiologic assessment to document ischemia before performing revascularization (Tonino 2009).	and stress MPI who were followed for a mean of 28 months. Cox regression models were used to determine the prognostic values of clinical, exercise, MPI and angiography data in predicting cardiac death or MI. Authors report that extent of perfusion abnormality had the higher chi-square value of any of the variables (gender, exercise work, cath data). Shaw 2002 was a retrospective cohort study that compared direct referral for angiography to stress myocardial perfusion imaging in women with stable chest pain. Cost per patient was calculated for both strategies and found to be $2490 for angiography and $1587 for MPI in low risk patients; for high risk patients, the costs were $3687 and $2585 respectively. Hachomovitch 2003 was a retrospective cohort study of patients without prior MI or revascularization who received SPECT. Patients were assigned to groups based on treatment received at 60 days after SPECT (revascularization or medical therapy). Patients were then followed approx. 2 years and outcomes of cardiac death and all-cause death were calculated. Cardiac death was higher in the revascularization group (2.8% vs 1.3%). However, authors state that "with increasing amounts of inducible ischemia, mortality rates progressively increased in patients undergoing medical therapy", and that in patients with > 20% myocardium ischemic, revascularization had a lower cardiac death rate than medical therapy. Tonino 2009 evaluated fractional flow reserve calculated from angiography; MPI was not utilized. None of these studies would meet the inclusion criteria of the WA HTA review, which included only RCTs or

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Ident.	#	Comment	Disposition
			observational studies comparing alternative testing strategies; none of them compare the diagnostic value of ECHO with SPECT. *For EbGS discussion*
	10	Summary • Stress echo, MPI and cardiac PET have AUC which have been rigorously developed, endorsed by multiple specialty societies, and utilized by the medical community successfully for years. There are certainly circumstances where patients referred for imaging may meet AUC for both stress echo and MPI. Selecting the appropriate test in these circumstances is generally best left to the ordering physician, using the factors described above, along with their knowledge of the individual patient.	Selection of the appropriate test is always left to the ordering physician; that does not obviate the need for coverage policy development.
	11	Again, we support the HERC adopting the NCI guidance based on the AUC and the Washington State Health Care Authority Technology Assessment. Thank you for this opportunity to comment on the Health Evidence Review Commission's Coverage Guidance on Nuclear Cardiac Imaging.	*For EbGS discussion*

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HEALTH EVIDENCE REVIEW COMMISSION (HERC)

COVERAGE GUIDANCE: ABLATION FOR ATRIAL FIBRILLATION

DRAFT for EbGS Meeting Materials 9/4/2014

HERC COVERAGE GUIDANCE

AV node ablation is recommended for coverage only in persons with inadequate ventricular rate control resulting in symptoms, left ventricular systolic dysfunction or substantial risk of left ventricular systolic dysfunction. Coverage is recommended only when pharmacological therapy for rate control is ineffective or not tolerated *(weak recommendation)*

Transcatheter pulmonary vein isolation is recommended for coverage for those who remain~~are persistently~~ symptomatic from atrial fibrillation despite rate control medications and antiarrhythmic medications (*strong recommendation)*

Surgical ablation (pulmonary vein isolation or Maze procedure) for atrial fibrillation~~Pulmonary vein isolation~~ is recommended for coverage at the time of other cardiac surgery for patients who remain ~~are persistently~~ symptomatic despite rate control medications (*weak recommendation*).

~~The Maze procedure is recommended for coverage at the time of other cardiac surgery for patients with significant symptoms from atrial fibrillation *(weak recommendation)*~~

Note: Definitions for strength of recommendation are provided in Appendix A GRADE Element Description

RATIONALE FOR GUIDANCE DEVELOPMENT

The HERC selects topics for guideline development or technology assessment based on the following principles:

- Represents a significant burden of disease
- Represents important uncertainty with regard to efficacy or harms
- Represents important variation or controversy in clinical care
- Represents high costs, significant economic impact
- Topic is of high public interest

Coverage guidance development follows to translate the evidence review to a policy decision. Coverage guidance may be based on an evidence-based guideline developed by the Evidence-based Guideline Subcommittee or a health technology assessment developed by the Heath Technology Assessment Subcommittee. In addition, coverage guidance may utilize an existing evidence report produced by one of HERC's trusted sources, generally within the last three years.

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EVIDENCE SOURCES

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The summary of evidence in this document is derived directly from these evidence sources, and portions are extracted verbatim.

SUMMARY OF EVIDENCE

Clinical Background

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of mechanical function. Different systems have been proposed to classify AF. Although the type of AF can change over time, it is often helpful to characterize it at a given moment, as this may guide treatment. Types of AF include first-detected, paroxysmal (arrhythmia terminates spontaneously within 7 days), persistent (arrhythmia is sustained beyond 7 days), longstanding persistent (patients who have been in AF for any period longer than 1 year when attempts at achieving sinus rhythm are planned or are in progress~~usually lasting~~

~~for more than 1 year~~), and permanent AF (in which cardioversion has failed or has not been attempted).

It is estimated that more than 2.3 million Americans have AF. The prevalence of AF increases with age and approaches 8 percent in patients older than 80 years of age. AF is the most common sustained arrhythmia seen in clinical practice. The impact of AF is compounded by its known association with significant mortality, morbidity, and health care costs. Not only is the risk of death in patients with AF twice that of patients without AF, but AF can result in myocardial ischemia or even infarction, heart failure exacerbation, and tachycardia-induced cardiomyopathy if the ventricular rate is not well controlled. The most dreaded complication of AF is thromboembolism, especially stroke. The risk of stroke in patients with AF is up to 8 percent per year, depending on the presence of stroke risk factors. Importantly, when ischemic stroke occurs in patients with AF, it is either fatal or of moderate to high severity in the majority of patients. The management of AF and its complications is responsible for almost $16 billion in costs to the U.S. health care system each year.

Treatment Strategies

Management of AF involves three distinct areas: rate control (treatments to slow the heart rate to a normal range), rhythm control (treatments to revert the heart rhythm back to normal), and prevention of thromboembolic events. Whether or not a rhythm-control strategy is adopted, current treatment guidelines suggest that adequate rate control should be achieved in all patients with AF to prevent myocardial infarction (if significant coronary artery disease is present), exacerbation of heart failure, and tachycardia-induced cardiomyopathy; to alleviate symptoms; and to improve exercise tolerance and quality of life.

Rate Control

If pharmacological therapy is insufficient for rate control and symptom management or is associated with side effects, the 2006 ACC/AHA/ESC Guidelines recommend ablation of the atrioventricular node (AVN) in conjunction with permanent pacemaker implantation to control heart rate. As the latter involves implantation of an indwelling device that is not reversible, it is considered a treatment of last resort for patients for whom initial pharmacotherapy was ineffective.

Another clinical dilemma is whether patients with AF do better with strict or lenient rate control. In theory, strict control could reduce symptoms and prevent complications. However, stricter control requires more intensive use of medications, which carry their own side effects. The 2011 Focused Update on the Management of Patients With Atrial Fibrillation by the American College of Cardiology Foundation (ACCF), the AHA, and the Heart Rhythm Society (HRS) addressed the issue of strict versus lenient rate control in patients with AF. Specifically, these guidelines emphasized the following Class III

recommendation (evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful): “Treatment to achieve strict rate control of heart rate (<80 bpm at rest or <110 bpm during a 6-minute walk) is not beneficial compared with achieving a resting heart rate <110 bpm in patients with persistent AF who have stable ventricular function (left ventricular ejection fraction >0.40) and no or acceptable symptoms related to the arrhythmia.”

Rhythm Control

If patients with AF continue to have significant symptoms despite adequate rate control through either pharmacological therapy or AVN ablation, then a rhythm-control strategy (either pharmacological or electrical) is currently recommended. For pharmacological cardioversion of AF, the 2014 ACC/AHA/ESC Guidelines recommend flecainide, dofetilide, propafenone, and ibutilide as Class I recommendations, and amiodarone as a Class IIa recommendation (weight of evidence/opinion is in favor of usefulness/efficacy). To enhance direct-current cardioversion, the 2014 ACC/AHA/ESC Guidelines recommend pretreatment with amiodarone, flecainide, ibutilide, propafenone, or sotalol. For maintenance of sinus rhythm after cardioversion, the 2014 ACC/AHA/ESC Guidelines list different antiarrhythmic medications for different clinical settings.

In addition to pharmacological and direct-current cardioversion, a number of surgical interventions are used for rhythm control. Catheter ablation for the treatment of AF, with pulmonary vein isolation (PVI) being the most commonly used ablation, has evolved rapidly from a highly experimental procedure to its current status as a commonly performed procedure that is widely regarded as a clinically useful treatment option for symptomatic patients with AF in whom medications are not effective or not tolerated.

Several other procedures for the treatment of AF have been investigated. One such procedure is the surgical Maze procedure, which appears to confer some benefit to selected patients with AF. ~~Implantation of a cardiac resynchronization therapy (CRT) device is another procedure that may decrease the burden of AF in patients who are eligible for this device based on a left ventricular ejection fraction ≤35 percent, a wide QRS complex, and heart failure symptoms despite optimal medical therapy. Secondary analyses of major clinical trials have provided conflicting findings on the effect of CRT on AF burden.~~

Although several studies of rate- and rhythm-control strategies exist, to date no study has shown that maintaining patients with AF in sinus rhythm provides a long-term survival benefit. It is also unknown whether the risks and benefits of different therapies vary by AF type.

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Evidence Review

Rate-Control Procedures Versus Drugs or Versus Other Procedures in Patients for Whom Initial Pharmacotherapy Was Ineffective

Al-Khatib 2013 reports on ~~six~~four RCTs (~~two~~one good, two~~hree~~ fair, and one poor quality) involving a total of 211~~537~~ patients that compared the effectiveness of a procedural intervention versus a primarily pharmacological intervention for rate control of AF~~ or comparing two primarily procedural interventions~~. All ~~F~~four studies recruited patients with permanent ~~only one specific type of~~ AF, ~~either permanent (three studies) or persistent (one study); one study recruited patients with~~(referred to as "resistant chronic" AF in one study)~~; and one study recruited patients with permanent or paroxysmal AF~~. ~~These studies, however, evaluated and compared different types of treatments, preventing conclusions about whether effectiveness varied by type of AF.~~ All studies included at least one treatment arm with radiofrequency ablation of either the AVN or His bundle~~, most often~~ in conjunction with pacemaker placement. The comparison arms included a pharmacological intervention whose main purpose was to control ventricular heart rate rather than converting the underlying rhythm of AF~~; this was combined with a procedure in some studies~~.

Based on three studies reported in Al-Khatib 2013 (one good, one fair, one~~two~~ poor quality) involving ~~175~~211 patients, patients undergoing a procedural intervention had a significantly lower heart rate at 12 months than those receiving a primarily pharmacological intervention. This was measured differently in all three studies. In one, the mean heart rate in the intervention group was 71 ±6 bpm compared to 83 ± 8 bpm in the medication group ($p<0.01$). In this study, maximum heart rate did not differ between groups. In the second study, those in the ablation group had higher minimum (70±9 vs. 39±9 bpm; $p<0.05$) and mean (76±7 vs. 71±11 bpm; $p<0.05$) heart rates than the medication group, but lower maximum heart rates (117 ± 16 bpm vs. 152 ± 37 bpm; $p<0.05$). The third study reported the percent of each group who had either a normal or uncontrolled ventricular rate; in the ablation group, 100% had a normal ventricular rate (50-90 bpm) compared to 58% in the medication group. Similarly, none of the ablation group had an uncontrolled heart rate (>90 bpm at rest or > 130 bpm on exertion), while 42% of the medication group did. There was no difference by treatment arm in all-cause mortality (two studies [one good, one fair quality], 201 patients); cardiovascular mortality (one study [good quality], 102 patients); or exercise capacity (two studies [one good, one fair quality], 135 patients) (all low strength of evidence). There was insufficient strength of evidence to support findings for other outcomes, including quality of life.

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Rhythm-Control Procedures and Drugs for Maintenance of Sinus Rhythm

Al-Khatib 2013 included 65 studies enrolling 6,739 patients that evaluated procedures for rhythm control. Of those that specified type of AF, eleven included only patients with longstanding persistent AF, 17 studies included only patients with paroxysmal AF, and 4 studies included only patients with persistent AF.

Transcatheter PVI versus antiarrhythmic drugs

Al-Khatib 2013 concluded, based on eight RCTs (five good, three fair quality) involving 921 patients, that transcatheter PVI is superior to antiarrhythmic drugs for **maintenance of sinus rhythm** over 12 months of follow up in patients with AF (one RCT reported 48 months of follow up). All trials had statistically significant results, as did meta-analysis of all eight trials (OR 6.51, 95% CI 3.22 to 13.16). This evidence is strongest in younger patients with little to no structural heart disease and with mild or no enlargement of the left atrium. Only one trial was limited to patients receiving ablation as first line therapy (Wazni 2005), while five specifically required failure of at least one AAD to be included in the study. The Wazni trial included 70 patients who experienced monthly episodes of symptomatic AF for at least three months, and found that at one year follow up, 63% of those treated with AADs had at least one recurrence of AF, compared to 13% of those who received PVI. Another trial included only in Hashimoto 2013 included only patients with persistent AF (MacDonald 2011), and reported that at final follow up (6 months), 50% of patients in the PVI group were in sinus rhythm while none of the control group were (no statistical testing done). This latter trial was limited to patients with advanced heart failure. (Note: This outcome is reported as freedom from recurrence in Hashimoto 2013, but results are similar.)

Al-Khatib 2013 concluded, based on two RCTs (Pappone 2006, Forleo 2009, both good quality) involving 268 patients, that transcatheter PVI is superior to antiarrhythmic medications in **reducing cardiovascular hospitalizations** (moderate strength of evidence). Both of these trials were also included in Hashimoto 2013. A third study, Stabile 2006, reported only in Hashimoto 2013, found a lower number of hospitalizations in the PVI group which did not reach statistical significance. A fourth RCT, Wazni 2005, reported only in Al-Khatib 2013, found the rate of hospitalization specifically for AF was higher in the AAD arm (15 of 35) than the PVI arm (3 of 32, $p < 0.001$) in the first 12 months of follow up.

Chen 2012 reported that only one trial (Stabile 2006) reported all-cause **mortality**. There were no statistically significant differences between groups for this outcome. In this trial, the one death that occurred in the PVI group was from a stroke that occurred during the procedure and was followed by a brain hemorrhage 9 months later. There were two deaths in the AAD group (diagnosis not specified).

Al-Khatib 2013 also reported only one study for the outcome of all-cause mortality, however, it was a different study than was reported by Chen. This study (Oral 2006) reported one death in the PVI arm at 12 months compared to none in the AAD arm; no statistical testing was done.

Hashimoto 2013 reported that four RCTs (Jais 2008, Wilbur 2010, Stabile 2006, Oral 2006) reported overall mortality rates (not procedure related) at 9 to 12 months of follow up. Mortality rate in the PVI arm ranged from 1% to 3%, while in the AAD arm a rate of 3% was reported in two studies. According to Hashimoto, Stabile 2006 was the only RCT to report mortality in both arms. Two cohort studies included in Hashimoto 2013 did report an increased risk of death in the AAD group at follow up times ranging from 1 to 3 years (Pappone 2003: 6.5% in the PVI group vs. 14.3% in the AAD group, $p < 0.001$) or at a mean follow up of 69 months (Sonne 2009: 2.1% in the PVI group vs. 16.5% in the AAD group, $p = 0.001$).

Eight studies evaluated **quality of life (QOL) or functional status**, three RCTs reported in all three source reports, two additional RCTs reported in both Hashimoto 2013 and Al-Khatib 2013, two additional RCTs in Hashimoto 2013 only and one cohort study reported in Al-Khatib 2013 only. In general, there was greater improvement from baseline in these scores in patients randomized to the PVI arm, compared to the AAD arm, and in most of these studies, results were statistically significant for at least some measures.

Harms were reported in eight RCTs, but for the most part, were not statistically analyzed. Complications reported in each study are summarized in the Table below:

Author	N	PVI Arm	AAD Arm
Krittayaphong	30	1 stroke, 1 groin hematoma	AE in 7 patients (47%): GI AE in 6 pts, corneal deposits in 2 pts, hypothyroidism in 2 pts, abnormal LFTs in 2 pts, hyperthyroidism in 1 pt, sinus node dysfunction in 1 pt
Wazni	70	No TE events, no bradycardia, 1 asymptomatic PV stenosis	No TE events, 8.6% bradycardia
Pappone	198	No serious AE	Sig AE leading to drug withdrawal in 23 pts,
Oral	146	None	None
Stabile	137	4.4% major complications (stroke, phrenic paralysis, pericardial effusion)	1 TIA, 2 cancer, 1 sudden death
Jais	112	2 cardiac tamponade, 2 groin hematomas, 1 PV stenosis requiring stent	1 hyperthyroidism, 2 deaths (unrelated)

Forleo	70	1 groin hematoma	17% sig drug AE (bradycardia, atrial flutter, sinus node dysfunction
Wilber	167	5 major AE (pericardial effusion, pulmonary edema, pneumonia, vascular complication, heart failure)	5 major AE (2 life-threatening arrhythmias, 3 disabling drug intolerance requiring discontinuation)

TE = thromboembolic; PV = pulmonary vein

Cryoablation PVI vs. AAD

One RCT reported in Hashimoto 2013 found that patients randomized to receive cryoablation had significantly greater freedom from recurrence compared with those patients randomized to receive AADs alone (69.9% versus 7%, respectively; P < .001). There was one death (0.6%) in the cryoablation PVI group and none in the AAD group at 12 months, which was not statistically significant.

Surgical Maze versus standard of care (mitral valve surgery)

Al-Khatib 2013 included seven RCTs (one good, six fair quality) involving 361 patients for this comparison. Surgical Maze at the time of other cardiac surgery (specifically mitral valve surgery) is superior to mitral valve surgery alone for **maintenance of sinus rhythm** over at least 12 months of followup in patients with persistent AF (OR 5.80, 95% CI 1.79 to 18.81). Six studies reported on all cause mortality; meta-analysis found an OR of 1.97 (95% CI 0.81 to 4.80) suggesting an increased risk of death with the Maze procedure, but this did not reach statistical significance.

PVI done at the time of cardiac surgery versus cardiac surgery alone or cardiac surgery in combination with antiarrhythmic drugs (AADs) or catheter ablation

Al-Khatib 2013 included eight RCTs (five good, three fair quality) involving 532 patients for this comparison. Pulmonary vein isolation done at the time of cardiac surgery is superior to cardiac surgery alone or cardiac surgery in combination with AADs or catheter ablation for **maintenance of sinus rhythm** over 12 months of followup in patients with persistent AF (OR 3.91, 95% CI 1.54 to 9.91). Two studies reported no difference between groups in all-cause mortality or stroke.

There are insufficient data on the effect of rhythm control with PVI or surgical Maze on final outcomes, such as all-cause mortality, stroke, heart failure, and left ventricular ejection fraction, and on the safety and durability of the effectiveness of these procedures beyond 12 months.

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Other comparisons

There are a variety of other comparisons included in Al-Khatib 2013 and Chen 2012, most of which had a limited number of studies and were considered outside the scope of this guidance document. These include the following:

- Circumferential PVI versus Segmental PVI
- Transcatheter PVI with complex fractionated atrial electrogram (CFAE) ablation versus transcatheter PVI without CFAE ablation
- Transcatheter PVI using different types of ablation catheters
- Transcatheter PVI with Cavotricuspid isthmus (CTI) ablation vs. transcatheter PVI without CTI ablation
- Transcatheter PVI vs transcatheter PVI with ablation sites other than CTI and CFAE and transcatheter PVI involving all four PVs vs transcatheter PVI involving arrhythmogenic PVs only
- Transcatheter PVI Alone vs transcatheter PVI plus postablation antiarrhythmic drugs
- Left atrial ablation vs. bi-atrial ablation
- PVI, circumferential PVI or left atrium ablation vs. ablation plus additional linear ablation
- PV-left atrium junction ablation vs. PV-left atrium junction ablation combined with CTI ablation
- Circumferential PV ablation vs. circumferential PV ablation plus PVI
- Superior PV ablation vs. four-PV ablation
- Small area isolation vs. large area isolation around PVs in circumferential PV ablation
- CFAE plus PV atrum isolation vs. PV atrum isolation alone
- Circumferential PV ablation vs. modified circumferential PV ablation
- Arrhythmogenic PVI vs all PVI

[Evidence Source]

Evidence Summary

Ablation of the AV node or bundle of His in patients with AF results in lower heart rate at 12 months than pharmacologic treatment (moderate SOE), although there is no difference in mortality or exercise capacity (low SOE). Pulmonary vein isolation (PVI) results in a greater likelihood of maintaining sinus rhythm at 12 months than pharmacologic treatment (high SOE); most of the evidence for this finding is in patients with AF who have failed at least one AAD. This procedure (PVI) also results in lower risk of hospitalization over 12 months (moderate SOE) and improved QOL (moderate SOE), but the evidence is insufficient to assess the impact of PVI on mortality.

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The surgical Maze procedure, when done at the time of other cardiac surgery, results in a higher likelihood of maintaining sinus rhythm than not performing the Maze (moderate SOE). Similarly, PVI done at the time of other cardiac surgery results in a higher likelihood of maintaining sinus rhythm than not performing PVI (high SOE), and no apparent difference in all-cause mortality or stroke (low SOE).

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GRADE-INFORMED FRAMEWORK

The HERC develops recommendations by using the concepts of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. GRADE is a transparent and structured process for developing and presenting evidence and for carrying out the steps involved in developing recommendations. There are four elements that determine the strength of a recommendation, as listed in the table below. The HERC reviews the evidence and makes an assessment of each element, which in turn is used to develop the recommendations presented in the coverage guidance box. Balance between desirable and undesirable effects, and quality of evidence, are derived from the evidence presented in this document, while estimated relative costs, values and preferences are assessments of the HERC members.

Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Variability in values and preferences	Coverage recommendation	Rationale
Ablation of AV node/bundle of His compared to rate control medications in patients for whom initial pharmacotherapy was ineffective	Lower heart rate, no difference in mortality/exercise capacity	Moderate/Low based on 1 to 3 poor to good quality studies, depending on the outcome	High	High	AV node ablation is recommended for coverage only in symptomatic persons when pharmacological therapy for rate control is ineffective or not tolerated. *(weak recommendation)*	Studies show mixed clinical significance of a lower heart rate. In those with persistently uncontrolled heart rate despite AADs, AV node ablation is a reasonable alternative to prevent the negative consequences of an uncontrolled rate such as MI, exacerbation of CHF or cardiomyopathy.
Transcatheter PVI vs. AAD	Better maintenance of SR, fewer	High/Moderate, based on 1 to	High	Moderate	Transcatheter PVI is recommended for	Transcatheter PVI produces

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Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Variability in values and preferences	Coverage recommendation	Rationale
	hospitalizations, better QOL, possibly lower mortality	8 fair to good quality studies, depending on the outcome			coverage when a rhythm control strategy is desired *(strong recommendation)*	superior clinical outcomes to antiarrhythmic drugs alone when a rhythm control strategy is pursued
Maze procedure	Better maintenance of SR; possible (nonsignificant) increase in mortality	Moderate based on 1 good and six fair quality studies	Moderate (concurrent with other cardiac surgery)	Moderate	The Maze procedure is recommended for coverage at the time of other cardiac surgery if the benefits of maintenance of sinus rhythm are thought to outweigh the potential risk of increased mortality *(weak recommendation)*	Maze may help maintain sinus rhythm but concerning nonsignificant increased risk of mortality
PVI done with other cardiac surgery	Better maintenance of SR	High based on 5 good and 3 fair quality studies	Moderate (concurrent with other cardiac surgery)	Low	PVI is recommended for coverage *(weak recommendation)*	PVI may help maintain sinus rhythm without significant additional risks

SR = sinus rhythm PVI = pulmonary vein isolation AAD = anti-arrhythmic drugs

*The Quality of Evidence rating was assigned by the primary evidence source, not the HERC Subcommittee

Note: GRADE framework elements are described in Appendix A

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POLICY LANDSCAPE

Nine quality measures pertaining to atrial fibrillation were identified when searching the National Quality Measures Clearinghouse; however, none of them referenced ablation.

Choosing Wisely® is part of a multi-year effort of the ABIM Foundation to help physicians be better stewards of finite health care resources. Originally conceived and piloted by the National Physicians Alliance through a Putting the Charter into Practice grant, more than 50 medical specialty organizations, along with Consumer Reports, have identified a number of tests or procedures commonly used in their field, whose necessity should be questioned and discussed. Each participating organization was free to determine how to create its own list, provided that it used a clear methodology and adhered to the following set of shared guidelines:

- Each item should be within the specialty's purview and control.
- The tests and/or interventions should be used frequently and/or carry a significant cost.
- Each recommendation should be supported by generally accepted evidence.
- The selection process should be thoroughly documented and publicly available on request.

One of the organizations that chose to participate in the *Choosing Wisely*® campaign is the Heart Rhythm Society. The most recent list created by this organization states the following:

> **"Don't ablate the atrioventricular node in patients with atrial fibrillation when both symptoms and heart rate are acceptably controlled by well-tolerated medical therapy.**
>
> Atrioventricular node ablation and pacemaker implantation may provide benefit in some patients when rate and related symptoms cannot be controlled by medication therapy,(Class IIa, indicated) or when there is concern for possible tachycardia-induced cardiomyopathy (Class IIb, may be considered). However, according to current professional society clinical guidelines, the risks of AV node ablation outweigh the benefits among patients with no symptoms and who have appropriate rate control with well-tolerated medical therapy."

They cite the 2011 publication of the ACCF/AGA guidelines on the management of patient with AF as supporting evidence. These guidelines were recently updated (2014), and are rated fair quality using the MED standard criteria,

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primarily because study selection criteria was not specified and the quality of included studies was not assessed. These guidelines state the following with regard to AV node ablation for rate control in AF:

Class IIa
3. AV nodal ablation with permanent ventricular pacing is reasonable to control the heart rate when pharmacological therapy is inadequate and rhythm control is not achievable. *(Level of Evidence: B)*

Class III: Harm
1. AV nodal ablation with permanent ventricular pacing should not be performed to improve rate control without prior attempts to achieve rate control with medications. *(Level of Evidence: C)*

For catheter ablation for rhythm control (e.g. PVI), the guidelines state the following:

Class I
1. AF catheter ablation is useful for symptomatic paroxysmal AF refractory or intolerant to at least 1 class I or III antiarrhythmic medication when a rhythm control strategy is desired. *(Level of Evidence: A)*

2. Prior to consideration of AF catheter ablation, assessment of the procedural risks and outcomes relevant to the individual patient is recommended. *(Level of Evidence: C)*

Class IIa
1. AF catheter ablation is reasonable for selected patients with symptomatic persistent AF refractory or intolerant to at least 1 class I or III antiarrhythmic medication. *(Level of Evidence: A)*

2. In patients with recurrent symptomatic paroxysmal AF, catheter ablation is a reasonable initial rhythm control strategy prior to therapeutic trials of antiarrhythmic drug therapy, after weighing risks and outcomes of drug and ablation therapy. *(Level of Evidence: B)*

Class IIb
1. AF catheter ablation may be considered for symptomatic long-standing (>12 months) persistent AF refractory or intolerant to at least 1 class I or III antiarrhythmic medication, when a rhythm control strategy is desired. *(Level of Evidence: B)*

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2. AF catheter ablation may be considered prior to initiation of antiarrhythmic drug therapy with a class I or III antiarrhythmic medication for symptomatic persistent AF, when a rhythm control strategy is desired. *(Level of Evidence: C)*

Class III: Harm

1. AF catheter ablation should not be performed in patients who cannot be treated with anticoagulant therapy during and following the procedure. *(Level of Evidence: C)*

2. AF catheter ablation to restore sinus rhythm should not be performed with the sole intent of obviating the need for anticoagulation. *(Level of Evidence: C)*

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 (the Center). This document is intended to guide public and private purchasers in Oregon in making informed decisions about health care services.

The Center is not engaged in rendering any clinical, legal, business or other professional advice. The statements in this document do not represent official policy positions of the Center. Researchers involved in preparing this document have no affiliations or financial involvement that conflict with material presented in this document.

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Appendix A. GRADE Element Descriptions

Element	Description
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
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—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

Strong recommendation

In Favor: The subcommittee is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Against: The subcommittee is confident that the undesirable effects of adherence to a recommendation outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Weak recommendation

In Favor: The subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Against: The subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Quality or strength of evidence rating across studies for the treatment/outcome[1]

***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 RCTs with few or no limitations and the estimate of effect is likely stable.

***Moderate*:** The subcommittee is moderately confident in the effect estimate: 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 effect estimate 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 effect estimate: 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.

[1] Includes risk of bias, precision, directness, consistency and publication bias

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Appendix B. Applicable Codes

CODES	DESCRIPTION
ICD-9 Diagnosis Codes	
427.31	Atrial fibrillation
ICD-10 Diagnosis Codes	
I48.0	Paroxysmal atrial fibrillation
I48.1	Persistent atrial fibrillation
I48.2	Chronic atrial fibrillation
I48.91	Unspecified atrial fibrillation
ICD-9 Volume 3 (Procedure Codes)	
None	
CPT Codes	
33250	Operative ablation of supraventricular arrhythmogenic focus or pathway (eg, Wolff-Parkinson-White, atrioventricular node re-entry), tract(s) and/or focus (foci); without cardiopulmonary bypass (For intraoperative pacing and mapping by a separate provider, use 93631) Codes 33254-33256 are only to be reported when there is no concurrently performed procedure that requires median sternotomy or cardiopulmonary bypass.
33251	…with cardiopulmonary bypass
33254	Operative tissue ablation and reconstruction of atria, limited (eg, modified maze procedure)
33255	Operative tissue ablation and reconstruction of atria, extensive (eg, maze procedure); without cardiopulmonary bypass
33256	…with cardiopulmonary bypass
33257	Operative tissue ablation and reconstruction of atria, performed at the time of other cardiac procedure(s), limited (eg, modified maze procedure) (List separately in addition to code for primary procedure)
33258	Operative tissue ablation and reconstruction of atria, performed at the time of other cardiac procedure(s), extensive (eg, maze procedure), without cardiopulmonary bypass (List separately in addition to code for primary procedure)
33259	Operative tissue ablation and reconstruction of atria, performed at the time of other cardiac procedure(s), extensive (eg, maze procedure), with cardiopulmonary bypass (List separately in addition to code for primary procedure)
33261	Operative ablation of ventricular arrhythmogenic focus with cardiopulmonary bypass
33265	Endoscopy, surgical; operative tissue ablation and reconstruction of atria, limited (eg, modified maze procedure), without cardiopulmonary bypass
33266	…operative tissue ablation and reconstruction of atria, extensive (eg, modified maze procedure), without cardiopulmonary bypass
93613	Intracardiac electrophysicologic 3-dimensional mapping (List separately in addition to code for primary procedure)
93650	Intracardiac catheter ablation of atrioventricular node function, atrioventricular conduction for creation of complete heart block, with or without temporary pacemaker placement
93653	Comprehensive electrophysiologic evaluation including insertion and repositioning of multiple electrode catheters with induction or attempted induction of an arrhythmia with right atrial pacing and recording, right ventricular pacing and recording, His recording with intracardiac catheter ablation of arrhythmogenic focus; with treatment

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CODES	DESCRIPTION
	of supraventricular tachycardia by ablation of fast or slow atrioventricular pathway, accessory atrioventricular connection, cavo-tricuspid isthmus or other single atrial focus or source of atrial re-entry (Do not report 93653 in conjunction with 93600-93603, 93610, 93612, 93618-93620, 93642, 93654)
93655	Intracardiac catheter ablation of a discrete mechanism of arrhythmia which is distinct from the primary ablated mechanism, including repeat diagnostic maneuvers, to treat a spontaneous or induced arrhythmia (List separately in addition to code for primary procedure) (Use 93655 in conjunction with 93653, 93654, 93656)
93656	Comprehensive electrophysiologic evaluation including transseptal catheterizations, insertion and repositioning of multiple electrode catheters with induction or attempted induction of an arrhythmia with atrial recording and pacing, when possible, right ventricular pacing and recording, His bundle recording with intracardiac catheter ablation of arrhythmogenic focus, with treatment of atrial fibrillation by ablation by pulmonary vein isolation
93657	Additional linear or focal intracardiac catheter ablation of the left or right atrium for treatment of atrial fibrillation remaining after completion of pulmonary vein isolation (List separately in addition to code for primary procedure)
93799	Unlisted cardiovascular service or procedure
HCPCS Level II Codes	
None	

Note: Inclusion on this list does not guarantee coverage

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Appendix C. HERC Guidance Development Framework

HERC Guidance Development Framework Principles

This framework was developed to assist with the decision making process for the Oregon policy-making body, the HERC and its subcommittees. It is a general guide, and must be used in the context of clinical judgment. It is not possible to include all possible scenarios and factors that may influence a policy decision in a graphic format. While this framework provides a general structure, factors that may influence decisions that are not captured on the framework include but are not limited to the following:

- Estimate of the level of risk associated with the treatment, or any alternatives;
- Which alternatives the treatment should most appropriately be compared to;
- Whether there is a discrete and clear diagnosis;
- The definition of clinical significance for a particular treatment, and the expected margin of benefit compared to alternatives;
- The relative balance of benefit compared to harm;
- The degree of benefit compared to cost; e.g., if the benefit is small and the cost is large, the committee may make a decision different than the algorithm suggests;
- Specific indications and contraindications that may determine appropriateness;
- Expected values and preferences of patients.

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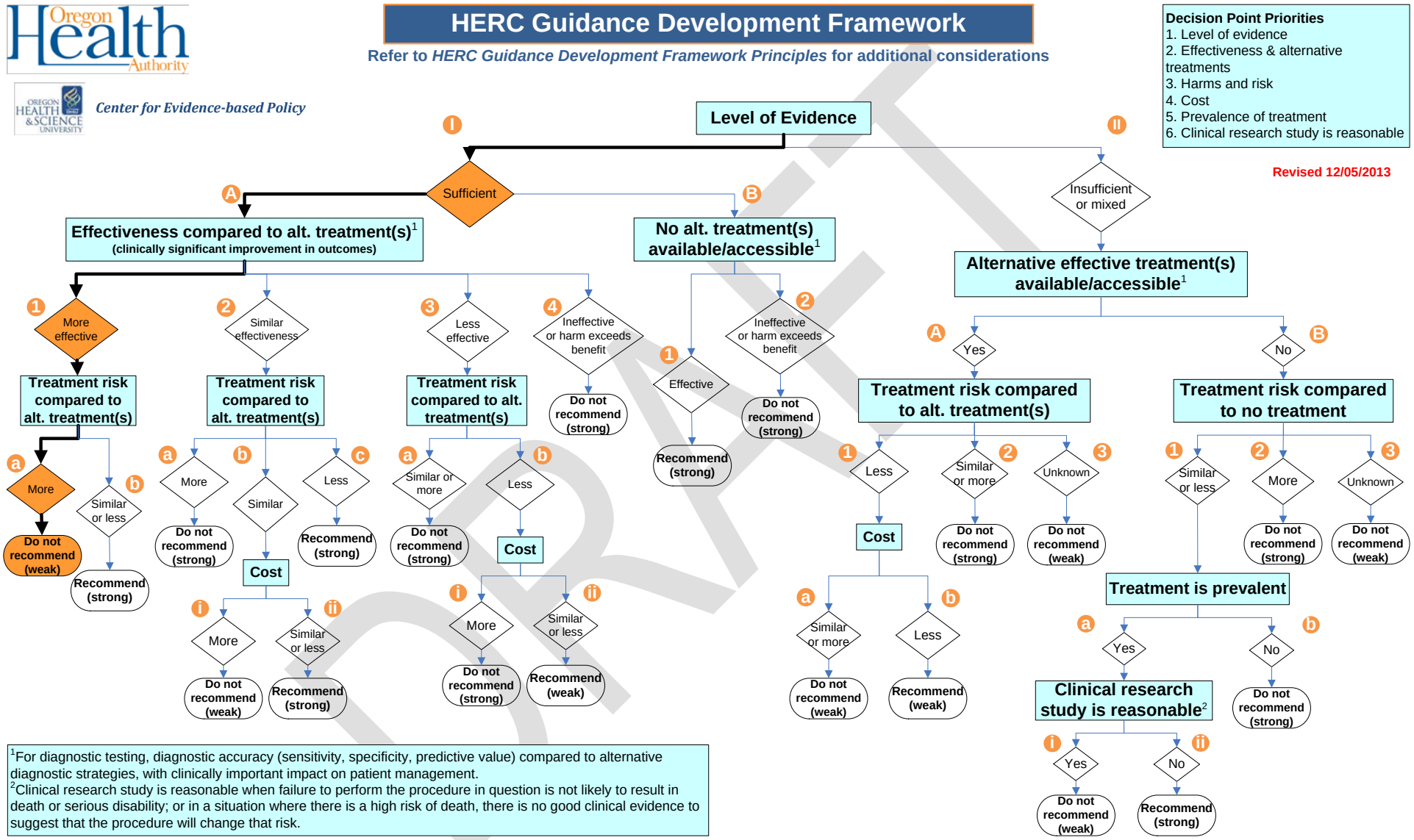
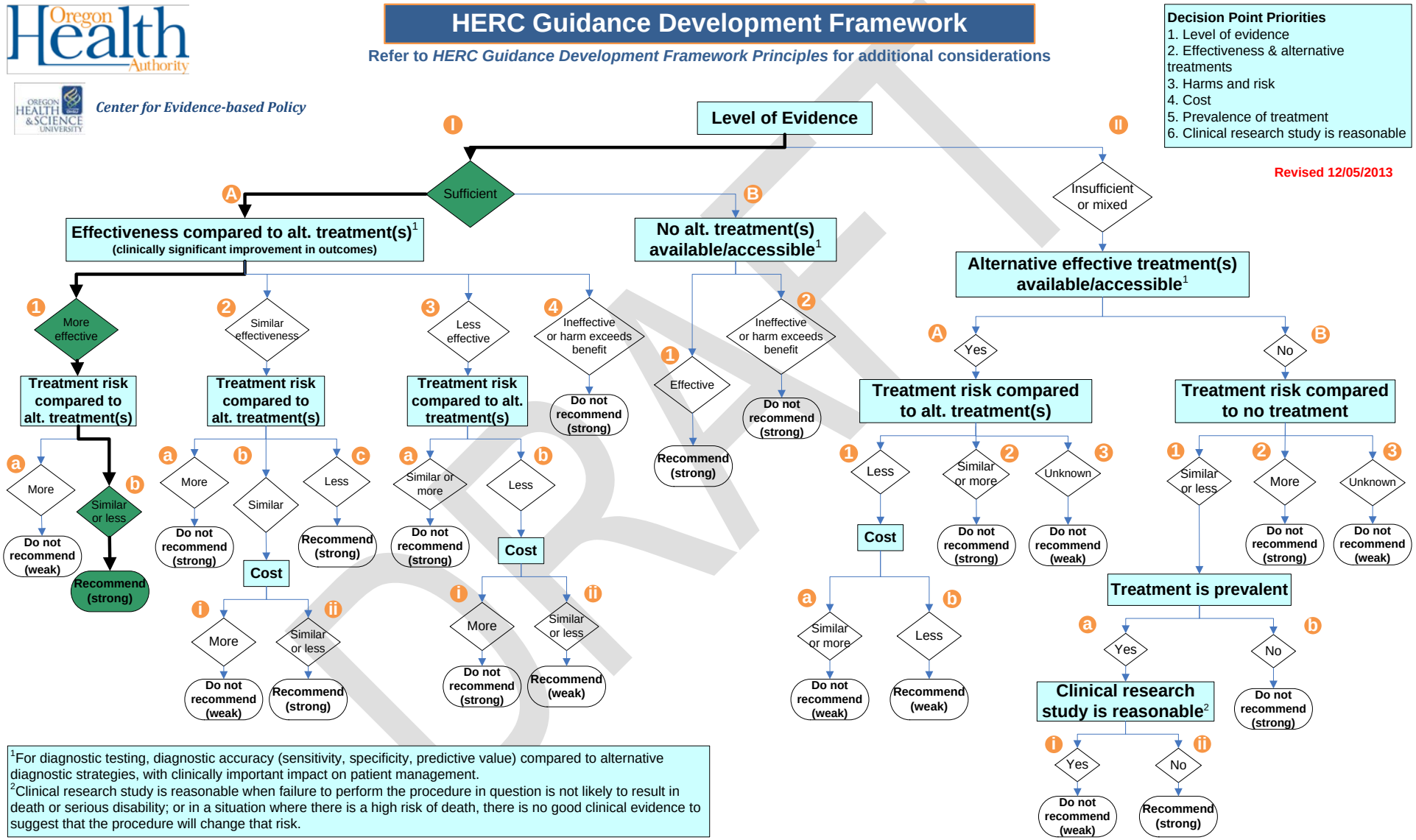
Ablation of AV node/bundle of His vs. rate control medications



Transcatheter pulmonary vein isolation (PVI) vs. antiarrhythmic drugs (AAD); Surgical ablation (Maze procedure or PVI done with other cardiac surgery)



[1]For diagnostic testing, diagnostic accuracy (sensitivity, specificity, predictive value) compared to alternative diagnostic strategies, with clinically important impact on patient management.
[2]Clinical research study is reasonable when failure to perform the procedure in question is not likely to result in death or serious disability; or in a situation where there is a high risk of death, there is no good clinical evidence to suggest that the procedure will change that risk.

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HERC Coverage Guidance – Ablation for Atrial Fibrillation
Disposition of Public Comments

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Commenters

Identification	Stakeholder
A	Family Physician, Reedsport, OR [*Submitted June 26, 2014*]
B	Oregon Chapter of the American College of Cardiology, Portland, OR [*Submitted July 22, 2014*]
C	Medtronic, Inc., Mounds View, MN [*Submitted July 21, 2014*]

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Public Comments

Ident.	#	Comment	Disposition
A	1	Agree with recommendations. They appear to be well-researched. Choosing Wisely recommendation adds weight; these have been researched by others and are endorsed by the specialty society.	Thank you for your comment.
B	1	The Oregon Chapter of the American College of Cardiology appreciates the opportunity to provide comments on the Health Evidence Review Commission's Coverage Guidance for Ablation for the Treatment of Atrial Fibrillation. We are of the opinion that the coverage guidance is well written and appropriate and agree with the overall conclusions and coverage decisions. However, there are several points worth revising, as detailed below.	Thank you for your comment.
B	2	Page 1: Box labeled "HERC Coverage Guidance", the third and fourth points are redundant, i.e., PVI at time of other cardiac surgery and surgical MAZE procedure at time of other cardiac surgery are the same. This error is repeated several times in the document. Although Al-Khatib distinguishes these two terms in her paper, these are generally used as synonyms in clinical practice, and thus comparisons between them are not valid. We recommend that the definitions of PVI and MAZE be included in the guidance.	PVI and surgical Maze are discussed separately in the AHRQ review, with different studies informing conclusions. Neither procedure is defined or described in this report. Given that both procedures have similar recommendations, box language changed to the generic term "surgical ablation".
B	3	Page 2: First paragraph under "clinical background", the term "permanent afib" is now rarely used and signifies afib that is always present and that no attempts are being made to restore sinus rhythm. We suggest clarifying that if attempts are made, then the afib is referred to as "longstanding persistent".	Current description of atrial fibrillation varieties is from the AHRQ report, and states the following: "Types of AF include first-detected, paroxysmal (arrhythmia terminates spontaneously within 7 days), persistent (arrhythmia is sustained beyond 7 days), longstanding persistent (usually lasting for more than 1 year ~~when attempts at achieving sinus rhythm are planned or are in progress~~), and permanent AF (in which cardioversion has failed or has not been attempted)." Suggested clarification made to the text.
B	4	Page 3: Top, "the risk of stroke is up to 8%, depending on other stroke risk factors". To more appropriately classify this risk, we recommend the statement be revised to state a range, such as 1-8%.	Current language is verbatim from the AHRQ report. No citation provided for the range. AHA guideline reports 5X

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Ident.	#	Comment	Disposition
			increase in stroke risk, but does not list an actual %. No change to guidance document.
B	5	Page 4: Middle, cardiac resynchronization therapy (CRT) is presented as a potential treatment for afib. CRT can be used in conjunction with AV node ablation, but the goal is not to decrease afib burden, as is currently discussed. Existing practice guidelines and current clinical practice do not include CRT as an appropriate treatment for afib, and we recommend removing it as a treatment option.	Language is from the background section and is verbatim from the AHRQ report; there is no evidence pertaining to CRT in the evidence review section. Sentence deleted.
B	6	Page 5: Top, AV node ablation is always in conjunction with placement of a permanent pacemaker (or previous placement of such). We suggest revision to reflect this.	This language is verbatim from the AHRQ report; five of the six included studies evaluated AV node ablation with pacemaker placement. The sixth study compared two different approaches (anterior and posterior) to "AV junction modification". In this study, no pacemaker was used, as AV node pacing function remained intact. Text of document revised to eliminate reference to studies that did not compare a primarily pharmacologic intervention to a primarily procedural intervention; this allows deletion as follows: "All studies included at least one treatment arm with radiofrequency ablation of either the AVN or His bundle, ~~most often~~ in conjunction with pacemaker placement."
B	7	Page 8: There are separate paragraphs dealing with surgical PVI v. MAZE procedure at time of other cardiac surgery. Again, see page 1 comments above.	See comment #B2. Box language changed to surgical ablation. However, because these two procedures are addressed discretely in the AHRQ report, with different studies supporting PVI and Maze, text of the document

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Ident.	#	Comment	Disposition
			other than the box not revised.
B	8	Page 9: Bottom, again, surgical PVI and MAZE are the same thing.	See comment #B7
C	1	Medtronic appreciates this opportunity to comment on Oregon Health Evidence Review Commission's (HERC's) draft coverage guidance on ablation for atrial fibrillation (AF).[1] Medtronic has extensive clinical expertise and offers innovative products across several areas of cardiovascular care, including AF. We applaud the efforts of HERC to develop evidence-based coverage guidance on treatments for AF. The guidance clearly summarizes and evaluates the robust body of evidence for AF treatment strategies.	Thank you for your comment.
C	2	To ensure alignment with the clinical guidelines and avoid potential confusion, we request clarification of the term "persistently symptomatic" in the draft coverage language for pulmonary vein isolation (PVI). The coverage guidance currently states: *"Transcatheter pulmonary vein isolation is recommended for coverage for those who are persistently symptomatic despite rate control medications and antiarrhythmic medications (strong recommendation)."* This language may suggest coverage is limited to patients with *persistent* AF and does not include patients with *paroxysmal* AF. We believe this may not be HERC's intention as such language would be counter to the prevailing clinical guidelines and clinical trial evidence cited in the coverage guidance document. The 2014 AHA/ACC/HRS Atrial Fibrillation Guideline (referenced on page 13 of the coverage guidance document) strongly recommends PVI for patients with symptomatic paroxysmal or symptomatic persistent AF who are refractory or intolerant to at least 1 class I or III antiarrhythmic medication (January 2014). We propose the following revised coverage language: *Transcatheter pulmonary vein isolation is recommended for coverage for those who are symptomatic (paroxysmal AF or persistent AF) despite rate control medications or antiarrhythmic medications (strong recommendation).*	EbGS agrees that the recommendation as written can be confusing and has modified the language to clarify: Transcatheter pulmonary vein isolation is recommended for coverage for those who remain ~~are persistently~~ remain symptomatic from atrial fibrillation despite rate control medications and antiarrhythmic medications (strong recommendation)
C	3	This revised language will help to ensure alignment with current clinical practice guidelines and that the appropriate patients have access to the right treatment strategies.	EbGS agrees.

DRAFT

References Provided by Commenters

Commenter	References
C	(1) January, C. T., Calkins, H., Murray, K. T., Cigarroa, J. E., & Stevenson, W. G. (2014). 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation. *Circulation*, *129*, 000-00.

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Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society

Craig T. January, L. Samuel Wann, Joseph S. Alpert, Hugh Calkins, Joseph C. Cleveland, Jr, Joaquin E. Cigarroa, Jamie B. Conti, Patrick T. Ellinor, Michael D. Ezekowitz, Michael E. Field, Katherine T. Murray, Ralph L. Sacco, William G. Stevenson, Patrick J. Tchou, Cynthia M. Tracy and Clyde W. Yancy

Circulation. published online March 28, 2014;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society

Developed in Collaboration With the Society of Thoracic Surgeons

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This document was approved by the American College of Cardiology Board of Trustees, the American Heart Association Science Advisory and Coordinating Committee, and the Heart Rhythm Society Board of Trustees in March 2014.

The online-only Comprehensive Relationships Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000041/-/DC1.

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January, CT et al.
2014 AHA/ACC/HRS Atrial Fibrillation Guideline

The American Heart Association requests that this document be cited as follows: January CT, Wann LS, Alpert JS, Calkins H, Cleveland JC, Cigarroa JE, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation 2014;129:●●●●–●●●●.

This article is copublished in *Journal of the American College of Cardiology*.

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(*Circulation*. 2014;129:000–000.)

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DOI: 10.1161/CIR.0000000000000041

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Circulation
Journal of the American Heart Association

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Preamble

The medical profession should play a central role in evaluating the evidence related to drugs, devices, and procedures for the detection, management, and prevention of disease. When properly applied, expert analysis of available data on the benefits and risks of these therapies and procedures can improve the quality of care, optimize patient outcomes, and favorably affect costs by focusing resources on the most effective strategies. An organized and directed approach to a thorough review of evidence has resulted in the production of clinical practice guidelines that assist clinicians in selecting the best management strategy for an individual patient. Moreover, clinical practice guidelines can provide a foundation for other applications, such as performance measures, appropriate use criteria, and both quality improvement and clinical decision support tools.

The American College of Cardiology (ACC) and the American Heart Association (AHA) have jointly engaged in the production of guidelines in the area of cardiovascular disease since 1980. The ACC/AHA Task Force on Practice Guidelines (Task Force), whose charge is to develop, update, or revise practice guidelines for cardiovascular diseases and procedures, directs this effort. Writing committees are charged with the task of performing an assessment of the evidence and acting as an independent group of authors to develop, update or revise written recommendations for clinical practice.

Experts in the subject under consideration are selected from both organizations to examine subject-specific data and write guidelines. Writing committees are specifically charged to perform a literature review, weigh the strength of evidence for or against particular tests, treatments, or procedure, and include estimates of expected health outcomes where such data exist. Patient-specific modifiers, comorbidities, and issues of patient preference that may influence the choice of tests or therapies are considered, as well as frequency of follow-up and cost effectiveness. When available, information from studies on cost is considered; however, review of data on efficacy and outcomes constitutes the primary basis for preparing recommendations in this guideline.

In analyzing the data, and developing recommendations and supporting text, the writing committee uses evidence-based methodologies developed by the Task Force (1). The Class of Recommendation (COR) is an estimate of the size of the treatment effect, with consideration given to risks versus benefits, as well as evidence and/or agreement that a given treatment or procedure is or is not useful/effective or in some situations may cause harm; this is defined in Table 1. The Level of Evidence (LOE) is an estimate of the certainty or precision of the treatment effect. The writing committee reviews and ranks evidence supporting each recommendation, with the weight of evidence ranked as LOE A, B, or C, according to specific definitions that are included in Table 1. Studies are identified as observational, retrospective, prospective, or randomized, as appropriate. For certain conditions for which inadequate data are available, recommendations are based on expert consensus and clinical experience and are ranked as LOE C. When recommendations at LOE C are supported by historical clinical data, appropriate references (including clinical reviews) are cited if available. For issues for which sparse data are available, a survey of current practice among the clinician members of the writing committee is the basis for LOE C recommendations and no references are cited. The schema for COR and LOE is summarized in Table 1, which also provides suggested phrases for writing recommendations within each COR.

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A new addition to this methodology is separation of the Class III recommendations to delineate whether the recommendation is determined to be of "no benefit" or is associated with "harm" to the patient. In addition, in view of the increasing number of comparative effectiveness studies, comparator verbs and suggested phrases for writing recommendations for the comparative effectiveness of one treatment or strategy versus another are included for COR I and IIa, LOE A or B only.

In view of the advances in medical therapy across the spectrum of cardiovascular diseases, the Task Force has designated the term *guideline-directed medical therapy* (GDMT) to represent optimal medical therapy as defined by ACC/AHA guideline (primarily Class I)-recommended therapies. This new term, GDMT, is used herein and throughout subsequent guidelines.

Because the ACC/AHA practice guidelines address patient populations (and clinicians) residing in North America, drugs that are not currently available in North America are discussed in the text without a specific COR. For studies performed in large numbers of subjects outside North America, each writing committee reviews the potential impact of different practice patterns and patient populations on the treatment effect and relevance to the ACC/AHA target population to determine whether the findings should inform a specific recommendation.

The ACC/AHA practice guidelines are intended to assist clinicians in clinical decision making by describing a range of generally acceptable approaches to the diagnosis, management, and prevention of specific diseases or conditions. The guidelines attempt to define practices that meet the needs of most patients in most circumstances. The ultimate judgment about care of a particular patient must be made by the clinician and patient in light of all the circumstances presented by that patient. As a result, situations may arise in which deviations from these guidelines may be appropriate. Clinical decision making should involve consideration of the quality and availability of expertise in the area where care is provided. When these guidelines are used as the basis for regulatory or payer decisions, the goal should be improvement in quality of care. The Task Force recognizes that situations arise in which additional data are needed to inform patient care more effectively; these areas are identified within each respective guideline when appropriate.

Prescribed courses of treatment in accordance with these recommendations are effective only if followed. Because lack of patient understanding and adherence may adversely affect outcomes, clinicians should make every effort to engage the patient's active participation in prescribed medical regimens and lifestyles. In addition, patients should be informed of the risks, benefits, and alternatives to a particular treatment and should be involved in shared decision making whenever feasible, particularly for COR IIa and IIb, for which the benefit-to-risk ratio may be lower.

The Task Force makes every effort to avoid actual, potential, or perceived conflicts of interest that may arise as a result of relationships with industry and other entities (RWI) among the members of the writing committee. All writing committee members and peer reviewers of the guideline are required to disclose all

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current healthcare-related relationships, including those existing 12 months before initiation of the writing effort.

In December 2009, the ACC and AHA implemented a new RWI policy that requires the writing committee chair plus a minimum of 50% of the writing committee to have no relevant RWI (Appendix 1 includes the ACC/AHA definition of *relevance*). The Task Force and all writing committee members review their respective RWI disclosures during each conference call and/or meeting of the writing committee, and members provide updates to their RWI as changes occur. All guideline recommendations require a confidential vote by the writing committee and require approval by a consensus of the voting members. Members may not draft or vote on any recommendations pertaining to their RWI. Members who recused themselves from voting are indicated in the list of writing committee members, and specific section recusals are noted in Appendix 1. Authors' and peer reviewers' RWI pertinent to this guideline are disclosed in Appendixes 1 and 2. In addition, to ensure complete transparency, writing committee members' comprehensive disclosure information—including RWI not pertinent to this document—is available as an online supplement (http://jaccjacc.cardiosource.com/DataSupp/2014_AF_GL_RWI_Table_Comprehensive_Only_0319.pdf). Comprehensive disclosure information for the Task Force is also available online at http://www.cardiosource.org/en/ACC/About-ACC/Who-We-Are/Leadership/Guidelines-and-Documents-Task-Forces.aspx. The ACC and AHA exclusively sponsor the work of the writing committee, without commercial support. Writing committee members volunteered their time for this activity. Guidelines are official policy of both the ACC and AHA.

In an effort to maintain relevance at the point of care for clinicians, the Task Force continues to oversee an ongoing process improvement initiative. As a result, in response to pilot projects, several changes to these guidelines will be apparent, including limited narrative text, a focus on summary and evidence tables (with references linked to abstracts in PubMed), and more liberal use of summary recommendation tables (with references that support LOE) to serve as a quick reference.

In April 2011, the Institute of Medicine released 2 reports: *Finding What Works in Health Care: Standards for Systematic Reviews* and *Clinical Practice Guidelines We Can Trust* (2, 3). It is noteworthy that the Institute of Medicine cited ACC/AHA practice guidelines as being compliant with many of the proposed standards. A thorough review of these reports and of our current methodology is under way, with further enhancements anticipated.

The recommendations in this guideline are considered current until they are superseded by a focused update, the full-text guideline is revised or until a published addendum declares it out of date and no longer official ACC/AHA policy.

Jeffrey L. Anderson, MD, FACC, FAHA
Chair, ACC/AHA Task Force on Practice Guidelines

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Table 1. Applying Classification of Recommendations and Level of Evidence

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT: CLASS I	CLASS IIa	CLASS IIb	CLASS III *No Benefit* or CLASS III *Harm*
	Benefit >>> Risk Procedure/Treatment **SHOULD** be performed/administered	***Benefit >> Risk*** *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	***Benefit ≥ Risk*** *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	Procedure/Test — Treatment COR III: No benefit — Not Helpful — No Proven Benefit COR III: Harm — Excess Cost w/o Benefit or Harmful — Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit: is not recommended; is not indicated; should not be performed/administered/other; is not useful/beneficial/effective COR III: Harm: potentially harmful; causes harm; associated with excess morbidity/mortality; should not 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	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes mellitus, history of prior myocardial infarction, history of heart failure, and prior aspirin use.
†For comparative-effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

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1. Introduction

1.1. Methodology and Evidence Review

The recommendations listed in this document are, whenever possible, evidence based. An extensive evidence review, focusing on 2006 to the present, was conducted through October 2012, and selected other references through February 2014. Searches were extended to studies, reviews, and other evidence that were conducted in human subjects, published in English, and accessible via PubMed, EMBASE, Cochrane, Agency for Healthcare Research and Quality Reports, and other selected databases relevant to this guideline. Key search words included but were not limited to the following: *age, antiarrhythmic, atrial fibrillation, atrial remodeling, atrioventricular conduction, atrioventricular node, cardioversion, classification, clinical trial, complications, concealed conduction, cost-effectiveness, defibrillator, demographics, epidemiology, experimental, heart failure, hemodynamics, human, hyperthyroidism, hypothyroidism, meta-analysis, myocardial infarction, pharmacology, postoperative, pregnancy, pulmonary disease, quality of life, rate control, rhythm control, risks, sinus rhythm, symptoms,* and *tachycardia-mediated cardiomyopathy.* Additionally, the committee reviewed documents related to atrial fibrillation (AF) previously published by the ACC and AHA. References selected and published in this document are representative and not all-inclusive.

To provide clinicians with a comprehensive set of data, whenever deemed appropriate or when published, the absolute risk difference and number needed to treat or harm are provided in the guideline, along with confidence intervals (CI) and data related to the relative treatment effects such as the odds ratio (OR), relative risk (RR), hazard ratio, or incidence rate ratio.

1.2. Organization of the Writing Committee

The 2014 AF writing committee was composed of clinicians with broad expertise related to AF and its treatment, including adult cardiology, electrophysiology, cardiothoracic surgery, and heart failure (HF). The committee was assisted by staff from the ACC and AHA. Under the guidance of the Task Force, the Heart Rhythm Society was invited to be a partner organization and has provided representation. The writing committee also included a representative from the Society of Thoracic Surgeons. The rigorous methodological policies and procedures noted in the Preamble differentiate ACC/AHA guidelines from other published guidelines and statements.

1.3. Document Review and Approval

This document was reviewed by 2 official reviewers each nominated by the ACC, the AHA, and the Heart Rhythm Society, as well as 1 reviewer from the Society of Thoracic Surgeons, and 43 individual content reviewers (from the ACC Electrophysiology Committee, Adult Congenital and Pediatric Cardiology Council, Association of International Governors, Heart Failure and Transplant Council, Imaging Council, Interventional Council, Surgeons Council, and the HRS Scientific Documents Committee). All information on reviewers' RWI was distributed to the writing committee and is published in this document (Appendix 2).

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This document was approved for publication by the governing bodies of the ACC, AHA, and Heart Rhythm Society, and endorsed by the Society of Thoracic Surgeons.

1.4. Scope of the Guideline

The task of the 2014 writing committee was to establish revised guidelines for optimum management of AF. The new guideline incorporates new and existing knowledge derived from published clinical trials, basic science, and comprehensive review articles, along with evolving treatment strategies and new drugs. This guideline supersedes the "2006 ACC/AHA/ESC Guideline for the Management of Patients With Atrial Fibrillation" (4) and the 2 subsequent focused updates from 2011 (5, 6). In addition, the ACC/AHA, American College of Physicians, and American Academy of Family Physicians submitted a proposal to the Agency for Healthcare Research and Quality to perform a systematic review on specific questions related to the treatment of AF. The data from that report were reviewed by the writing committee and incorporated where appropriate (7).

The 2014 AF guideline is organized thematically with recommendations, where appropriate, provided with each section. Some recommendations from earlier guidelines have been eliminated or updated, as warranted by new evidence or a better understanding of earlier evidence. In developing the 2014 AF guideline, the writing committee reviewed prior published guidelines and related statements. Table 2 is a list of these publications and statements deemed pertinent to this effort and is intended for use as a resource.

Table 2. Associated Guidelines and Statements

Title	Organization	Publication Year/ Reference
Guidelines		
Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII)	NHLBI	2003 (8)
Assessment of Cardiovascular Risk in Asymptomatic Adults	ACCF/AHA	2010 (9)
Coronary Artery Bypass Graft Surgery	ACCF/AHA	2011 (10)
Hypertrophic Cardiomyopathy	ACCF/AHA	2011 (11)
Percutaneous Coronary Intervention	ACCF/AHA/SCAI	2011 (12)
Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease	AHA/ACCF	2011 (13)
Atrial Fibrillation*	CCS	2011 (14)
Atrial Fibrillation	ESC	2012 (15)
Device-Based Therapy	ACCF/AHA/HRS	2012 (16)
Stable Ischemic Heart Disease	ACCF/AHA/ACP/ AATS/PCNA/SCAI/STS	2012 (17)
Antithrombotic Therapy	ACCP	2012 (18)
Heart Failure	ACCF/AHA	2013 (19)
ST-Elevation Myocardial Infarction	ACCF/AHA	2013 (20)
Non–ST-Elevation Acute Coronary Syndromes	ACC/AHA	2014 In Press (21)
Valvular Heart Disease	AHA/ACC	2014 (22)
Assessment of Cardiovascular Risk	ACC/AHA	2013 (23)

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Lifestyle Management to Reduce Cardiovascular Risk	AHA/ACC	2013 (24)
Management of Overweight and Obesity in Adults	AHA/ACC/TOS	2013 (25)
Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults	ACC/AHA	2013 (26)
Statements		
Treatment of Atrial Fibrillation	AHRQ	2012 (7)
Oral Antithrombotic Agents for the Prevention of Stroke in Nonvalvular Atrial Fibrillation: a Science Advisory for Healthcare Professionals	AHA/ASA	2012 (27)
Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Patient Selection, Procedural Techniques, Patient Management and Follow-Up, Definitions, Endpoints, and Research Trial Design	HRS/EHRA/ECAS	2012 (28)

*Includes the following sections: Catheter Ablation for AF/Atrial Flutter, Prevention and Treatment of AF Following Cardiac Surgery; Rate and Rhythm Management, Prevention of Stroke and Systemic Thromboembolism in AF and Flutter; Management of Recent-Onset AF and Flutter in the Emergency Department; Surgical Therapy; The Use of Antiplatelet Therapy in the Outpatient Setting; and Focused 2012 Update of the CCS AF Guidelines: Recommendations for Stroke Prevention and Rate/Rhythm Control.

AATS indicates American Association for Thoracic Surgery; ACC, American College of Cardiology; ACCF, American College of Cardiology Foundation; ACP, American College of Physicians; ACCP, American College of Chest Physicians; AHA, American Heart Association; AHRQ, Agency for Healthcare Research and Quality; ASA, American Stroke Association; AF, atrial fibrillation; CCS, Canadian Cardiology Society; ECAS, European Cardiac Arrhythmia Society; EHRA, European Heart Rhythm Association; ESC, European Society of Cardiology; HRS, Heart Rhythm Society; JNC, Joint National Committee; NHLBI, National Heart, Lung, and Blood Institute; PCNA, Preventive Cardiovascular Nurses Association; SCAI, Society for Cardiac Angiography and Interventions; STS, Society of Thoracic Surgeons, and TOS, The Obesity Society.

2. Background and Pathophysiology

AF is a common cardiac rhythm disturbance and increases in prevalence with advancing age. Approximately 1% of patients with AF are <60 years of age, whereas up to 12% of patients are 75 to 84 years of age (29). More than one third of patients with AF are ≥80 years of age (30, 31). In the United States, the percentage of Medicare Fee-for-Service beneficiaries with AF in 2010 was reported as 2% for those <65 years of age and 9 % for those ≥65 years of age (32). For individuals of European descent, the lifetime risk of developing AF after 40 years of age is 26% for men and 23% for women (33). In African Americans, although risk factors for AF are more prevalent, the AF incidence appears to be lower (34). AF is often associated with structural heart disease and other co-occurring chronic conditions (Table 3; see also http://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Chronic-Conditions/Downloads/2012Chartbook.pdf). The mechanisms causing and sustaining AF are multifactorial, and AF can be complex and difficult for clinicians to manage. AF symptoms range from non-existent to severe. Frequent hospitalizations, hemodynamic abnormalities, and thromboembolic events related to AF result in significant morbidity and mortality. AF is associated with a 5-fold increased risk of stroke (35) and stroke risk increases with age (36). AF-related stroke is likely to be more severe than non–AF-related stroke (37). AF is also associated with a 3-fold risk of HF (38-40), and 2-fold increased risk of both dementia (41) and mortality (35). Hospitalizations with AF as the primary diagnosis are

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>467,000 annually in the United States, and AF is estimated to contribute to >99,000 deaths per year. Patients with AF are hospitalized twice as often as patients without AF; are 3 times more likely to have multiple admissions; and 2.1% of patients with AF died in the hospital compared to 0.1% without it (42, 43). AF is also expensive, adding approximately $8,700 per year (estimate from 2004 to 2006) for a patient with AF compared to a patient without AF. It is estimated that treating patients with AF adds $26 billion to the U.S. healthcare bill annually. AF affects between 2.7 million and 6.1 million American adults, and that number is expected to double over the next 25 years, adding further to the cost burden (42, 43).

AF web-based tools are available, including several risk calculators and clinical decision aids (http://www.cardiosource.org/Science-And-Quality/Clinical-Tools/Atrial-Fibrillation-Toolkit.aspx); however, these tools must be used with caution because validation across the broad range of AF patients encountered in clinical practice is incomplete.

Table 3. 10 Most Common Comorbid Chronic Conditions Among Medicare Beneficiaries With AF

Beneficiaries ≥65 y of age (N=2,426,865)				**Beneficiaries <65 y of age (N=105,878)**		
(mean number of conditions=5.8; median=6)				*(mean number of conditions=5.8; median=6)*		
	N	%			N	%
Hypertension	2,015,235	83.0		Hypertension	85,908	81.1
Ischemic heart disease	1,549,125	63.8		Ischemic heart disease	68,289	64.5
Hyperlipidemia	1,507,395	62.1		Hyperlipidemia	64,153	60.6
HF	1,247,748	51.4		HF	62,764	59.3
Anemia	1,027,135	42.3		Diabetes mellitus	56,246	53.1
Arthritis	965,472	39.8		Anemia	48,252	45.6
Diabetes mellitus	885,443	36.5		CKD	42,637	40.3
CKD	784,631	32.3		Arthritis	34,949	33.0
COPD	561,826	23.2		Depression	34,900	33.0
Cataracts	546,421	22.5		COPD	33,218	31.4

AF indicates atrial fibrillation; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disorder; and HF, heart failure.
Reproduced with permission from the Centers for Medicare and Medicaid Services (44).

2.1. Definitions and Pathophysiology of AF

AF is a supraventricular tachyarrhythmia with uncoordinated atrial activation and consequently ineffective atrial contraction (4, 28, 30). Electrocardiogram (ECG) characteristics include: 1) irregular R-R intervals (when atrioventricular [AV] conduction is present), 2) absence of distinct repeating P waves, and 3) irregular atrial activity.

Hemodynamic consequences of AF can result from a variable combination of suboptimal ventricular rate control (either too rapid or too slow), loss of coordinated atrial contraction, beat-to-beat variability in ventricular filling, and sympathetic activation (45-47). Consequences for individual patients vary, ranging from no symptoms to fatigue, palpitations, dyspnea, hypotension, syncope, or HF (48). The most common symptom

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of AF is fatigue. The appearance of AF is often associated with exacerbation of underlying heart disease, either because AF is a cause or consequence of deterioration, or because it contributes directly to deterioration (49, 50). For example, initially asymptomatic patients may develop tachycardia-induced ventricular dysfunction and HF (tachycardia-induced cardiomyopathy) when the ventricular rate is not adequately controlled (51, 52). AF also confers an increased risk of stroke and/or peripheral thromboembolism owing to the formation of atrial thrombi, usually in the left atrial appendage (LAA).

In the absence of an accessory AV pathway, the ventricular rate is determined by the conduction and refractory properties of the AV node and the sequence of wave fronts entering the AV node (53-55). L-type calcium channels are responsible for the major depolarizing current in AV nodal cells. Beta-adrenergic receptor stimulation enhances AV nodal conduction, whereas vagal stimulation (muscarinic receptor activation by acetylcholine) impedes AV nodal conduction (55). Sympathetic activation and vagal withdrawal such as with exertion or illness, accelerates the ventricular rate. Each atrial excitation wave front that depolarizes AV nodal tissue renders those cells refractory for a period of time, preventing successive impulses from propagating in the node—an effect called concealed conduction (55). This effect of concealed conduction into the AV node explains why the ventricular rate can be faster and more difficult to slow when fewer atrial wave fronts are entering the AV node, as in atrial flutter, compared to AF (53).

Loss of atrial contraction may markedly decrease cardiac output, particularly when diastolic ventricular filling is impaired by mitral stenosis, hypertension, hypertrophic cardiomyopathy (HCM), or restrictive cardiomyopathy (50, 56, 57). After restoration of sinus rhythm, atrial mechanical function fails to recover in some patients, likely as a consequence of remodeling or underlying atrial disease and duration of AF (58). Ventricular contractility is not constant during AF because of variable diastolic filling time and changes in the force-interval relationship (59, 60). Overall, cardiac output may decrease and filling pressures may increase compared to a regular rhythm at the same mean rate. In patients undergoing AV nodal ablation, irregular right ventricular (RV) pacing at the same rate as regular ventricular pacing resulted in a 15% reduction in cardiac output (60). Irregular R-R intervals also promote sympathetic activation (45, 46).

2.1.1. AF—Classification

AF may be described in terms of the duration of episodes and using a simplified scheme revised from the 2006 AF full-revision guideline, which is given in Table 4 (28, 30). Implanted loop recorders, pacemakers, and defibrillators offer the possibility of reporting frequency, rate, and duration of abnormal atrial rhythms, including AF (61, 62). Episodes often increase in frequency and duration over time.

Table 4. AF Definitions: A Simplified Scheme

Term	Definition
Paroxysmal AF	• AF that terminates spontaneously or with intervention within 7 d of onset. • Episodes may recur with variable frequency.
Persistent AF	• Continuous AF that is sustained >7 d.

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Longstanding persistent AF	• Continuous AF of >12 mo duration.
Permanent AF	• Permanent AF is used when there has been a joint decision by the patient and clinician to cease further attempts to restore and/or maintain sinus rhythm. • Acceptance of AF represents a therapeutic attitude on the part of the patient and clinician rather than an inherent pathophysiological attribute of the AF. • Acceptance of AF may change as symptoms, the efficacy of therapeutic interventions, and patient and clinician preferences evolve.
Nonvalvular AF	• AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair.

AF indicates atrial fibrillation.

The characterization of patients with AF by the duration of their AF episodes (Table 4) has clinical relevance in that outcomes of therapy, such as catheter ablation, are better for paroxysmal AF than for persistent AF (28). When sinus rhythm is restored by cardioversion, however, the ultimate duration of the AF episode(s) is not known. Furthermore, both paroxysmal and persistent AF may occur in a single individual.

"Lone AF" is a historical descriptor that has been variably applied to younger individuals without clinical or echocardiographic evidence of cardiopulmonary disease, hypertension, or diabetes mellitus (63). Because definitions are variable, the term "lone AF'" is potentially confusing and should not be used to guide therapeutic decisions.

2.1.1.1. Associated Arrhythmias

Other atrial arrhythmias are often encountered in patients with AF. Atrial tachycardias are characterized by an atrial rate of ≥100 bpm with discrete P waves and atrial activation sequences. Atrial activation is most commonly the same from beat to beat.

Focal atrial tachycardia is characterized by regular, organized atrial activity with discrete P waves, typically with an isoelectric segment between P waves (Figure 1) (64, 65). Electrophysiological mapping reveals a focal point of origin. The mechanism can be automaticity or a micro–re-entry circuit (66, 67). In multifocal atrial tachycardia, the atrial activation sequence and P-wave morphology vary (64).

2.1.1.2. Atrial Flutter and Macro–Re-Entrant Atrial Tachycardia

Early studies designated atrial flutter with a rate of 240 bpm to 340 bpm as "type I flutter," and this term has commonly been applied to typical atrial flutter (65, 68). An ECG appearance of atrial flutter with a rate faster than 340 bpm was designated as "type II flutter," the mechanism of which remains undefined (69). It is now recognized that tachycardias satisfying either of these descriptions can be due to re-entrant circuits or to rapid focal atrial tachycardia.

Typical atrial flutter is a macro–re-entrant atrial tachycardia that usually proceeds up the atrial septum, down the lateral atrial wall, and through the cavotricuspid (subeustachian) isthmus between the tricuspid valve annulus and inferior vena cava, where it is commonly targeted for ablation. It is also known as "common atrial flutter" or "cavotricuspid isthmus-dependent atrial flutter" (64). This sequence of activation (also referred to as "counterclockwise atrial flutter") produces predominantly negative "saw tooth" flutter waves in ECG leads II,

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III, and aVF, and a positive deflection in V1 (Figure 1). The atrial rate is typically 240 bpm to 300 bpm, but conduction delays in the atrial circuit due to scars from prior ablation, surgery, or antiarrhythmic drugs, can slow the rate to <150 bpm in some patients (65). When the circuit revolves in the opposite direction, flutter waves typically appear positive in the inferior ECG leads and negative in V1 (reverse typical atrial flutter, also referred to as "clockwise typical atrial flutter") (65). Unusual flutter wave morphologies occur in the presence of substantial atrial disease, prior surgery, or radiofrequency catheter ablation; the P-wave morphology is not a reliable indicator of the type of macro–re-entrant atrial tachycardia in these situations (70-72). Atrial flutter is often a persistent rhythm that requires electrical cardioversion or radiofrequency catheter ablation for termination. It is often initiated by a brief episode of atrial tachycardia or by AF (69, 73). This relationship between AF and atrial flutter may explain why ≥80% of patients who undergo radiofrequency catheter ablation of typical atrial flutter will have AF within the following 5 years (74).

AF may be misdiagnosed as atrial flutter when AF activity is prominent on ECG (75, 76). Atrial flutter may also arise during treatment with antiarrhythmic agents prescribed to prevent recurrent AF (77), particularly sodium channel blocking antiarrhythmic drugs such as flecainide or propafenone. Catheter ablation of the cavotricuspid isthmus is effective for prevention of recurrent atrial flutter in these patients while allowing continued antiarrhythmic treatment to prevent recurrent AF (78).

Atypical flutter, or "noncavotricuspid isthmus-dependent macro–re-entrant atrial tachycardia," describes macro–re-entrant atrial tachycardias that are not one of the typical forms of atrial flutter that use the cavotricuspid isthmus (64). A variety of re-entrant circuits has been described, including "perimitral flutter" re-entry involving the roof of the left atrium (LA), and re-entry around scars in the left or right atrium, often from prior surgery or ablation (65, 67, 79). Complex re-entry circuits with >1 re-entry loop or circuit can occur and often coexist with common atrial flutter. These arrhythmias are not abolished by ablation of the cavotricuspid isthmus, but their recognition and distinction from common atrial flutter usually requires electrophysiologic study with atrial mapping (65). A variety of terms has been applied to these arrhythmias according to the re-entry circuit location, including "LA flutter" and "LA macro–re-entrant tachycardia" (65, 67, 79, 80).

Figure 1. Atrial Tachycardias

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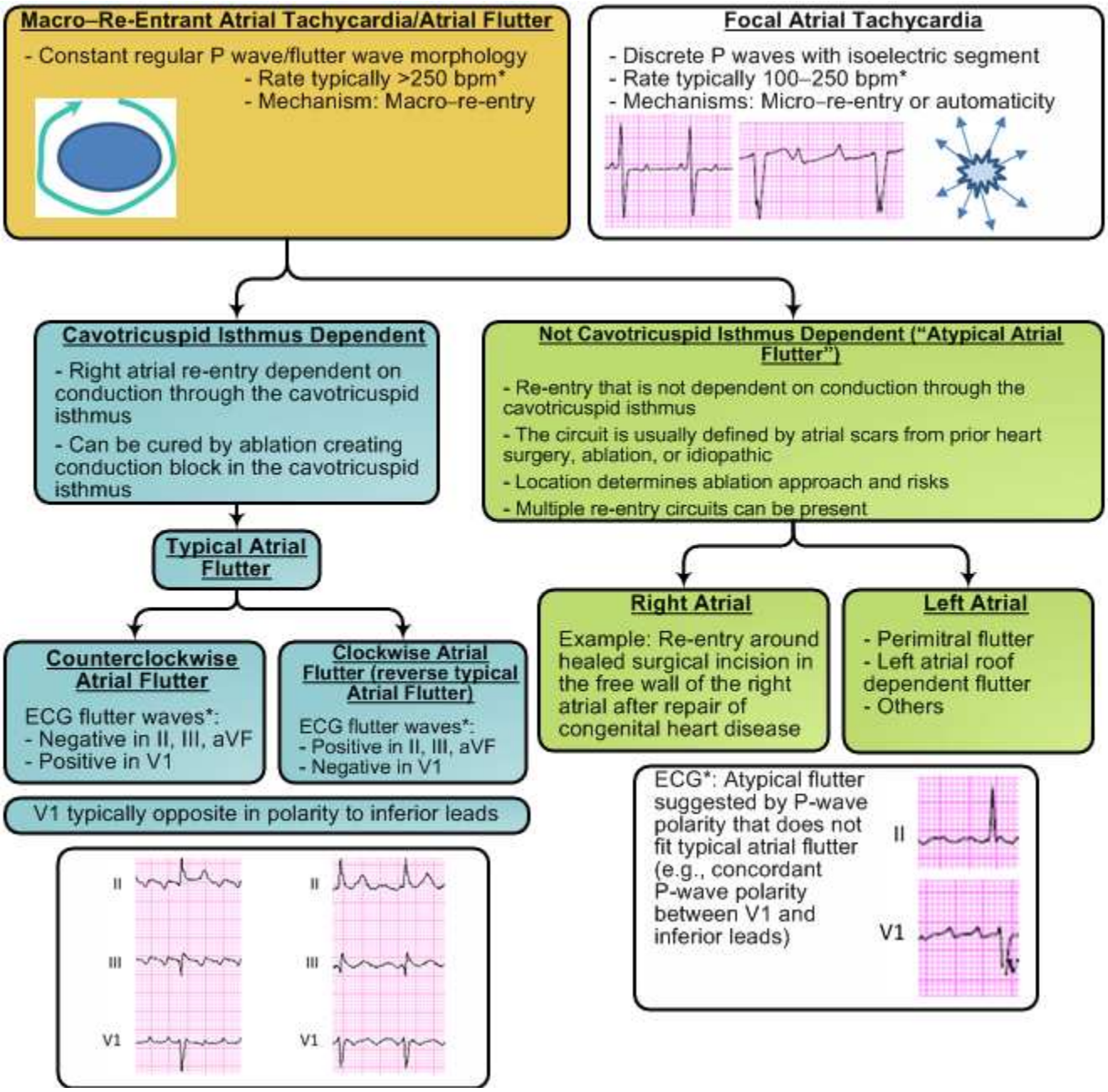

Diagram summarizing types of atrial tachycardias often encountered in patients with a history of AF, including those seen after catheter or surgical ablation procedures. P-wave morphologies are shown for common types of atrial flutter; however, the P-wave morphology is not always a reliable guide to the re-entry circuit location or to the distinction between common atrial flutter and other macro–re-entrant atrial tachycardias.
*Exceptions to P-wave morphology and rate are common in scarred atria.

AF indicates atrial fibrillation and ECG, electrocardiogram (72, 80).

2.2. Mechanisms of AF and Pathophysiology

AF occurs when structural and/or electrophysiologic abnormalities alter atrial tissue to promote abnormal impulse formation and/or propagation (Figure 2). These abnormalities are caused by diverse pathophysiologic

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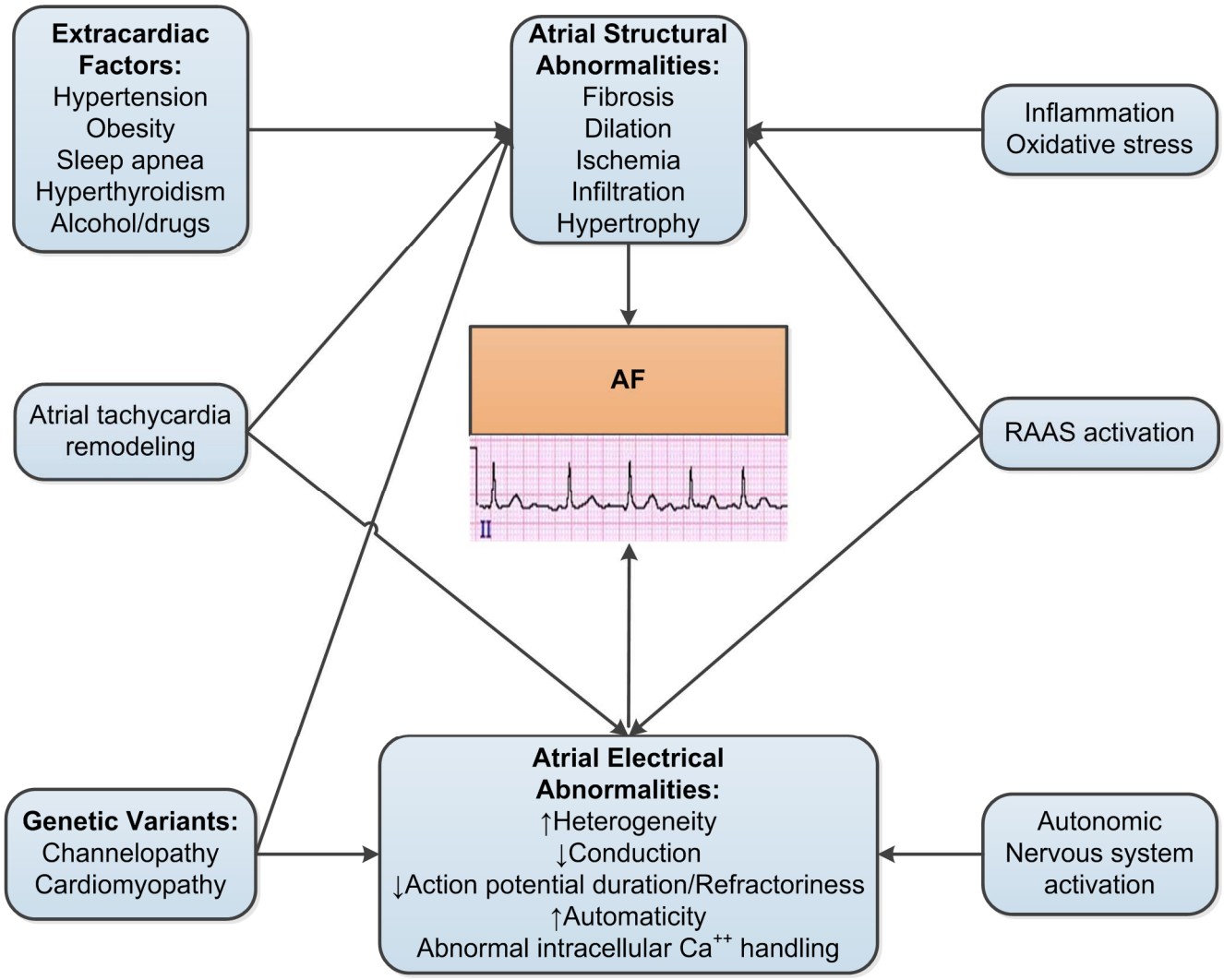
mechanisms (28, 81, 82), such that AF represents a final common phenotype for multiple disease pathways and mechanisms that are incompletely understood.

Figure 2. Mechanisms of AF



AF indicates atrial fibrillation; Ca^{++} ionized calcium; and RAAS, renin-angiotensin-aldosterone system.

2.2.1. Atrial Structural Abnormalities

Any disturbance of atrial architecture potentially increases susceptibility to AF (83). Such changes (e.g., inflammation, fibrosis, hypertrophy) occur most commonly in the setting of underlying heart disease associated with hypertension, coronary artery disease (CAD), valvular heart disease, cardiomyopathies, and HF which tend to increase LA pressure, cause atrial dilation, and alter wall stress. Similarly, atrial ischemia from CAD and infiltrative diseases such as amyloidosis, hemochromatosis, and sarcoidosis, can also promote AF. Additional promoters include extracardiac factors such as hypertension, sleep apnea, obesity, alcohol/drugs, and hyperthyroidism, which have pathophysiologic effects on atrial cellular structure and/or function. Even in patients with paroxysmal AF without recognized structural heart disease, atrial biopsies have revealed

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inflammatory infiltrates consistent with myocarditis and fibrosis (84). In addition, prolonged rapid atrial pacing increases arrhythmia susceptibility and forms the basis for a well-studied model of AF. In the atria of patients with established AF and of animals subjected to rapid atrial pacing, there is evidence of myocyte loss from glycogen deposits and of mitochondrial disturbances and gap-junction abnormalities that cause cell necrosis and apoptosis (85-87). These structural abnormalities can heterogeneously alter impulse conduction and/or refractoriness, generating an arrhythmogenic substrate.

A common feature of both experimental and human AF is myocardial fibrosis (88). The atria are more sensitive to profibrotic signaling and harbor a greater number of fibroblasts than the ventricles. Atrial stretch activates the renin-angiotensin-aldosterone system, which generates multiple downstream profibrotic factors, including transforming growth factor-beta$_1$. Additional mechanisms, including inflammation and genetic factors, can also promote atrial fibrosis. The canine rapid ventricular pacing model of HF causes extensive atrial fibrosis and increases AF susceptibility (89). Fibrosis also occurs in the rapid atrial pacing model of AF. Late gadolinium-enhancement magnetic resonance imaging is used to image and quantitate atrial fibrosis noninvasively (90-95). Human studies show a strong correlation between regions of low voltage on electro-anatomic mapping and areas of late enhancement on magnetic resonance imaging. Preliminary results suggest that the severity of atrial fibrosis correlates with the risk of stroke (91) and decreased response to catheter ablation (90).

2.2.2. Electrophysiologic Mechanisms

AF requires both a trigger for initiation and an appropriate anatomic substrate for maintenance, both of which are potential targets for therapy. Several hypotheses have been proposed to explain the electrophysiologic mechanisms that initiate and maintain AF (28). In humans, the situation is complex, and it is likely that multiple mechanisms coexist in an individual patient.

2.2.2.1. Triggers of AF

Ectopic focal discharges often initiate AF (96-98). Rapidly firing foci initiating paroxysmal AF arise most commonly from LA myocardial sleeves that extend into the pulmonary veins. These observations led to the development of pulmonary vein isolation as the cornerstone for radiofrequency catheter ablation strategies (28). Unique anatomic and electrophysiologic features of the pulmonary veins and atriopulmonary vein junctions may account for their arrhythmogenic nature. Atrial myocardial fibers are oriented in disparate directions around the pulmonary veins and the posterior LA, with considerable anatomic variability among individuals. Conduction abnormalities that promote re-entry are likely due to relatively depolarized resting potentials in pulmonary vein myocytes that promote sodium channel inactivation and to the abrupt changes in fiber orientation. Re-entry is further favored by abbreviated action potentials and refractoriness in pulmonary vein myocytes (99). Isolated pulmonary vein myocytes also demonstrate abnormal automaticity and triggered activity that could promote rapid focal firing. Additional potential sources for abnormal activity include interstitial cells (similar to pacemaker cells in the gastrointestinal tract) (100) and melanocytes (101), both of which have been identified in

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pulmonary veins. Although the pulmonary veins are the most common sites for ectopic focal triggers, triggers can also arise elsewhere, including the posterior LA, ligament of Marshall, coronary sinus, venae cavae, septum, and appendages.

Abnormal intracellular calcium handling may also play a role in AF owing to diastolic calcium leak from the sarcoplasmic reticulum, which can trigger delayed after depolarizations (102-106).

2.2.2.2. Maintenance of AF

Theories proposed to explain the perpetuation and maintenance of AF include 1) multiple independent re-entrant wavelets associated with heterogeneous conduction and refractoriness; 2) ≥1 rapidly firing foci, which may be responsive to activity from cardiac ganglion plexi; and 3) ≥1 rotors, or spiral wave re-entrant circuits (28, 82, 88, 107-113). With a single rapid focus or rotor excitation, wave fronts may encounter refractory tissue and break up during propagation, resulting in irregular or fibrillatory conduction (28, 107, 110). Both rapid focal firing and re-entry may be operative during AF.

These presumed mechanisms have driven the development of therapies. The atrial maze procedure and ablation lines may interrupt paths for multiple wavelets and spiral re-entry. Using a biatrial phase mapping approach, a limited number of localized, rapid drivers (mean of approximately 2 per patient) were identified in a small group of patients with various types of AF (112). In most cases, these localized sources appeared to be re-entrant, while in others they were consistent with focal triggers and radiofrequency catheter ablation targeting of these sites often terminated or slowed AF. Other investigators, using a noninvasive continuous biatrial mapping system, report contrasting results, observing mostly evidence for multiple wavelets and focal sites rather than rotor activity (114).

Some investigators targeted regions in which electrogram recordings show rapid complex atrial fractionated electrograms, which are felt to be indicative of the substrate for AF or markers for ganglion plexi (see Section 2.2.2.3. for ablation of AF) (109). The relation of complex atrial fractionated electrograms to AF remains controversial.

2.2.2.3. Role of the Autonomic Nervous System

Autonomic stimulation can provoke AF (28, 98, 115). Activation of the parasympathetic and/or sympathetic limbs can provoke atrial arrhythmias (108, 116). Acetylcholine activates a specific potassium current, $I_{K,ACh}$, that heterogeneously shortens atrial action potential duration and refractoriness, increasing susceptibility to re-entry. Sympathetic stimulation increases intracellular calcium, which promotes automaticity and triggered activity. Increased parasympathetic and/or sympathetic activity prior to onset of AF has been observed in some animal models and humans (117, 118).

Plexi of autonomic ganglia that constitute the intrinsic cardiac autonomic nervous system are located in epicardial fat near the pulmonary vein-LA junctions and the ligament of Marshall. Stimulation of the ganglia in animals elicits repetitive bursts of rapid atrial activity. These plexi are often located in proximity to atrial sites

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where complex atrial fractionated electrograms are recorded. Ablation targeting these regions improved outcomes over pulmonary vein isolation alone in some but not all studies (119-121).

In some patients with structurally normal hearts, AF is precipitated during conditions of high-parasympathetic tone, such as during sleep and following meals, and is referred to as "vagally mediated AF" (122). Avoidance of drugs, such as digoxin, that enhance parasympathetic tone has been suggested in these patients, but this remains an unproven hypothesis. Catheter ablation targeting ganglion plexi involved in vagal responses abolished AF in only 2 of 7 patients in 1 small series (120). Adrenergic stimulation, as during exercise, can also provoke AF in some patients (123).

2.2.3. Pathophysiologic Mechanisms

2.2.3.1. Atrial Tachycardia Remodeling

AF often progresses from paroxysmal to persistent over a variable period of time. Cardioversion of AF and subsequent maintenance of sinus rhythm are more likely to be successful when AF duration is <6 months (124). The progressive nature of AF is consistent with studies demonstrating that AF causes electrical and structural remodeling such that "AF begets AF" (125, 126).

2.2.3.2. Inflammation and Oxidative Stress

Inflammation (e.g., associated with pericarditis and cardiac surgery), may be linked to AF and can be correlated with a rise in plasma concentrations of C-reactive protein (81). Inflammatory infiltrates consistent with myocarditis are often present in the atria of patients with AF and in animals with atrial dilation. Plasma concentrations of C-reactive protein and interleukin-6 are elevated in AF; increased C-reactive protein predicts the development of AF and relapse after cardioversion; and genetic variants in the interleukin-6 promoter region may influence the development of postoperative AF. In the canine pericarditis and atrial tachypacing models, prednisone suppresses AF susceptibility and reduces plasma concentrations of C-reactive protein (127).

Aging, environmental stress, inflammation, and activation of the renin-angiotensin-aldosterone system can cause oxidative damage in the atrium. Oxidative changes are present in the atrial tissue of patients with AF and are associated with upregulation of genes involved in the production of reactive oxygen species. In human AF and a porcine model of atrial tachypacing, atrial superoxide production increased, with an apparent contribution of NAD(P)H oxidase (128). The antioxidant ascorbate attenuated electrical remodeling in the canine atrial tachypacing model and reduced postoperative AF in a small study in humans (129).

2.2.3.3. The Renin-Angiotensin-Aldosterone System

Stimulation of the renin-angiotensin-aldosterone system promotes structural and likely electrophysiologic effects in the atrium and ventricle that increase arrhythmia susceptibility (130-133). In addition to adverse hemodynamic effects, activation of multiple cell signaling cascades promotes increased intracellular calcium, hypertrophy, apoptosis, cytokine release and inflammation, oxidative stress, and production of growth-related factors that also stimulate fibrosis, as well as possible modulation of ion channel and gap-junction dynamics.

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Components of the renin-angiotensin-aldosterone system (including angiotensin II, angiotensin-converting enzyme [ACE], and aldosterone) are synthesized locally in the atrial myocardium and are increased during atrial tachypacing and AF. Variants in the ACE gene that increase angiotensin II plasma concentrations can elevate risk of AF, while selective cardiac overexpression of ACEs causes atrial dilation, fibrosis, and increased susceptibility of AF. Therapy with these agents can reduce the occurrence of AF in patients with hypertension or left ventricular (LV) dysfunction but does not help prevent recurrence of AF in the absence of these other indications for these drugs (Section 6.2.1).

Aldosterone plays an important role in angiotensin II-mediated inflammation and fibrosis; in patients with primary hyperaldosteronism, the incidence of AF is increased. In experimental models of HF, spironolactone and eplerenone decreased atrial fibrosis and/or susceptibility of AF. Eplerenone therapy is associated with decreased AF in patients with HF (134).

2.2.3.4. Risk Factors and Associated Heart Disease

Multiple clinical risk factors, electrocardiographic and echocardiographic features, and biochemical makers are associated with an increased risk of AF (Table 5). One epidemiologic analysis found that 56% of the population-attributable risk of AF could be explained by ≥1 common risk factor (135). Thus, it may be possible to prevent some cases of AF through risk factor modification such as blood pressure control or weight loss.

Many potentially "reversible" causes of AF have been reported, including binge drinking, cardiothoracic and noncardiac surgery, myocardial infarction (MI), pericarditis, myocarditis, hyperthyroidism, electrocution, pneumonia, and pulmonary embolism (10, 49, 136-138). AF that occurs in the setting of Wolff-Parkinson-White (WPW) syndrome, AV nodal re-entrant tachycardia, or atrial ectopic tachycardia may resolve after catheter ablation for these arrhythmias (69). It is important to recognize that there are few data to support the notion that patients with AF that occurs in the setting of 1 of these potentially "reversible" conditions are, in fact, cured of AF after effective treatment or elimination of the condition. Since long-term follow-up data are not available in these clinical scenarios and AF may recur, these patients should receive careful follow-up.

Table 5. Selected Risk Factors and Biomarkers for AF

Clinical Risk Factors	References
Increasing age	(139)
Hypertension	(139)
Diabetes mellitus	(139)
MI	(139)
VHD	(139)
HF	(38, 139)
Obesity	(140-142)
Obstructive sleep apnea	(142)
Cardiothoracic surgery	(137)
Smoking	(143)
Exercise	(144-146)
Alcohol use	(147-149)
Hyperthyroidism	(150-152)

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Increased pulse pressure	(153)
European ancestry	(154)
Family history	(155)
Genetic variants	(156-159)
Electrocardiographic	
LVH	(35)
Echocardiographic	
LA enlargement	(35, 160)
Decreased LV fractional shortening	(35)
Increased LV wall thickness	(35)
Biomarkers	
Increased CRP	(86, 161)
Increased BNP	(162, 163)

AF indicates atrial fibrillation; BNP, B-type natriuretic peptide; CRP, C-reactive protein; HF, heart failure; LA, left atrial; LV, left ventricular; LVH, left ventricular hypertrophy; MI, myocardial infarction; and VHD, valvular heart disease.

See Online Data Supplements 1 and 2 for additional data on electrophysiologic and pathophysiologic mechanisms (http://jaccjacc.cardiosource.com/DataSupp/MASTER_2014_AF_Evidence_Table_Supplement_03182014.pdf).

3. Clinical Evaluation: Recommendation

Class I

1. **Electrocardiographic documentation is recommended to establish the diagnosis of AF. *(Level of Evidence: C)***

The diagnosis of AF in a patient is based on the patient's clinical history and physical examination and is confirmed by ECG, ambulatory rhythm monitoring (e.g., telemetry, Holter monitor, event recorders), implanted loop recorders, pacemakers or defibrillators, or, in rare cases, by electrophysiological study. The clinical evaluations, including additional studies that may be required, are summarized in Appendix 4.

3.1. Basic Evaluation of the Patient With AF

3.1.1. Clinical History and Physical Examination

The initial evaluation of a patient with suspected or proven AF involves characterizing the pattern of the arrhythmia (paroxysmal, persistent, longstanding persistent, or permanent), determining its cause, defining associated cardiac and extracardiac disease, and assessing thromboembolic risk. Symptoms, prior treatment, family history, and a review of associated conditions and potentially reversible risk factors as outlined in Table 5 should be recorded.

The physical examination suggests AF by the presence of an irregular pulse, irregular jugular venous pulsations, and variation in the intensity of the first heart sound or absence of a fourth sound previously heard during sinus rhythm. Physical examination may also disclose associated valvular heart disease or myocardial

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abnormalities. The pulse in atrial flutter is often regular and rapid, and venous oscillations may be visible in the jugular pulse.

3.1.2. Investigations

An ECG, or other electrocardiographic recording, is the essential tool for confirming AF. A chest radiograph should be done if pulmonary disease or HF is suspected and may also detect enlargement of the cardiac chambers. As part of the initial evaluation, all patients with AF should have a 2-dimensional transthoracic echocardiogram to detect underlying structural heart disease, assess cardiac function, and evaluate atrial size. Additional laboratory evaluation should include assessment of serum electrolytes; thyroid, renal, and hepatic function; and a blood count.

Transesophageal Echocardiography (TEE): TEE is the most sensitive and specific technique to detect LA thrombi as a potential source of systemic embolism in AF and can be used to guide the timing of cardioversion or catheter ablation procedures (Section 6.1.1). TEE can also identify features associated with an increased risk of LA thrombus formation, including reduced LAA flow velocity, spontaneous LA contrast, and aortic atheroma. In 5% to 15% of patients with AF, a TEE before planned cardioversion revealed a LA or LAA thrombus (164, 165).

Electrophysiological Study: An electrophysiological study can be helpful when initiation of AF is due to a supraventricular tachycardia, such as AV node re-entrant tachycardia, AV re-entry involving an accessory pathway, or ectopic atrial tachycardia. Ablation of the supraventricular tachycardia may prevent or reduce recurrences of AF. Electrophysiological study is often warranted in patients with a delta wave on the surface ECG indicating pre-excitation. Some patients with AF also have atrial flutter that may benefit from treatment with radiofrequency catheter ablation. AF associated with rapid ventricular rates and a wide-complex QRS (aberrant conduction) may sometimes be mislabeled as ventricular tachycardia, and an electrophysiological study can help establish the correct diagnosis.

Additional Investigation of Selected Patients With AF: Plasma levels of B-type natriuretic peptide or N-terminal pro- B-type natriuretic peptide may be elevated in patients with paroxysmal and persistent AF in the absence of clinical HF, and levels decrease rapidly after restoration of sinus rhythm. A sleep study may be useful if sleep apnea is suspected (166).

3.1.3. Rhythm Monitoring and Stress Testing

Prolonged or frequent monitoring may be necessary to reveal episodes of asymptomatic AF. ECG, ambulatory rhythm monitoring (e.g., telemetry, Holter monitor, and event recorders), and exercise testing can be useful to judge the adequacy of rate control. Patient-activated ECG event recorders can help assess the relation to symptoms, whereas auto-triggered event recorders may detect asymptomatic episodes. These technologies may also provide valuable information to guide drug dosage for rate control or rhythm management.

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4. Prevention of Thromboembolism

4.1. Risk-Based Antithrombotic Therapy: Recommendations

See Table 6 for a summary of recommendations from this section.

Class I

1. **In patients with AF, antithrombotic therapy should be individualized based on shared decision-making after discussion of the absolute and RRs of stroke and bleeding, and the patient's values and preferences.** ***(Level of Evidence: C)***
2. **Selection of antithrombotic therapy should be based on the risk of thromboembolism irrespective of whether the AF pattern is paroxysmal, persistent, or permanent (167-170).** ***(Level of Evidence: B)***
3. **In patients with nonvalvular AF, the CHA_2DS_2-VASc score is recommended for assessment of stroke risk (171-173).** ***(Level of Evidence: B)***
4. **For patients with AF who have mechanical heart valves, warfarin is recommended and the target international normalized ratio (INR) intensity (2.0 to 3.0 or 2.5 to 3.5) should be based on the type and location of the prosthesis (174-176).** ***(Level of Evidence: B)***
5. **For patients with nonvalvular AF with prior stroke, transient ischemic attack (TIA), or a CHA_2DS_2-VASc score of 2 or greater, oral anticoagulants are recommended. Options include: warfarin (INR 2.0 to 3.0) (171-173)** ***(Level of Evidence: A)*****, dabigatran (177)** ***(Level of Evidence: B)*****, rivaroxaban (178)** ***(Level of Evidence: B)*****, or apixaban (179).** ***(Level of Evidence: B)***
6. **Among patients treated with warfarin, the INR should be determined at least weekly during initiation of antithrombotic therapy and at least monthly when anticoagulation (INR in range) is stable (180-182).** ***(Level of Evidence: A)***
7. **For patients with nonvalvular AF unable to maintain a therapeutic INR level with warfarin, use of a direct thrombin or factor Xa inhibitor (dabigatran, rivaroxaban, or apixaban) is recommended.** ***(Level of Evidence: C)***
8. **Re-evaluation of the need for and choice of antithrombotic therapy at periodic intervals is recommended to reassess stroke and bleeding risks.** ***(Level of Evidence: C)***
9. **Bridging therapy with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) is recommended for patients with AF and a mechanical heart valve undergoing procedures that require interruption of warfarin. Decisions regarding bridging therapy should balance the risks of stroke and bleeding.** ***(Level of Evidence: C)***
10. **For patients with AF without mechanical heart valves who require interruption of warfarin or newer anticoagulants for procedures, decisions about bridging therapy (LMWH or UFH) should balance the risks of stroke and bleeding and the duration of time a patient will not be anticoagulated.** ***(Level of Evidence: C)***
11. **Renal function should be evaluated prior to initiation of direct thrombin or factor Xa inhibitors and should be re-evaluated when clinically indicated and at least annually (183-185).** ***(Level of Evidence: B)***
12. **For patients with atrial flutter, antithrombotic therapy is recommended according to the same risk profile used for AF.** ***(Level of Evidence: C)***

Class IIa

1. **For patients with nonvalvular AF and a CHA_2DS_2-VASc score of 0, it is reasonable to omit antithrombotic therapy (183, 184).** ***(Level of Evidence: B)***
2. **For patients with nonvalvular AF with a CHA_2DS_2-VASc score of 2 or greater and who have end-stage CKD (creatinine clearance [CrCl] <15 mL/min) or are on hemodialysis, it is reasonable to prescribe warfarin (INR 2.0 to 3.0) for oral anticoagulation (185).** ***(Level of Evidence: B)***

Class IIb

1. **For patients with nonvalvular AF and a CHA_2DS_2-VASc score of 1, no antithrombotic therapy or treatment with an oral anticoagulant or aspirin may be considered.** ***(Level of Evidence: C)***

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2. **For patients with nonvalvular AF and moderate-to-severe CKD with CHA_2DS_2-VASc scores of 2 or greater, treatment with reduced doses of direct thrombin or factor Xa inhibitors may be considered (e.g., dabigatran, rivaroxaban, or apixaban), but safety and efficacy have not been established.** ***(Level of Evidence: C)***
3. **In patients with AF undergoing percutaneous coronary intervention,* bare-metal stents may be considered to minimize the required duration of dual antiplatelet therapy. Anticoagulation may be interrupted at the time of the procedure to reduce the risk of bleeding at the site of peripheral arterial puncture.** ***(Level of Evidence: C)***
4. **Following coronary revascularization (percutaneous or surgical) in patients with AF and a CHA_2DS_2-VASc score of 2 or greater, it may be reasonable to use clopidogrel (75 mg once daily) concurrently with oral anticoagulants but without aspirin (186).** ***(Level of Evidence: B)***

Class III: No Benefit

1. **The direct thrombin inhibitor, dabigatran, and the factor Xa inhibitor, rivaroxaban, are not recommended in patients with AF and end-stage CKD or on hemodialysis because of the lack of evidence from clinical trials regarding the balance of risks and benefits (177-179, 187-189).** ***(Level of Evidence: C)***

Class III: Harm

1. **The direct thrombin inhibitor, dabigatran, should not be used in patients with AF and a mechanical heart valve (190).** ***(Level of Evidence: B)***

*See the 2011 percutaneous coronary intervention guideline for type of stent and duration of dual antiplatelet therapy recommendations (12).

Table 6. Summary of Recommendations for Prevention of Thromboembolism in Patients With AF

Recommendations	COR	LOE	References
Antithrombotic therapy based on shared decision-making, discussion of risks of stroke and bleeding, and patient's preferences	I	C	N/A
Antithrombotic therapy selection based on risk of thromboembolism	I	B	(167-170)
CHA_2DS_2-VASc score recommended to assess stroke risk	I	B	(171-173)
Warfarin recommended with mechanical heart valves. Target INR intensity should be based on the type and location of prosthesis	I	B	(174-176)
With prior stroke, TIA, or CHA_2DS_2-VASc score ≥2, oral anticoagulants recommended. Options include:			
• Warfarin	I	A	(171-173)
• Dabigatran, rivaroxaban, or apixaban	I	B	(177-179)
With warfarin, determine INR at least weekly during initiation and monthly when stable	I	A	(180-182)
Direct thrombin or factor Xa inhibitor recommended, if unable to maintain therapeutic INR	I	C	N/A
Re-evaluate the need for anticoagulation at periodic intervals	I	C	N/A
Bridging therapy with LMWH or UFH recommended with a mechanical heart valve if warfarin is interrupted. Bridging therapy should balance risks of stroke and bleeding	I	C	N/A
Without a mechanical heart valve, bridging therapy decisions should balance stroke and bleeding risks against the duration of time patient will not be anticoagulated	I	C	N/A
Evaluate renal function prior to initiation of direct thrombin or factor Xa inhibitors, and re-evaluate when clinically indicated and at least annually	I	B	(183-185)

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For atrial flutter, antithrombotic therapy is recommended as for AF	I	C	N/A
With nonvalvular AF and CHA_2DS_2-VASc score of 0, it is reasonable to omit antithrombotic therapy	IIa	B	(183, 184)
With CHA_2DS_2-VASc score ≥2 and end-stage CKD (CrCl <15 mL/min) or on hemodialysis, it is reasonable to prescribe warfarin for oral anticoagulation	IIa	B	(185)
With nonvalvular AF and a CHA_2DS_2-VASc score of 1, no antithrombotic therapy or treatment with an oral anticoagulant or aspirin may be considered	IIb	C	N/A
With moderate-to-severe CKD and CHA_2DS_2-VASc scores of ≥2, reduced doses of direct thrombin or factor Xa inhibitors may be considered	IIb	C	N/A
For PCI,* BMS may be considered to minimize duration of DAPT	IIb	C	N/A
Following coronary revascularization in patients with CHA_2DS_2-VASc score of ≥2, it may be reasonable to use clopidogrel concurrently with oral anticoagulants, but without aspirin	IIb	B	(186)
Direct thrombin, dabigatran, and factor Xa inhibitor, rivaroxaban, are not recommended with AF and end-stage CKD or on hemodialysis because of the lack of evidence from clinical trials regarding the balance of risks and benefits	III: No Benefit	C	(177-179, 187-189)
Direct thrombin inhibitor, dabigatran, should not be used with a mechanical heart valve	III: Harm	B	(190)

*See the 2011 percutaneous coronary intervention guideline for type of stent and duration of dual antiplatelet therapy recommendations (12).
AF indicates atrial fibrillation; BMS, bare-metal stent; CKD, chronic kidney disease; COR, Class of Recommendation; CrCl, creatinine clearance; DAPT, dual antiplatelet therapy; INR, international normalized ratio; LOE, Level of Evidence; LMWH, low-molecular-weight heparin; N/A, not applicable; PCI, percutaneous coronary intervention; TIA, transient ischemic attack; and UFH, unfractionated heparin.

4.1.1. Selecting an Antithrombotic Regimen—Balancing Risks and Benefits

AF, whether paroxysmal, persistent, or permanent, and whether symptomatic or silent, significantly increases the risk of thromboembolic ischemic stroke (191-194). Nonvalvular AF increases the risk of stroke 5 times and AF in the setting of mitral stenosis increases the risk of stroke 20 times (195) over patients in sinus rhythm. Thromboembolism occurring with AF is associated with a greater risk of recurrent stroke, more severe disability, and mortality (196). Silent AF is also associated with ischemic stroke (191-194). The appropriate use of antithrombotic therapy, and the control of other risk factors including hypertension, and hypercholesterolemia, substantially reduces stroke risk.

Antithrombotic agents in routine use for the prevention of thromboembolism in patients with nonvalvular AF include anticoagulant drugs (UFH and LMWH, warfarin, and direct thrombin and factor Xa inhibitors) and antiplatelet drugs (aspirin and clopidogrel). While anticoagulants have been effective in reducing ischemic stroke in multiple randomized controlled trials (RCTs), their use is associated with an increased risk of bleeding, ranging from minor bleeding to fatal intracranial or extracranial hemorrhage. Platelet inhibitors (alone or in combination) are less effective than warfarin, better tolerated by some patients, and are associated with a lower risk of intracerebral hemorrhage. However, they have similar overall rates of major bleeding in some studies (184, 189, 197-199). Careful consideration is required to balance the benefits and the risks of bleeding in each individual patient.

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4.1.1.1. Risk Stratification Schemes ($CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED)

One meta-analysis has stratified ischemic stroke risk among patients with nonvalvular AF using the AF Investigators (200); the ($CHADS_2$) Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Prior Stroke or TIA or Thromboembolism (doubled) score (201); or the (CHA_2DS_2-VASc) Congestive heart failure, Hypertension, Age ≥75 years (doubled), Diabetes mellitus, Prior Stroke or TIA or thromboembolism (doubled), Vascular disease, Age 65 to74 years, Sex category point score systems (Table 7) (15).

Table 7. Comparison of the $CHADS_2$ and CHA_2DS_2-VASc Risk Stratification Scores for Subjects With Nonvalvular AF

Definition and Scores for $CHADS_2$ and CHA_2DS_2-VASc	
	Score
$CHADS_2$ acronym	
Congestive HF	1
Hypertension	1
Age ≥75 y	1
Diabetes mellitus	1
Stroke/TIA/TE	2
Maximum Score	6
CHA_2DS_2-VASc acronym	
Congestive HF	1
Hypertension	1
Age ≥75 y	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (prior MI, PAD, or aortic plaque)	1
Age 65–74 y	1
Sex category (i.e., female sex)	1
Maximum Score	9

Stroke Risk Stratification With the $CHADS_2$ and CHA_2DS_2-VASc scores	
	Adjusted stroke rate (% per y)
$CHADS_2$ acronym*	
0	1.9%
1	2.8%
2	4.0%
3	5.9%
4	8.5%
5	12.5%
6	18.2%
CHA_2DS_2-VASc acronym†	
0	0%
1	1.3%
2	2.2%
3	3.2%
4	4.0%
5	6.7%
6	9.8%
7	9.6%
8	6.7%
9	15.20%

*These adjusted-stroke rates are based on data for hospitalized patients with AF and were published in 2001 (201). Because stroke rates are decreasing, actual stroke rates in contemporary nonhospitalized cohorts might vary from these estimates.
†Adjusted-stroke rate scores are based on data from Lip and colleagues (202). Actual rates of stroke in contemporary cohorts might vary from these estimates.

AF indicates atrial fibrillation; $CHADS_2$, Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Prior Stroke or TIA or Thromboembolism (doubled); CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 years (doubled), Diabetes mellitus, Prior Stroke or TIA or thromboembolism (doubled), Vascular disease, Age 65–74 years, Sex category; HF, heart failure; LV, left ventricular; MI, myocardial infarction; PAD, peripheral artery disease; TE, thromboembolic; and TIA, transient ischemic attack (202, 203).

The $CHADS_2$ score has been validated in multiple nonvalvular AF cohorts, with findings indicating approximately a 2.0% increase in stroke rate for each 1-point increase in $CHADS_2$ score (from 1.9% with a score

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of 0 to 18.2% with a score of 6) (201, 204). A limitation of the $CHADS_2$ score is that a $CHADS_2$ score of 1 is considered an "intermediate" risk and those at lowest risk may not be well identified. Furthermore, patients whose only risk factor is a $CHADS_2$ score of 2 due to prior stroke may have a greater risk than a score of 2 would indicate.

Compared to the $CHADS_2$ score, the CHA_2DS_2-VASc score (15) for nonvalvular AF has a broader score range (0 to 9) and includes a larger number of risk factors (female sex, 65 to 74 years of age, and vascular disease) (202, 203). In this scheme, women cannot achieve a CHA_2DS_2-VASc score of 0. In a nationwide Danish registry from 1997 to 2008, the CHA_2DS_2-VASc index better discriminated stroke risk among subjects with a baseline $CHADS_2$ score of 0 to 1 with an improved predictive ability (172). In another study among patients with AF, the CHA_2DS_2-VASc score more clearly defined anticoagulation recommendations than did the $CHADS_2$ score (173). More patients, particularly older women, were redistributed from the low- to high-risk categories. In a study of Swedish patients with nonvalvular AF, women again had a moderately increased stroke risk compared with men, however, women younger than 65 years of age and without other AF risk factors had a low risk for stroke and it was concluded that anticoagulant treatment was not required (205). However, the continued evolution of AF-related thromboembolic risk evaluation is needed.

Bleeding risk scores to quantify hemorrhage risk include HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol concomitantly), RIETE (Computerized Registry of Patients With Venous Thromboembolism), HEMORR2HAGES (Hepatic or Renal Disease, Ethanol Abuse, Malignancy, Older Age, Reduced Platelet Count or Function, Rebleeding, Hypertension, Anemia, Genetic Factors, Excessive Fall Risk and Stroke), and ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) (206-208). Although these scores may be helpful in defining patients at elevated bleeding risk, their clinical utility is insufficient for use as evidence for the recommendations in this guideline. The RIETE score was developed from a large venous thromboembolism cohort and includes 2 points for recent bleeding, 1.5 points for abnormal creatinine levels or anemia, and 1 point for each of the following: >75 years of age, cancer, or pulmonary embolism at baseline. HEMORR2HAGES includes the following variables: hepatic or renal disease, ethanol abuse, malignancy, older age, reduced platelet count or function, rebleeding, hypertension, anemia, genetic factors, excessive fall risk, and stroke. The ATRIA score assigns points to the following variables: anemia, 3; severe renal disease, 3; >75 years of age, 2; prior hemorrhage, 1; and hypertension, 1.

HAS-BLED (14, 30) is a score based on the presence of hypertension (systolic blood pressure >160 mm Hg), abnormal liver or renal function, history of stroke or bleeding, labile INRs, elderly age (age >65 years), use of drugs that promote bleeding, or excess alcohol (209). A score of ≥3 indicates potentially "high risk" for bleeding and may require closer observation of a patient for adverse risks, closer monitoring of INRs, or differential dose selections of oral anticoagulants or aspirin. HAS-BLED better discriminates risk than the

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HEMORR2HAGES or ATRIA scoring systems but all 3 scores had C-indexes <0.70 in their receiver operating curves, indicating only modest performance and poor predictive accuracy (210).

4.2. Antithrombotic Options

Antithrombotic medications prevent strokes and systemic emboli among patients with AF in part by reducing the formation of platelet-rich or thrombotic clots in the LA or LAA, from which they can embolize through the systemic circulation to the brain or other sites. Stroke prevention trials (Figure 3) compared warfarin or aspirin with placebo, and aspirin with warfarin or clopidogrel and aspirin. Warfarin was also compared with dual antiplatelet agents (clopidogrel and aspirin). Trials have also compared direct thrombin inhibitors and factor Xa inhibitors with warfarin and, in 1 case, with aspirin. Both primary and secondary stroke prevention have been evaluated. The selection of an antithrombotic agent should be based on shared decision-making that takes into account risk factors, cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including time in INR therapeutic range if the patient has been on warfarin, irrespective of whether the AF pattern is paroxysmal, persistent, or permanent.

Meta-analyses have summarized the effect of antithrombotic therapies for stroke prevention in nonvalvular AF. The largest meta-analysis identified 29 RCTs from 1996 to 2007 that tested antithrombotic therapies of >12 weeks duration among 28,044 patients (184). Nine trials were double-blind designs with a mean follow-up of 1.5 years per patient. The average age of the subjects was 71 years and 35% were women. Among 12 of the trials, there were nearly 3,003 subjects randomized to placebo or control with an average stroke rate of 4.1% per year among the primary prevention studies and 13% per year among those with prior stroke or TIA.

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4.2.1. Antiplatelet Agents

No studies, with the exception of the SPAF (Stroke Prevention in Atrial Fibrillation)-1 trial, show benefit for aspirin alone in preventing stroke among patients with AF (183, 184, 211). Antiplatelet therapy was compared to placebo or no treatment in 8 trials with a total of 4,876 subjects (184) (Figure 3). Seven of these 8 trials compared different doses of aspirin ranging from 25 mg twice a day to 1,300 mg once a day (184). For primary prevention, aspirin was associated with a 19% reduction (95% CI: -1% to 35%) in stroke incidence with an absolute risk reduction of 0.8% per year (number needed to treat: 125). The 95% CI encompassed 0, which includes the possibility that aspirin has no real effect on stroke reduction. For secondary prevention among those with TIA or strokes, aspirin was associated with an absolute risk reduction of 2.5% per year and a corresponding number needed to treat of 40. It is important to recognize that the 19% reduction in stroke incidence observed in this meta-analysis was driven by positive results from only 1 of these RCTs—the SPAF-1 trial. In this trial, aspirin was prescribed at 325 mg once daily and the impact of aspirin was very heterogeneous between groups. Aspirin was ineffective in preventing strokes in those >75 years of age and did not prevent severe strokes. Moreover, aspirin has not been studied in a low-risk AF population.

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Clopidogrel plus aspirin was evaluated for stroke prevention in the ACTIVE (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events)-W trial (198). This trial was terminated early (before planned follow-up was completed) on the recommendation of the Data Safety and Monitoring Board because the combination of antiplatelet agents, clopidogrel (75 mg once daily) plus aspirin (75 mg to 100 mg once daily), proved inferior to warfarin (target INR 2.0 to 3.0) in patients with a mean $CHADS_2$ score of 2. ACTIVE-W found a 40% RR reduction (95% CI: 18% to 56%; p<0.001) for stroke with warfarin compared with the dual antiplatelet regimen. ACTIVE-A compared clopidogrel combined with aspirin versus aspirin alone in patients with AF who were unsuitable for oral anticoagulation and who had ≥1 additional stroke risk factor (199). The combination of clopidogrel and aspirin resulted in a 28% RR reduction (95% CI: 17% to 38%; p<0.0002) in all strokes compared with aspirin alone. Major bleeding was significantly greater with the combination and was increased by 57% (95% CI: 29% to 92%; p<0.001). The absolute differences between the treatment arms were small, with major vascular events decreased by 0.8% per year and major hemorrhages increased by 0.7% per year. The results of ACTIVE-W and ACTIVE-A demonstrate that adjusted-dose warfarin for stroke prevention is significantly better than clopidogrel plus aspirin, and clopidogrel plus aspirin is superior to aspirin alone. The latter benefits are dampened by the significant increase in major bleeding events. No direct comparisons have been made between clopidogrel and aspirin and the new oral anticoagulants that have lower bleeding risks than warfarin. However, there is a direct comparison between aspirin and the factor Xa inhibitor apixaban in the AVERROES (Apixaban Versus Acetylsalicylic Acid to Prevent Strokes) study, a double-blind study of 5,599 patients deemed unsuitable for warfarin therapy (189). Subjects were randomized to apixaban 5 mg twice daily (2.5 mg twice daily for those who had 2 of the following 3: age ≥80 years, weight ≤60 kg, serum creatinine ≥1.5 mg/dL) or to aspirin 81 mg or 325 mg once daily. The primary outcome of the study was the occurrence of any stroke or systemic embolism. After a mean follow-up of 1.1 years, the study was prematurely terminated owing to the superiority of apixaban over aspirin for preventing the primary outcome. Major bleeding risk between the 2 treatments was similar.

Figure 3. Antithrombotic Therapy to Prevent Stroke in Patients who Have Nonvalvular AF (Meta-Analysis)

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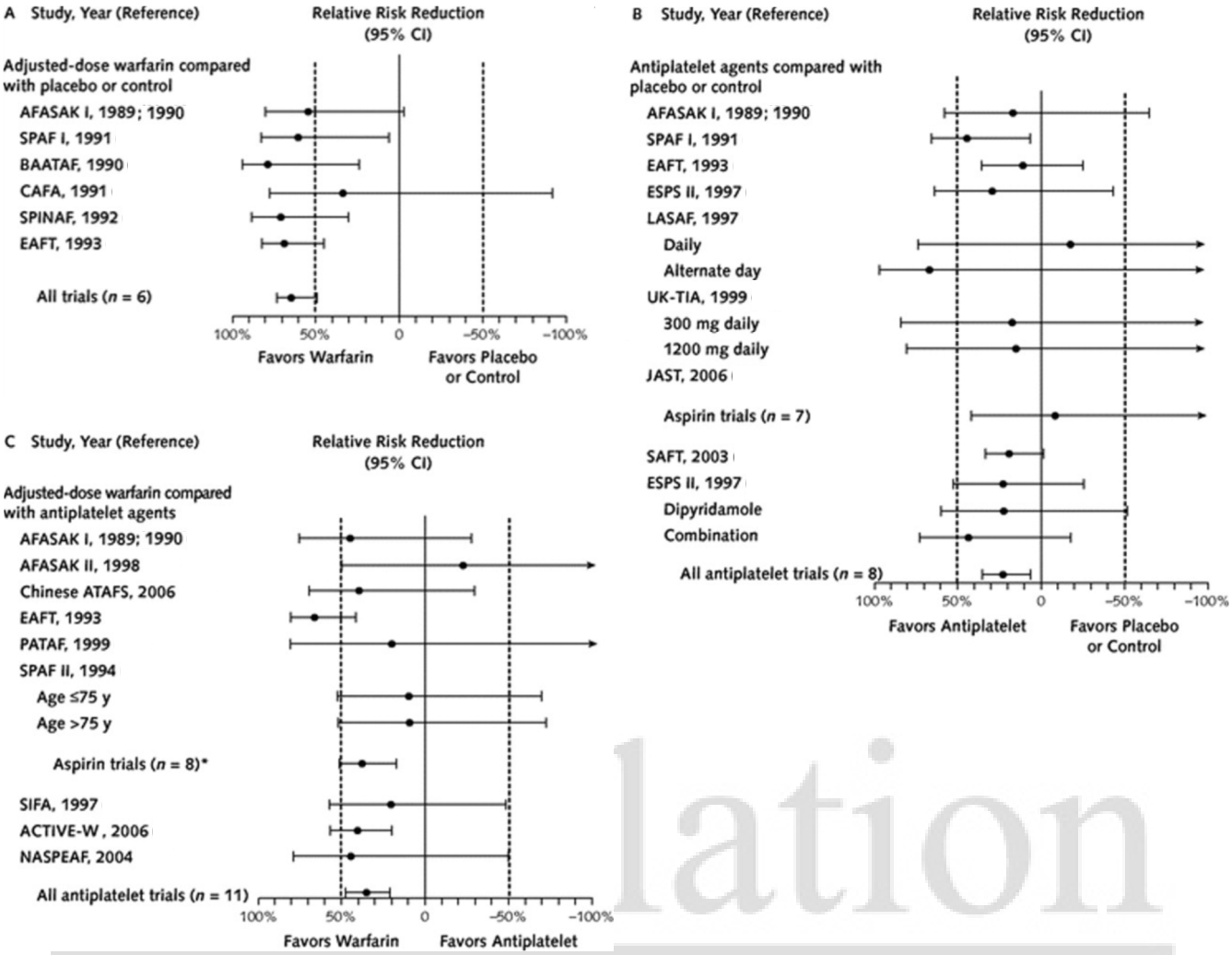

ACTIVE-W indicates Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events-W; AF, Atrial Fibrillation; AFASAK, Atrial Fibrillation, Aspirin and Anticoagulant Therapy Study; BAATAF, Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA, Canadian Atrial Fibrillation Anticoagulation; CI, confidence interval; EAFT, European Atrial Fibrillation Trial; ESPS, European Stroke Prevention Study; JAST, Japan AF Stroke Prevention Trial; LASAF, Low-Dose Aspirin, Stroke, Atrial Fibrillation; NASPEAF, National Study for Prevention of Embolism in Atrial Fibrillation; PATAF, Primary Prevention of Arterial Thromboembolism in Nonrheumatic Atrial Fibrillation; SAFT, Swedish Atrial Fibrillation Trial; SIFA, Studio Italiano Fibrillazione Atriale; SPAF I, Stroke Prevention in Atrial Fibrillation Study; SPINAF, Stroke Prevention in Atrial Fibrillation; and UK-TIA, United Kingdom-Transient Ischemic Attack.
Adapted with permission from Hart et al. (184).

4.2.2. Oral Anticoagulants

See Online Data Supplement 3 for additional data and evidence tables on warfarin versus aspirin and the new oral anticoagulants (http://jaccjacc.cardiosource.com/DataSupp/MASTER_2014_AF_Evidence_Table_Supplement_03182014.pdf).

4.2.2.1. Warfarin

Warfarin is a vitamin K antagonist in use since the 1950s as an oral anticoagulant for stroke prevention in patients with AF. Its multiple sites of action in the coagulation cascade are shown in Figure 4. Among 6 RCTs of 2,900 subjects in which adjusted-dose warfarin was compared with placebo or no treatment, the mean INR

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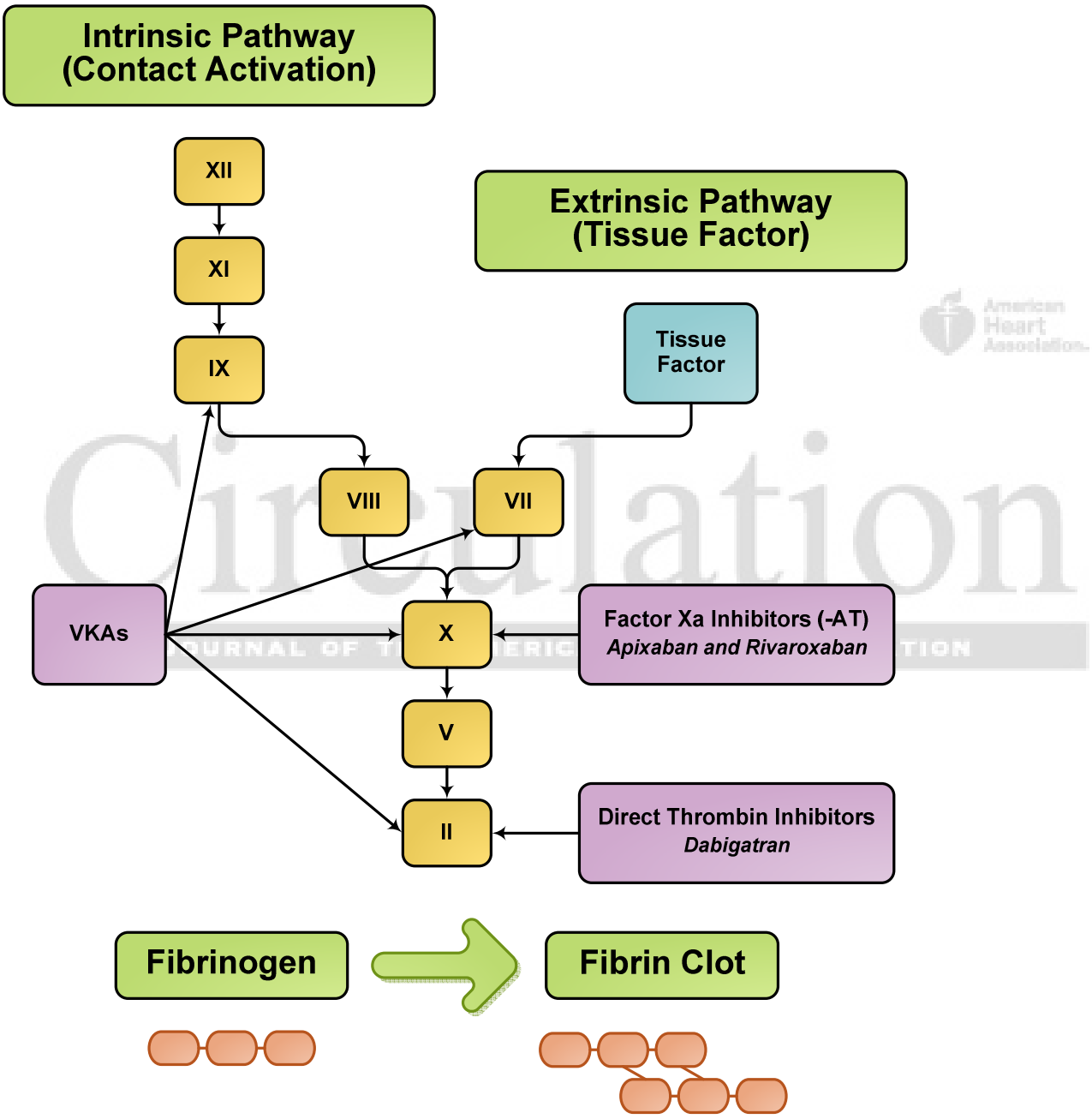
ranged from 2.0 to 2.9 (184, 212). Adjusted-dose warfarin resulted in a 64% RR reduction (95% CI: 49% to 74%) for ischemic and hemorrhagic stroke compared with the placebo. The absolute risk reduction was 2.7% per year which yielded a number needed to treat of 37 for 1 year to prevent 1 stroke and 12 for patients with prior stroke or TIA (184).

Figure 4. Coagulation Cascade



AT indicates antithrombin and VKAs, vitamin K antagonists.
Adapted with permission from Nutescu et al. (213).

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A Cochrane Collaboration review of warfarin versus placebo among subjects without prior cerebral events found that warfarin was associated with a significant risk reduction in all strokes, ischemic stroke, and the combined endpoint of stroke, MI, or vascular death (214). With an ischemic stroke rate of 4% per year in the control group, the absolute reduction was about 2.6% per year for those with no prior stroke or TIA, or about 25 ischemic strokes prevented in 1 year per 1,000 subjects treated with warfarin. The RR reductions were consistent across the trials. Intracranial hemorrhage was not significantly increased among the subjects randomized to warfarin, but the patient numbers were small and the CI wide.

For nonvalvular AF, 2 separate Cochrane reviews evaluated the efficacy and safety of oral anticoagulants compared to antiplatelet agents (215, 216). One review included those with no history of stroke or TIA and the other those with a history of stroke or TIA. Among 9,598 subjects with AF, the majority (90%) of whom had no prior stroke or TIA, oral anticoagulants were associated with a significant reduction in all strokes and ischemic strokes compared with antiplatelet agents. Assuming an absolute stroke risk of 4% per year with antiplatelet agents, approximately 19 strokes could be prevented per year for every 1,000 patients with AF treated with oral anticoagulants. The risk of intracranial hemorrhage was significantly increased among those treated with oral anticoagulants, but major extracranial hemorrhages were not significantly different. After excluding the ACTIVE-W trial, which used clopidogrel and aspirin as the antiplatelet agent comparison, oral anticoagulants were significantly associated with an increased risk of bleeding (OR: 1.90; 95% CI: 1.07 to 3.39) (215). Similarly, among patients with a prior history of stroke or TIA, oral anticoagulants compared with antiplatelet agents were associated with significant reductions in all major vascular events and recurrent stroke. Bleeding risks—including for any intracranial bleeds and major extracranial bleeds—were increased with oral anticoagulants.

The BAFTA (Birmingham Atrial Fibrillation Treatment of the Aged) study also evaluated the efficacy of warfarin among higher-risk elderly subjects >75 years of age (197). BAFTA was designed to compare warfarin with aspirin for the prevention of fatal and nonfatal stroke, intracranial hemorrhage, and other clinically significant arterial embolism in a primary care population of patients ≥75 years of age who had AF. Warfarin was superior in preventing stroke or systemic embolism without a significant increase in bleeding risk. The annual risk of extracranial hemorrhage was 1.4% in the warfarin group and 1.6% in the aspirin group.

Despite strong evidence for the efficacy of warfarin, several limitations have led to its underutilization (217-221). The narrow therapeutic window and increased risk of bleeding, including in the brain, have hindered broader use, especially among the elderly. Interactions with other drugs, effects of alterations in diet, and the requirement for close monitoring with frequent blood tests have also made the dosing of warfarin challenging for clinicians and patients. Even in well-conducted clinical trials, the time in therapeutic range (TTR) of those taking warfarin were reported as 55% to 66% (177-179), whereas in some community settings, TTR has been reported as approximately 50% (222, 223). Despite underutilization of warfarin among eligible persons due to a

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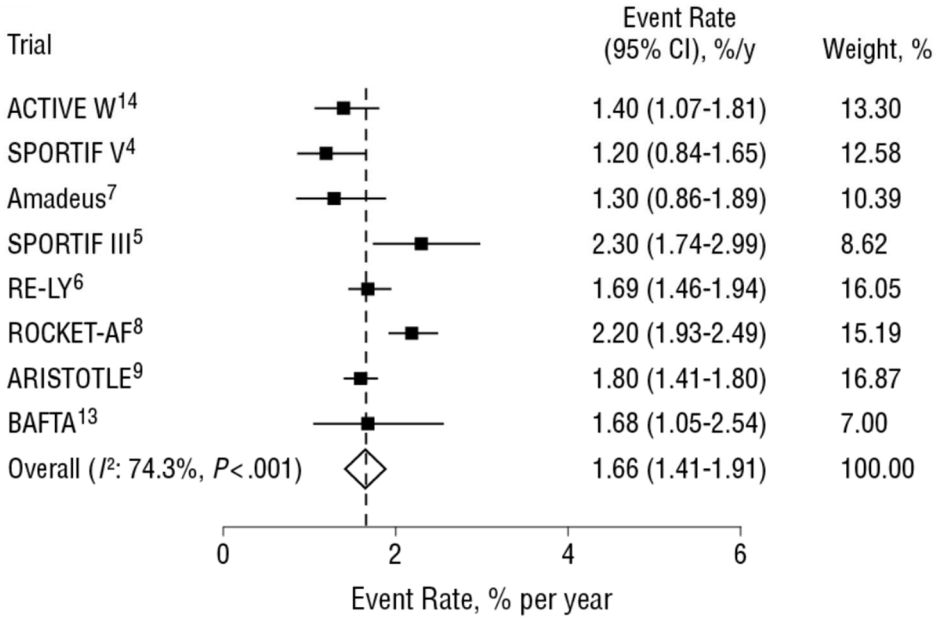
variety of factors (217-221), a meta-analysis of contemporary studies found risk of stroke or systemic embolism estimated to be at 1.66% per year for warfarin in patients with AF (224) (Figure 5).

Figure 5. Pooled Estimates of Stroke or Systemic Embolism in Patients With AF Treated With Warfarin



ACTIVE W indicates Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events-W; Amadeus, Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation; ARISTOTLE, Apixaban Versus Warfarin in Patients With AF; BAFTA, Birmingham Atrial Fibrillation Treatment of the Aged Study; CI, confidence interval; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET AF, Rivaroxaban Versus Warfarin in Nonvalvular Atrial Fibrillation; and SPORTIF, Stroke Prevention Using Oral Thrombin Inhibitor in Atrial Fibrillation.
Adapted with permission from Agarwal et al. (224).

See Online Data Supplements 4 and 5 for additional data on warfarin and antiplatelet therapy (http://jaccjacc.cardiosource.com/DataSupp/MASTER_2014_AF_Evidence_Table_Supplement_03182014.pdf).

4.2.2.2. Newer Oral Anticoagulants

Dabigatran is the first new oral anticoagulant approved by the U.S. Food and Drug Administration (FDA) to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF, and is a direct thrombin inhibitor. Its site of action in the coagulation cascade is shown in Figure 4. Dabigatran was compared with warfarin in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial, which was an open-label randomized comparison of dabigatran (110 mg or 150 mg twice daily in a blinded fashion) with adjusted-dose warfarin in 18,113 patients over a median follow-up period of 2 years (177). The mean $CHADS_2$ score was 2.1 and the primary outcome was stroke (of any type) and systemic embolism, with any major hemorrhage being the primary safety outcome. Half of the patients were naïve to oral anticoagulants. The mean TTR for those randomized to warfarin was 64%. The primary outcome was assessed first for noninferiority

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followed by superiority. For the primary outcomes, dabigatran 150 mg twice daily was superior to warfarin, and dabigatran 110 mg twice daily was noninferior to warfarin. Compared with warfarin, the risk of hemorrhagic strokes was also significantly lower (74% lower) with both the 110 mg and 150 mg doses. Major bleeding was significantly decreased with the 110 mg dose but not with the 150 mg dose. Both doses had lower rates of intracranial bleeding and life-threatening bleeding, whereas gastrointestinal bleeding was higher in the 150 mg dose (1.6% versus 1.0% per year) group. Dyspepsia was more frequent for both doses. For secondary prevention of stroke, the results were similar to the primary analysis but statistically weaker because of smaller sample size (225).

Dabigatran is renally excreted and patients with CrCl <30 mL/min were excluded from the RE-LY trial. CKD is associated with increased bleeding risk during both dabigatran therapy and warfarin therapy (226). The FDA approved the higher dose of 150 mg twice daily but not the lower dose of 110 mg twice daily. The FDA also approved a dose of 75 mg twice daily for those with low CrCl (15 mL/min to 30 mL/min) based on pharmacological modeling, but that dose was never clinically studied.

The RE-LY trial included subjects distributed equally across stroke risk strata ($CHADS_2$ score 0 to 1 in 31% of subjects, 2 in 33%, and >2 in 32%). For the primary efficacy endpoint and intracranial bleeding, there was similar efficacy across the range of $CHADS_2$ scores (177). In patients <75 years of age, both doses of dabigatran were associated with less intracranial and extracranial bleeding than warfarin; in patients ≥75 years of age, both doses reduced intracranial bleeding. However, extracranial bleeding was similar or more frequent compared to warfarin (227). Higher $CHADS_2$ scores were associated with increased risks for stroke or systemic embolism, bleeding, and death in patients with AF receiving oral anticoagulants (228). The benefits of dabigatran compared with warfarin in terms of efficacy and safety were similar in patient groups with paroxysmal, persistent, and permanent AF (169). A FDA postmarket analysis of gastrointestinal and intracranial bleeding of dabigatran versus warfarin indicates that bleeding rates do not appear to be higher for dabigatran (229).

A post hoc analysis of 1,989 electrical cardioversions found a very low rate of stroke within 30 days after the procedure (0.6% for warfarin, 0.3% for dabigatran 150 mg twice daily, and 0.8% for dabigatran 110 mg twice daily) (230). Most subjects were treated with their assigned medication for ≥3 weeks before cardioversion. TEE was performed in 25% of subjects. There was no significant difference in the incidence of LAA thrombus (1.1% for warfarin and for dabigatran 1.2% for 150 mg twice daily and 1.8% for 110 mg twice daily) (230).

In the RE-LY trial, there appeared to be an imbalance of MIs; 0.8%, 0.8%, and 0.6% per year for patients randomized to dabigatran 150 mg twice daily, or 110 mg twice daily and warfarin, respectively (p=0.09) (72). Absolute events were low in a population in which 31% of randomized patients had objective evidence of CAD. A meta-analysis of a RCT of dabigatran found a statistically significant increase in risk of MI and acute coronary syndromes (ACSs) in patients randomized to dabigatran (231). Interpretation of these results

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should be made with caution given the multiple limitations of this type of analysis, which includes the use of different controls and different patient populations.

Rivaroxaban is the second new oral anticoagulant approved by the FDA for reduction of risk of stroke and systemic embolism in patients with nonvalvular AF and is a direct factor Xa inhibitor (Figure 4). It should be administered as a single daily dose with the evening meal to ensure adequate absorption. It is predominantly excreted by the kidneys. The evidence leading to approval was based on the ROCKET AF (Rivaroxaban Versus Warfarin in Nonvalvular Atrial Fibrillation) trial, which was an RCT comparing rivaroxaban (20 mg once daily, 15 mg once daily if CrCl was 30 mL/min to 49 mL/min) with warfarin among 14,264 patients (178). ROCKET AF differed from RE-LY in that it selected higher-risk patients with AF (≥2 risk factors for stroke compared with 1 risk factor). Patients in ROCKET AF were older and had a greater mean $CHADS_2$ score of 3.47. Similar to other AF trials, the primary outcome was any stroke or systemic embolism and the primary hypothesis was noninferiority. Although the primary analysis was prespecified as a per protocol analysis, the intention-to-treat analysis was also presented. The main safety outcome was clinically relevant bleeding events. This was a double-blind trial and the patients receiving warfarin had a lower mean TTR of 55%. The trial demonstrated noninferiority for rivaroxaban compared with warfarin; however, in the intention-to-treat analysis, superiority was not achieved (p=0.12). Major bleeding was similar for rivaroxaban and warfarin, but less fatal bleeding and less intracranial hemorrhage, were found for rivaroxaban. At the end of the trial, patients transitioning to open-label therapy had more strokes with rivaroxaban than with warfarin. However, the risk of stroke or noncentral nervous system embolism after elective temporary discontinuation of rivaroxaban compared with warfarin in the ROCKET AF trial did not differ significantly in a post hoc analysis (232). The risk of stroke was similar for patients assigned to rivaroxaban and warfarin. In ROCKET AF, a decline in renal function was an independent predictor of stroke risk.

Apixaban is the third new oral anticoagulant approved by the FDA for reduction of risk of stroke and systemic embolism with nonvalvular AF and is another direct factor Xa inhibitor (Figure 4). It is predominantly eliminated hepatically and is highly protein bound. It has been investigated in 2 clinical trials. In the ARISTOTLE (Apixaban Versus Warfarin in Patients With Atrial Fibrillation) trial, apixaban (5 mg twice daily) was compared with warfarin in a double-blind RCT of 18,201 patients with AF and a mean $CHADS_2$ score of 2.1 (179). Apixaban 2.5 mg twice daily was used among patients with ≥2 of the following conditions: ≥80 years of age, weight ≤60 kg, or a serum creatinine level ≥1.5 mg/dL. As with the other newer anticoagulant trials, the primary outcome was any stroke or systemic embolism and the primary safety outcome was major bleeding. Patients were followed for a mean of 1.8 years and the mean age was 70 years. For warfarin-treated patients, the TTR was 62%. Apixaban was significantly better than warfarin, with fewer overall strokes (both ischemic and hemorrhagic), systemic emboli, and major bleeding events. Patients treated with apixaban had significantly fewer intracranial bleeds, but gastrointestinal bleeding complications were similar between the 2 study groups. Patients treated with apixaban had fewer deaths than those on warfarin. In ARISTOTLE, apixaban's benefit was

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independent of type of AF, risk profile, $CHADS_2$ or CHA_2DS_2-VASc score, and whether there was a prior stroke.

Apixaban was also compared with aspirin in the AVERROES study, a double-blind study of 5,599 patients deemed unsuitable for warfarin therapy (189) (Section 4.2). The mean $CHADS_2$ score was 2 and 36% of the subjects had a $CHADS_2$ score of 0 to 1. After a mean follow-up of 1.1 years, the study was prematurely terminated owing to the superiority of apixaban compared with aspirin for preventing the occurrence of any stroke or systemic embolism, whereas bleeding risk between the 2 treatments was similar.

Patients with severe and end-stage CKD (serum creatinine >2.5 mg/dL or CrCl <25 mL/min) were excluded from the ARISTOTLE and AVERROES trials (179, 189). Based on new pharmacokinetic profiles in a limited data set (233), apixaban prescribing recommendations were revised for use in patients with end-stage CKD maintained on stable hemodialysis with the recommended dose of 5 mg twice daily with a reduction in dose to 2.5 mg twice daily for either ≥80 years of age or body weight ≤60 kg. For patients with severe or end-stage CKD not on dialysis a dose recommendation was not provided. There are no published data for the use of apixaban in these clinical settings.

Other factor Xa inhibitors, including edoxaban (234) and betrixaban (235), are in evaluation but not yet approved by the FDA.

4.2.2.3. Considerations in Selecting Anticoagulants

Selection of agents for antithrombotic therapy depends on a large number of variables, including clinical factors, clinician and patient preference, and, in some circumstances, cost. The newer agents are currently considerably more expensive than warfarin. However, dietary limitations and the need for repeated INR testing are eliminated with the newer agents. If patients are stable, easily controlled, and satisfied with warfarin therapy, it is not necessary to change to 1 of the newer agents. However, it is important to discuss this option with patients who are candidates for the newer agents.

All 3 new oral anticoagulants represent important advances over warfarin because they have more predictable pharmacological profiles, fewer drug–drug interactions, an absence of major dietary effects, and less risk of intracranial bleeding than warfarin. They have rapid onset and offset of action such that bridging with parenteral anticoagulant therapy is not needed during initiation, and bridging may not be needed in patients on chronic therapy requiring brief interruption of anticoagulation for invasive procedures. However, strict compliance with these new oral anticoagulants is critical. Missing even 1 dose could result in a period without protection from thromboembolism. As a result, the FDA issued black box warnings regarding discontinuation of these newer agents that can increase the risk of thromboembolism, and coverage with another anticoagulant may be needed. In addition, reversal agents, while under development, are not presently available, although the short half-lives lessen the need for an antidote. Although dose adjustments may be warranted for those with CKD or body weight extremes, these new agents do not require regular INR or activated partial thromboplastin time monitoring.

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Importantly, patients with mechanical heart valves or hemodynamically significant mitral stenosis were excluded from all 3 major trials (RE-LY, ROCKET AF, and ARISTOTLE) (80, 89, 90); therefore, these patients should be managed with warfarin. Patients with aortic stenosis or aortic insufficiency who, in the estimation of the local RCT principal investigator, would not need a surgical procedure before the conclusion of the trial were included. The RE-ALIGN (Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients After Heart Valve Replacement) trial, a phase 2 dose-ranging study of the use of dabigatran compared with warfarin in patients with mechanical heart valves, was stopped because dabigatran users were more likely to experience strokes, MI, and thrombus forming on the mechanical heart valves than were warfarin users (190, 236, 237). There was also more bleeding after valve surgery in the dabigatran users than in the warfarin users, thus dabigatran is contraindicated for use in patients with mechanical heart valves. Similar drug safety and efficacy information is lacking for rivaroxaban and apixaban and mechanical heart valves. Bioprosthetic heart valves have not been studied with any of the newer anticoagulants. None of the 3 major trials included pregnant or lactating women, children, patients with reversible causes of AF, or patients with severe hypertension (systolic blood pressure >180 mm Hg or diastolic blood pressure >100 mm Hg). Patients with a recent stroke (within 7 to 14 days), patients with significant liver disease, and complex patients with multiple chronic conditions were excluded from all trials.

For patients with CKD, dose modifications of the new agents are available (Table 8); however, for those with severe or end-stage CKD, warfarin remains the anticoagulant of choice, as there are no or very limited data for these patients. Among patients on hemodialysis, warfarin has been used with acceptable risks of hemorrhage (185).

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Table 8. Dose Selection of Oral Anticoagulant Options for Patients with Nonvalvular AF and CKD (Based on Prescribing Information for the United States)*

Renal Function	**Warfarin** (238)	**Dabigatran**† (177)	**Rivaroxaban**† (178)	**Apixaban**† (179)
Normal/Mild Impairment	Dose adjusted for INR 2.0–3.0	150 mg BID (CrCl >30 mL/min)	20 mg QD with the evening meal (CrCl >50 mL/min)	5.0 or 2.5 mg BID‡
Moderate Impairment	Dose adjusted for INR 2.0–3.0	150 mg BID or 75 mg BID§ (CrCl >30 mL/min)	15 mg QD with the evening meal (CrCl 30–50 mL/min)	5.0 or 2.5 mg BID‡
Severe Impairment	Dose adjusted for INR 2.0–3.0‖	75 mg BID§ (CrCl 15–30 mL/min)	15 mg QD with the evening meal (CrCl 15–30 mL/min)	No recommendation, See section 4.2.2.2.¶
End-Stage CKD Not on Dialysis	Dose adjusted for INR 2.0–3.0‖	Not recommended¶ (CrCl <15 mL/min)	Not recommended¶ (CrCl <15 mL/min)	No recommendation, See section 4.2.2.2.¶
End-Stage CKD on Dialysis	Dose adjusted for INR 2.0–3.0‖	Not recommended¶ (CrCl <15 mL/min)	Not recommended¶ (CrCl <15 mL/min)	No recommendation, See section 4.2.2.2.¶#

*Renal function should be evaluated prior to initiation of direct thrombin or factor Xa inhibitors and should be re-evaluated when clinically indicated and at least annually. CrCl should be measured using the Crockoft-Gault method.
†The concomitant use of P-glycoprotein inducers or inhibitors with dabigatran, or the concomitant use of dual P-glycoprotein and strong *CYP3A4* inducers or inhibitors with either rivaroxaban or apixaban, particularly in the setting of

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CKD, may require dosing adjustment or avoidance of concomitant drug use (see the FDA drug label at http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202155s002lbl.pdf; Section 8.6).
‡Use apixaban 2.5 mg BID if any 2 patient characteristics present: Cr ≥1.5 mg/dL, ≥80 years of age, body weight ≤60 kg (179). Apixaban is not recommended in patients with severe hepatic impairment.
§Modeling studies suggest that dabigatran 75 mg BID might be safe for patients with CrCl 15–30mL/min, but this has not been validated in a prospective cohort. Some countries outside the United States use 110 mg BID (177).
‖Dose-adjusted warfarin has been used, but observational data regarding safety and efficacy are conflicting.
¶No published studies support a dose for this level of renal function.
#In patients with end-stage CKD on stable hemodialysis, prescribing information indicates the use of apixaban 5 mg BID with dose reduction to 2.5 mg BID if the patient is either ≥80 years of age or body weight ≤60 kg.

AF indicates atrial fibrillation; BID, twice daily; CKD, chronic kidney disease; Cr, creatinine; CrCl, creatinine clearance; INR, international normalized ratio; and QD, once daily.

The price of an effective anticoagulant is the risk of bleeding, which, if extracranial, is usually not life-threatening. Although INR and activated partial thromboplastin time increase with dabigatran, this is not in a linear fashion and cannot be used to monitor the level of anticoagulation. The Hemoclot thrombin clotting time is a more accurate measure of anticoagulation levels, but the test is not approved in the United States nor is it widely available elsewhere (94). If bleeding or overdose occurs, the anticoagulant agent should be discontinued. The use of activated charcoal to reduce absorption may be considered. Dabigatran is dialyzable, but both apixaban and rivaroxaban are not dialyzable and are highly plasma protein bound.

Dabigatran, rivaroxaban, and apixaban are substrates for the efflux transporter P-glycoprotein. P-glycoprotein inhibitors, such as ketoconazole, verapamil, amiodarone, dronedarone, quinidine, and clarithromycin, may increase plasma concentrations. In addition, P-glycoprotein inducers (such as phenytoin, carbamazepine, rifampin, and St. John's wort) can decrease levels of these drugs to subtherapeutic blood levels and coadministration should be avoided. Absorbed dabigatran etexilate is "pumped" back into the intestinal tract; therefore, proton pump inhibitors may reduce absorption of dabigatran (239). Rivaroxaban and apixaban are contraindicated with drugs that inhibit cytochrome *P450 3A4* (*CYP3A4*), such as azole antimycotics, ritonavir, and clarithromycin.

Although the newer oral anticoagulant trials were similar in design and inclusion/exclusion criteria, it is difficult to make comparisons between the agents to judge differential efficacy in the absence of direct comparisons.

4.2.2.4. Silent AF and Stroke

Clinically unrecognized and asymptomatic AF is a potentially important cause of stroke, supporting efforts for early detection of AF in at-risk individuals. Episodes of asymptomatic AF are potentially detectable from implantable arrhythmia management devices (pacemakers or defibrillators) that have an atrial lead and can be programmed to record the number, duration, and frequency of atrial rates that exceed a certain threshold and, in some cases, also provide stored electrograms for analysis. These devices typically report "atrial high-rate events." Whether the high-rate event is AF, atrial flutter, or an atrial tachycardia is not necessarily discernible.

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Patients receiving arrhythmia management devices often have risk factors for AF. Atrial high-rate episodes have been observed in 10% to 28% of patients who have no prior history of AF (61, 191).

The ASSERT (Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial) trial enrolled 2,580 patients ≥65 years of age with hypertension and no history of AF in whom a pacemaker or defibrillator was recently implanted. During the first 3 months, atrial high-rate episodes >190 bpm for >6 minutes occurred in 10% of subjects (61). These high-rate episodes were associated with a >5-fold increase in subsequent diagnosis of atrial arrhythmia on ECG and a 1.60% per year rate of stroke or systemic embolism compared to 0.69% per year rate for those without high-rate episodes during the first 3 months. In a subgroup analysis of the MOST (Mode Selection Trial in Sinus Node Dysfunction) trial, patients with atrial high-rate episodes (rate >220 bpm for >10 beats detected by a pacemaker) were more than 2 times as likely to die or have a stroke and 6 times as likely to be subsequently diagnosed with AF as similar patients without atrial high-rate events (193). In a prospective study of 2,486 patients receiving arrhythmia management devices and who had ≥1 AF risk factor for stroke—20% of whom had a history of AF—patients with atrial tachycardia/AF burden (defined as the longest total atrial tachycardia/AF duration on any given day during the prior 30-day period) >5.5 hours had a thromboembolism rate of 2.4% per year as compared to 1.1% per year for those with no or less atrial tachycardia/AF burden (194). In a study of 560 patients with HF, the recording of atrial high-rate events lasting >3.8 hours in 1 day was associated with a 9-fold increased thromboembolic event rate (240).

Additional studies are needed to further clarify the relationship between stroke risk and atrial high-rate episodes detected by implanted devices and to define key characteristics of atrial high-rate episodes in patients who warrant further investigation or potentially therapy (192, 194).

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4.3. Interruption and Bridging Anticoagulation

Interruption of anticoagulation is often considered for patients with AF who have episodes of bleeding or require surgical or interventional procedures associated with a bleeding risk. There is sparse evidence on which to base specific recommendations on the use of bridging of oral anticoagulants among patients with nonvalvular AF with adjusted-dose heparin or LMWH (241); however, additional studies (e.g., BRIDGE [Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery]) are on-going (242). The duration of interruption and timing of resumption of anticoagulation after the procedure is guided by individualized consideration of the risk of thrombotic events and the severity of the operative and perioperative bleeding risk. For patients who are treated with warfarin and who are at low risk of thromboemboli, or are back in normal sinus rhythm and are undergoing surgical or diagnostic procedures that carry a risk of bleeding, stopping warfarin for up to 1 week and allowing the INR to normalize without substituting UFH is a recognized approach. Warfarin is then resumed after adequate hemostasis has been achieved. For patients at higher risk of thromboembolism (mechanical valves, prior stroke, CHA_2DS_2-VASc score ≥2), bridging with UFH or LMWH is a common practice, although data for LMWH are

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limited (22). An increasingly common approach, especially for pacemaker or implantable cardioverter-defibrillator implantation, catheter ablation, coronary angiography, and other vascular interventions, is to perform the procedure without interrupting warfarin (241, 243-247). Radiofrequency catheter ablation of AF performed with a therapeutic INR does not increase bleeding risk and reduces the risk of emboli (243, 244). Pacemaker or defibrillator implantation with a therapeutic INR has a lower risk of postoperative bleeding than discontinuing warfarin and initiating bridging anticoagulation with UFH or LMWH, and may be considered in those patients requiring device implantation who also have a moderate-to-high thromboembolic risk (241, 245-250).

For oral factor Xa inhibitors and direct thrombin inhibitors, there is limited experience with drug withdrawal prior to surgical procedures (244). In the ROCKET AF trial, rivaroxaban was held for 2 days prior to elective surgery or invasive procedure and for 24 hours prior to semiurgent procedures (60). The increased risk of bleeding should be weighed carefully against the urgency of surgery or an invasive procedure. Interruption of anticoagulation should be guided by the pharmacologic properties of the drug. The timing of resumption should take into account the fact that anticoagulation, in contrast to warfarin, is achieved promptly, and that reversal agents are not yet available for these agents, which complicates management if bleeding occurs. For elective surgery, holding these agents for 1 day (2 doses for dabigatran and apixaban; 1 dose for rivaroxaban) prior to the procedure is generally sufficient for patients with normal renal function (239). The need for complete hemostasis (e.g., for spinal puncture, spinal/epidural catheter, or major surgery) will demand a longer period of discontinuation of ≥48 hours for patients with normal renal function. An activated partial thromboplastin time for dabigatran and prothrombin time for apixaban and rivaroxaban may provide useful information; a level close to control suggests a low serum concentration of these agents. For patients undergoing catheter ablation, or any procedure in which perforation of the heart chamber is possible, these new agents need to be used with caution because of the lack of approved antidotes in the event of cardiac tamponade. In some cases, activated prothrombin complex concentrate and recombinant factor VIIa have been used to reverse the anticoagulant effects of these new agents. Specific reversing agents are not currently available but are under development. Whether hemostasis will be easier and safer for coronary interventions done by a radial artery approach rather than a femoral approach is not known. The use of bare-metal stents or coronary artery bypass surgery in preference to drug-eluting stents where concomitant long-term use of dual antiplatelet agents is anticipated and might increase bleeding risk is a reasonable consideration when long-term therapy with these anticoagulants is desired.

In patients undergoing percutaneous coronary intervention, dual antiplatelet therapy with aspirin and clopidogrel is indicated to prevent stent thrombosis. The combination of oral anticoagulants and antiplatelet therapy ("triple therapy") is associated with a high annual risk of fatal and nonfatal bleeding episodes (251-254). Recently, in patients taking oral anticoagulants undergoing percutaneous coronary intervention, the efficacy and safety of antiplatelet therapy with aspirin and clopidogrel versus clopidogrel alone were studied (186). The use

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of clopidogrel without aspirin was associated with a reduction in bleeding and no increase in the rate of thrombotic events.

4.4. Nonpharmacologic Stroke Prevention

4.4.1. Percutaneous Approaches to Occlude the LAA

The LAA is the primary source for thromboembolism in AF (255). Exclusion of the LAA, both surgically and with devices, has been attempted with the goal of reducing thromboembolism in patients with AF. There are 2 general approaches to occlude the LAA using percutaneous approaches. The first strategy involves implantable devices that are inserted percutaneously into the LAA with the goal of occluding or plugging the LAA. Devices for LAA occlusion include the WATCHMAN Device and the Amplatzer Cardiac Plug. The WATCHMAN Device is deployed percutaneously via transeptal puncture and has a polyethylene membrane that covers a self-expanding nitinol cage with barbs to anchor the device in the LAA (256). The early WATCHMAN Device findings suggest noninferiority to warfarin for the composite endpoint of stroke, systemic embolism, and cardiovascular death; however, early adverse events occur in approximately 10% of patients including pericardial bleeding. Longer-term follow-up of the WATCHMAN Device at 1,588 patient years suggests noninferiority of this device to warfarin (256). A subsequent registry study demonstrated that the WATCHMAN Device achieved noninferiority to patients who could not receive warfarin (257). Lastly, data from subsequent experience with the WATCHMAN Device suggest that the earlier device-related complications were mitigated with increasing operator experience (258).

The Amplatzer Cardiac Plug, which has Conformité Européenne Mark approval, consists of a small proximal disc, a central polyester patch, and a larger distal disc with hooks to anchor the device in the LAA. It does not require anticoagulation and a European-based trial found a 96% success rate for deployment/implantation but with a 7% incidence of serious complications (259). The second strategy is to tie off the LAA using an epicardial snare, referred to as the LARIAT device. This device received FDA approval in 2009 for facilitation of suture placement and knot tying for use in surgical applications in which soft tissues are being approximated. It has been adapted for use in AF and combines a percutaneous epicardial and endocardial approach. The initial experience with this device appeared promising, with 97% acute obliteration of the LAA as confirmed by TEE and a favorable safety profile (260). The LARIAT device's long-term outcomes, requiring RCTs to study reduced stroke risk and safety, are not yet defined. The device requires subxiphoid pericardial access that may not be achievable in the presence of pericardial adhesions, it can provoke pericarditis that can be severe, and it is not suitable for all LAA anatomies. It is not yet clear if occluding the LAA with the LARIAT device lowers stroke risk. Additional devices are in development.

4.4.2. Cardiac Surgery—LAA Occlusion/Excision: Recommendation

Class IIb

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1. **Surgical excision of the LAA may be considered in patients undergoing cardiac surgery.** ***(Level of Evidence: C)***

Surgical-based procedures to exclude the LAA during cardiac surgery are controversial for several reasons. What should seem technically simple and reproducible—removal of the LAA—yields inconsistent results and the anatomy of the LAA is quite variable (261). The circumflex coronary artery lies proximate to the base of the LAA and epicardial and endocardial-based surgical techniques to occlude the LAA are often inadequate because of surgeon concern regarding damage to the circumflex artery during a suture-based closure of the appendage. Epicardial techniques include simple suture ligation, oversewing the base without excision, excising the appendage and oversewing the base, and surgical stapling and excision (262). One device, the Gillinov-Cosgrove clip LAA excluder system, has FDA approval (263). Endocardial techniques include inversion of the appendage, amputation, and then oversewing the base from the endocardial aspect (262).

The results of surgical occlusion of the LAA remain suboptimal, with echocardiographic follow-up suggesting incomplete occlusion in ≥50% of subjects. In the largest study to examine the success of LAA ligation, 2,546 patients undergoing TEE between 1993 and 2004 were retrospectively examined (264); 137 patients underwent a surgical attempt at LAA occlusion. Of these 137 patients, 52 underwent excision and 85 underwent exclusion (either suture or stapled). TEE-defined unsuccessful closures were defined by either persistent flow into the LAA, a remnant stump of >1.0 cm of the LAA, or color Doppler flow into the LAA. Overall, 50 of 137 closures were successful (40%). Success varied with the technique employed: excision (73% success rate), suture exclusion (23% success rate), and stapling (0% success rates). Particularly noteworthy is that thrombus was identified in ≥25% of patients with unsuccessful LAA occlusion with suture exclusion or stapled LAA remnants. This latter finding constitutes important data guiding the continued need for anticoagulation in patients who have undergone surgical LAA ligation.

Success of LAA occlusion and efficacy with stroke prevention remains unclear regarding whether the appendage should be occluded at the time of concomitant heart surgery. The LAAOS (Left Atrial Appendage Occlusion Study) randomized 77 patients with risk factors for stroke to LAA closure or control at the time of coronary artery bypass surgery (265). During this trial, suture-based or stapler-based occlusion was permitted and the success of LAA closure in the suture group was 45% versus 72% in the stapled group. Nine appendage tears occurred during the trial (1 control and 8 treatments), but these tears did not contribute to mortality or morbidity. There were 2 thromboembolic events in the occlusion group and none in the control. The authors concluded that LAA occlusion could be performed safely; however, larger randomized studies are needed to determine whether LAA occlusion could reduce stroke risk in patients with risk factors for AF who undergo non–AF-related cardiac surgery. In a retrospective cohort of 205 patients with echocardiography following mitral valve replacement, 58 patients underwent LAA ligation as judged by transthoracic echocardiogram. Of these 58 patients, 52 had a complete ligation of the LAA, as defined by lack of color Doppler flow from the body of the LA into the appendage, and 6 had persistent flow. The principal finding was that a lack of or an

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incomplete LAA occlusion were both strongly associated with the occurrence of a thromboembolic event (266).

In summary, the current data regarding LA occlusion at the time of concomitant cardiac surgery reveals a lack of clear consensus because of the inconsistency of techniques used for surgical excision, the highly variable rates of successful LAA occlusion, and the unknown impact LAA occlusion may or may not have upon future thromboembolic events.

5. Rate Control: Recommendations

See Table 9 for a summary of recommendations for this section.

Class I

1. **Control of the ventricular rate using a beta blocker or nondihydropyridine calcium channel antagonist is recommended for patients with paroxysmal, persistent, or permanent AF (267-269). *(Level of Evidence: B)***
2. **Intravenous administration of a beta blocker or nondihydropyridine calcium channel blocker is recommended to slow the ventricular heart rate in the acute setting in patients without pre-excitation. In hemodynamically unstable patients, electrical cardioversion is indicated (270-273). *(Level of Evidence: B)***
3. **In patients who experience AF-related symptoms during activity, the adequacy of heart rate control should be assessed during exertion, adjusting pharmacological treatment as necessary to keep the ventricular rate within the physiological range. *(Level of Evidence: C)***

Class IIa

1. **A heart rate control (resting heart rate <80 bpm) strategy is reasonable for symptomatic management of AF (269, 274). *(Level of Evidence: B)***
2. **Intravenous amiodarone can be useful for rate control in critically ill patients without pre-excitation (275-277). *(Level of Evidence: B)***
3. **AV nodal ablation with permanent ventricular pacing is reasonable to control the heart rate when pharmacological therapy is inadequate and rhythm control is not achievable (278-280). *(Level of Evidence: B)***

Class IIb

1. **A lenient rate-control strategy (resting heart rate <110 bpm) may be reasonable as long as patients remain asymptomatic and LV systolic function is preserved (274). *(Level of Evidence: B)***
2. **Oral amiodarone may be useful for ventricular rate control when other measures are unsuccessful or contraindicated. *(Level of Evidence: C)***

Class III: Harm

1. **AV nodal ablation with permanent ventricular pacing should not be performed to improve rate control without prior attempts to achieve rate control with medications. *(Level of Evidence: C)***
2. **Nondihydropyridine calcium channel antagonists should not be used in patients with decompensated HF as these may lead to further hemodynamic compromise. *(Level of Evidence: C)***
3. **In patients with pre-excitation and AF, digoxin, nondihydropyridine calcium channel antagonists, or intravenous amiodarone should not be administered as they may increase the ventricular response and may result in ventricular fibrillation (281). *(Level of Evidence: B)***
4. **Dronedarone should not be used to control the ventricular rate in patients with permanent AF as it increases the risk of the combined endpoint of stroke, MI, systemic embolism, or cardiovascular death (282, 283). *(Level of Evidence: B)***

Table 9. Summary of Recommendations for Rate Control

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Recommendations	COR	LOE	References
Control ventricular rate using a beta blocker or nondihydropyridine calcium channel antagonist for paroxysmal, persistent, or permanent AF	I	B	(267-269)
IV beta blockers or nondihydropyridine calcium channel blocker recommended to slow ventricular heart rate in the acute setting in patients without pre-excitation. In hemodynamically unstable patients, electrical cardioversion is indicated	I	B	(270-273)
For AF, assess heart rate control during exertion, adjusting pharmacological treatment as necessary	I	C	N/A
A heart rate control (resting heart rate <80 bpm) strategy is reasonable for symptomatic management of AF	IIa	B	(269, 274)
IV amiodarone can be useful for rate control in critically ill patients without pre-excitation	IIa	B	(275-277)
AV nodal ablation with permanent ventricular pacing is reasonable when pharmacological management is inadequate and rhythm control is not achievable	IIa	B	(278-280)
Lenient rate control strategy (resting heart rate <110 bpm) may be reasonable with asymptomatic patients and LV systolic function is preserved	IIb	B	(274)
Oral amiodarone may be useful for ventricular rate control when other measures are unsuccessful or contraindicated	IIb	C	N/A
AV nodal ablation should not be performed without prior attempts to achieve rate control with medications	III: Harm	C	N/A
Nondihydropyridine calcium channel antagonists should not be used in decompensated HF	III: Harm	C	N/A
With pre-excitation and AF, digoxin, nondihydropyridine calcium channel antagonists, or amiodarone, should not be administered	III: Harm	B	(281)
Dronedarone should not be used to control ventricular rate with permanent AF	III: Harm	B	(282, 283)

AF indicates atrial fibrillation; AV, atrioventricular; COR, Class of Recommendation; HF, heart failure; IV, intravenous; LOE, Level of Evidence; LV, left ventricular; and N/A, not applicable.

Rate control in AF is an important strategy. It impacts quality of life, reduces morbidity, and decreases the potential for developing tachycardia-induced cardiomyopathy. Multiple agents, including beta blockers, nondihydropyridine calcium channel blockers, digoxin, and certain antiarrhythmic drugs, including amiodarone and sotalol, have been evaluated with regard to efficacy in attaining rate control and. This information is summarized in Table 10. When considering which agent(s) to use, clinicians must consider the patient's degree of symptoms, hemodynamic status, presence or absence of HF, and potential precipitants of AF. When evaluating the evidence supporting different agents, clinicians must recognize that most clinical trials were performed in the 1980s and 1990s and have study design limitations that include variable endpoints, small sample sizes, and single-site study and observational trial designs. Issues to consider include the acuity of attaining rate control, which agent(s) to administer, and the degree of rate control required. Over the last 40 years, several themes have emerged. In general, beta blockers are the most common agents utilized for rate control, followed by nondihydropyridine calcium channel blockers, digoxin, and amiodarone. Patient comorbidities must be understood in order to avoid medications that may precipitate adverse events such as decompensation of HF, exacerbation of chronic obstructive pulmonary disease, or acceleration of conduction in patients with pre-excitation.

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When rapid control of ventricular rate during AF is required, intravenous medications or electrical cardioversion may be used. Electrical cardioversion is preferred in patients with decompensated HF, ongoing myocardial ischemia, or hypotension, although this may carry an increased thromboembolic risk in patients inadequately anticoagulated or for whom AF is of uncertain duration. In hemodynamically stable patients with a rapid ventricular response, oral medications may be administered.

Table 10. AF Rate Control Common Medication Dosage

	Intravenous Administration	Usual Oral Maintenance Dose
Beta blockers		
Metoprolol tartrate	2.5–5.0 mg IV bolus over 2 min; up to 3 doses	25–100 mg BID
Metoprolol XL (succinate)	N/A	50–400 mg QD
Atenolol	N/A	25–100 mg QD
Esmolol	500 mcg/kg IV bolus over 1 min, then 50–300 mcg/kg/min IV	N/A
Propranolol	1 mg IV over 1 min, up to 3 doses at 2 min intervals	10–40 mg TID or QID
Nadolol	N/A	10–240 mg QD
Carvedilol	N/A	3.125–25 mg BID
Bisoprolol	N/A	2.5–10 mg QD
Nondihydropyridine calcium channel antagonists		
Verapamil	(0.075-0.15 mg/kg) IV bolus over 2 min, may give an additional 10.0 mg after 30 min if no response, then 0.005 mg/kg/min infusion	180–480 mg QD (ER)
Diltiazem	0.25 mg/kg IV bolus over 2 min, then 5-15 mg/h	120–360 mg QD (ER)
Digitalis glycosides		
Digoxin	0.25 mg IV with repeat dosing to a maximum of 1.5 mg over 24 h	0.125–0.25 mg QD
Others		
Amiodarone	300 mg IV over 1 h, then 10–50 mg/h over 24 h	100–200 mg QD

AF indicates atrial fibrillation; BID, twice daily; ER, extended release; IV, intravenous; N/A, not applicable; QD, once daily; QID, four times a day; and TID, three times a day.

5.1. Specific Pharmacological Agents for Rate Control

5.1.1. Beta Adrenergic Receptor Blockers

By blocking sympathetic tone, beta blockers are useful for ventricular rate control in patients with AF. Beta blockers, including esmolol, propranolol, and metoprolol, are effective when administered intravenously in the setting of acute AF (270, 273, 284). Orally administered beta blockers including atenolol, metoprolol, nadolol, propranolol, and sotalol have all been effectively utilized for ongoing ventricular rate control in patients with chronic AF. There is less published literature on rate control of AF with additional beta blockers. In the

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AFFIRM (Atrial Fibrillation Follow-Up Investigation of Rhythm Management) study, beta blockers were the most effective and commonly used drug class for rate control (70% on beta blocker versus 54% on calcium channel blocker) (269). In patients with HF, carvedilol had efficacy for heart rate control and, in combination with digoxin, resulted in improved LV function (285). Combination therapy of beta blockers with other agents, including digoxin, is effective in ventricular rate control; however, drugs should be titrated to avoid excessive bradycardia (267).

See Online Data Supplement 6 for additional data on beta blockers (http://jaccjacc.cardiosource.com/DataSupp/MASTER_2014_AF_Evidence_Table_Supplement_03182014.pdf).

5.1.2. Nondihydropyridine Calcium Channel Blockers

Diltiazem and verapamil have direct AV nodal effects, blocking L-type calcium channels, and are used for ventricular rate control in both acute and chronic AF. In the setting of acute AF, intravenous administration of diltiazem was safe and effective in controlling ventricular response in 83% of patients (271). Intravenous verapamil is also effective in establishing acute ventricular rate control (273, 286, 287). Unless immediate rate control is required or an enteral route of administration is not available, oral administration is appropriate. Both verapamil and diltiazem reduce resting and exercise heart rate and can improve exercise tolerance (288). These nondihydropyridine calcium channel blockers should not be used in patients with LV systolic dysfunction and decompensated HF owing to their negative inotropic effects, but they may be used in patients with HF with preserved LV systolic function. In addition, these agents should not be used in patients with pre-excitation and AF due to the potential for shortening bypass tract refractoriness which may accelerate the ventricular rate to precipitate hypotension or ventricular fibrillation (281, 289) (Section 7.8).

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See Online Data Supplement 7 for additional data on nondihydropyridine calcium channel blockers (http://jaccjacc.cardiosource.com/DataSupp/MASTER_2014_AF_Evidence_Table_Supplement_03182014.pdf).

5.1.3. Digoxin

Digoxin is not usually first-line therapy for ventricular rate control in patients with AF, despite its common use. Although intravenous digoxin does slow the ventricular response, onset of action requires >1 hour and the effect does not peak until approximately 6 hours after initial administration. Therefore, it is not an optimal agent when rapid rate control is desired (290). During chronic oral therapy, digoxin reduces the resting heart rate but it is ineffective at controlling the ventricular response during exercise (267). Digoxin may be combined with beta blockers or nondihydropyridine calcium channel blockers to improve ventricular rate control during exercise (267, 291, 292), and it has been used in HF as 1 of the few rate control agents that does not have negative inotropic effects. Adverse effects of digoxin include AV block, ventricular arrhythmias, and infrequently aggravation of sinus node dysfunction. Dose adjustment is required in patients with renal dysfunction, the elderly, and in the presence of drugs that reduce its excretion such as amiodarone, propafenone, or nondihydropyridine calcium channel blockers. Therefore, periodic assessment of serum levels is warranted in

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many patients. Studies finding an association between digoxin therapy and mortality raise further concern about its use, particularly long term (293, 294). In the AFFIRM trial, digoxin was associated with an increase in mortality, which in post hoc analysis was irrespective of sex or HF (295). Arrhythmias, which are dose related, are a potential source of mortality; in the DIG (Digitalis Investigation Group) trial, serum levels >0.9 ng/mL were associated with increased mortality (296). However, in another AFFIRM subgroup propensity-matched analysis with paroxysmal and persistent AF there was no increase in mortality or hospitalization in those taking digoxin as baseline initial therapy (297). Because it can shorten cardiac action potential duration, digoxin should not be employed as sole therapy in patients with pre-excitation.

See Online Data Supplement 8 for additional data on digoxin (http://jaccjacc.cardiosource.com/DataSupp/MASTER_2014_AF_Evidence_Table_Supplement_03182014.pdf).

5.1.4. Other Pharmacological Agents for Rate Control

Amiodarone exerts sympatholytic and calcium antagonistic properties that can depress AV nodal conduction. Although intravenous amiodarone can be used in critically ill patients without pre-excitation to attain ventricular rate control, it is less effective than nondihydropyridine calcium channel blockers (272, 298) and requires a longer time to achieve rate control (7 hours versus 3 hours for diltiazem). There are limited data on the efficacy of chronic oral therapy with amiodarone for rate control during persistent AF, but in 1 small trial it had similar efficacy to digoxin (299). Amiodarone is uniquely lipid soluble. Its onset of action can be accelerated by a high-dose amiodarone-loading regimen, but there is the potential for worsening hemodynamics in patients with recent decompensated HF or hypotension. Intravenous amiodarone does not have the same electrophysiologic effects as oral amiodarone (300), and intravenous amiodarone has the potential to accelerate the ventricular response and precipitate fatal arrhythmias in patients with AF and pre-excitation (301, 302). Amiodarone has many potential toxicities and drug interactions that limit its long-term use for control of ventricular rate.

Dronedarone, which lacks iodine moieties of amiodarone, slows the resting rate in AF by an average of 12 bpm and also improves the exercise heart rate control (303); however, it should not be used for rate control in permanent AF as it was found to increase rates of HF, stroke, cardiovascular death, and unplanned hospitalization (282). Furthermore, dronedarone should not be used for ventricular rate control in patients with HF and LV systolic dysfunction as it increases the likelihood of the combined endpoint of stroke, MI, systemic embolism, or cardiovascular death (282, 283).

See Online Data Supplement 9 for additional data on pharmacological agents for rate control (http://jaccjacc.cardiosource.com/DataSupp/MASTER_2014_AF_Evidence_Table_Supplement_03182014.pdf).

5.2. AV Nodal Ablation

AV nodal ablation with permanent pacemaker implantation effectively controls and regularizes ventricular heart rate and, in selected patients, improves symptoms. Patients most likely to benefit include those with tachycardia-

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induced cardiomyopathy with ventricular rate control refractory to medical therapy (280, 304-307). AV nodal ablation is usually reserved for elderly patients as it leads to pacemaker dependency. Patients with symptoms refractory to medical therapy who are treated with AV nodal ablation and permanent pacemaker implantation have an improvement in cardiac symptoms, quality of life, and health care utilization. With this approach, no rate control medications are necessary, but anticoagulation to prevent thromboembolism is required based on the patient's stroke risk as assessed by the CHA_2DS_2-VASc system. When this approach is under consideration, the patient must receive counseling to understand that this is an irreversible measure that results in a lifelong pacemaker dependency with its potential complications. Time-permitting, pacemaker implantation may be performed 4 to 6 weeks prior to the AV node ablation to ensure proper pacemaker function as malfunction due to lead dislodgement can be catastrophic. Sudden death secondary to torsades de pointes or ventricular fibrillation has been reported after AV junction ablation. This outcome is possibly related to increased dispersion of ventricular refractoriness produced by sudden heart rate slowing and ventricular pacing (308). Postablation, the ventricular pacing rate is usually set between 90 bpm and 100 bpm and then gradually tapered over several months (309, 310, 310). RV apical pacing also creates a ventricular activation sequence that can lead to depressed ventricular function. In patients with left ventricular ejection fraction (LVEF) <35% and symptoms of HF, implantation of a biventricular pacing system is recommended. This procedure should also be considered for patients with less severe ventricular dysfunction (16). In the BLOCK HF (Biventricular Versus Right Ventricular Pacing in Heart Failure Patients With Atrioventricular Block) trial, patients with advanced AV block with LVEF <50% had improved clinical outcomes when treated with a biventricular pacemaker as compared with RV apical pacing (311). Upgrading to a biventricular pacing system should be considered for patients who have undergone AV nodal ablation coupled with a RV pacing system who develop moderate-to-severe LV systolic dysfunction (312).

See Online Data Supplement 10 for additional data on AV junction ablation (http://jaccjacc.cardiosource.com/DataSupp/MASTER_2014_AF_Evidence_Table_Supplement_03182014.pdf).

5.3. Selecting and Applying a Rate Control Strategy

5.3.1. Broad Considerations in Rate Control

The optimal heart rate targets for rate control are controversial. The target used in the AFFIRM trial was a resting heart rate of either ≤80 bpm or averaging ≤100 bpm on ambulatory monitoring, without a rate >100% of the maximum age-adjusted predicted exercise heart rate. These conditions were achieved in 58% of patients during initial drug therapy (269). One RCT, the RACE (Rate Control Efficacy in Permanent Atrial Fibrillation)-II trial assessed lenient versus strict rate control (274). In this trial, 614 patients with permanent AF were randomized to a lenient rate control (resting heart rate <110 bpm) strategy or a strict rate control (resting heart rate <80 bpm) strategy. At 3 years the primary composite endpoint of cardiovascular death, hospitalization for HF, stroke, embolism, bleeding, or life-threatening arrhythmic events was similar between the 2 groups (12.9%

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lenient rate control versus 14.9% strict rate control); thus, a strict rate control strategy did not improve outcomes. Several considerations warrant a cautious approach to extrapolating these findings to the general AF population. The majority of patients in the RACE-II trial had preserved LV systolic function. RACE-II was a single noninferiority trial with a 90% CI for a composite endpoint. The resting heart rate achieved in both groups only differed by 10 bpm and 78% of patients in the lenient control group had resting rates <100 bpm. This single RCT does not provide sufficient evidence to assess definitive results of the impact on all-cause mortality, HF symptoms, hospitalizations, or quality of life. The degree of rate control, however, remains an area of uncertainty and controversy that requires further study.

See Online Data Supplement 11 for additional data on rate control (http://jaccjacc.cardiosource.com/DataSupp/MASTER_2014_AF_Evidence_Table_Supplement_03182014.pdf).

5.3.2. Individual Patient Considerations

Optimal ventricular rate control may differ and is impacted by the degree of patient symptoms and comorbidities including the presence of valvular heart disease, LV systolic dysfunction, HF, and presence of pre-excitation. Figure 6 provides a brief outline of the approach(es) to rate control in different patient populations.

Figure 6. Approach to Selecting Drug Therapy for Ventricular Rate Control*

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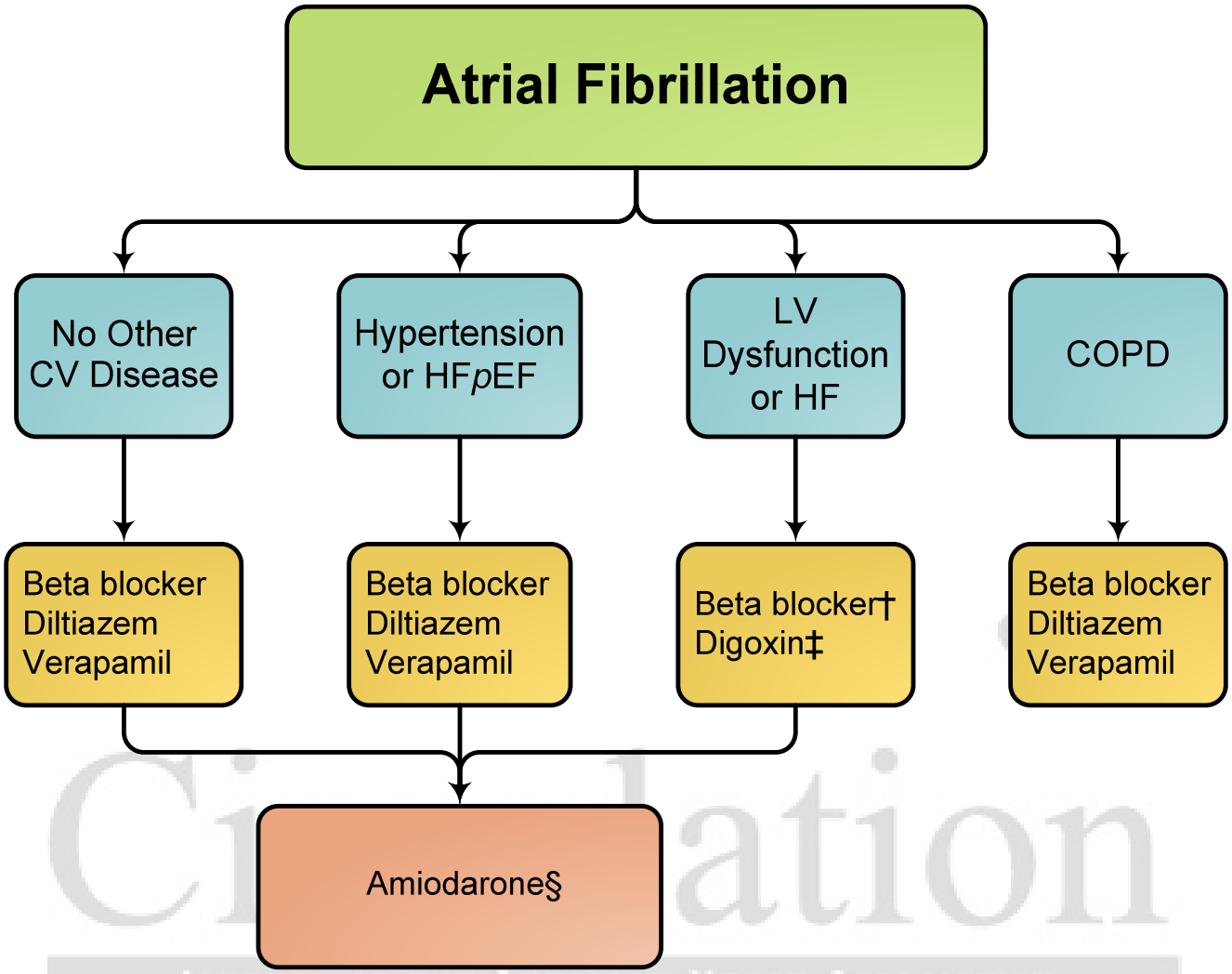

*Drugs are listed alphabetically.
†Beta blockers should be instituted following stabilization of patients with decompensated HF. The choice of beta blocker (cardio-selective, etc.) depends on the patient's clinical condition.
‡Digoxin is not usually first-line therapy. It may be combined with a beta blocker and/or a nondihydropyridine calcium channel blocker when ventricular rate control is insufficient and may be useful in patients with HF.
§In part because of concern over its side-effect profile, use of amiodarone for chronic control of ventricular rate should be reserved for patients who do not respond to or are intolerant of beta blockers or nondihydropyridine calcium antagonists.

COPD indicates chronic obstructive pulmonary disorder; CV, cardiovascular; HF, heart failure; HF*p*EF, heart failure with preserved ejection fraction; and LV, left ventricular.

6. Rhythm Control

Long-term AF management may employ attempts to restore and maintain sinus rhythm, commonly referred to as "a rhythm-control strategy"; utilizing a combination of approaches, including cardioversion, antiarrhythmic drugs and radiofrequency catheter ablation in the setting of appropriate anticoagulation and rate control. RCTs comparing outcomes of a rhythm-control strategy using antiarrhythmic drugs with a rate-control strategy in patients with AF failed to show a superiority of rhythm control for either strategy on mortality (269, 313). Furthermore, when applied in patients who are candidates for both treatment strategies (rhythm or rate control),

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a rhythm-control strategy results in more hospitalizations. Therefore, the routine use of a rhythm-control strategy is not warranted for some patients. Catheter ablation has not been studied in this context.

Although an initial rate-control strategy is reasonable for many patients, several considerations favor pursuing a rhythm-control strategy. Successful sinus rhythm maintenance is associated with improvements in symptoms and quality of life for some patients (314, 315). Persistent symptoms associated with AF remain the most compelling indication for a rhythm-control strategy. Other factors that may favor attempts at rhythm control include difficulty in achieving adequate rate control, younger patient age, tachycardia-mediated cardiomyopathy, first episode of AF, AF that is precipitated by an acute illness, and patient preference. AF progresses from paroxysmal to persistent in many patients and subsequently results in electrical and structural remodeling that becomes irreversible with time (126, 316). For this reason, accepting AF as permanent in a patient may render future rhythm-control therapies less effective. This may be more relevant for a younger individual who wishes to remain a candidate for future developments in rhythm-control therapies. Early intervention with a rhythm-control strategy to prevent the progression of AF may be beneficial (317-319).

6.1. Electrical and Pharmacological Cardioversion of AF and Atrial Flutter

See Table 11 for a summary of recommendations from this section.

6.1.1. Thromboembolism Prevention: Recommendations

Class I

1. **For patients with AF or atrial flutter of 48-hour duration or longer, or when the duration of AF is unknown, anticoagulation with warfarin (INR 2.0 to 3.0) is recommended for at least 3 weeks prior to and 4 weeks after cardioversion, regardless of the CHA_2DS_2-VASc score and the method (electrical or pharmacological) used to restore sinus rhythm (320-323). *(Level of Evidence: B)***
2. **For patients with AF or atrial flutter of more than 48 hours or unknown duration that requires immediate cardioversion for hemodynamic instability, anticoagulation should be initiated as soon as possible and continued for at least 4 weeks after cardioversion unless contraindicated. *(Level of Evidence: C)***
3. **For patients with AF or atrial flutter of less than 48-hour duration and with high risk of stroke, intravenous heparin or LMWH, or administration of a factor Xa or direct thrombin inhibitor, is recommended as soon as possible before or immediately after cardioversion, followed by long-term anticoagulation therapy. *(Level of Evidence: C)***
4. **Following cardioversion for AF of any duration, the decision regarding long-term anticoagulation therapy should be based on the thromboembolic risk profile (Section 4). *(Level of Evidence: C)***

Class IIa

1. **For patients with AF or atrial flutter of 48-hour duration or longer or of unknown duration who have not been anticoagulated for the preceding 3 weeks, it is reasonable to perform a TEE prior to cardioversion and proceed with cardioversion if no LA thrombus is identified, including in the LAA, provided that anticoagulation is achieved before TEE and maintained after cardioversion for at least 4 weeks (164). *(Level of Evidence: B)***
2. **For patients with AF or atrial flutter of 48-hour duration or longer, or when the duration of AF is unknown, anticoagulation with dabigatran, rivaroxaban, or apixaban is reasonable for at least 3 weeks prior to and 4 weeks after cardioversion (230, 324, 325). *(Level of Evidence: C)***

Class IIb

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1. **For patients with AF or atrial flutter of less than 48-hour duration who are at low thromboembolic risk, anticoagulation (intravenous heparin, LMWH, or a new oral anticoagulant) or no antithrombotic therapy may be considered for cardioversion, without the need for postcardioversion oral anticoagulation (326). *(Level of Evidence: C)***

6.1.2. Direct-Current Cardioversion: Recommendations

Class I

1. **In pursuing a rhythm-control strategy, cardioversion is recommended for patients with AF or atrial flutter as a method to restore sinus rhythm. If cardioversion is unsuccessful, repeated direct-current cardioversion attempts may be made after adjusting the location of the electrodes or applying pressure over the electrodes, or following administration of an antiarrhythmic medication (327). *(Level of Evidence: B)***
2. **Cardioversion is recommended when a rapid ventricular response to AF or atrial flutter does not respond promptly to pharmacological therapies and contributes to ongoing myocardial ischemia, hypotension, or HF. *(Level of Evidence: C)***
3. **Cardioversion is recommended for patients with AF or atrial flutter and pre-excitation when tachycardia is associated with hemodynamic instability. *(Level of Evidence: C)***

Class IIa

1. **It is reasonable to perform repeated cardioversions in patients with persistent AF provided that sinus rhythm can be maintained for a clinically meaningful period between cardioversion procedures. Severity of AF symptoms and patient preference should be considered when embarking on a strategy requiring serial cardioversion procedures. *(Level of Evidence: C)***

6.1.3. Pharmacological Cardioversion: Recommendations

Class I

1. **Flecainide, dofetilide, propafenone, and intravenous ibutilide are useful for pharmacological cardioversion of AF or atrial flutter provided contraindications to the selected drug are absent (328-333). *(Level of Evidence: A)***

Class IIa

1. **Administration of oral amiodarone is a reasonable option for pharmacological cardioversion of AF (334, 335). *(Level of Evidence: A)***
2. **Propafenone or flecainide ("pill-in-the-pocket") in addition to a beta blocker or nondihydropyridine calcium channel antagonist is reasonable to terminate AF outside the hospital once this treatment has been observed to be safe in a monitored setting for selected patients (328). *(Level of Evidence: B)***

Class III: Harm

1. **Dofetilide therapy should not be initiated out of hospital owing to the risk of excessive QT prolongation that can cause torsades de pointes (332, 336). *(Level of Evidence: B)***

Table 11. Summary of Recommendations for Electrical and Pharmacological Cardioversion of AF and Atrial Flutter

Recommendations	COR	LOE	References
Thromboembolism prevention			
With AF or atrial flutter for ≥48 h, or unknown duration, anticoagulate with warfarin for at least 3 wk prior to and 4 wk after cardioversion	I	B	(320-323)

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With AF or atrial flutter for >48 h or unknown duration requiring immediate cardioversion, anticoagulate as soon as possible and continue for at least 4 wk	I	C	N/A
With AF or atrial flutter <48 h and high stroke risk, IV heparin or LMWH, or factor Xa or direct thrombin inhibitor, is recommended before or immediately after cardioversion, followed by long-term anticoagulation	I	C	N/A
Following cardioversion of AF, long-term anticoagulation should be based on thromboembolic risk	I	C	N/A
With AF or atrial flutter for ≥48 h or unknown duration and no anticoagulation for preceding 3 wk, it is reasonable to perform a TEE prior to cardioversion, and then cardiovert if no LA thrombus is identified, provided anticoagulation is achieved before TEE and maintained after cardioversion for at least 4 wk	IIa	B	(164)
With AF or atrial flutter ≥48 h, or unknown duration, anticoagulation with dabigatran, rivaroxaban, or apixaban is reasonable for ≥3 wk prior to and 4 wk after cardioversion	IIa	C	(230, 324, 325)
With AF or atrial flutter <48 h and low thromboembolic risk, IV heparin, LMWH, a new oral anticoagulant, or no antithrombotic may be considered for cardioversion	IIb	C	(326)
Direct-current cardioversion			
Cardioversion is recommended for AF or atrial flutter to restore sinus rhythm. If unsuccessful, repeat cardioversion attempts may be made	I	B	(327)
Cardioversion is recommended for AF or atrial flutter with RVR, that does not respond to pharmacological therapies	I	C	N/A
Cardioversion is recommended for AF or atrial flutter and pre-excitation with hemodynamic instability	I	C	N/A
It is reasonable to repeat cardioversions in persistent AF when sinus rhythm is maintained for a clinically meaningful time period between procedures	IIa	C	N/A
Pharmacological cardioversion			
Flecainide, dofetilide, propafenone, and IV ibutilide are useful for cardioversion of AF or atrial flutter provided contraindications to the selected drug are absent	I	A	(328-333)
Amiodarone is reasonable for pharmacological cardioversion of AF	IIa	A	(334, 335)
Propafenone or flecainide ("pill-in-the-pocket") to terminate AF out of hospital is reasonable once observed to be safe in a monitored setting	IIa	B	(328)
Dofetilide should not be initiated out of hospital	III: Harm	B	(332, 336)

AF indicates atrial fibrillation; COR, Class of Recommendation; IV, intravenous; LA, left atrial; LOE, Level of Evidence; LMWH, low-molecular-weight heparin; N/A, not applicable; RVR, rapid ventricular response; and TEE, transesophageal echocardiogram.

Direct-current cardioversion involves the delivery of an electrical shock synchronized with the QRS complex to avoid inducing ventricular fibrillation as can occur by a shock applied during ventricular repolarization on the T wave. It is clinically relevant to differentiate between a cardioversion in which sinus rhythm was not restored, even transiently, and a cardioversion in which sinus rhythm was restored but AF recurs. In the former scenario, approaches that improve energy delivery and may allow for successful cardioversion include increasing shock strength, delivering a biphasic rather than monophasic waveform, changing the shock vector by altering the electrode pad position, improving energy transfer via pressure on the anterior electrode pad, or using a drug such as ibutilide to lower defibrillation threshold. In the latter scenario, when sinus rhythm is restored but AF returns,

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pretreatment with selected antiarrhythmic drugs may increase the likelihood of maintenance of sinus rhythm (327, 337).

A number of technical factors influence cardioversion efficacy, including energy, waveform, and electrode placement (7). A biphasic waveform is more effective than a monophasic waveform (338). Antero-posterior electrode placement is superior to anterolateral placement in some but not all studies (7, 339). If an attempt at cardioversion using 1 electrode placement fails, another attempt using the alternative placement is recommended. The initial use of a higher-energy shock is more effective and may minimize the number of shocks required as well as the duration of sedation (340). The risks associated with cardioversion include thromboembolism, sedation-related complications, ventricular tachycardia and fibrillation, bradyarrhythmias, skin burn or irritation from electrodes, muscle soreness, and reprogramming or altering implanted cardiac device function. Elective cardioversion should not be performed in patients with evidence of digoxin toxicity, severe hypokalemia, or other electrolyte imbalances until these factors are corrected.

Appropriate anticoagulation management around the time of a cardioversion is essential for reducing thromboembolic risk. Results of observational studies suggest that thromboembolic risk after cardioversion is highest in the first 72 hours and that the majority of events occur within 10 days (341, 342). Thromboembolism after cardioversion can be due to migration of thrombi present at the time of cardioversion or to the formation and subsequent migration of de novo thrombi that form while atrial function is still depressed in the postcardioversion period. This guideline's Class I recommendation for anticoagulation with warfarin for ≥3 weeks prior to and continuing for ≥4 weeks after cardioversion is based on pathophysiological and observational data (322, 323). For new oral anticoagulants, available data supporting similar use at cardioversion consist of subgroup analyses of dabigatran from RE-LY, rivaroxaban from ROCKET AF, and apixaban from ARISTOTLE in patients who were receiving long-term anticoagulation (>3 weeks) around the time of cardioversion (230, 324, 325).

TEE guidance is an alternative to 3 weeks of anticoagulation prior to cardioversion (164, 343). Therapeutic anticoagulation is achieved, followed by a TEE; if no thrombus is seen (including in the LAA), cardioversion is performed and anticoagulation is continued for a ≥4 weeks. The absence of left atrial thrombus on TEE does not preclude the need for anticoagulation during and after cardioversion. In the ACUTE (Assessment of Cardioversion Using Transesophageal Echocardiography) trial, hospitalized patients were typically started on intravenous heparin prior to cardioversion whereas outpatients were typically started on warfarin 5 days before cardioversion and anticoagulation status was verified at the time of cardioversion (164). Alternative strategies for achieving rapid anticoagulation include administration of LMWH (344) or a new oral anticoagulant. If thrombus is identified on TEE, the cardioversion should be postponed followed by ≥3 to 4 weeks of anticoagulation. A repeat TEE to ensure thrombus resolution is an option prior to another cardioversion attempt (322). If thrombus remains on repeat TEE, an alternative strategy such as rate control in conjunction with appropriate anticoagulation may be considered.

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Data on cardioversion risks for atrial flutter are limited. Atrial flutter can, however, be associated with thrombi and episodes of AF. Therefore, it is recommended that the anticoagulation management strategy for cardioversion of atrial flutter be the same as for AF.

In patients with AF clearly of <48 hours duration, it is common practice to perform a cardioversion without TEE or antecedent anticoagulation (345). No RCTs comparing anticoagulation strategies in patients with AF duration <48 hours exist (342). If high-risk features are present, such as mitral stenosis or prior history of thromboembolism, long-term anticoagulation should be considered. Decisions regarding whether to initiate long-term systemic anticoagulation at the time of cardioversion in a patient with AF of <48 hours should be based on the patient's long-term risk of stroke using the CHA_2DS_2-VASc risk score discussed in Section 4.1.

For patients with AF requiring emergency cardioversion because of hemodynamic instability, the initiation of anticoagulation should not delay interventions to stabilize the patient. No RCTs have evaluated optimal anticoagulation strategies in this patient population. It is reasonable to administer heparin (intravenous bolus of UFH followed by infusion, or LMWH) or newer anticoagulant and to continue this after the cardioversion unless contraindicated. For patients with AF or atrial flutter of ≥48 hours or uncertain duration, oral anticoagulation is recommended for ≥4 weeks after emergency cardioversion (similar to patients undergoing elective cardioversion). If warfarin is used, bridging with UFH or LMWH is indicated until the INR is therapeutic. For patients with AF and thromboembolic risks factors, oral long-term anticoagulation is recommended.

Antiarrhythmic drugs can be administered for attempted conversion of AF to sinus rhythm or to facilitate electrical cardioversion. Pharmacological cardioversion is most likely effective when initiated within 7 days after the onset of an episode of AF. The most commonly effective antiarrhythmic drugs are specified in Table 12. In patients with recent onset AF, intravenous administration of ibutilide restored sinus rhythm in about 50% of patients with an average conversion time of <30 minutes. The rates of successful termination were higher in those patients with atrial flutter than in those with AF (346). Ibutilide pretreatment also improves the efficacy of transthoracic electrical cardioversion of AF (327). The major risk is excessive QT prolongation, which can cause polymorphic ventricular tachycardia/torsades de pointes. The latter occurs in up to 3% to 4% of patients. ECG monitoring should be continued for ≥4 hours after administration and resuscitation equipment must be immediately available. Ibutilide should be avoided in patients with QT prolongation, marked hypokalemia, or a very low ejection fraction (EF) (<30%) because of the risk of ventricular proarrhythmia (327). Some experts administer magnesium sulfate intravenously prior to administering ibutilide in an attempt to lower this risk (331). Intravenous amiodarone may facilitate slowing of the ventricular rate in AF, but the effect to restore sinus rhythm is often delayed. In 1 study, oral amiodarone loaded over the course of several weeks resulted in conversion of persistent AF to sinus rhythm in about 25% of patients (314). An oral dose of flecainide or propafenone can be used as a "pill-in-the-pocket" strategy to attempt to restore sinus rhythm shortly after the onset of symptomatic AF (328, 330). Because termination of AF may be associated with

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bradycardia owing to sinus node or AV node dysfunction or a proarrhythmic response, an initial conversion trial in a monitored setting is recommended before this approach is used in the unmonitored outpatient setting. A beta blocker or nondihydropyridine calcium channel antagonist should be administered ≥30 minutes before administering the Vaughan Williams Class IC agent to prevent a rapid ventricular response due to 1:1 AV conduction during atrial flutter (328).

Table 12. Recommended Drug Doses for Pharmacological Cardioversion of AF

Drug	Route of Administration	Dosage		Potential Adverse Effects	References
Amiodarone	Oral	600–800 mg daily in divided doses to a total load of up to 10 g, then 200 mg QD as maintenance		Phlebitis (IV), hypotension, bradycardia, QT prolongation, torsades de pointes (rare), GI upset, constipation, increased INR	(334, 335)
	IV	150 mg over 10 min, then 1 mg/min for 6 h, then 0.5 mg/min for 18 h or change to oral dosing			
Dofetilide	Oral	CrCl (mL/min)	Dose (mcg BID)	QT prolongation, torsades de pointes; adjust dose for renal function, body size, and age	(332)
		>60 40–60 20–40 <20	500 250 125 Not recommended		
Flecainide	Oral	200–300 mg x 1*		Hypotension, atrial flutter with 1:1 AV conduction, ventricular proarrhythmia; avoid in patients with CAD and significant structural heart disease	(328)
Ibutilide	IV	1 mg over 10 min; may repeat 1 mg once if necessary (weight <60 kg use 0.01 mg/kg)		QT prolongation, torsades de pointes, hypotension	(329, 333, 346)
Propafenone	Oral	450–600 mg x 1*		Hypotension, atrial flutter with 1:1 AV conduction, ventricular proarrhythmia; avoid in patients with CAD and significant structural heart disease	(328, 330)

*Recommended given in conjunction with a beta blocker or nondihydropyridine calcium channel antagonist administered ≥30 minutes before administering the Vaughan Williams Class IC agent (328).

AF indicates atrial fibrillation; AV, atrioventricular; BID, twice a day; CAD, coronary artery disease; CrCl, creatinine clearance; GI, gastrointestinal; INR, international normalized ratio; IV, intravenous; and QD, once daily.
Adapted with permission from Fuster et al. (4).

6.2. Pharmacological Agents for Preventing AF and Maintaining Sinus Rhythm

6.2.1. Antiarrhythmic Drugs to Maintain Sinus Rhythm: Recommendations

Class I

1. **Before initiating antiarrhythmic drug therapy, treatment of precipitating or reversible causes of AF is recommended. *(Level of Evidence: C)***
2. **The following antiarrhythmic drugs are recommended in patients with AF to maintain sinus rhythm, depending on underlying heart disease and comorbidities *(Level of Evidence: A)*:**
    a. **Amiodarone (314, 347-349)**

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   b. **Dofetilide (332, 336)**
   c. **Dronedarone (350-352)**
   d. **Flecainide (347, 353)**
   e. **Propafenone (347, 354-357)**
   f. **Sotalol (347, 355, 358)**
3. **The risks of the antiarrhythmic drug, including proarrhythmia, should be considered before initiating therapy with each drug.** ***(Level of Evidence: C)***
4. **Owing to its potential toxicities, amiodarone should only be used after consideration of risks and when other agents have failed or are contraindicated. (314, 354, 359-362).** ***(Level of Evidence: C)***

Class IIa

1. **A rhythm-control strategy with pharmacological therapy can be useful in patients with AF for the treatment of tachycardia-induced cardiomyopathy.** ***(Level of Evidence: C)***

Class IIb

1. **It may be reasonable to continue current antiarrhythmic drug therapy in the setting of infrequent, well-tolerated recurrences of AF, when the drug has reduced the frequency or symptoms of AF.** ***(Level of Evidence: C)***

Class III: Harm

1. **Antiarrhythmic drugs for rhythm control should not be continued when AF becomes permanent** ***(Level of Evidence: C)*** **including dronedarone (282).** ***(Level of Evidence: B)***
2. **Dronedarone should not be used for treatment of AF in patients with New York Heart Association (NYHA) class III and IV HF or patients who have had an episode of decompensated HF in the past 4 weeks (283).** ***(Level of Evidence: B)***

When a rhythm-control strategy is desired, antiarrhythmic drug therapy may be selected to reduce the frequency and duration of AF and improve quality of life. Before antiarrhythmic drug treatment is initiated, reversible precipitants of AF should be identified and corrected. After the first episode of AF that resolves, it is reasonable to address the underlying causes of AF and need for anticoagulation, and to not initiate antiarrhythmic drug treatment until warranted by AF recurrences. Decisions regarding anticoagulation should be based on the patient's individual stroke risk profile and not on the response to antiarrhythmic drug therapy. Antiarrhythmic drug efficacy is modest and asymptomatic AF recurrences are common. Therefore, a rhythm-control strategy should not result in cessation of antithrombotic therapy, rate control therapy, or treatment of underlying heart disease.

Drug selection is guided to a greater extent by safety concerns than by drug efficacy. A common approach is to identify available drug choices by first eliminating, on the basis of clinical parameters, drugs that have absolute or relative contraindications. Patients with CAD, significant LV hypertrophy, and HF have more restricted options than those with no or minimal structural heart disease. Several other important factors must be considered, including the risk for bradyarrhythmias, risk factors for excessive QT prolongation and torsades de pointes (e.g., baseline QT prolongation, history of torsades de pointes during therapy with a QT interval-prolonging drug, potassium wasting syndromes), and factors that influence drug disposition such as patient age, and renal or hepatic dysfunction. Because of its toxicity profile, amiodarone should only be used after consideration of risks and when other agents have failed or are contraindicated.

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Table 13 summarizes antiarrhythmic drugs useful in the maintenance of sinus rhythm along with toxicity profiles. In general, antiarrhythmic drugs have the potential to precipitate or worsen bradycardia due to sinus node dysfunction or abnormal AV conduction. A history of syncope, sinus bradycardia, PR interval prolongation, and bundle-branch block raise concerns for a risk of bradyarrhythmia during antiarrhythmic drug therapy. Depending on the specific agent selected, a pacemaker may be required for patients with significant bradyarrhythmias.

In selecting a strategy of rhythm control with an antiarrhythmic drug, providing for adequate rate control in the event of AF recurrence should also be considered. Once antiarrhythmic drug therapy is initiated, patient symptoms may improve without complete AF suppression. The transition from frequent AF to infrequent, well-tolerated recurrence of AF is a reasonable outcome and does not necessarily indicate that the therapy should be discontinued. However, if attempts at rhythm control are abandoned (e.g., after AF has been declared permanent), the antiarrhythmic drug should be discontinued.

Several systematic reviews have summarized the efficacy and safety of antiarrhythmic drugs for treating AF (347, 359, 363, 364). In a meta-analysis of 44 trials, antiarrhythmic drug therapy significantly reduced recurrence of AF (with a number needed to treat ranging from 2 to 9). All drugs may require discontinuation of therapy owing to adverse effects (number needed to harm ranging from 9 to 27) and all but amiodarone and propafenone increased proarrhythmia in this analysis (number needed to harm ranging from 17 to 119). Vaughan Williams Class IA drugs (quinidine and disopyramide, pooled data) were associated with increased mortality compared with controls, whereas no other antiarrhythmic drug showed a significant effect on mortality (365). Most of the trials in this meta-analysis had relatively short duration of follow-up and enrolled relatively healthy patients; therefore it is difficult to extrapolate these data to other patient populations. Conclusions about other important clinical outcomes such as stroke and HF were not analyzed and dronedarone was not included.

Antiarrhythmic drugs that prolong the QT interval, notably sotalol, dofetilide, and disopyramide (all of which block the rapidly activating delayed rectifier potassium current I_{Kr}) have a risk of causing torsades de pointes and should be avoided in patients at increased risk of this form of proarrhythmia. Amiodarone and dronedarone have rarely been associated with prolongation of the QT interval and torsades de pointes (366, 367). General risk factors associated with increased risk of torsades de pointes include bradycardia, advanced age, hypokalemia, hypomagnesemia, female sex, baseline prolonged QT interval, congenital long-QT syndrome, concomitant use of other QT-prolonging therapies, HF, and possibly LV hypertrophy.

Structural heart disease has been associated with an increased risk of drug-induced proarrhythmia that may manifest as life-threatening ventricular arrhythmias. Manifestations of heart disease sufficient to warrant consideration include prior MI, HF, and significant LV hypertrophy. Drugs that have prominent sodium channel-blocking effects (e.g., flecainide, Vaughan Williams Class IC drug) increase mortality in patients with MI from CAD (368). This consideration has been inferred for propafenone (Vaughan Williams Class IC agents), and these drugs should be avoided in patients with MI from CAD.

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Table 13. Dosage and Safety Considerations for Maintenance of Sinus Rhythm in AF

Drug	Usual Doses	Exclude/Use with Caution	Major Pharmacokinetic Drug Interactions
Vaughan Williams Class IA			
Disopyramide	• Immediate release: 100–200 mg once every 6 h • Extended release: 200–400 mg once every 12 h	• HF • Prolonged QT interval • Prostatism, glaucoma • Avoid other QT interval-prolonging drugs	• Metabolized by *CYP3A4*: caution with inhibitors (e.g., verapamil, diltiazem, ketoconazole, macrolide antibiotics, protease inhibitors, grapefruit juice) and inducers (e.g., rifampin, phenobarbital, phenytoin)
Quinidine	• 324–648 mg every 8 h	• Prolonged QT interval • Diarrhea	• Inhibits *CYP2D6*: ↑concentrations of tricyclic antidepressants, metoprolol, antipsychotics; ↓efficacy of codeine • Inhibits P-glycoprotein: ↑digoxin concentration
Vaughan Williams Class IC			
Flecainide	• 50–200 mg once every 12 h	• Sinus or AV node dysfunction • HF • CAD • Atrial flutter • Infranodal conduction disease • Brugada syndrome • Renal or liver disease	• Metabolized by *CYP2D6* (inhibitors include quinidine, fluoxetine, tricyclics; also genetically absent in 7%–10% of population) and renal excretion (dual impairment can ↑↑plasma concentration)
Propafenone	• Immediate release: 150–300 mg once every 8 h • Extended release: 225–425 mg once every 12 h	• Sinus or AV node dysfunction • HF • CAD • Atrial flutter • Infranodal conduction disease • Brugada syndrome • Liver disease • Asthma	• Metabolized by *CYP2D6* (inhibitors include quinidine, fluoxetine, tricyclics; also genetically absent in 7%–10% of population)—poor metabolizers have ↑beta blockade • Inhibits P-glycoprotein: ↑digoxin concentration • Inhibits *CYP2C9*: ↑warfarin concentration (↑INR 25%)
Vaughan Williams Class III			
Amiodarone	• Oral: 400–600 mg daily in divided doses for 2-4 wk; maintenance typically 100-200 mg QD • IV: 150 mg over 10 min; then 1 mg/min for 6 h; then 0.5 mg/min for 18 h or change to oral dosing; after 24 h, consider decreasing dose to 0.25 mg/min	• Sinus or AV node dysfunction • Infranodal conduction disease • Lung disease • Prolonged QT interval	• Inhibits most CYPs to cause drug interaction:↑concentrations of warfarin (↑INR 0%–200%), statins, many other drugs • Inhibits P-glycoprotein: ↑digoxin concentration
Dofetilide	• 125–500 mcg once every 12 h	• Prolonged QT interval • Renal disease • Hypokalemia • Diuretic therapy	• Metabolized by *CYP3A*: verapamil, HCTZ, cimetidine, ketoconazole, trimethoprim, prochlorperazine, and

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		• Avoid other QT interval prolonging drugs	megestrol are contraindicated; discontinue amiodarone at least 3 mo before initiation
Dronedarone	• 400 mg once every 12 h	• Bradycardia • HF • Long-standing persistent AF/flutter • Liver disease • Prolonged QT interval	• Metabolized by *CYP3A*: caution with inhibitors (e.g., verapamil, diltiazem, ketoconazole, macrolide antibiotics, protease inhibitors, grapefruit juice) and inducers (e.g., rifampin, phenobarbital, phenytoin) • Inhibits *CYP3A*, *CYP2D6*, P-glycoprotein: ↑concentrations of some statins, sirolimus, tacrolimus, beta blockers, digoxin
Sotalol	• 40–160 mg once every 12 h	• Prolonged QT interval • Renal disease • Hypokalemia • Diuretic therapy • Avoid other QT interval prolonging drugs • Sinus or AV nodal dysfunction • HF • Asthma	• None (renal excretion)

AF indicates atrial fibrillation; AV, atrioventricular; CAD, coronary artery disease; HCTZ, hydrochlorothiazide; HF, Heart Failure; INR, international normalized ratio; IV, intravenous; and QD, once daily.
Adapted from Roden et al. (369).

6.2.1.1. Specific Drug Therapy

Amiodarone is an iodinated compound that, along with its metabolites, blocks multiple ion channels (e.g., I_{Kr}, I_{Na}, I_{Kur}, I_{to}, I_{CaL}, I_{KAch}, and I_{Ks}). It is a noncompetitive beta-adrenergic antagonist. It has a long half-life of weeks and large volume of distribution into adipose tissue. While suppression of sinus and AV nodal function can occur early within the first few days of oral therapy, the antiarrhythmic effect and QT prolongation can be delayed for days or weeks. A loading phase accelerates the onset of its antiarrhythmic activity, and administration in divided doses and with food minimizes the gastrointestinal symptoms associated with large doses (≥600 mg) during the loading phase. Administration with food also significantly increases the rate and extent of amiodarone absorption. Use of oral amiodarone for AF is associated with the added benefit of effective rate control, frequently eliminating the need for other drugs to control the ventricular rate for AF recurrences. Drug interactions and toxicities, however, are sufficient to preclude its routine use as a rate-controlling agent.

Amiodarone is known to inhibit *CYP3A*, *CYP2C9*, and P-glycoprotein and, consequently, the elimination of multiple other medications. In patients also taking warfarin or digoxin, dose reduction in these drugs may be needed upon amiodarone initiation in anticipation of a rise in INR (that can be variable) and serum digoxin level. Doses of other medications for rate control should be reduced when the rate slows after initiation of amiodarone and stopped if the rate slows excessively.

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Amiodarone is the most effective available antiarrhythmic drug for maintenance of sinus rhythm in patients with paroxysmal or persistent AF. In direct comparisons, it is more effective than dronedarone, sotalol, or propafenone (314, 360, 362, 370). A mixed treatment comparison of amiodarone, dronedarone, flecainide, propafenone, and sotalol for the treatment of AF or atrial flutter found that amiodarone had the largest reduction of AF recurrence (OR: 0.22; 95% CI: 0.16 to 0.29) but was associated with the highest rate of patients experiencing ≥1 serious adverse event (OR: 2.41; 95% CI: 0.96 to 6.06) and treatment withdrawals due to adverse events (OR: 2.91; 95% CI: 1.66 to 5.11) (359). Trends for increased mortality (OR: 2.17; 95% CI: 0.63 to 7.51) were found, which were stronger when small studies randomizing <100 subjects per group were excluded from the analysis. Amiodarone therapy was associated with an increase in noncardiac mortality in patients with NYHA class III HF in SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) (371).

The major cardiovascular side effect of amiodarone is bradycardia. Marked QT prolongation can occur, but it is very rarely associated with torsades de pointes (366). Extracardiac toxicities, including thyroid, liver, pulmonary, and ocular and skin discoloration, are a major problem with amiodarone, so it not a first-choice agent (especially in younger patients) when other antiarrhythmic drugs are an option. The risk of many toxicities, including pulmonary toxicity, is dose-related and can be fatal. Chronic oral doses of ≤200 mg daily may be effective and result in fewer side effects than higher-dose regimens. In patients with left ventricular hypertrophy, HF, CAD, and/or previous MI, amiodarone is associated with a low risk of proarrhythmia, making it an appropriate initial choice to prevent recurrent AF in these clinical settings. Appropriate surveillance for lung, liver, and thyroid toxicity is warranted.

Flecainide and Propafenone are Vaughan Williams Class 1C drugs that may be considered for rhythm control in patients with AF without structural heart disease. Flecainide, along with other potent sodium channel-blocking drugs, increased mortality in patients with prior MI and therefore should be avoided in patients with ischemic heart disease (368) In addition, both drugs are negative inotropes and should be avoided in patients with LV dysfunction.

These medications can cause slowing of the atrial rate in atrial flutter, resulting in 1:1 AV conduction and an increased ventricular rate; therefore, concomitant AV nodal blocking medication is recommended. Drug-induced, use-dependent increases in the PR and QRS durations of up to 25% compared with baseline can also occur during sinus rhythm. However, a greater increase in the QRS duration may be a marker for proarrhythmia risk (372). These agents should be used with caution in the presence of significant conduction system disease, including intraventricular conduction delay or bundle branch block in the absence of a pacing system. Noncardiac side effects are uncommon and include dizziness and visual disturbance, and propafenone can cause a metallic taste. The parent compound has beta-blocker properties and its metabolites are electrophysiologically active with weak beta-blocking activity. Propafenone is a substrate for *CYP2D6*, which is genetically absent in approximately 7% of patients (poor metabolizers) and is inhibited by quinidine, fluoxetine, tricyclic

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antidepressants, among others. Thus, drug interactions and genetic susceptibility can cause abnormally increased plasma concentrations of propafenone, resulting in significant beta blockade.

Sotalol, a I_{Kr} inhibitor and beta blocker, is not effective for conversion of AF to sinus rhythm, but it may be used to prevent recurrent AF. Much like with other antiarrhythmic drugs, with the exception of amiodarone, the rates of maintaining sinus rhythm at 1 year for sotalol are in the range of 30% to 50% (347). Sotalol is renally cleared and should be used with caution or avoided in patients with CKD or unstable renal function. Sotalol causes drug-induced QT interval prolongation, so it should be administered with caution or avoided when administered with other drugs known to prolong the QT interval. During follow-up, serum potassium and magnesium levels and renal function should be checked periodically. Trends toward increased mortality for sotalol (OR: 3.44; 95% CI: 1.02 to 11.59) were observed in a comparison study (359) and it is likely that proarrhythmia is a contributing mechanism. Some experts initiate sotalol in hospital with electrocardiographic monitoring to observe for QT prolongation and proarrhythmia in the absence of an implanted cardioverter-defibrillator.

Dofetilide is a potent and selective inhibitor of I_{Kr} that may be considered for rhythm control in patients who are low risk for torsades de pointes induced by QT interval prolongation. Dofetilide has minimal noncardiac side effects. In the SAFIRE-D (Symptomatic Atrial Fibrillation Investigative Research on Dofetilide) trial, dofetilide (500 mcg twice daily) exhibited 58% efficacy in maintaining sinus rhythm at 1 year after cardioversion, compared with only 25% in the placebo group (332). Torsades de pointes occurred with an incidence of 0.8%. Dofetilide was discontinued owing to excessive QT prolongation in 5% of patients. In the DIAMOND (Danish Investigations of Arrhythmia and Mortality on Dofetilide) study of patients with reduced LV function, sinus rhythm was maintained at 1 year in 79% of the dofetilide group compared with 42% of the placebo group (336). In the United States, for initiation or dose escalation of therapy, inpatient ECG monitoring is mandatory, as was the case in clinical trials. Under these circumstances, dofetilide does not increase mortality in HF and post-MI populations (373). It is renally cleared, dosed according to CrCl, and adjusted or discontinued depending on degree of QT prolongation. It should not be administered concomitantly with multiple other drugs that influence dofetilide disposition (Table 13) or can prolong the QT interval.

Dronedarone may be considered for rhythm control in patients who do not have HF. Dronedarone is a structural analogue of amiodarone but lacks amiodarone's iodine moieties. It is associated with a lower incidence of adverse events than amiodarone but is also less efficacious (360). Its multiple electrophysiologic actions include sympatholytic effects as well as blocking of calcium, sodium, and potassium currents. Dronedarone reduced the combined endpoint of death and cardiovascular complications (largely by reducing hospitalizations for AF) in patients with paroxysmal or persistent AF or atrial flutter and risk factors for thromboembolism (350).

Dronedarone increases mortality in patients with recently decompensated HF and depressed LV function (283) and is contraindicated in patients with NYHA class III or IV HF and in patients who have had an

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episode of decompensated HF in the past 4 weeks, especially if they have depressed LV function. In patients with permanent AF, dronedarone increases the combined endpoint of stroke, cardiovascular death, and hospitalization (282). Therefore, dronedarone is contraindicated in patients who are not restored to sinus rhythm.

The major cardiac adverse effects of dronedarone are bradycardia and QT prolongation. Torsades de pointes is rare but has been reported. Like amiodarone, dronedarone inhibits renal tubular secretion of creatinine, which can increase plasma creatinine levels. However, there is no reduction in the glomerular filtration rate. Dronedarone is metabolized by *CYP3A4* and is a moderate inhibitor of *CYP2D6* and P-glycoprotein. Consequently, it increases levels of digoxin and dabigatran and should not be administered with strong inhibitors of *CYP3A4* (e.g., ketoconazole and macrolide antibiotics), which may potentiate its effects. Dronedarone can be administered with verapamil or diltiazem, which are moderate *CYP3A4* inhibitors, but low doses of these agents should be used initially and titrated according to response and tolerance. Dronedarone does not alter the INR when used with warfarin. Dronedarone has been associated with rare case reports of severe hepatotoxicity occurring within 6 months of initiation; therefore monitoring of hepatic serum enzymes, especially during the first 6 months of treatment, should be performed.

Disopyramide is a sodium channel-blocking drug with potent anticholinergic and negative inotropic effects that can be considered for rhythm control in patients with AF. Disopyramide can reduce AF recurrence after direct-current cardioversion (374). Because of its prominent vagolytic pharmacological effects, disopyramide is useful in AF that occurs in the setting of high vagal tone ("vagally mediated AF"), such as sleep and in response to stimuli that elicit a vagal response, but there is little supporting evidence for this approach. Its negative inotropic effects may be desirable in patients with HCM associated with dynamic outflow tract obstruction (375). Otherwise, it is avoided in structural heart disease. Disopyramide can also prolong the QT interval.

Quinidine has a sodium channel-blocking effect at rapid heart rates and a potassium channel-blocking effect at slower heart rates as well as vagolytic and alpha-adrenergic receptor blocking effects, and was among the first antiarrhythmic drugs used to treat AF. It prolongs the QT interval, can cause torsades de pointes, and is used infrequently. Cumulative evidence from a systematic review suggests that quinidine and disopyramide may increase mortality slightly (365). Quinidine has no negative inotropic effects and can be used when there is advanced renal dysfunction. Quinidine requires close ECG monitoring at initiation and may be an alternative treatment for AF when other, newer antiarrhythmic drugs cannot be used.

Beta blockers are usually not considered effective for maintaining sinus rhythm in patients with AF. One placebo-controlled study of 394 patients with persistent AF found a lower risk of early recurrence after cardioversion and slower ventricular response with sustained-release metoprolol than with placebo (376). Combining an antiarrhythmic drug with a beta blocker may be helpful in some patients. These agents are useful to prevent AF in patients following cardiac surgery and during a high-adrenergic state, such as exercise and thyrotoxicosis-related AF. At least theoretically, they can aggravate vagally mediated AF.

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See Online Data Supplement 12 for additional data on antiarrhythmic drug therapy (http://jaccjacc.cardiosource.com/DataSupp/MASTER_2014_AF_Evidence_Table_Supplement_03182014.pdf).

6.2.1.2. Outpatient Initiation of Antiarrhythmic Drug Therapy

Drug-related proarrhythmia is most common during the initiation phase of drug therapy. Serial ECGs are important to detect excessive QT prolongation (such as with dofetilide or sotalol), the appearance of "giant" U waves, or QRS prolongation >25% (such as with flecainide or propafenone), and should be performed near the time of peak drug concentration (377). Inpatient initiation or dose escalation of dofetilide in an electrocardiographically monitored environment is required because of the risk of untoward QT interval prolongation and arrhythmia provocation (332, 336). Sotalol also results in QT prolongation and may cause proarrhythmia. Its initiation and dose escalation during hospitalization with electrocardiographic monitoring should be considered; the package insert has a corresponding black box warning. There is considerable experience, however, initiating sotalol in an outpatient setting. Some experts allow outpatient initiation when sotalol is started with the patient in sinus rhythm provided the QT interval and serum potassium are normal and no other QT interval-prolonging medications are present but require inpatient hospitalization when sotalol is initiated while a patient is in AF (316). Other experts always initiate sotalol in an inpatient monitored setting. Practice patterns vary widely both in terms of which patients are hospitalized for initiation of antiarrhythmic drug therapy and in the length of hospitalization. The decision about whether to initiate other antiarrhythmic drugs in an inpatient or outpatient setting should be carefully individualized (378). Data supporting the outpatient initiation of antiarrhythmic drug therapy are best established for amiodarone and dronedarone (Table 13).

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See Online Data Supplement 13 for additional data on antiarrhythmic drug therapy (http://jaccjacc.cardiosource.com/DataSupp/MASTER_2014_AF_Evidence_Table_Supplement_03182014.pdf).

6.2.2. Upstream Therapy: Recommendations

Class IIa

1. **An ACE inhibitor or angiotensin-receptor blocker (ARB) is reasonable for primary prevention of new-onset AF in patients with HF with reduced LVEF (130, 379, 380). *(Level of Evidence: B)***

Class IIb

1. **Therapy with an ACE inhibitor or ARB may be considered for primary prevention of new-onset AF in the setting of hypertension (381). *(Level of Evidence: B)***
2. **Statin therapy may be reasonable for primary prevention of new-onset AF after coronary artery surgery (136, 382). *(Level of Evidence: A)***

Class III: No Benefit

1. **Therapy with an ACE inhibitor, ARB, or statin is not beneficial for primary prevention of AF in patients without cardiovascular disease (383). *(Level of Evidence: B)***

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The goal of "upstream" therapy (i.e., ACE inhibitors, ARBs, statins, and n-3 polyunsaturated fatty acids) is to modify the atrial substrate to reduce susceptibility to, or progression of, AF. Agents delivered as upstream drug therapy might have the ability to halt or delay the cellular processes leading to AF either before (primary prevention) or after (secondary prevention) the development of AF.

A number of prospective trials investigating ARBs and polyunsaturated fatty acids for prevention of recurrent AF have been disappointing (81, 383-388). Although upstream therapies may be valuable strategies for primary prevention of cardiac changes leading to AF in selected patients, reversal of AF substrate has not been demonstrated and such therapy is not recommended for the prevention of AF recurrence in patients without another indication. In retrospective studies and studies in which AF was a prespecified secondary endpoint, ACE inhibitors or ARBs slightly reduce the development of AF in patients with HF and LV dysfunction and possibly those with hypertension and LV hypertrophy (81). Several systematic reviews of statin therapy to prevent AF have been performed (136, 384, 389, 390). The administration of statins may reduce postoperative AF in patients undergoing coronary artery bypass grafting (136, 382, 391).

See Online Data Supplement 14 for additional data on upstream therapy (http://jaccjacc.cardiosource.com/DataSupp/MASTER_2014_AF_Evidence_Table_Supplement_03182014.pdf).

6.3. AF Catheter Ablation to Maintain Sinus Rhythm: Recommendations

Class I

1. **AF catheter ablation is useful for symptomatic paroxysmal AF refractory or intolerant to at least 1 class I or III antiarrhythmic medication when a rhythm control strategy is desired (363, 392-397). *(Level of Evidence: A)***
2. **Prior to consideration of AF catheter ablation, assessment of the procedural risks and outcomes relevant to the individual patient is recommended. *(Level of Evidence: C)***

Class IIa

1. **AF catheter ablation is reasonable for selected patients with symptomatic persistent AF refractory or intolerant to at least 1 class I or III antiarrhythmic medication (394, 398-400). *(Level of Evidence: A)***
2. **In patients with recurrent symptomatic paroxysmal AF, catheter ablation is a reasonable initial rhythm control strategy prior to therapeutic trials of antiarrhythmic drug therapy, after weighing risks and outcomes of drug and ablation therapy (401-403). *(Level of Evidence: B)***

Class IIb

1. **AF catheter ablation may be considered for symptomatic long-standing (>12 months) persistent AF refractory or intolerant to at least 1 class I or III antiarrhythmic medication, when a rhythm control strategy is desired (363, 404). *(Level of Evidence: B)***
2. **AF catheter ablation may be considered prior to initiation of antiarrhythmic drug therapy with a class I or III antiarrhythmic medication for symptomatic persistent AF, when a rhythm control strategy is desired. *(Level of Evidence: C)***

Class III: Harm

1. **AF catheter ablation should not be performed in patients who cannot be treated with anticoagulant therapy during and following the procedure. *(Level of Evidence: C)***

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2. **AF catheter ablation to restore sinus rhythm should not be performed with the sole intent of obviating the need for anticoagulation.** ***(Level of Evidence: C)***

The role of catheter ablation in the management of AF continues to evolve rapidly, with improvements in the efficacy and safety of the procedure (28). The efficacy of radiofrequency catheter ablation for maintaining sinus rhythm is superior to current antiarrhythmic drug therapy for maintenance of sinus rhythm in selected patient populations. A number of systematic reviews of the efficacy of AF catheter ablation versus antiarrhythmic drug therapy have been performed (363, 392-395, 405, 406). Cryoballoon ablation is an alternative to point-by-point radiofrequency ablation to achieve pulmonary vein isolation (407). The evidence supporting the efficacy of catheter ablation is strongest for paroxysmal AF in younger patients with little to no structural heart disease (408) and in procedures performed in highly experienced centers. Studies have demonstrated a reduction of AF-related symptoms in these contexts (409). Evidence is insufficient to determine whether AF catheter ablation reduces all-cause mortality, stroke, and HF (7). Ongoing clinical trials (CABANA [Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation] and EAST [Early Therapy of Atrial Fibrillation for Stroke Prevention Trial]) should provide new information for assessing whether AF catheter ablation is superior to standard therapy with either rate- or rhythm-control drugs for reducing total mortality and other secondary outcome measures, and whether early application of a rhythm-control therapy involving ablation, antiarrhythmic drugs, or both, can impact endpoints of stroke, cardiovascular death, or HF compared with usual care. These important trials will help to address whether catheter ablation provides benefit beyond improvements in quality of life.

See Online Data Supplements 15 and 16 for additional data on maintaining sinus rhythm and AF catheter ablation (http://jaccjacc.cardiosource.com/DataSupp/MASTER_2014_AF_Evidence_Table_Supplement_03182014.pdf).

6.3.1. Patient Selection

The decision whether to pursue catheter ablation depends on a large number of variables, including the type of AF (paroxysmal versus persistent verses longstanding persistent), degree of symptoms, presence of structural heart disease, candidacy for alternative options such as rate control or antiarrhythmic drug therapy, likelihood of complications, and patient preference (28). It is important to recognize that most patients enrolled in trials of AF catheter ablation have generally been younger, healthy individuals with symptomatic paroxysmal AF refractory to ≥1 antiarrhythmic medication. The safety and efficacy of catheter ablation are less well established for other populations of patients, especially patients with longstanding persistent AF, very elderly patients, and patients with significant HF including tachycardia-induced cardiomyopathy (28) (Section 6.3). Figure 7 shows an approach to the integration of antiarrhythmic drugs and catheter ablation of AF in patients without and with structural heart disease.

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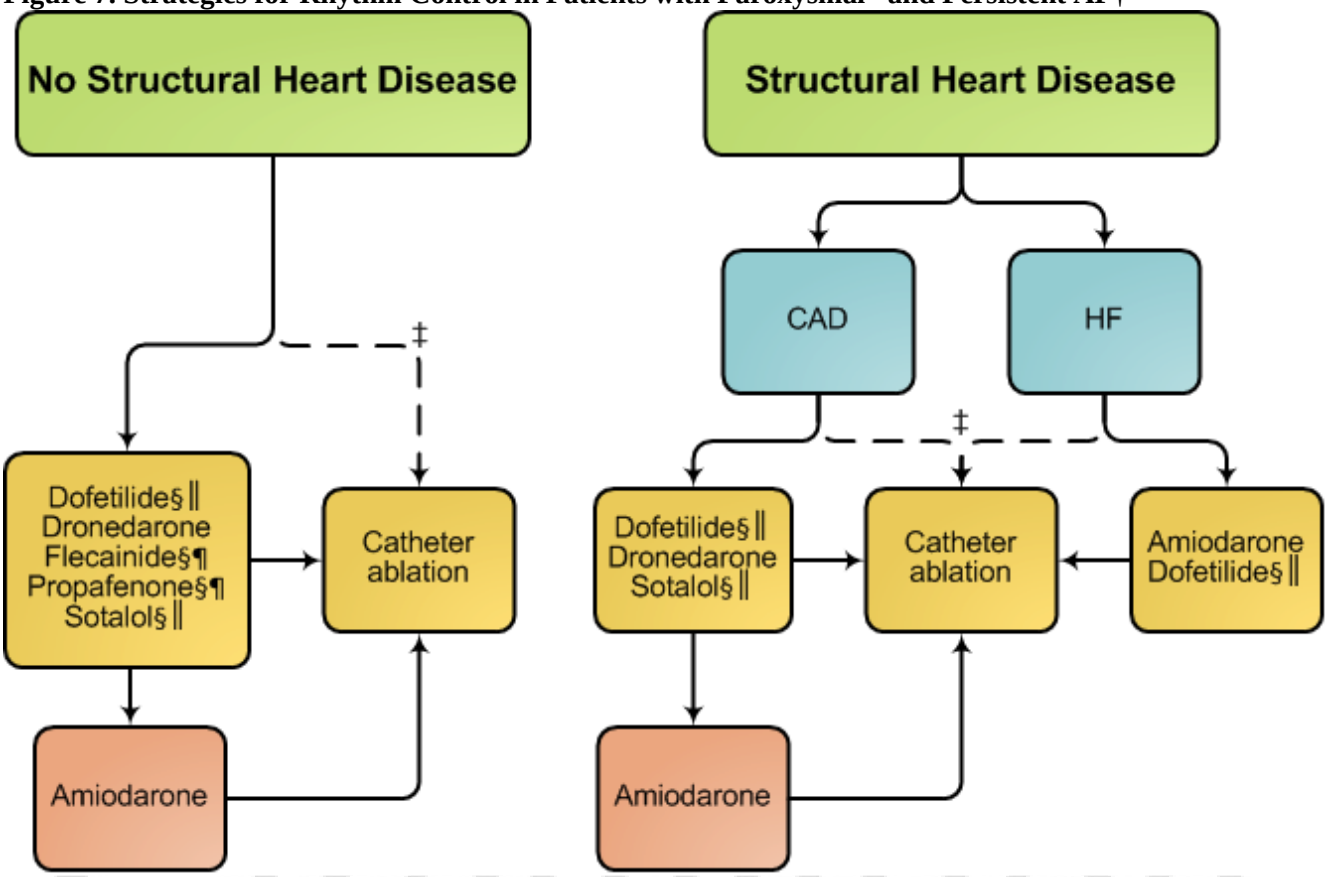
Figure 7. Strategies for Rhythm Control in Patients with Paroxysmal* and Persistent AF†



*Catheter ablation is only recommended as first-line therapy for patients with paroxysmal AF (Class IIa recommendation).
†Drugs are listed alphabetically.
‡Depending on patient preference when performed in experienced centers.
§Not recommended with severe LVH (wall thickness >1.5 cm).
‖Should be used with caution in patients at risk for torsades de pointes ventricular tachycardia.
¶Should be combined with AV nodal blocking agents.
AF indicates atrial fibrillation; CAD, coronary artery disease; HF, heart failure; and LVH, left ventricular hypertrophy.

Two RCTs compared radiofrequency catheter ablation with antiarrhythmic drug therapy as a first-line rhythm control treatment. The RAAFT (Radiofrequency Ablation Versus Antiarrhythmic Drug for Atrial Fibrillation Treatment) II trial compared the efficacy of AF catheter ablation with that of antiarrhythmic drug therapy as first-line therapy for rhythm control in 127 patients (88% paroxysmal AF) with a higher 1-year freedom from AF (45% versus 28%; p=0.02) (402). The MANTRA-PAF (Medical Antiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation) trial compared AF catheter ablation with antiarrhythmic drug therapy as first-line therapy in 294 patients (410). At the 24-month follow-up, more patients in the ablation group were free from any AF or symptomatic AF and quality of life was significantly better (403). However, total AF burden was not significantly different between the 2 groups and major complications requiring intervention were more common in the ablation group. On the basis of these data, radiofrequency catheter ablation may be considered as first-line therapy in select patients prior to a trial of antiarrhythmic drug therapy when a rhythm control strategy is desired.

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6.3.2. Recurrence After Catheter Ablation

Recurrences of AF after catheter ablation are common during the first 3 months and do not preclude long-term success, although they are associated with an increased risk of procedural failure and rehospitalization. Therefore, when AF occurs early after catheter ablation, a pharmacologic rhythm control approach rather than early repeat ablation should be considered (28). Patients who have had AF catheter ablation and develop persistent AF within the 3 months following ablation may require cardioversion. Recurrent AF after 3 months is usually an indication of recovery of pulmonary vein conduction and may respond to repeat ablation or initiation of an antiarrhythmic drug (411). A number of centers have reported late AF recurrences >1 year after catheter ablation (78, 412-415).

6.3.3. Anticoagulation Therapy Periablation

Because of the well-established risk of periprocedure stroke or TIA associated with AF catheter ablation, there is consensus that anticoagulation is indicated to prevent thromboembolism around the time of radiofrequency catheter ablation regardless of the patient's baseline thromboembolic risk. Detailed consensus recommendations have been published regarding the approach to anticoagulation prior to, during, and following catheter ablation (28). Both intraprocedural heparin and oral anticoagulation for ≥2 months postprocedure are recommended. AF catheter ablation should not be performed in patients who cannot be treated with anticoagulant therapy during and following the procedure.

Several reports indicate that AF catheter ablation may be performed with fewer complications when oral warfarin anticoagulation is continued as an alternative to a bridging approach with UFH or LMWH (243, 416-418). Several centers reported their experience with the use of direct thrombin and factor Xa inhibitors (mainly dabigatran) around the time of AF catheter ablation (244, 324, 419-422). Typically, dabigatran was held for 1 or 2 doses prior to the ablation procedure, in part reflecting the lack of a reversal agent. These reports suggest that the use of dabigatran is associated with a similar risk of bleeding and thromboembolic complications compared with uninterrupted warfarin; however, this is not a uniform finding (244).

Continuation of anticoagulation >2 months following AF catheter ablation, if the procedure is perceived successful, should be based on consideration of the patient's thromboembolic risk profile (Section 4.1), bleeding risk, and patient choice. Recurrence of AF following ablation is 3- to 7-fold more likely to be asymptomatic compared with prior to ablation (423, 424), and late recurrences of AF can occur. Several large case series have reported a low risk of stroke after AF ablation (425-428). Although the stroke rate is low in these series, few patients at high risk of stroke were monitored after anticoagulation was stopped for a significant period of time.

6.3.4. Catheter Ablation in HF

A number of smaller clinical trials have evaluated the role of AF catheter ablation in selected patients with LV dysfunction and HF and demonstrate a reasonable rate of successful sinus rhythm maintenance with improvements in LVEF and symptoms (47, 307, 429). The degree to which LVEF improves varies according to patient characteristics (430). In cases where the LV dysfunction is thought to be due to AF itself, AF catheter

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ablation and maintenance of sinus rhythm may result in a marked improvement. It may be difficult to determine in this population whether symptoms are related to AF or the underlying HF and whether the AF itself has contributed to the decline in LVEF. Improved rate control or cardioversion with antiarrhythmic drug therapy may help determine the causality. Because of the extent of remodeling and underlying heart disease, recurrence rates (431) and complication rates are higher in this population. A meta-analysis reported that the single-procedure efficacy of AF catheter ablation was lower in patients with systolic dysfunction, but a similar success rate could be achieved among patients with and without systolic dysfunction with repeat procedures (432). Patient selection biases likely influence reported outcomes. Taken as a whole, catheter ablation may be reasonable to treat symptomatic AF in selected patients with significant LV dysfunction and HF.

6.3.5. Complications Following AF Catheter Ablation

AF catheter ablation is associated with important risks of major complications. A 2010 international survey of radiofrequency catheter ablation procedures reported a 4.5% incidence of major complications, including a 1.3% rate of cardiac tamponade, a 0.94% rate of stroke or TIA, a 0.04% rate of atrial-esophageal fistula, and a 0.15% rate of death (433). A European observational multinational registry reported a complication rate of 7.7%, of which 1.7% were major complications (434). A report from a state-wide inpatient database described a complication rate of 5% with a 9% readmission rate (435). Much of the data regarding rates of complications is derived from experienced centers or voluntary registries.

Table 14 lists the complications associated with radiofrequency catheter ablation for AF. A detailed summary of definitions and prevention of specific complications is covered elsewhere (28). Factors associated with complication rates include older age, female sex, and a $CHADS_2$ score of ≥2 (435-437). Also, LA catheter ablation results in a small incidence of asymptomatic cerebral embolism detectable on cranial magnetic resonance imaging. Most of these lesions resolve or disappear over time. Further research is needed to better define the relationship between ablation strategy and risk, and to determine methods to eliminate them (28, 438, 439).

Table 14. Complications of Radiofrequency Catheter Ablation for AF

Complication	Symptoms/Signs	Treatment
Air embolism	Acute ischemia, cardiac arrest, AV block, hypotension	Supplemental oxygen, fluids, CPR, or pacing if indicated
Atrial-esophageal fistula	Usually 1–4 wk after ablation, dysphagia, unexplained fever, chills, sepsis, neurological events (septic emboli)	CT or MRI of esophagus, avoiding endoscopy, immediate surgical correction
Cardiac tamponade/perforation	Abrupt or gradual fall in BP	Pericardiocentesis, emergent surgical drainage if pericardiocentesis fails
Phrenic nerve injury resulting in diaphragmatic paralysis	Shortness of breath, elevated hemidiaphragm	None, usually resolves spontaneously
Iatrogenic atrial flutter	Tachycardia	Cardioversion, antiarrhythmic drugs, or repeat ablation

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Gastric motility disorder	Nausea, vomiting, bloating, abdominal pain	Depends on severity of symptoms
Mitral valve injury requiring surgery	Entrapment of catheter	Advance sheath with gentle catheter retraction, surgical removal
MI	Chest pain, ST changes, hypotension	Standard therapy
Pericarditis	Chest pain, typical quality	NSAIDs, colchicine, steroids
Pulmonary vein stenosis	Shortness of breath, cough, hemoptysis	PV dilation/stent or no therapy
Radiation injury	Pain and reddening at radiation site, can present late	Treat as burn injury
Stroke or TIA	Neurological deficit	Consider lysis therapy
Vascular access complication • Femoral pseudo aneurysm	Pain or pulsatile mass at groin	Observation, compression, thrombin injection, possible surgery
• Arteriovenous fistula	Pain, bruit at groin site	Observation, compression, possible surgery
• Hematoma	Pain, swelling	Compression
Death	N/A	N/A

AF indicates atrial fibrillation; AV, atrioventricular; BP, blood pressure; CPR, cardiopulmonary resuscitation; CT, computed tomography; MI, myocardial infarction; MRI, magnetic resonance imaging; N/A, not applicable; NSAIDs, nonsteroidal anti-inflammatory drugs; PV, pulmonary valve; and TIA, transient ischemic attack.

6.4. Pacemakers and Implantable Cardioverter-Defibrillators for the Prevention of AF

The primary role of pacemakers in the treatment of patients with AF is for treatment of symptomatic bradycardia, which is often related to underlying sick sinus syndrome. Antiarrhythmic therapy may exacerbate sick sinus syndrome and require pacemaker implantation. For patients with sick sinus syndrome who need pacing, atrial or dual chamber pacing significantly decreases the incidence of subsequent AF compared with RV pacing (16). Attempts to prevent AF episodes by proprietary overdrive atrial pacing algorithms that react to premature atrial complexes are inconsistent (16). Therefore, permanent pacing is not indicated for the prevention of AF in patients without other indications for pacemaker implantation. Atrial defibrillators to automatically cardiovert AF do not have clinical value; most patients find discharge energies >1 J uncomfortable and early recurrence of AF following a shock is common. Implanted defibrillators are not indicated for rhythm control of AF.

6.5. Surgery Maze Procedures: Recommendations

Class IIa

1. **An AF surgical ablation procedure is reasonable for selected patients with AF undergoing cardiac surgery for other indications.** ***(Level of Evidence: C)***

Class IIb

1. **A stand-alone AF surgical ablation procedure may be reasonable for selected patients with highly symptomatic AF not well managed with other approaches (440).** ***(Level of Evidence: B)***

The surgical maze procedure was introduced in 1987. The initial 2 iterations were associated with high rates of pacemaker implantation and are no longer performed. The third version (Cox maze III) became the standard surgical procedure to restore sinus rhythm in patients with AF (441) but is not widely performed because of

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surgeons' reluctance to perform this complicated "cut and sew" atrial lines of ablation operation approach in association with valve or coronary artery bypass procedures or as a stand-alone procedure. The Cox maze IV operation is less invasive, using radiofrequency or cryoablation to replicate surgical lines of ablation (442).

Data regarding long-term outcomes in patients undergoing stand-alone AF surgery are limited. Of 282 patients prospectively studied from 2002 to 2009 undergoing the Cox maze IV procedure, 42% had paroxysmal AF and 58% had either persistent or longstanding persistent AF (442). Ninety-five of 282 patients (34%) had a stand-alone procedure and 187 of 282 patients (66%) had a concomitant AF procedure. Overall operative mortality was 2% (1% in stand-alone maze procedures) and freedom from atrial tachyarrhythmias was 89%, 93%, and 89% at 3, 6, and 12 months, respectively. Freedom from atrial tachyarrhythmias off all antiarrhythmic drugs was 63%, 79%, and 78% at 3, 6, and 12 months, respectively. In the period of the study subsequent to 2006, 24-hour Holter monitoring or pacemaker interrogation was performed in these patients. In this cohort, 92% were free of atrial tachyarrhythmias and 78% were not taking antiarrhythmic drugs (442).

Nine RCTs comparing patients who undergo concomitant AF surgery with patients who undergo mitral valve surgery alone suggest greater freedom from AF in treated patients (443-451); however, in the composite body of evidence, there was no consistent surgical technique, patient populations in the trial were quite varied, a consistent endpoint defining procedural success was lacking, and long-term clinical endpoints were often missing as well.

The Society of Thoracic Surgeons Adult Cardiac Surgery Database from 2005 to 2010 recorded 91,801 AF surgical ablations, of which 4,893 (5.3%) were stand-alone procedures (452). Propensity matching of 1,708 patients with and without cardiopulmonary bypass showed no difference in mortality risk between groups, but the "off bypass group" had fewer reoperations for bleeding, shorter hospital stay, and less prolonged ventilation. Minimally invasive stand-alone operations, bilateral pulmonary vein isolation, intraoperative confirmation of mapping, ablation of ganglionic plexi, and exclusion of the LAA procedures have been developed. Of 114 patients undergoing bilateral mini-thoracotomy surgical ablation of AF, 2 patients (1.8%) died within the perioperative period and the overall complication rate was 10% (453). At the 6-month follow-up (ECG, Holter monitor, event monitor, or pacemaker interrogation), 52 of 60 patients (87%) with paroxysmal AF were in sinus rhythm and 43 of 60 patients (72%) were off antiarrhythmic drugs. In patients with persistent or long-standing persistent AF, the success rates of freedom from AF were lower, at 18 of 32 patients (56%) and 11 of 22 patients (50%), respectively.

The FAST (Atrial Fibrillation Catheter Ablation Versus Surgical Ablation Treatment) trial compared the outcomes of catheter ablation and surgical ablation in a randomized study design (440). Patients either had left atrial dilation and hypertension (42 patients, 33%) or failed prior catheter ablation (82 patients, 67%). Freedom from atrial arrhythmias was greater after surgical ablation compared with catheter ablation, but the complication rate after surgical ablation was higher. Decisions regarding the choice of catheter-based or surgical ablation

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must be made on the basis of patient preference, and institutional experience and outcomes with each therapy (28).

7. Specific Patient Groups and AF

See Table 15 for a summary of recommendations for this section and Online Data Supplement 17 for additional data on specific patient groups and AF (http://jaccjacc.cardiosource.com/DataSupp/MASTER_2014_AF_Evidence_Table_Supplement_03182014.pdf).

7.1. Athletes

Paroxysmal or persistent AF is common in athletes and may be autonomically mediated or triggered by other supraventricular tachycardias (454). Contributing conditions such as hypertension and CAD should be considered, particularly for older athletes, and a transthoracic echocardiogram is helpful to evaluate for structural heart disease. Evaluation of the rate of ventricular response during an episode of AF is warranted and may require ambulatory ECG monitoring and/or exercise testing to a level of exertion similar to that of the intended sport. Other therapies such as radiofrequency catheter ablation or a "pill-in-the-pocket" approach can be considered in athletes. Specifics of these therapies are considered in Section 6.1.3 (455).

7.2. Elderly

The prevalence of AF increases with age and approximately 35% of patients with AF are ≥80 years of age (30, 31). The elderly are a heterogeneous group with potential for multiple comorbidities (Table 3). It is critical to consider the implications of comorbidities to ensure that the patient's overall goals of care are factored into management decisions. For the older patient with AF, symptoms may be minimal and somewhat atypical. The risk of stroke is increased in the elderly. It is for this reason that the CHA_2DS_2-VASc risk scoring system identifies 65 to 74 years of age as a minor risk factor for stroke and ≥75 years of age as a major stroke risk factor (Section 4.1).

Because AF is often associated with minimal or no symptoms in this population, and the clearance of antiarrhythmic medications is diminished, sensitivity to proarrhythmic effects, including bradyarrhythmias, is often increased. Therefore a rate control strategy is often preferred (30), and direct-current cardioversion is less often warranted (456). Typically, rate control can be achieved with beta blockers or nondihydropyridine calcium channel antagonists. Care must be taken in these patients as they are often more susceptible to orthostatic hypotension or bradyarrhythmias and when AF is paroxysmal and sinus node dysfunction is more common. Comorbidities should also be considered. Digoxin can be useful for rate control in the relatively sedentary individual, but there are concerns about its risks (Section 5.1.3).

7.3. Hypertrophic Cardiomyopathy: Recommendations

Class I

1. **Anticoagulation is indicated in patients with HCM with AF independent of the CHA_2DS_2-VASc score (50, 457). *(Level of Evidence: B)***

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Class IIa

1. **Antiarrhythmic medications can be useful to prevent recurrent AF in patients with HCM. Amiodarone, or disopyramide combined with a beta blocker or nondihydropyridine calcium channel antagonists are reasonable therapies.** ***(Level of Evidence: C)***
2. **AF catheter ablation can be beneficial in patients with HCM in whom a rhythm-control strategy is desired when antiarrhythmic drugs fail or are not tolerated (458-461).** ***(Level of Evidence: B)***

Class IIb

1. **Sotalol, dofetilide, and dronedarone may be considered for a rhythm-control strategy in patients with HCM (11).** ***(Level of Evidence: C)***

Patients with HCM are considered separately because their unique pathology serves to distinguish them from other patients with LV hypertrophy. HCM is defined on the basis of standard criteria such as the echocardiographic identification of a hypertrophied, nondilated LV in the absence of another cardiac or systemic disease capable of producing the magnitude of hypertrophy evident (462). AF is relatively common in HCM, increases with age, and is often poorly tolerated symptomatically (50). The incidence of AF is estimated at 2% per year in patients with HCM and approximately two-thirds of patients with both HCM and AF are paroxysmal (50). AF is associated with increased mortality in patients with HCM (3% in patients with AF versus 1% in sinus rhythm per year) (50, 463) and is primarily due to HF. The HF risk associated with AF in patients with HCM is worse in patients with outflow obstruction and those who develop AF before 50 years of age (50).

There is an important risk of stroke and systemic embolism in patients with HCM and AF (50, 464, 465). In a study of 480 patients with HCM, the OR for stroke in those with AF was 17.7 (50). Although no randomized studies of anticoagulant therapy have been reported, the incidence of thromboembolism in patients with HCM and AF is high and anticoagulation is indicated for these patients independent of their other CHA_2DS_2-VASc (or $CHADS_2$) score. Anticoagulation with direct thrombin or factor Xa inhibitors may represent another option to reduce the risk of thromboembolic events, but data for patients with HCM are not available (50, 177, 457).

Given the poor tolerance of AF in patients with HCM, a rhythm-control strategy is preferred. However, for those patients for whom a rate-control strategy is chosen, a nondihydropyridine calcium channel blocker, a beta blocker, or a combination of the 2 is preferable. Digoxin, a positive inotrope, may increase the outflow gradient in HCM patients and should be avoided. There have been no systematic studies of the treatment of AF in patients with HCM, but various antiarrhythmic agents have been used, including disopyramide, propafenone, amiodarone, sotalol, dofetilide, and dronedarone. An implantable cardioverter-defibrillator may provide added safety with QT interval-prolonging drugs. Amiodarone or disopyramide in combination with ventricular rate-controlling agents are generally preferred (11, 466).

Success and complication rates for AF catheter ablation appear to be similar for HCM and other forms of heart disease, but reported outcomes are likely influenced by selection bias (11, 458, 460). The surgical maze

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procedure for AF shows some success (467); however, the role of a surgical maze procedure for patients undergoing other open chest surgical procedures (i.e., septal myectomy) is unresolved (11, 467).

7.4. AF Complicating ACS: Recommendations

Class I

1. **Urgent direct-current cardioversion of new-onset AF in the setting of ACS is recommended for patients with hemodynamic compromise, ongoing ischemia, or inadequate rate control. *(Level of Evidence: C)***
2. **Intravenous beta blockers are recommended to slow a rapid ventricular response to AF in patients with ACS who do not display HF, hemodynamic instability, or bronchospasm. *(Level of Evidence: C)***
3. **For patients with ACS and AF with CHA_2DS_2-VASc score of 2 or greater, anticoagulation with warfarin is recommended unless contraindicated. *(Level of Evidence: C)***

Class IIb

1. **Administration of amiodarone or digoxin may be considered to slow a rapid ventricular response in patients with ACS and AF associated with severe LV dysfunction and HF or hemodynamic instability. *(Level of Evidence: C)***
2. **Administration of nondihydropyridine calcium antagonists might be considered to slow a rapid ventricular response in patients with ACS and AF only in the absence of significant HF or hemodynamic instability. *(Level of Evidence: C)***

The incidence of AF in patients with ACS ranges from 10% to 21% and increases with patient age and severity of MI (138, 468). In the Medicare population, AF is associated with increased in-hospital mortality (25.3% with AF versus 16.0% without AF), 30-day mortality (29.3% versus 19.1%), and 1-year mortality (48.3% versus 32.7%) (138). With multivariate adjustment, AF remains an independent predictor of mortality: in-hospital (OR: 1.21), 30-day (OR: 1.20), and 1-year (OR: 1.34) (138). Patients who develop AF during hospitalization have a worse prognosis than those with AF on admission (138). Stroke rates are increased in patients with MI and AF compared with rates in those without AF (3.1% for those with AF versus 1.3% for those in normal sinus rhythm) (468). Thus, AF is an independent predictor of poor long-term outcome in patients with ACS (469, 470). Specific recommendations for management of patients with AF in the setting of ACS are based primarily on consensus because no adequate trials have tested alternative strategies (20).

Patients treated for ACS normally require dual antiplatelet therapy with aspirin plus other platelet inhibitors, such as clopidogrel, and may require the addition of warfarin or a novel oral anticoagulant ("triple therapy") as treatment of AF (186) (Section 4.3). In patients with long-standing AF or a moderate-to-high CHA_2DS_2-VASc score, efforts should be directed to minimize duration of triple therapy and the decisions about stent insertion should consider the potential requirement for long-term anticoagulant therapy. For patients who develop transient AF as a complication of ACS and who do not have a prior history of AF, the need for anticoagulation and the duration of oral anticoagulation should be based on the patient's CHA_2DS_2-VASc score. Use of dual antiplatelet therapy alone may be considered for patients with ACS who have AF and a low CHA_2DS_2-VASc score, with reconsideration of the indications for anticoagulation over time (199, 323). An

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option is to consider the use of oral anticoagulation plus clopidogrel with or without aspirin (186). The novel oral anticoagulants have not been evaluated in the context of AF and ACS and thus no recommendation for their use can be made.

Urgent direct-current cardioversion is appropriate in patients with ACS presenting with new-onset AF and intractable ischemia, hemodynamic instability, or inadequate rate control. Intravenous administration of a beta blocker is indicated for rate control in patients with ACS to reduce myocardial oxygen demands. Intravenous amiodarone is an appropriate alternative for rate control and may facilitate conversion to normal sinus rhythm. Digoxin may be considered in those with severe LV dysfunction and HF or hemodynamic instability. Systemic anticoagulation is indicated in those with large anterior infarcts and in survivors of ACS who develop persistent AF. Treatment with ACE inhibitors appears to reduce the incidence of AF in patients with LV dysfunction after ACS (471, 472).

7.5. Hyperthyroidism: Recommendations

Class I

1. **Beta blockers are recommended to control ventricular rate in patients with AF complicating thyrotoxicosis unless contraindicated. *(Level of Evidence: C)***
2. **In circumstances in which a beta blocker cannot be used, a nondihydropyridine calcium channel antagonist is recommended to control the ventricular rate. *(Level of Evidence: C)***

AF is the most common arrhythmia in patients with hyperthyroidism (5% to 15% of patients) and is more frequent amongst those >60 years of age (152, 473, 474). Complications of AF in hyperthyroidism include HF and thromboembolism, although the correlation with thromboembolic disease is controversial (473-481). Treatment is directed primarily toward restoring an euthyroid state, which is usually associated with a spontaneous reversion of AF to sinus rhythm. Antiarrhythmic drugs and cardioversion often fail to achieve sustained sinus rhythm while thyrotoxicosis persists (482); therefore, efforts to restore normal sinus rhythm may be deferred until the patient is euthyroid. Beta blockers are effective in controlling the ventricular rate in this situation, and treatment with beta blockers is particularly important in cases of thyroid storm; nondihydropyridine calcium channel antagonists are recommended for rate control (483). Although several studies reported thromboembolism in patients with thyrotoxicosis and AF, evidence suggests that embolic risk was not necessarily increased independent of other stroke risk factors (484, 485). Anticoagulation for the patient with thyrotoxicosis and AF should be guided by CHA_2DS_2-VASc risk factors (Section 4. 1 and 4.1.1.).

Hyperthyroidism and thyrotoxicosis can infrequently result from long-term amiodarone use. In the event of iatrogenic hyperthyroidism during treatment with amiodarone, the drug should be discontinued. The risks and benefits of treating patients with AF with a known history of thyroid disease with amiodarone should be carefully weighed prior to initiation of therapy and patients should be monitored closely (486).

7.6. Acute Noncardiac Illness

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A number of acute noncardiac conditions are associated with AF (e.g., hypertension, postoperative state, pulmonary embolism, viral infections). Management of the underlying condition and correction of contributing factors as first-line treatment is common to all of these scenarios (487) and many of these patients will spontaneously convert with correction of the underlying condition. However, during acute illness, patients may require rate control with cardioversion, AV nodal blockers, and/or antiarrhythmic drugs if AF is poorly tolerated or rate control is not feasible. The specific rate or rhythm control agent(s) will depend on the underlying medical condition. Of note is that an elevated catecholamine state is common to many of these clinical circumstances, and unless contraindicated, a beta blocker is the preferred initial drug. The role of anticoagulation is less clear and likely disease-specific, and needs to be addressed on the basis of risk profile and duration of AF.

7.7. Pulmonary Disease: Recommendations

Class I

1. **A nondihydropyridine calcium channel antagonist is recommended to control the ventricular rate in patients with AF and chronic obstructive pulmonary disease. *(Level of Evidence: C)***
2. **Direct-current cardioversion should be attempted in patients with pulmonary disease who become hemodynamically unstable as a consequence of new onset AF. *(Level of Evidence: C)***

Supraventricular arrhythmias, including AF, are common in patients with chronic obstructive pulmonary disorder (488-490). AF should be distinguished from multifocal atrial tachycardia, which is unlikely to respond to electrical cardioversion, but will often slow with treatment of the underlying disease and in response to nondihydropyridine calcium channel blockers (491). Treatment of the underlying lung disease and correction of hypoxia and acid-base imbalance are of primary importance in this situation and represent first-line therapy. Antiarrhythmic drug therapy and cardioversion may be ineffective against AF until respiratory decompensation has been corrected. Theophylline and beta adrenergic agonists can precipitate AF and make control of the ventricular response rate difficult. Non–beta-1 selective blockers, sotalol, propafenone, and adenosine are contraindicated in patients with bronchospasm. However, beta blockers, sotalol, or propafenone may be considered in patients with obstructive lung disease who develop AF and do not have bronchospasm. Rate control can usually be achieved safely with nondihydropyridine calcium channel antagonists or possibly amiodarone (275). Digoxin can be used with calcium channel blockers, particularly in those with preserved LVEF (492). In patients refractory to drug therapy, AV nodal ablation and ventricular pacing may be necessary to control the ventricular rate. Anticoagulation, while not specifically studied in patients with AF due to pulmonary disease, is discussed in Section 4.2. for risk-based antithrombotic therapy.

7.8. WPW and Pre-Excitation Syndromes: Recommendations

Class I

1. **Prompt direct-current cardioversion is recommended for patients with AF, WPW, and rapid ventricular response who are hemodynamically compromised (64). *(Level of Evidence: C)***

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2. **Intravenous procainamide or ibutilide to restore sinus rhythm or slow the ventricular rate is recommended for patients with pre-excited AF and rapid ventricular response who are not hemodynamically compromised (64).** ***(Level of Evidence: C)***
3. **Catheter ablation of the accessory pathway is recommended in symptomatic patients with pre-excited AF, especially if the accessory pathway has a short refractory period that allows rapid antegrade conduction (64).** ***(Level of Evidence: C)***

Class III: Harm

1. **Administration of intravenous amiodarone, adenosine, digoxin (oral or intravenous), or nondihydropyridine calcium channel antagonists (oral or intravenous) in patients with WPW syndrome who have pre-excited AF is potentially harmful as they accelerate the ventricular rate (493-495).** ***(Level of Evidence: B)***

AF is of specific concern in patients with WPW because of the potential for degeneration to ventricular fibrillation related to rapidly conducting anterograde accessory pathways. The risk of developing AF over 10 years in patients with WPW is estimated at 15%, although the mechanism of increased AF risk is poorly understood (496, 497). Approximately 25% of patients with WPW syndrome have accessory pathways with short anterograde refractory periods (<250 ms), which are associated with a risk of rapid ventricular rates and ventricular fibrillation (498, 499). Patients with multiple accessory pathways are also at greater risk of ventricular fibrillation (498). The safety and efficacy of catheter ablation of accessory pathway is established (64); however, ablation of the accessory pathway does not always prevent AF, especially in older patients, and additional pharmacological or ablative therapy may be required. Once the accessory pathway has been eliminated, the process of selecting pharmacological therapy is the same as for patients without pre-excitation.

Specifics of antiarrhythmic therapies are described in Section 6. During AF, the ventricular rate is determined by competing conduction over the AV node and the accessory pathway(s). As with any unstable arrhythmia, cardioversion is recommended for hemodynamic instability (64). Agents that slow AV nodal conduction without prolonging accessory pathway refractoriness can accelerate the ventricular rate and precipitate hemodynamic collapse and ventricular fibrillation in high-risk patients. Intravenous administration of ibutilide or procainamide may slow the rate of conduction over the accessory pathway, slow the ventricular rate, or may convert AF to sinus rhythm; it is recommended for hemodynamically stable patients in the setting of AF with conduction over an accessory pathway. Verapamil, diltiazem, adenosine, digoxin (oral or intravenous), and intravenous amiodarone can precipitate ventricular fibrillation and should not be used (493, 495). Similarly, lidocaine use in pre-excited AF is considered potentially harmful (500). Oral amiodarone can slow or block accessory pathway conduction during chronic oral therapy. Although beta blockers theoretically pose a similar potential risk, there are few data regarding administration of these agents in rapid AF in patients with WPW; nevertheless, they should be used with caution (494, 501).

7.9. Heart Failure: Recommendations

Class I

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1. **Control of resting heart rate using either a beta blocker or a nondihydropyridine calcium channel antagonist is recommended for patients with persistent or permanent AF and compensated HF with preserved EF (HF*p*EF) (269). *(Level of Evidence: B)***
2. **In the absence of pre-excitation, intravenous beta blocker administration (or a nondihydropyridine calcium channel antagonist in patients with HF*p*EF) is recommended to slow the ventricular response to AF in the acute setting, with caution needed in patients with overt congestion, hypotension, or HF with reduced LVEF (502-505). *(Level of Evidence: B)***
3. **In the absence of pre-excitation, intravenous digoxin or amiodarone is recommended to control heart rate acutely in patients with HF (277, 503, 506, 507). *(Level of Evidence: B)***
4. **Assessment of heart rate control during exercise and adjustment of pharmacological treatment to keep the rate in the physiological range is useful in symptomatic patients during activity. *(Level of Evidence: C)***
5. **Digoxin is effective to control resting heart rate in patients with HF with reduced EF. *(Level of Evidence: C)***

Class IIa

1. **A combination of digoxin and a beta blocker (or a nondihydropyridine calcium channel antagonist for patients with HF*p*EF), is reasonable to control resting and exercise heart rate in patients with AF (267, 503). *(Level of Evidence: B)***
2. **It is reasonable to perform AV node ablation with ventricular pacing to control heart rate when pharmacological therapy is insufficient or not tolerated (269, 508, 509). *(Level of Evidence: B)***
3. **Intravenous amiodarone can be useful to control the heart rate in patients with AF when other measures are unsuccessful or contraindicated. *(Level of Evidence: C)***
4. **For patients with AF and rapid ventricular response causing or suspected of causing tachycardia-induced cardiomyopathy, it is reasonable to achieve rate control by either AV nodal blockade or a rhythm-control strategy (51, 307, 510). (*Level of Evidence: B)***
5. **For patients with chronic HF who remain symptomatic from AF despite a rate-control strategy, it is reasonable to use a rhythm-control strategy. (*Level of Evidence: C)***

Class IIb

1. **Oral amiodarone may be considered when resting and exercise heart rate cannot be adequately controlled using a beta blocker (or a nondihydropyridine calcium channel antagonist in patients with HF*p*EF) or digoxin, alone or in combination. *(Level of Evidence: C)***
2. **AV node ablation may be considered when the rate cannot be controlled and tachycardia-mediated cardiomyopathy is suspected. *(Level of Evidence: C)***

Class III: Harm

1. **AV node ablation should not be performed without a pharmacological trial to achieve ventricular rate control. *(Level of Evidence: C)***
2. **For rate control, intravenous nondihydropyridine calcium channel antagonists, intravenous beta blockers, and dronedarone should not be administered to patients with decompensated HF. *(Level of Evidence: C)***

Patients with HF are more likely than the general population to develop AF (38) and there is a direct relationship between the NYHA class and the prevalence of AF in patients with HF, progressing from 4% in those who are NYHA class I to 40% in those who are NYHA class IV (511). AF is a strong independent risk factor for subsequent development of HF as well (38, 512). In addition to those with HF and depressed EFs, patients with HF due to diastolic dysfunction with HF*p*EF are also at greater risk for AF (513). HF and AF can interact to perpetuate and exacerbate each other through mechanisms such as rate-dependent worsening of cardiac function,

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fibrosis, and activation of neurohumoral vasoconstrictors. AF can worsen symptoms in patients with HF and conversely, worsened HF can promote a rapid ventricular response in AF.

Similar to other patient populations, the main goals of therapy for those with AF and HF are prevention of thromboembolism and symptom control. Most patients with AF and HF expect to be candidates for systemic anticoagulation unless contraindicated (Section 4). General principles of management include correction of underlying causes of AF and HF as well as optimization of HF management. As in other patient populations, the issue of rate control versus rhythm control has been investigated. For patients who develop HF as a result of AF, a rhythm-control strategy should be pursued. It is important to recognize that AF with a rapid ventricular response is 1 of the few potentially reversible causes of HF. Therefore a patient who presents with newly detected HF in the presence of AF with a rapid ventricular response should be presumed to have a rate-related cardiomyopathy until proved otherwise. In this situation, 2 strategies can be considered. One is to rate control the patient's AF and see if the HF and EF improve. The other strategy is to attempt to restore and maintain sinus rhythm. In this situation, it is common practice to initiate amiodarone and then arrange for cardioversion a month later. Amiodarone has the advantage of being both an effective rate-control medication and the most effective antiarrhythmic medication with a low risk of proarrhythmia.

In patients with HF who develop AF, a rhythm-control strategy is not superior to a rate-control strategy (514). If rhythm control is chosen, AF catheter ablation in patients with HF may lead to an improvement in LV function and quality of life but is less likely to be effective than in patients with intact cardiac function (47, 307).

Because of their favorable effect on morbidity and mortality in patients with systolic HF, beta blockers are the preferred agents for achieving rate control unless otherwise contraindicated. Digoxin may be an effective adjunct to a beta blocker. Nondihydropyridine calcium antagonists, such as diltiazem, should be used with caution in those with depressed EF because of their negative inotropic effect. For those with HF and preserved EF, nondihydropyridine calcium antagonists can be effective at achieving rate control but may be more effective when used in combination with digoxin. For those patients for whom a rate-control strategy is chosen, AV node ablation and cardiac resynchronization therapy device placement can be useful when rate control cannot be achieved either because of drug inefficacy or intolerance (515-520).

7.10. Familial (Genetic) AF: Recommendation

Class IIb

1. **For patients with AF and multigenerational family members with AF, referral to a tertiary care center for genetic counseling and testing may be considered. (*Level of Evidence: C*)**

AF is heritable and having an affected family member is associated with a 40% increased risk of the arrhythmia (155, 521-524). Premature AF, defined as a first-degree relative with an onset of AF prior to 66 years of age, is associated with a doubling in the risk of AF (155). Thus it is common, particularly among younger, healthier individuals with AF, to observe families with AF. In the last 10 years, many mutations have been identified in

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individuals and families with AF (525). The implicated genes include a wide-range of ion channels, signaling molecules, and related proteins; however, the role of these mutations in more common forms of AF appears limited. Population-based or genome-wide association studies identified ≥9 distinct genetic loci for AF (156-159). Furthermore, combinations of AF-associated single nucleotide polymorphisms may identify individuals at high risk for arrhythmia (526, 527). However, the role of these common genetic variants in risk stratification (155, 528, 529), assessment of disease progression, and determination of clinical outcomes (157, 530, 531) is currently limited. Routine genetic testing related to AF is not indicated (532).

7.11. Postoperative Cardiac and Thoracic Surgery: Recommendations

Class I

1. **Treating patients who develop AF after cardiac surgery with a beta blocker is recommended unless contraindicated (533-536). *(Level of Evidence: A)***
2. **A nondihydropyridine calcium channel blocker is recommended when a beta blocker is inadequate to achieve rate control in patients with postoperative AF (537). *(Level of Evidence: B)***

Class IIa

1. **Preoperative administration of amiodarone reduces the incidence of AF in patients undergoing cardiac surgery and is reasonable as prophylactic therapy for patients at high risk for postoperative AF (538-540). *(Level of Evidence: A)***
2. **It is reasonable to restore sinus rhythm pharmacologically with ibutilide or direct-current cardioversion in patients who develop postoperative AF, as advised for nonsurgical patients (541). *(Level of Evidence: B)***
3. **It is reasonable to administer antiarrhythmic medications in an attempt to maintain sinus rhythm in patients with recurrent or refractory postoperative AF, as advised for other patients who develop AF (537). *(Level of Evidence: B)***
4. **It is reasonable to administer antithrombotic medication in patients who develop postoperative AF, as advised for nonsurgical patients (542). *(Level of Evidence: B)***
5. **It is reasonable to manage well-tolerated, new-onset postoperative AF with rate control and anticoagulation with cardioversion if AF does not revert spontaneously to sinus rhythm during follow-up. *(Level of Evidence: C)***

Class IIb

1. **Prophylactic administration of sotalol may be considered for patients at risk of developing AF following cardiac surgery (536, 543). *(Level of Evidence: B)***
2. **Administration of colchicine may be considered for patients postoperatively to reduce AF following cardiac surgery (544). *(Level of Evidence: B)***

Postoperative AF occurs in 25% to 50% of patients after open heart surgery. Increased age is the most consistent risk factor (545). With the projected increase in the number of elderly patients undergoing cardiac operations, the incidence of postoperative AF is likely to increase. Postoperative AF is associated with stroke (546), increased cost (547), and mortality (548). Beta blockers, nondihydropyridine calcium channel blockers, and amiodarone are useful as treatments in patients with postoperative AF and may be initiated preoperatively in some patients (391, 544).

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In a meta-analysis of patients undergoing coronary revascularization, those who received preoperative statin therapy had less AF than those not treated with statins (391). No published data exist for patients undergoing valvular or other heart surgery.

The COPPS (Colchicine for the Prevention of the Postpericardiotomy Syndrome) substudy examined the efficacy and safety of colchicine for AF prevention (544). In this multicenter trial, patients were randomized to colchicine with standard therapy or standard therapy alone. The primary endpoint was incidence of AF at 1 month postoperatively. Patients receiving colchicine had a reduced incidence of AF (12% versus 22% at 30 days postoperatively). The colchicine group also had a shorter length of stay.

Table 15. Summary of Recommendations for Specific Patient Groups and AF

Recommendations	COR	LOE	References
Hypertrophic cardiomyopathy			
Anticoagulation indicated in HCM with AF independent of the CHA_2DS_2-VASc score	I	B	(50, 457)
Antiarrhythmic drugs can be useful to prevent recurrent AF in HCM. Amiodarone, or disopyramide combined with beta blockers or nondihydropyridine calcium channel antagonist are reasonable	IIa	C	N/A
AF catheter ablation can be beneficial for HCM to facilitate a rhythm-control strategy when antiarrhythmics fail or are not tolerated	IIa	B	(458-461)
Sotalol, dofetilide, and dronedarone may be considered for a rhythm-control strategy in HCM	IIb	C	(11)
AF complicating ACS			
Urgent cardioversion of new onset AF in setting of ACS is recommended for patients with hemodynamic compromise, ongoing ischemia, or inadequate rate control	I	C	N/A
IV beta blockers are recommended to slow RVR with ACS and no HF, hemodynamic instability, or bronchospasm	I	C	N/A
With ACS and AF with CHA_2DS_2-VASc (score $\geq$2), anticoagulation with warfarin is recommended unless contraindicated	I	C	N/A
Amiodarone or digoxin may be considered to slow a RVR with ACS and AF, and severe LV dysfunction and HF or hemodynamic instability	IIb	C	N/A
Nondihydropyridine calcium antagonists might be considered to slow a RVR with ACS and AF only in the absence of significant HF or hemodynamic instability	IIb	C	N/A
Hyperthyroidism			
Beta blockers are recommended to control ventricular rate with AF complicating thyrotoxicosis, unless contraindicated	I	C	N/A
Nondihydropyridine calcium channel antagonist is recommended to control the ventricular rate with AF and thyrotoxicosis when beta blocker cannot be used	I	C	N/A
Pulmonary diseases			
Nondihydropyridine calcium channel antagonist is recommended to control the ventricular rate with COPD and AF	I	C	N/A
Cardioversion should be attempted with pulmonary disease patients who become hemodynamically unstable with new onset AF	I	C	N/A
WPW and pre-excitation syndromes			
Cardioversion recommended with AF, WPW, and RVR who are hemodynamically compromised	I	C	(64)

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IV procainamide or ibutilide to restore sinus rhythm or slow ventricular rate recommended with pre-excited AF and RVR who are not hemodynamically compromised	I	C	(64)
Catheter ablation of accessory pathway is recommended in symptomatic patients with pre-excited AF, especially if the accessory pathway has a short refractory period	I	C	(64)
IV amiodarone, adenosine, digoxin, or nondihydropyridine calcium channel antagonists with WPW who have pre-excited AF is potentially harmful	III: Harm	B	(493-495)
Heart failure			
Beta blocker or nondihydropyridine calcium channel antagonist is recommended for persistent or permanent AF in patients with HF*p*EF	I	B	(269)
In the absence of pre-excitation, IV beta blocker (or a nondihydropyridine calcium channel antagonist with HF*p*EF) is recommended to slow ventricular response to AF in the acute setting, exercising caution in patients with overt congestion, hypotension or HF*r*EF	I	B	(502-505)
In the absence of pre-excitation, IV digoxin or amiodarone is recommended to acutely control heart rate	I	B	(277, 503, 506, 507)
Assess heart rate during exercise and adjust pharmacological treatment in symptomatic patients during activity	I	C	N/A
Digoxin is effective to control resting heart rate with HF*r*EF	I	C	N/A
Combination digoxin and beta blocker (or a nondihydropyridine calcium channel antagonist with HF*p*EF), is reasonable to control rest and exercise heart rate with AF	IIa	B	(267, 503)
Reasonable to perform AV node ablation with ventricular pacing to control heart rate when pharmacological therapy insufficient or not tolerated	IIa	B	(269, 508, 509)
IV amiodarone can be useful to control the heart rate with AF when other measures are unsuccessful or contraindicated	IIa	C	N/A
With AF and RVR, causing or suspected of causing tachycardia-induced cardiomyopathy, it is reasonable to achieve rate control by AV nodal blockade or rhythm control strategy	IIa	B	(51, 307, 510)
In chronic HF patients who remain symptomatic from AF despite a rate-control strategy, it is reasonable to use a rhythm-control strategy	IIa	C	N/A
Amiodarone may be considered when resting and exercise heart rate cannot be controlled with a beta blocker (or a nondihydropyridine calcium channel antagonist with HF*p*EF) or digoxin, alone or in combination	IIb	C	N/A
AV node ablation may be considered when rate cannot be controlled and tachycardia-mediated cardiomyopathy suspected	IIb	C	N/A
AV node ablation should not be performed without a pharmacological trial to control ventricular rate	III: Harm	C	N/A
For rate control, IV nondihydropyridine calcium channel antagonists, IV beta blockers and dronedarone should not be given with decompensated HF	III: Harm	C	N/A
Familial (Genetic) AF			
With AF and multigenerational AF family members, referral to a tertiary care center for genetic counseling and testing may be considered	IIb	C	N/A
Postoperative cardiac and thoracic surgery			
Beta blocker is recommended to treat postoperative AF unless contraindicated	I	A	(533-536)
A nondihydropyridine calcium channel blocker is recommended when a beta blocker is inadequate to achieve rate control with postoperative AF	I	B	(537)

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Preoperative amiodarone reduces AF with cardiac surgery and is reasonable as prophylactic therapy for high risk of postoperative AF	IIa	A	(538-540)
It is reasonable to restore sinus rhythm pharmacologically with ibutilide or direct-current cardioversion with postoperative AF	IIa	B	(541)
It is reasonable to administer antiarrhythmic medications to maintain sinus rhythm with recurrent or refractory postoperative AF	IIa	B	(537)
It is reasonable to administer antithrombotic medications for postoperative AF	IIa	B	(542)
It is reasonable to manage new-onset postoperative AF with rate control and anticoagulation with cardioversion if AF does not revert spontaneously to sinus rhythm during follow-up	IIa	C	N/A
Prophylactic sotalol may be considered for patients with AF risk following cardiac surgery	IIb	B	(536, 543)
Colchicine may be considered postoperatively to reduce AF following cardiac surgery	IIb	B	(544)

AF indicates atrial fibrillation; AV, atrioventricular; COPD, chronic obstructive pulmonary disease; COR, Class of Recommendation; HCM, hypertrophic cardiomyopathy; HF, heart failure; HF*p*EF, heart failure with preserved ejection fraction; HF*r*EF, heart failure with reduced ejection fraction; IV, intravenous; LOE, Level of Evidence; LV, left ventricular; N/A, not applicable; RVR, rapid ventricular response; and WPW, Wolff-Parkinson-White.

8. Evidence Gaps and Future Research Directions

The past decade has seen substantial progress in the understanding of AF mechanisms, clinical implementation of ablation for maintaining sinus rhythm, and new drugs for stroke prevention. Further studies are needed to better inform clinicians as to the risks and benefits of therapeutic options for an individual patient. Continued research is needed into the mechanisms that initiate and sustain AF. Better understanding of these tissue and cellular mechanisms will, hopefully, lead to more defined approaches to treating and abolishing AF. This includes new methodological approaches for AF ablation that would favorably impact survival, thromboembolism, and quality of life across different patient profiles. New pharmacologic therapies are needed, including antiarrhythmic drugs that have atrial selectivity and drugs that target fibrosis, which will hopefully reach clinical evaluation. The successful introduction of new anticoagulants is encouraging, and further investigations will better inform clinical practices for optimizing beneficial applications and minimizing the risks of these agents, particularly in the elderly, in the presence of comorbidities and in the periprocedural period. Further investigations must be performed to better understand the links between the presence of AF, AF burden, and stroke risk, and also to better define the relationship between AF and dementia. The roles of emerging surgical and procedural therapies to reduce stroke will be defined. Great promise lies in prevention. Future strategies for reversing the growing epidemic of AF will come from basic science and genetic, epidemiologic, and clinical studies.

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Key Words: ACC/AHA Practice Guidelines ■ atrial fibrillation ■ cardio-renal physiology/pathophysiology ■ cardiovascular surgery: transplantation, ventricular assistance, cardiomyopathy ■ epidemiology ■ full revision ■ health policy and outcome research ■ other atrial fibrillation.

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Appendix 1. Author Relationships With Industry and Other Entities (Relevant)—2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation

Committee Member	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section*
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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 ≥$10,000 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.

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†Indicates significant relationship.
‡No financial benefit.
§Dr. Sacco's relationship with Boehringer Ingelheim was added just after final balloting of the recommendations and prior to organizational review, so it was not relevant during the writing or voting stages of the guideline's development.

ACC indicates American College of Cardiology; AHA, American Heart Association; DSMB, data safety monitoring board; and HRS, Heart Rhythm Society.

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Appendix 2. Reviewer Relationships With Industry and Other Entities (Relevant)—2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation

Reviewer	Representation	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
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Jonathan Halperin	Official Reviewer—ACC/AHA Task Force on Practice Guidelines	Mt. Sinai Medical Center—Professor of Medicine	• AstraZeneca • Bayer • Biotronik* • Boehringer Ingelheim* • Boston Scientific • Bristol-Myers Squibb • Daiichi-Sankyo	None	None	None	None	None

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Stuart Winston	Official Reviewer—ACC Board of Trustees	Michigan Heart, P. C. Michigan Heart & Vascular Institute—Cardiologist	None	None	None	None	• Biotronik† • Medtronic†	None
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ACC indicates American College of Cardiology; AHA, American Heart Association; AIG, Association of International Governors; DSMB, data safety monitoring board; EP, electrophysiology; HF, heart failure; HHS, Health and Human Services; HRS, Heart Rhythm Society; ICD, implantable cardioverter-defibrillator; PharmD, doctor of pharmacy; PI, principal investigator; STS, Society of Thoracic Surgeons; UCLA, University of California, Los Angeles; USUHS, Uniformed Services University of the Health Sciences; UT, University of Texas; VA, Veterans Affairs; and VCU, Virginia Commonwealth University.

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Appendix 3. Abbreviations

ACE = angiotensin-converting enzyme

ACS = acute coronary syndrome

AF = atrial fibrillation

ARB = angiotensin-receptor blocker

AV = atrioventricular

CAD = coronary artery disease

CKD = chronic kidney disease

CrCl = creatinine clearance

ECG = electrocardiogram

EF = ejection fraction

GDMT = guideline-directed medical therapy

HCM = hypertrophic cardiomyopathy

HF = heart failure

HF*p*EF = heart failure with preserved ejection fraction

INR = international normalized ratio

LA = left atrium

LAA = left atrial appendage

LMWH = low-molecular-weight heparin

LV = left ventricular

LVEF = left ventricular ejection fraction

RCT = randomized controlled trial

RV= right ventricular

TEE = transesophageal echocardiography

TIA = transient ischemic attack

TTR = times in therapeutic range

UFH = unfractionated herparin

WPW = Wolff-Parkinson-White

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Appendix 4. Initial Clinical Evaluation in Patients With AF

Minimum Evaluation	
1. History and physical examination, to define	• Presence and nature of symptoms associated with AF
	• Clinical type of AF (paroxysmal, persistent, or permanent)
	• Onset of the first symptomatic attack or date of discovery of AF
	• Frequency, duration, precipitating factors, and modes of initiation or termination of AF
	• Response to any pharmacological agents that have been administered
	• Presence of any underlying heart disease or reversible conditions (e.g., hyperthyroidism or alcohol consumption)
2. ECG, to identify	• Rhythm (verify AF)
	• LVH
	• P-wave duration and morphology or fibrillatory waves
	• Pre-excitation
	• Bundle-branch block
	• Prior MI
	• Other atrial arrhythmias
	• To measure and follow the R-R, QRS, and QT intervals in conjunction with antiarrhythmic drug therapy
3. TTE, to identify	• VHD
	• LA and RA size
	• LV and RV size and function
	• Peak RV pressure (pulmonary hypertension)
	• LV hypertrophy
	• LA thrombus (low sensitivity)
	• Pericardial disease
4. Blood tests of thyroid, renal, and hepatic function	• For a first episode of AF
	• When the ventricular rate is difficult to control
Additional Testing (1 or several tests may be necessary)	
1. 6-min walk test	• If the adequacy of rate control is in question
2. Exercise testing	• If the adequacy of rate control is in question
	• To reproduce exercise-induced AF
	• To exclude ischemia before treatment of selected patients with a type IC* antiarrhythmic drug
3. Holter or event monitoring	• If diagnosis of the type of arrhythmia is in question
	• As a means of evaluating rate control
4. TEE	• To identify LA thrombus (in the LAA)
	• To guide cardioversion
5. Electrophysiological study	• To clarify the mechanism of wide-QRS-complex tachycardia
	• To identify a predisposing arrhythmia such as atrial flutter or paroxysmal supraventricular tachycardia
	• To seek sites for curative AF ablation or AV conduction block/modification

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6. Chest radiograph, to evaluate	• Lung parenchyma, when clinical findings suggest an abnormality
	• Pulmonary vasculature, when clinical findings suggest an abnormality

*Type IC refers to the Vaughan-Williams classification of antiarrhythmic drugs.

AF indicates atrial fibrillation; AV, atrioventricular; ECG, electrocardiogram; LA, left atrial; LAA, left atrial appendage; LV, left ventricular; LVH, left ventricular hypertrophy; MI, myocardial infarction; RA, right atrial; RV, right ventricular; TEE, transesophageal echocardiography; TTE, transthoracic echocardiogram; and VHD, valvular heart disease.
Modified from Fuster, et al. (4).

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2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation—ONLINE AUTHOR LISTING OF COMPREHENSIVE RELATIONSHIPS WITH INDUSTRY AND OTHERS (April 2012)

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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 ≥$10,000 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.

*Indicates significant relationship.
†No financial benefit.
‡Dr. Sacco's relationship with Boehringer Ingelheim was added just after final balloting of the recommendations and prior to organizational review, so it was not relevant during the writing or voting stages of the guideline's development.

AHA indicates American Heart Association; CIHR, Canadian Institutes for Health Research; CME, continuing medical education; DSMB, Data Safety Monitoring Board; IHD, ischemic heart disease; and PI, principal investigator; and SCD, sudden cardiac death.

2014 AHA/ACC/HRS Atrial Fibrillation Guideline Data Supplements

(Section numbers correspond to the full-text guideline.)

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Data Supplement 1. Electrophysiologic Mechanisms in the Initiation and Maintenance of AF (Section 2)

Mechanism	References	
	Experimental	Human
Multiple wavelet hypothesis	(1-3)	(4-8)
• Heterogeneity in atrial electrophysiology	(3, 9)	(10-13)
Focal firing	(14-17)	(18-21)
• Pulmonary vein foci		
○ Electrophysiology	(16, 22-28)	(29, 30)
○ Evidence for reentry	(24, 31-33)	(30, 34-36)
○ Evidence for focal firing	(32)	(35)
• Nonpulmonary vein foci	(17)	(19, 21, 37-42)
Rotor with fibrillatory conduction	(9, 31-33, 43-46)	(34-36, 47-50)
• Dominant frequency gradients	(9, 32, 43, 46, 51)	(34, 49-52)

AF indicates atrial fibrillation.

Data Supplement 2. Pathophysiologic Mechanisms Generating the AF Substrate (Section 2)

Mechanism	References	
	Experimental	Human
Atrial structural abnormalities	(9, 53-55)	(56-62)
• Fibrosis	(63-70)	(55, 56, 62, 63, 71-73)
• Noninvasive imaging of fibrosis	(74, 75)	(76-79)
Inflammation/oxidative stress	(80-83)	(59, 80, 82-88)
• Steroids	(89-91)	N/A
• Statins	(92-94)	N/A
• Omega-3 polyunsaturated fatty acids	(95-100)	(96, 101-103)
Renin-angiotensin-aldosterone system activation	(104-114)	(72, 115, 116)
• Aldosterone	(117, 118)	(119-121)
• Transforming growth factor-β_1	(68, 122, 123)	N/A
Autonomic nervous system	(3, 14-16, 27, 124-126)	(127-129)
Genetic variants	See Section 7.10	
Atrial tachycardia remodeling		
• Electrophysiologic	(9, 130-136)	(137, 138)
• Structural	(53, 132, 139-142)	N/A
• Intracellular calcium	(143-145)	(145-148)
Extracardiac factors	See Section 2.2	

AF indicates atrial fibrillation.

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Data Supplement 3. Oral Anticoagulants (Dabigatran, Rivaroxaban, Apixaban) vs. Warfarin (Section 4.2.2)

Study Name, Author, Year	Study Aim	Study Type/Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints			P Values, OR: HR: RR: & 95% CI:	Adverse Events	Study Limitations
				Inclusion Criteria	***Exclusion Criteria***		***Primary Endpoint & Results***	***Safety Endpoint & Results***	***Secondary Endpoint & Results***			
RE-LY Randomized Connolly SJ, et al., 2009 (149) 19717844	To compare 2 fixed doses of dabigatran with open-label use of warfarin in pts with AF at increased risk of stroke	RCT, open-label, blinded doses of dabigatran (18,113)	Dabigatran 110 mg (6,015) Dabigatran 150 mg (6,076) Warfarin (6,021)	AF and ≥1 of the following: prior stroke or TIA; LVEF<40%, NYHA class II or higher HF Sx, age ≥75 y or an age of 65-74 y plus DM, HTN, or CAD Mean CHADS2 of 2.1	Severe heart-valve disorder, stroke within 14 d or severe stroke within 6 mo, condition that increased hemorrhage risk, CrCl <20 mL/min, active liver disease, pregnancy	Dabigatran in 2 fixed doses – oral prodrug, direct competitive inhibitor of thrombin Warfarin INR 2-3, mean TTR 64%	Stroke or SE Dabigatran110 mg 1.53%/y Dabigatran 150 mg 1.11%/y Warfarin 1.69%/y	Major Hemorrhage Dabigatran 110 mg 2.71%/y Dabigatran 150 mg 3.11%/y Warfarin 3.36%/y Intracranial Bleeding Dabigatran 110 mg 0.23%/y Dabigatran 150 mg 0.30%/y Warfarin 0.74%/y Major GI	Stroke Dabigatran 110 mg 1.44%/y Dabigatran 150 mg 1.01%/y Warfarin 1.57%/y Stroke, ST elevation, PE, MI, death, or major bleeding Dabigatran 110 mg 7.09%/y Dabigatran 150 mg 6.91%/y Warfarin 7.64%/y	Dabigatran 110 mg RR: 0.91; 95% CI: 0.74-1.11; p<0.001 for noninferiority, p=0.34 for superiority Dabigatran 150 mg RR: 0.66; 95% CI: 0.53-0.83; p<0.001 for noninferiority, p<0.001 for superiority	Dyspepsia	Open-label Median duration of FU 2 y

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								Dabigatran 110 mg 1.12%/y Dabigatran 150 mg 1.51%/y Warfarin 1.02%/y				
ROCKET-AF Patel MR, et al., 2011 (150) 21830957	To compare QD oral rivaroxaban with dose-adjusted warfarin for the prevention of stroke and SE in pts with NVAF who were at moderate to high risk of stroke	RCT, double-dummy, double-blinded (14,264)	Rivaroxaban (7,131) Warfarin (7,133)	NVAF at moderate to high risk of stroke: Hx of stroke, TIA, or SE or ≥2 of the following (HF or LVEF<35%, HTN, age >75 y, DM (CHADS2 score of≥2) Mean CHADS2 score of 3.5	Severe valvular disease, transient AF caused by a reversible disorder, hemorrhage risk related criteria; severe, disabling stroke within 3 mo or any stroke within 14 d, TIA within 3 d; indication for anticoagulant Tx	Rivaroxaban Factor Xa inhibitor, 20 mg QD or 15 mg QD for those with CrCl of 39-40 mL/min Warfarin INR 2-3, mean TTR 55%	Any stroke or SE Per-protocol as treated Rivaroxaban 1.7%/y Warfarin 2.2%/y Intention to Treat Rivaroxaban 2.1%/y Warfarin 2.4%/y	Major and non-major clinically relevant bleeding Rivaroxaban 14.9/100 pt-years Warfarin 14.5/100 pt-years ICH Rivaroxaban 0.5/100 pt-years Warfarin 0.7/100 pt-years Major GI Rivaroxaban 3.15% Warfarin 2.16%	Stroke, SE, or VD Rivaroxaban 3.11/100 pt-years Warfarin 3.64/100 pt-years HR: 0.86; 95% CI: 0.74-0.99; p=0.034	Per-Protocol, as treated HR: 0.79; 95% CI: 0.66-0.96; p<0.001 for noninferiority Intention to treat HR: 0.88; 95% CI: 0.75-1.03; p<0.001 for noninferiority p=0.12 for superiority	N/A	Median duration of follow-up was 707 d Lower TTR in warfarin group 1° analysis was prespecified as a per-protocol analysis High-event rate after discontinuation of Tx

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ARISTOTLE Granger CB, et al., 2011 (151) 21870978	To determine whether apixaban was noninferior to warfarin in reducing the rate of stroke (ischemic or hemorrhagic) or SE among pts with AF and ≥1 other risk factor for stroke	RCT, double-dummy, double-blinded (18,201)	Apixaban (9,120) Warfarin (9,081)	AF and ≥1 stroke risk factor (age >75 y; previous stroke, TIA or SE; symptomatic HF within the prior 3 mo or LVEF≤40%; DM; or HTN) Mean CHADS2 score of 2.1	AF due to a reversible cause, moderate or severe mitral stenosis, conditions other than AF requiring OAC, stroke within the prior 7 d, a need for ASA>165 mg or for ASA and CP, or severe renal insufficiency (CrCl<25 mL/min)	Apixaban Factor Xa inhibitor 5 mg BID or 2.5 mg BID among pts with ≥2 of the following (≥80 y, body weight ≤60 kg, or serum Cr level of ≥1.5 mg/dL) Warfarin INR 2-3 Mean TTR 62.2%	Any stroke or SE Apixaban 1.27%/y Warfarin 1.6%/y	Major Bleeding Apixaban 2.13%/y Warfarin 3.09%/y ICH Apixaban 0.33%/y Warfarin 0.80%/y Major GI Apixaban 0.76%/y Warfarin 0.86%/y	Stroke, SE, major bleeding, or death from any cause Apixaban 6.13%/y Warfarin 7.20%/y	HR: 0.79; 95% CI: 0.66-0.95; p<0.001 for noninferiority, p=0.01 for superiority HR: 0.85; 95% CI: 0.78-0.92; p<0.001	No differences	Median duration of FU 1.8 y
AVERROES Connolly SJ, et al., 2011 (152) 21309657	To determine the efficacy and safety of apixaban, at a dose of 5 mg BID, as compared with ASA, at a dose of 81-324 mg QD, for the Tx of pts with AF for whom VKA Tx was considered unsuitable	RCT double-blind, double-dummy (5,559)	Apixaban (2,808) ASA (2,791)	≥50 y and AF and ≥1 of the following stroke risk factors: prior stroke or TIA, ≥75 y, HTN, DM, HF, LVEF≤35%, or PAD. Pts could not be receiving VKAs	Pts required long-term anticoagulation, VD requiring surgery, a serious bleeding event in the previous 6 mo or a high-risk bleeding, stroke	Apixaban Factor Xa inhibitor 5 mg BID or 2.5 mg BID among pts with ≥2 of the following (age ≤80 y, body weight ≤60 kg, or serum Cr level of ≥1.5 mg/dL) ASA	Any stroke or SE Apixaban 1.6%/y ASA 3.7%/y p<0.001	Major Bleeding Apixaban 1.4% ASA 1.2% Intracranial Bleeding Apixaban 0.4% ASA 0.4% Major GI	Stroke, SE, MI, VD or major bleeding event Apixaban 5.3%/y ASA 7.2%/y HR: 0.74; 95% CI: 0.60–0.90; p<0.003	HR: 0.45; 95% CI: 0.32-0.62; p<0.001	No differences	N/A

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				because it had already been demonstrated to be unsuitable or because it was expected to be unsuitable. Mean CHADS2 of 2.0	within the previous 10 d, severe renal insufficiency (a sCr>2.5 mg/dL) or a calculated CrCl<25 mL/min	81-325 mg/dL		Apixaban 0.4% ASA 0.4%				

1° indicates primary; AF, atrial fibrillation; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in AF; ASA, aspirin; AVERROES, Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; BID, twice daily; CAD, coronary artery disease; CHADS2, Congestive heart failure, Hypertension, Age 75 years, Diabetes mellitus, Stroke; ; CP, codeine phosphate; Cr, creatinine; CrCl, creatinine clearance; DM, diabetes mellitus; FU, follow-up; GI, gastrointestinal; HF, heart failure; HR, hazard ratio; HTN, hypertension; Hx, history; ICH, intracranial hemorrhage; INR, international normalized ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; N/A, not applicable; PAD, peripheral arterial disease; PE, pulmonary embolism; N/A, not applicable; NVAF, nonvalvular atrial fibrillation; NYHA, New York Heart Association; OAC, oral anticoagulation; pts, patient; QD, once daily; RCT, randomized controlled trial; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET-AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibitor Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial; RR, relative risk; sCr, serum creatinine; SE, systemic embolism; Sx, symptom; TIA, transient ischemic attack; TTR, time in therapeutic range; Tx, therapy; VD, valvular disease; and VKA, vitamin K antagonist.

Data Supplement 4. Warfarin vs. Control (Section 4.2)

Study Name, Author, Year	Study Aim	Study Type/ Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints			P Values, OR: HR: RR: & 95% CI:
				Inclusion Criteria	***Exclusion Criteria***		***Primary Endpoint & Results***	***Safety Endpoint & Results***	***Secondary Endpoint & Results***	
Aguilar MI, et al., 2005 (153) 16034869	To characterize the efficacy and safety of oral anticoagulants for the 1° prevention of stroke in pts with chronic AF	Cochrane Collaboration Systematic Review (AFASAK I, BAATAF, CAFA, SPAF I, SPINAF)	2,313 pts Warfarin 1,154 PC 1,159	AF (intermittent or sustained)	Prior stroke or TIA, mitral stenosis or prosthetic cardiac valves	Oral VKAs (warfarin) mean INR 2.0-2.6	All Stroke (ischemic or ICH) Warfarin 27 PC 71	ICH, Major extracranial bleeds ICH, Warfarin 5, PC 2 Extracranial bleeds, Warfarin	Stroke, MI or VD Warfarin 69 PC 118	All ischemic stroke or ICH OR: 0.39; 95% CI: 0.26-0.59 Ischemic stroke OR: 0.34; 95% CI: 0.23-0.52

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								17, PC 16		Stroke, MI, VD OR: 0.57; 95% CI: 0.42-0.77 All ICH OR: 2.38; 95% CI: 0.54-10.50) Major extracranial bleeds OR: 1.07; 95% CI: 0.53-2.12

1° indicates primary; AF, atrial fibrillation; AFASAK, Atrial Fibrillation, Aspirin and Anticoagulant Therapy Study; BAATAF, Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA, Canadian Atrial Fibrillation Anticoagulation ; ICH, intracranial hemorrhage; INR, international normalized ratio; MI, myocardial infarction; N/A, not applicable; OR, odds ratio; PC, placebo; Pts, patients; RR, relative risk; SPAF I, Stroke Prevention in Atrial Fibrillation Study; SPINAF, Stroke Prevention in Atrial Fibrillation; TIA, transient ischemic attack; VD, vascular death; and VKA, vitamin K antagonist.

Data Supplement 5. Warfarin vs. Antiplatelet Therapy (Section 4.2)

Study Name, Author, Year	Study Aim	Study Type/ Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints			P Values, OR: HR: RR: & 95% CI:	Study Limitations
				Inclusion Criteria	***Exclusion Criteria***		***Primary Endpoint & Results***	***Safety Endpoint & Results***	***Secondary Endpoint & Results***		
Aguilar MI, et al., 2007 (154) 17636831	To characterize the relative effect of long-term oral anticoagulant Tx compared with antiplatelet Tx in pts with AF and no Hx of stroke or TIA	Cochrane Collaboration Systematic Review (ACTIVE-W, AFASAK I, AFASAK II, ATHENS, NASPEAF, PATAF, SPAF IIa, SPAF IIb,	9,598 pts OAC 4,815 Antiplatelet 4,783	AF (intermittent or sustained)	Prior stroke or TIA, mitral stenosis or prosthetic cardiac valves	Adjusted dose warfarin or other coumarins; antiplatelet therapies	All Stroke (ischemic or ICH) OAC 132/4,815 Antiplatelet 190/4,783	ICH, major extracranial bleeds	Stroke, MI, or VD	All Stroke OR: 0.68; 95% CI: 0.54-0.85; p=0.00069 Ischemic stroke OR: 0.53; 95% CI: 0.41-0.69 ICH OR: 1.98; 95% CI: 1.20-3.28 Major Extracranial OR: 0.97; 95% CI: 0.74-1.28	N/A

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										Major Extracranial (exclude ACTIVE W with CP+A) OR: 1.90; 95% CI: 1.07-3.39 Stroke, MI, 485 VD OR: 0.74; 95% CI: 0.61-0.90	
Saxena R, et al., 2011 (155) 15494992	To compare the value of anticoagulants and antiplatelet Tx for the long term prevention of recurrent vascular events in pts with non-rheumatic AF and previous TIA or minor ischemic stroke	Cochrane Collaboration Systematic Review (EAFT, SIFA)	1,371 pts, warfarin 679, antiplatelet 692	AF and prior minor stroke or TIA	Rheumatic VD	Oral VKAs (warfarin) mean INR>2.0; Antiplatelets 300 mg ASA; indobufen 200 mg BID	All major vascular events (VD, recurrent stroke, MI, or SE)	Any ICH; major extracranial bleed	All fatal or nonfatal recurrent strokes	All Major Vasc Events OR: 0.67; 95% CI: 0.50-0.91 Recurrent Stroke OR: 0.49; 95% CI: 0.33-0.72 Any ICH OR: 1.99; 95% CI: 0.40-9.88 Major Extracranial bleed OR: 5.16; 95% CI: 2.08-12.83	N/A
Mant J, et al., 2007 BAFTA (156) 17693178	To compare the efficacy of warfarin with that of ASA for the prevention of fatal and nonfatal stroke, ICH, and other clinically significant arterial embolism in a 1° care	RCT (973 pts)	973 pts, ASA 485, warfarin 488	Age ≥75 y, AF or flutter by EKG within 2 y from 1° care practices	Rheumatic heart disease, a major nontraumatic hemorrhage within 5 y, ICH, documented peptic ulcer disease within the previous year, esophageal varices,	ASA 75 mg QD; Warfarin target INR 2.5, range 2-3	Fatal or nonfatal disabling stroke (ischemic or hemorrhagic), other ICH, or clinically significant arterial embolism Warfarin 24 (1.8%/y)	Hemorrhage Major extracranial Warfarin 18 (1.4%/y) ASA 20 (1.6%/y) All major hemorrhages Warfarin 25 (1.9%/y) ASA 25 (2.0%/y)	Major vascular events (stroke, MI, PE, VD) Warfarin 76 (5.9%/y) ASA 100 (8.1%/y) 1° events plus major hemorrhage Warfarin 39	RR: 0.48; 95% CI: 0.28-0.80; p=0.0027 Stroke RR: 0.46; 95% CI: 0.26-0.79; p=0.003 All major hemorrhages RR: 0.96; 95% CI: 0.53-1.75; p=0.90 Major vascular	Open-label with blind assessments 67% of the warfarin group remained on Tx TTR was 67%

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	population of pts aged ≥75 y who had AF				allergic hypersensitivity to study drugs, terminal illness, surgery within the last 3 mo, BP>180/110		ASA 48 (3.8%/y)		(3.0%/y) ASA 64 (5.1%/y)	events (stroke, MI, PE, VD) RR: 0.73; 95% CI: 0.53-0.99; p=0.03 1° events plus major hemorrhage RR: 0.59; 95% CI: 0.38-0.89; p=0.008	

1° indicates primary; AF, atrial fibrillation; ACTIVE-W, Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events-W; AFASAK, Atrial Fibrillation, Aspirin and Anticoagulant Therapy Study; ATHENS, Primary Prevention of Arterial Thromboembolism in the Oldest Old with Atrial Fibrillation; BID, twice daily; BP, blood pressure; EAFT, European Atrial Fibrillation Trial; EKG, electrocardiogram; Hx, history; ICH, intracranial hemorrhage; MI, myocardial infarction; N/A, not applicable; NASPEAF, National Study for Prevention of Embolism in Atrial Fibrillation; PATAF, Primary Prevention of Arterial Thromboembolism in Nonrheumatic Atrial Fibrillation; PE, pulmonary embolism; pts, patients; QD, once daily; RR, relative risk; SE, systemic embolism; SIFA, Studio Italiano Fibrillazione Atriale; SPAF, Stroke Prevention in Atrial Fibrillation Study; TIA, transient ischemic attack; TTR, time in therapeutic range; Tx, therapy; and VD, vascular death.

Data Supplement 6. Beta Blockers (Sections 5.1.1)

Study Name, Author, Year	Study Aim	Study Type/ Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints		P Values, OR: HR: RR: & 95% CI:	Adverse Events	Study Limitations
				Inclusion Criteria	***Exclusion Criteria***		***Primary Endpoint & Results***	***Secondary Endpoint & Results***			
Abrams J, et al., 1985 (157) 3904379	Evaluation of the efficacy and safety of esmolol in comparing to propranolol for the acute control of SVT	Randomized prospective, multicenter double-blind	IV esmolol vs. IV propranolol	Pts over age 18 y with ventricular rates >120 bpm 2° to AF, atrial flutter, SVT, atrial tachycardia, idiopathic sinus tachycardia and AV reentrant tachycardias	WPW syndrome, hypotension, sick sinus syndrome, AV conduction delay decompensated HF or noncardiac precipitated arrhythmias	Esmolol vs. propranolol	Composite endpoint of either ≥20% reduction from average baseline heart rate, reduction in heart rate to <100 bpm, or conversion to NSR esmolol 72% vs. propranolol 69%	N/A	No difference	Hypotension (esmolol 45% vs. propranolol 18%)	Small sample size Only 66% of pts had AF
Farshi R, et al., 1999 (158) 9973007	Comparison of the effects of 5 standard drug	Prospective, open-label crossover outpatient	N/A	Chronic AF pts who had a duration of ≥1 y	LVEF<0.35, WPW syndrome, sick sinus	Comparison of the effects of 5 standard drug	Comparison of 24 h mean ventricular rates	Peak ventricular response at 5 m of exercise:	p<0.01 for comparison of atenolol or atenolol and	N/A	N/A

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	regimens: digoxin, diltiazem, atenolol, digoxin plus diltiazem, and digoxin + atenolol on the mean 24-h heart rate				syndrome, pacemaker or clinically significant renal, thyroid or hepatic disease	regimens: digoxin, diltiazem, atenolol, digoxin plus diltiazem, and digoxin + atenolol on the mean 24-h heart rate	Digoxin: 78.9±16.3 Diltiazem: 80.0±15 Atenolol: 75.9±11.7 Digoxin + Diltiazem: 67.3±14.1 Digoxin + atenolol: 65±9.4	Digoxin: 175±36 Diltiazem: 151±27 Atenolol: 130±34 Digoxin + Diltiazem: 146±40 Digoxin + atenolol: 126±29	digoxin compared to digoxin alone		

1° indicates primary; 2°, secondary; AF, atrial fibrillation; AV, atrioventricular; HF, heart failure; HR, hazard ratio; IV, intravenous; LVEF, left ventricular ejection fraction; N/A, not applicable; NSR, normal sinus rhythm; pts, patients; SVT, supraventricular tachycardia; Tx, therapy; and WPW, Wolff-Parkinson-White.

Data Supplement 7. Nondihydropyridine Calcium Channel Blockers (Sections 5.1.2)

Study Name, Author, Year	Study Aim	Study Type/ Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints	P Values, OR: HR: RR: & 95% CI:	Study Limitations
				Inclusion Criteria	***Exclusion Criteria***		***Primary Endpoint & Results***		
Ellenbogen KA, et al., 1991 (159) 1894861	To demonstrate the safety and efficacy of a continuous IV diltiazem infusion for 24 h heart rate control	Randomized, double-blind, parallel, PC-controlled	IV diltiazem vs. PC	Pts >18 y with AF or atrial flutter with duration >24 h and HR>120 bpm	Severe CHF, sinus node dysfunction, 2nd or 3rd degree AV block, WPW syndrome or hypotension	IV diltiazem vs. PC	Therapeutic response (ventricular response <100 bpm, ≥20% decrease in heart rate from baseline or conversion to NSR 74% vs. 0%	p<0.001	Small sample size
Steinberg JS, et al., 1987 (160) 3805530	To determine the efficacy of diltiazem to control ventricular response at rest, during exercise, and during daily activities	Prospective, open-label	Oral diltiazem	Pts with chronic AF with a VR>100 bpm at 3 min of a standardized exercise test	UA, acute MI, WPW syndrome, hypotension, renal or hepatic failure, sick sinus syndrome without a pacemaker	Oral diltiazem	Ventricular response: Rest: 69±10 vs. 96±17 Exercise: 116±26 vs. 155±28+	p<0.001	Small sample size Most pts at entry were on digoxin and continued on digoxin

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Siu CW, 2009 et al., (161) 19487941	To compare the clinical efficacy of IV diltiazem, digoxin, and amiodarone for acute VR in symptomatic AF	Randomized, prospective, open-label	IV diltiazem vs. IV amiodarone vs. IV digoxin	Hospitalized pts with symptomatic AF<48 h with ventricular response >120 bpm	Ventricular response >200 bpm, pre-excitation syndrome, hypotension, CHF, implanted pacemaker/defibrillator, recent MI, UA or stroke	IV diltiazem vs. IV amiodarone vs. IV digoxin	VR control (<90 bpm) within 24 h: ventricular response <90 bpm sustained for ≥4 h Diltiazem 90% vs. amiodarone 74% vs. digoxin 74%	p<0.47	N/A

AF indicates atrial fibrillation; AV, atrioventricular; CHF, congestive heart failure; IV, intravenous; MI, myocardial infarction; N/A, not applicable; NSR, normal sinus rhythm; PC, placebo; pts, patients; RR, relative risk; UA, unstable angina; VR, ventricular rate; and WPW, Wolff-Parkinson-White.

Data Supplement 8. Digoxin (Sections 5.1.3)

Study Name, Author, Year	Study Aim	Study Type/ Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints		P Values, OR: HR: RR: & 95% CI:	Study Limitations
				Inclusion Criteria	***Exclusion Criteria***		***Primary Endpoint & Results***	***Secondary Endpoint & Results***		
IV Digoxin in Acute AF (162) 9129897	To examine the effects of IV digoxin in acute AF	Randomized, prospective, multicenter, double-blind PC-controlled	IV digoxin vs. PC	Pts >18 y with AF≤7d	Ongoing Tx with digoxin or antiarrhythmics, sick sinus syndrome or 2nd /3rd degree AV block without a pacemaker, WPW syndrome, heart rate <60 or >170 bpm, ongoing ischemia or recent MI	IV digoxin vs. PC	Conversion to sinus rhythm at 16 h Digoxin 46% vs. PC 51%	Effect on heart rate: 91.2±20 vs. 116.2±25	p=0.37 p<0.0001	N/A
AFFIRM Olshansky B, et al., 2004 (163) 15063430	To examine whether digoxin use was associated with adverse	Post hoc analysis	Nonrandomized comparison of digoxin vs. no digoxin	Pts with AF considered at high risk for stroke	N/A	Post hoc analysis including propensity analysis	Estimated HR of 1.41 for all-cause mortality for digoxin	Estimated HR of 1.61 for arrhythmic mortality Estimated HR	p<0.001 p<0.009 p<0.016	Post hoc analysis utilizing propensity scoring

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	mortality and morbidity							of 1.35 for CV mortality		

AF indicates atrial fibrillation; AFFIRM, Atrial Fibrillation Follow-up Investigation of Rhythm Management; AV, atrioventricular; HR, hazard ratio; IV, intravenous; MI, myocardial infarction; N/A, not applicable; PC, placebo; pts, patients; RR, relative risk; Tx, therapy; and WPW, Wolff-Parkinson-White.

Data Supplement 9. Other Pharmacological Agents for Rate Control (Sections 5.1.4)

Study Name, Author, Year	Study Aim	Study Type/ Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints			P Values, OR: HR: RR: & 95% CI:	Adverse Events
				Inclusion Criteria	*Exclusion Criteria*		*Primary Endpoint & Results*	*Safety Endpoint & Results*	*Secondary Endpoint & Results*		
Delle Karth G, et al., 2001 (164) 11395591	To compare the efficacy of IV diltiazem bolus/infusion vs. IV amiodarone bolus vs. IV amiodarone bolus/infusion for immediate (4 h) and 24-h rate control during AF	Randomized prospective, controlled	IV diltiazem bolus/infusion vs. IV amiodarone bolus vs. IV amiodarone bolus/infusion	Critically ill pts with recent-onset AF with ventricular rate >120 bpm	N/A	IV diltiazem bolus/ infusion vs. IV amiodarone bolus vs. IV amiodarone bolus/infusion	Sustained heart rate reduction ≥30% within 4 h 70% vs. 55% vs. 75%	Bradycardia or hypotension 35% vs. 0% vs. 5%	Uncontrolled tachycardia 0% vs. 45% vs. 5%	1° endpoint: NS 2° endpoint p<0.00016 Safety endpoint p=0.01	N/A
Connolly SJ, et al., 2011 (165) 22082198	Assess impact of dronedarone on major vascular events in high-risk permanent AF	Randomized prospective, multicenter, double-blind, PC-controlled trial (3,236)	Dronedarone 400 mg po BID vs. PC	Permanent AF / flutter, age ≥65 y with ≥1 risk factor: CAD, CVA or TIA, CHF, LVEF≤0.40, PAD or age ≥75 y with HTN and DM	Paroxysmal or persistent AF, ICD, heart rate <50 bpm, QT interval corrected >500 ms	Dronedarone vs. PC	Composite of stroke, MI, SE, or CV death Composite of unplanned hospitalization for CV event/ death	N/A	N/A	HR: 2.29; 95% CI: 1.34-3.94 HR: 1.95; 95% CI: 1.45-2.62	Stroke HR: 2.32; 95% CI: 1.11-4.88 Unplanned hospitalization for CV event HR: 1.81; 95% CI: 1.44-2.70

1° indicates primary; 2°, secondary; AF, atrial fibrillation; BID, twice daily; CAD, coronary artery disease; CHF, congestive heart failure; CV, cardiovascular; CVA, cerebrovascular accident; DM, diabetes mellitus; HR, hazard ratio; HTN, hypertension; ICD, implantable cardioverter defibrillator; IV, intravenous; LVEF, left ventricular ejection fraction; MI, myocardial infarction; N/A, not applicable; NS, not significant; PAD, peripheral artery disease; PC, placebo; po, orally; pts, patients; RR, relative risk; SE systemic embolism; and TIA, transient ischemic attack.

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Data Supplement 10. AV Junction Ablation (Sections 5.2)

Study Name, Author, Year	Study Aim	Study Type/ Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints *Primary Endpoint & Results*	P Values, OR: HR: RR: & 95% CI:	Study Limitations
				Inclusion Criteria	***Exclusion Criteria***				
Ozcan C, et al., 2001 (166) 11287974	Assess effect of radio-frequency ablation of the AV node and implantation of a permanent pacemaker on long-term survival in pts with AF refractory to drug Tx	Observational single site	Comparison to 2 control populations Age/sex matched from minnesota population Consecutive pts with AF who received drug Tx	All pts who underwent AV nodal ablation and pacemaker implantation for medically refractory AF between 1990 and 1998	N/A	AV nodal ablation pacemaker compared to 2 control groups	No difference in survival between ablation/pacemaker group and control group treated with drugs Excess observed death in ablation/ pacemaker group relative to age/sex matched population	N/A	Observation, nonrandomized trial

AF indicates atrial fibrillation; AV, atrioventricular; N/A, not applicable; pts, patients; RR, relative risk; and Tx, therapy.

Data Supplement 11. Broad Considerations in Rate Control (Sections 5.3.1)

Study Name, Author, Year	Study Aim	Study Type/ Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Endpoints		P Values, OR: HR: RR: & 95% CI:	Adverse Events
				Inclusion Criteria	***Exclusion Criteria***		***Primary Endpoint & Results***	***Secondary Endpoint & Results***		
Van Gelder IC, et al., 2010 (167) 20231232	Lenient rate control is noninferior to strict rate control in permanent AF	Randomized, prospective, multicenter, open label N=614	Lenient rate control (resting heart rate <110) vs. strict rate control (resting heart rate <80)	Age <80 y, permanent AF, oral anticoagulant or ASA Tx	N/A	N/A	Composite of CV death and morbidity at 12.9% vs. 14.9%	Death, components of 1° endpoint, Sx, and functional status	1° endpoint, 3 y, HR: 0.84; 95% CI: 0.58-1.21	HF (3.8% vs. 4.1%); HR: 0.97; 95% CI: 0.48-1.96 Stroke 1.6% vs. 3.9%, HR: 0.35; 95% CI: 0.13-0.92 CV death 2.9% vs. 3.9%, HR: 0.79; 95% CI: 0.38-1.65

1° indicates primary; AF, atrial fibrillation; ASA, aspirin; CV, cardiovascular; HF, heart failure; HR, hazard ratio; N/A, not applicable; pts, patients; RACE, Rate Control Efficacy in Permanent Atrial Fibrillation; RR, relative risk; Sx, symptom; and Tx, therapy.

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Data Supplement 12. Antiarrhythmic Drug Therapy (Section 6.2.1)

Study Name, Author, Year	Study Aim	Study Type/ Size (N)	Intervention vs. Comparator (n)	Patient Population	Endpoints		Adverse Events	Comments
					Primary Endpoint & Results	***Secondary Endpoint & Results***		
ADONIS, Singh BN, et al., 2007 (168) 17804843	To assess the efficacy of dronedarone in maintenance of SR in pts with AF	RCT, double-blind (625)	Dronedarone 400 mg BID (417) PC (208)	Age ≥21 y ≥1 episode AF in previous 3 mo	Time to the 1st recurrence of AF or atrial flutter Dronedarone 158 d PC 59 d (p=0.002)	Ventricular rate after recurrence, dronedarone 104.6 bpm PC 116.6 bpm (p<0.001).	N/A	Dronedarone was more effective than PC in maintaining SR and in reducing ventricular rate during recurrent AF
AFFIRM Substudy, 2003 (169) 12849654	To evaluate the efficacy of antiarrhythmic drugs for AF	RCT, open-label (410)	Amiodarone 200 mg/d vs. class I drug vs. sotalol	Substudy of pts randomized to rhythm control	1° – proportion at 1 y alive, on Tx drug, and in SR 62% amiodarone vs. 23% class I drug (p<0.001) 60% amiodarone vs. 38% sotalol (p=0.002) 34% sotalol vs. 23% class I drug (p=0.488)	N/A	AEs leading to drug discontinuation 12.3% amiodarone 11.1% sotalol 28.1% class I agent Amiodarone pulmonary toxicity 1.3% at 1 y and 2.0% at 2 y 1 case torsade de pointes - quinidine	Amiodarone more effective than sotalol or class I agent for SR without cardioversion AEs were common
Aliot E, et al., 1996 (170) 8607394	To assess the safety and efficacy of flecainide vs. propafenone in PAF or atrial flutter	RCT, open-label (97)	Flecainide 100-200 mg/d (48) Propafenone 600 mg/d (49)	Inclusion: >18 y with symptomatic PAF or atrial flutter Exclusion: AF last >72 h, Hx of MI or UA, Hx of VT, Hx of HF (NYHA class III or IV), LVEF<35%, PR>280 ms, QRS>150 ms, sick sinus syndrome or AV block in absence of pacemaker	Probability of SR at 1 y 0.619 flecainide 0.469 propafenone (p=0.79)	N/A	8.5% flecainide group had neurologic side effects 16.7% propafenone group GI side effects	Flecainide and propafenone similar efficacy (although small sample size and open-label design) Nonsignificant trend toward higher side-effects with propafenone

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ANDROMEDA, Kober L, et al., 2008 (171) 18565860	To evaluate the efficacy of dronedarone in HF pts	RCT, double-blind (627)	Dronedarone (310) PC (317)	Age >18 y, hospitalized for HF, LVEF<35%, NYHA class III or IV (Did not require AF Dx, Hx of AF 37-40%)	Death from any cause or HF hospitalization 17.1% dronedarone 12.6% PC HR: 1.38; 95% CI: 0.92-2.09; p=0.12	N/A	Death 8.1% dronedarone 3.8% PC HR: 2.13; 95% CI: 1.07-4.25; p=0.03	Dronedarone is associated with increased mortality in pts with severe HF and reduced LVEF related to worsening of HF
ASAP, Page RL, et al., 2003 (172) 12615792	To assess the frequency of asymptomatic AF in pts treated with azimilide	RCT, double-blind (1,380)	Azimilide 35-125 mg/d (891) PC (489)	Inclusion: Symptomatic AF in SR at time of randomization Exclusion: Rest angina or UA, class IV CHF, Hx of torsade de pointes, QTc >440 ms, resting SR<50 bpm	Time to 1st documented asymptomatic AF – no significant difference 40% reduction in asymptomatic AF episodes in the 100 mg or 125 mg azimilide group vs. PC (p=0.03)	N/A	N/A	N/A
ATHENA, Hohnloser SH, et al., 2009 (173) 19213680	N/A	RCT, double-blind (4,628)	Dronedarone 400 mg BID (2,301) PC (2,327)	Inclusion: AF (paroxysmal or persistent) and ≥1 of these: >70 y, HTN, DM, LVEF<40%, LAD>50 mm, Hx of TIA/stroke/embolism	1° – 1st hospitalization due to CV event or death 31.9% dronedarone 39.4% PC HR: 0.76; p<0.001	Death due to any cause CV death CV hospitalization	N/A	N/A
Bellandi F, et al., 2001 (174) 11564387	To evaluate the long-term efficacy and safety of propafenone and sotalol for maintaining SR	RCT, double-blind (194)	Propafenone HCL 900 mg/d (102) Sotalol HCL 240 mg/d (106) PC (92)	≥18 y, recurrent AF (≥4 episodes previous 12 mo) and episode of AF at enrollment <48 h	Proportion of pts remaining in SR at 1 y FU 63% propafenone 73% sotalol 35% PC (p=0.001)	N/A	4% ventricular arrhythmia with sotalol Drug discontinuation due to AEs – 9% propafenone, 10% sotalol, 3% PC	Sotalol and propafenone appear to have similar efficacy and are superior to PC at maintaining SR at 1 y
Benditt DG, et al., 1999 (175) 10496434	To evaluate the efficacy of sotalol for maintaining of SR	RCT, double-blind (253)	Sotalol 80 mg BID (59) Sotalol 120 mg BID (63) Sotalol 160 mg	Inclusion: symptomatic AF or atrial flutter and SR at time of randomization Dose reduction in presence of renal dysfunction	Time to first recurrent symptomatic AF or atrial flutter after steady state (intention to treat) 27 d PC	Proportion of pts free of AF 12 mo 28% PC 30% sotalol 80 mg 40% sotalol 120	Bradycardia and fatigue most common AEs No cases of torsade de pointes in this study	Outpatient initiation in 27%

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			BID (62) PC (69)	Exclusion: QT>450 ms, sinus rate <50, other QT prolonging drugs, renal failure (CrCl<40 mL/min), Hx of HF, uncorrected hypokalemia, asymptomatic AF, sick sinus syndrome without pacer, MI<2 mo, syncope, TIA/stroke	106 d sotalol 80 mg 229 d sotalol 120 mg 175 d sotalol 160 mg	mg 45% sotalol 160 mg		
Byrne-Quinn E, et al., 1970 (176) 4911757	To evaluate the efficacy of quinidine for maintenance of SR	RCT, double-blind (65)	Quinidine 1.2 g/d (28) PC (37)	Inclusion: Pts hospitalized for AF with plan for cardioversion Exclusion: digoxin stopped 24 h prior	Percentage of pts at FU in SR 24.3% PC 57% quinidine	N/A	1 death presumed related to quinidine	Small sample size, variable FU period (5-15 mo)
Carunchio A, et al., 1995 (177) 7642012	To evaluate the efficacy and safety of flecainide and sotalol for maintenance of SR	RCT, open-label (66)	Flecainide acetate 200 mg/d (20) Sotalol HCL 240 mg/d (20) PC (26)	N/A	Arrhythmia free survival at 12 mo 70% flecainide 60% sotalol 27% PC p=0.002 AAD vs. PC p=0.163 flecainide vs. sotalol	N/A	N/A	Flecainide and sotalol have similar efficacy in prevention of recurrence of AF Side effects common but serious AE uncommon in this FU period
Channer KS, et al., 2004 (178) 14720531	To evaluate the efficacy of amiodarone to prevent recurrent AF after cardioversion	RCT, double-blind (161)	Amiodarone (short-term) 200 mg/d for 8 wk after DCCV (62) Amiodarone (long-term) 200 mg/d for 52 wk after DCCV (61) PC (38)	Inclusion: Age >18 y and sustained AF>72 h Exclusion: LVEF<20%, significant valve disease, female <50 y, thyroid, lung or liver disease, contraindication to anticoagulation	Percentage in SR at 1 y 49% long-term amiodarone 33% short-term (8 wk after DCCV) amiodarone 5% PC	Spontaneous conversion to SR 21% amiodarone and 0% in PC SR rhythm at 8 wk after DCCV – 16% PC, 47% short-term amiodarone, 56% long-term amiodarone	AEs leading to discontinuation 3% PC 8% short-term amiodarone 18% long-term amiodarone	Amiodarone pre-Tx allows chemical cardioversion in 1/5 of pts with persistent AF and is more effective at maintaining SR after DCCV Given the long-term AEs with amiodarone, 8 wk of adjuvant Tx suggested as option by authors

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CTAF, Roy D, et al., 2000 (179) 10738049	Low dose amiodarone would be more efficacious in preventing recurrent AF than sotalol or propafenone	RCT (403)	Amiodarone 200 mg/d (201) Sotalol 160 mg BID (101) Propafenone 150 QID (101)	Symptomatic AF within previous 6 mo but not persistent AF>6mo	Recurrence of AF during FU (mean 16 mo) 35% amiodarone 63% sotalol or propafenone (p<0.001)	N/A	AEs requiring drug discontinuation 18% amiodarone vs. 11% sotalol or propafenone group (p=0.06)	Amiodarone is more effective than sotalol or propafenone in preventing recurrent AF (with a trend toward higher side-effects)
DAFNE, Touboul P, et al., 2003 (180) 12919771	To determine the most appropriate dose of dronedarone for prevention of AF after DCCV	RCT, double-blind (199)	Dronedarone 800 mg/d (54) Dronedarone 1,200 mg/d (54) Dronedarone 1600 mg/d (43) PC (48)	Inclusion: age 21-85 y, pts with persistent AF (>72 h and <12 mo) scheduled for DCCV Exclusion: Hx of torsade de pointes, QT>500 ms, severe bradycardia, AV block, NYHA class III or IV HF, LVEF<35, ICD, WPW syndrome	Time to first documented AF recurrence at 6 mo 60 d for dronedarone 400 mg BID 5.3 d for PC (p=0.001)	Spontaneous conversion of AF with dronedarone 5.8 to 14.8% pts	Premature discontinuation 22.6% 1600 mg, 3.9% 800 mg	Small sample size, dose-finding study
DIAMOND, Pedersen OD, et al., 2001 (181) 11457747	To evaluate the efficacy of dofetilide to maintain SR in pt with LV dysfunction	RCT, double-blind (506)	Dofetilide 500 mcg/d (249) PC (257)	Inclusion: Persistent AF associated with either HF or recent acute MI Dose reduction for renal insufficiency Exclusion: HR: <50 bpm, QTc>460 ms (500 ms with BBB), K<3.6 or >5.5, CrCl<20 mL/min	Probability of maintaining SR at 1 y 79% dofetilide 42% with PC (p<0.001)	No effect on all-cause mortality Dofetilide associated with reduced rate of rehospitalization	Torsade de pointes occurred in 4 dofetilide pts (1.6%)	N/A
DIONYSOS, Le Heuzey JY, et al., 2010 (182) 20384650	To evaluate the efficacy and safety of amiodarone and dronedarone in pts with persistent AF	RCT, double-blind (504)	Amiodarone 600 mg QD for 28 d then 200 mg QD (255) Dronedarone 400 mg BID (249)	Age ≥21 y with documented AF for >72 h for whom CV and AAD were indicated and oral anticoagulation	Recurrence of AF (including unsuccessful CV) or premature study discontinuation at 12 mo 75.1% dronedarone, 58.8% amiodarone, HR: 1.59; 95% CI: 1.28-1.98; p<0.0001	N/A	Drug discontinuation less frequent with dronedarone (10.4 vs. 13.3%). MSE was 39.3% and 44.5% with dronedarone and amiodarone, respectively, at 12 mo (HR: 0.80;	Dronedarone was less effective than amiodarone in decreasing AF recurrence, but had a better safety profile

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					Mainly driven by AF recurrence with dronedarone compared with amiodarone (63.5 vs. 42.0%)		95% CI: 0.60 to 1.07; p=0.129), and mainly driven by fewer thyroid, neurologic, skin, and ocular events in the dronedarone group	
Dogan A, et al., 2004 (183) 15255456	To evaluate the efficacy of propafenone for maintenance of SR after cardioversion	RCT, Single-blind (110)	Propafenone 450 mg/d (58) PC (52)	Recent onset or persistent AF Exclusion: MI, HF, CABG<6 mo, severe COPD, LA thrombus, thyroid disease, inability to consent to DCCV	Percentage of AF recurrences at 15 mo 39% propafenone 65% PC	Spontaneous conversion with drug predicted lower chance of recurrence	Discontinuation due to side effects: 4 pts on propafenone and 1 PC (p=0.36)	Propafenone is more effective than PC for prevention of recurrent AF
EURIDIS, Singh BN, et al., 2007 (168) 17804843	To assess the efficacy of dronedarone in maintenance of SR in pts with AF	RCT, double-blind (612)	Dronedarone 400 mg BID (411) PC (201)	≥1 episode AF in previous 3 mo, Age ≥2y	Time to the 1st recurrence of AF or atrial flutter 96 d dronedarone 41 d in the PC (p=0.01)	After AF recurrence, mean rate=117.5 bpm, PC=102.3 bpm, dronedarone (p<0.001)	N/A	Dronedarone was more effective than PC in maintaining SR and in reducing ventricular rate during recurrent AF
FAPIS, Chimienti M, et al., 1996 (184) 8607393	To compare the safety of flecainide to propafenone for Tx of PAF	RCT, open-label (200)	Flecainide acetate 200 mg/d (97) Propafenone HCL 450-900 mg/d (103)	Paroxysmal AF without structural heart disease	Probability of remaining free of AEs at 12 mo 77% flecainide 75% propafenone 1 VT in propafenone group 2 accelerated ventricular response with flecainide	Drug discontinuation 4 flecainide 5 propafenone	N/A	AEs appear occur at similar rate with propafenone and flecainide in this population with AF and without evidence of structural disease
GEFACA, Galperin J, et al., 2001 (185) 11907636	To evaluate the efficacy of amiodarone for restoration and maintenance of SR	RCT, double-blind (50)	Amiodarone 200 mg/d (47) PC (48)	Persistent AF>2 mo duration Exclusion: paroxysmal AF, age >75 y, HR<50 bpm, LA>60 mm	Recurrent AF in 37% amiodarone and 80% PC group Spontaneous conversion 34% with amiodarone and 0% PC	N/A	AEs 15% of pts on amiodarone	Amiodarone restored SR in 1/3 pts, increased success of DCCV, reduced and delayed recurrence of AF

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Kalusche D, et al., 1994 (186) 7846939	To compare the efficacy of sotalol to a fixed combination of quinidine and verapamil	RCT, open-label (82)	Quinidine sulfate 1000 mg/d Sotalol HCL 240-400 mg/d	N/A	SR at 6 and 12 mo 75.7% and 67.3% quinidine/verapamil 63.4 and 49.9% sotalol p=NS	N/A	5 pts quinidine/verapamil discontinued Tx due to noncardiac AEs, 3 pts in sotalol discontinued due to bradycardia No proarrhythmia noted	N/A
Kochiadakis GE, et al., 2004 (187) 15589019	Compare the efficacy and safety of sotalol and propafenone for prevention of recurrent AF	RCT, single-blind (254)	Propafenone HCL 240 mg/d (86) Sotalol HCL 320 mg/d (85) PC (83)	Symptomatic AF, successful chemical or DCCV if persistent	Percentage recurrence AF during FU 69/85 sotalol 45/86 propafenone 73/83 PC (p<0.001)	N/A	N/A	Long-term results show superiority of propafenone (question methods of comparison)
Kuhlkamp, et al., 2000 (188) 10898425	To evaluate the efficacy of metoprolol XL to reduce AF recurrence after cardioversion	RCT, double-blind (394)	Metoprolol XL 100 mg/d (197) PC (197)	Inclusion: Persistent AF with successful cardioversion (DC or chemical) Exclusion: Concomitant Tx with any class I or class 3 AAD, beta blocker or CCB	Percentage of pts with recurrent AF during FU (up to 6 mo) 48.7% metoprolol XL 59.9% PC (p=0.005)	Mean HR was lower with recurrent AF in pts on metoprolol (107 vs. 98; p=0.015)	SAEs similar with metoprolol or PC	Metoprolol XL prevents recurrent AF after cardioversion Short duration of FU
Naccarelli GV, et al., 1996 (189) 8607392	To compare the efficacy of flecainide to quinidine for PAF	RCT, open-label (239)	Flecainide acetate 200-300 mg/d (122) Quinidine sulfate 1000-1500 mg/d (117)	Symptomatic PAF	Percentage of pts with reported episodes of symptomatic AF 72% flecainide 74.3% quinidine (p=0.54)	Combined endpoint efficacy and tolerability at 1 y 70% flecainide vs. 55.4% quinidine (p<0.007)	N/A	Flecainide and quinidine have similar efficacy but flecainide is better tolerated
PAFAC, Fetsch T, et al., 2004 (190) 15302102	To compare the efficacy of quinidine and sotalol to PC for maintenance of SR in pt with persistent AF	RCT, double-blind (848)	Quinidine sulfate 480 mg/d Sotalol HCL 320 mg/d	Persistent AF lasting >7 d (mean duration: 15 mo), N=848, male: 66%, age (mean, SD): 63, ±9, structural heart disease: NS, left anterior descending: 45 mm, LVEF: 60%	At 12 mo: Mortality Pro-arrhythmia AEs AF recurrence	N/A	N/A	N/A

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			PC					
PALLAS, Connolly SJ, et al., 2011 (165) 22082198	To assess whether dronedarone would reduce major vascular events in high-risk permanent AF	RCT, double-blind (3236)	Dronedarone 400 mg BID PC	Age >65 y with permanent AF or atrial flutter with no plan to restore SR and high risk feature: CAD, previous stroke or TIA, HF class II or III Sx, LVEF<40%, PAD or age >75 y, HTN & DM	Coprimary outcomes: Stroke, MI, SE, or CV death, 43 pts receiving dronedarone and 19 receiving PC (HR: 2.29; 95% CI: 1.34-3.94; p=0.002 Unplanned CV hospitalization or death, 127 pts receiving dronedarone and 67 pts receiving PC (HR: 1.95; 95% CI: 1.45-2.62; p<0.001)	Hospitalization for HF occurred in 43 pts in the dronedarone group and 24 in the PC group (HR: 1.81; 95% CI: 1.10- 2.99; p=0.02)	Most common AEs were diarrhea, asthenic condition, nausea and vomiting, dizziness, dyspnea, and bradycardia ALT>3x upper limit normal range occurred in 22 of 1,481 (1.5%) pts receiving dronedarone and in 7 of 1,546 (0.5%) receiving PC p=0.02	Dronedarone increased rates of HF, stroke, and death from CV causes in pts with permanent AF who were at risk for major vascular events.
Piccini JP, et al., 2009 (191) 19744618	To evaluate randomized trials of amiodarone and dronedarone for safety and efficacy in AF	Meta-analysis	4 trials of amiodarone vs. PC 4 trials of dronedarone vs. PC 1 comparison of amiodarone vs. dronedarone	Randomized PC-controlled trials of amiodarone and dronedarone for maintenance of SR in pts with AF	OR: 0.12 amiodarone vs. PC (95% CI: 0.08-0.19) OR: 0.79 dronedarone vs. PC (95% CI: 0.33-1.87)	N/A	Amiodarone trend towards increased mortality Amiodarone greater number AEs than dronedarone	Dronedarone is less effective than amiodarone but has fewer AEs

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Plewan A, et al., 2001 (192) 11482924	N/A	RCT, open-label (128)	Sotalol 160 mg/d Bisoprolol fumarate 5 mg/d	Persistent AF (mean duration: 9 mo). N=128 Male: 62%. Age (mean, SD): 59, ±10 Structural heart disease: 72%. LAD: 48 mm. LVEF: 41%	At 8 mo: Mortality Pro-arrhythmia AEs AF recurrence	N/A	N/A	N/A
PRODIS, Crijns HJ, et al., 1996 (193) 8842506	N/A	RCT, double-blind (56)	Disopyramide phosphate 750 mg/d Propafenone HCL 900 mg/d	Persistent AF (mean duration: 5 mo). N=56 Male: 68%. Age (mean, SD): 60, ±11 Structural heart disease: 65%. LAD: 46 mm. LVEF: NS	At 6 mo: Mortality Pro-arrhythmia AEs AF recurrence	N/A	N/A	N/A
RAFT, Pritchett EL, et al., 2003 (194) 14556870	Assess the efficacy and safety of sustained-released propafenone for maintenance of SR	RCT, double-blind (523)	Propafenone hydrochloride 450-850 mg/d (397) PC (126)	Inclusion: Symptomatic AF (type not specified) SR at time of randomization Exclusion: Permanent AF, NYHA class III or IV HF, cardiac surgery <6 mo, MI<12 mo, WPW syndrome, 2nd or 3rd degree AV block, QRS>160 ms, HR<50 bpm, Hx of VF, VT or ICD	At 9 mo: Mortality Pro-arrhythmia AEs AF recurrence	N/A	N/A	N/A
Reimold SC, et al., 1993 (195) 8438741	To compare the efficacy of propafenone and sotalol for maintenance of SR	RCT, open-label (100)	Propafenone HCL 675 mg/d (50) Sotalol HCL 320 mg/d (50)	Pts with AF with previous AAD failure	Percentage with SR at 3, 6, and 12 mo 46%, 41%, 30% propafenone 49%, 46% sotalol	N/A	N/A	Propafenone and sotalol similar efficacy
Richiardi E, et al., 1992 (196) 1600529	To evaluate the efficacy and safety of oral propafenone vs. quinidine at preventing AF	RCT, open-label (200)	Propafenone 900 mg/d Quinidine 1000 mg/d	≥3 AF episodes in past 6 mo Exclusion: LA size >55 mm, hepatic or renal insufficiency, MI<30 d, pregnant, decompensated HF, thyroid dysfunction	SR at 6 mo 60% propafenone 56% quinidine SR at 1 y 48% propafenone 42% quinidine	p=NS	N/A	10% side effects propafenone 24% side-effects quinidine (p=0.02)
SAFE-T, Singh BN, et	To assess the efficacy of	RCT, double-blind	Amiodarone 300 mg/d	Inclusion: Persistent AF>72 h including at time of	Pharmacological Conversion to SR	Sustained SR improved QOL	NS difference in AEs among the 3 groups	N/A

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al., 2005 (197) 15872201	amiodarone and sotalol in converting AF and maintenance of SR	(665)	Sotalol 320 mg/d PC	randomization & on oral anticoagulation Exclusion: Paroxysmal AF or atrial flutter, NYHA class III or IV HF, CrCl<60 mL/min, intolerance to beta blockers, Hx of long QT syndrome	27.1% amiodarone 24.2% sotalol 0.8% PC Median Time to Recurrence AF (intention to treat) 487 d amiodarone 74 d sotalol 6 d PC p<0.001	and exercise capacity		
SAFIRE-D, Singh S, et al., 2000 (198) 11067793	To determine the efficacy and safety of dofetilide in converting AF or atrial flutter to SR and maintaining SR for 1 y	RCT, double-blind (250)	Dofetilide 250-1000 mcg/d PC	Inclusion: Age 18-85 y with AF or atrial flutter 2-26 wk duration Exclusion: Sinus node dysfunction, QRS>180 ms, QT interval>400 ms (QT>500 ms with BBB), sinus rate<50 bpm, Hx of renal or hepatic disease, use of verapamil, diltiazem, QT prolonging drugs	Pharmacological Conversion Rate 6.1% 125 mcg BID 9.8% 250 mcg BID 29.9% 500 mcg BID 1.2% PC p=0.015 250 mcg and p<0.001 500 mcg (vs. PC) Probability of SR at 1 y 0.40 125 mcg BID 0.37 250 mcg BID 0.58 500 mcg BID 0.25 PC	N/A	2 cases of torsade de pointes during initiation phase (0.8%) 1 sudden death (proarrhythmic) on Day 8 (0.4%)	In-hospital initiation and dosage adjustment based on QTc and CrCl to minimize proarrhythmic risk
SOPAT, Patten M, et al., 2004 (199) 15321697	To assess the effectiveness of 2 AAD on frequency of AF	RCT, double-blind (1033)	High-dose Quinidine sulfate 480 mg/d and verapamil 240 mg/d (263) Low-dose Quinidine sulfate 320 mg/d and	Age 18-80 y, symptomatic PAF Exclusion: cardiogenic shock, LA thrombus, MI or cardiac surgery <3 mo, UA, valve disease requiring surgery, ICD or pacemaker, sick sinus syndrome, 2nd or 3rd degree AV block, QTc>440 ms, bradycardia,	Time to 1st recurrence of symptomatic PAF or premature discontinuation 105.7 d PC 150.4 d high-dose quinidine/verapamil 148.9 d low-dose quinidine/verapamil	AF burden (% says with symptomatic AF) 6.1% PC 3.4% high dose 4.5% low dose 2.9% sotalol (p=0.026)	1 death and 1 VT event related to high-dose quinidine/verapamil 2 syncopal events related to sotalol	Quinidine/verapamil fixed combination similar efficacy to sotalol but with risk of SAEs

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			verapamil 160 mg/d (255) Sotalol HCL 320 mg/d (264) PC (251)	renal or liver dysfunction, hypokalemia, bundle branch block Mean time under Tx 233 d	145.6 d sotalol (p<0.001)			
Stroobandt R, et al., 1997 (200) 9052343	To assess the efficacy of propafenone at maintaining sinus rhythm	RCT, double-blind (102)	Propafenone HCL 150 mg TID (77) PC (25)	Age >18 y with AF, enrolled in maintenance phase after attempt at pharmacological conversion with IV propafenone (and if unsuccessful DCCV)	Proportion of pts free from recurrent symptomatic AF at 6 mo 67% propafenone 35% PC (p<0.001)	N/A	NS difference in AEs	Evidence for the efficacy of propafenone in maintaining sinus rhythm after cardioversion. Short duration of FU (6 mo)
SVA-3, Pritchett EL, et al., 2000 (201) 10987602	To assess the effectiveness of azimilide in reducing symptomatic AF or atrial flutter	RCT, double-blind (384)	Azimilide 50 mg, 100 mg, or 125 mg PC	Inclusion: Age ≥18 y, Symptomatic AF in SR at time of randomization Exclusion: Rest angina or UA, class IV CHF, Hx of torsade de pointes, QTc>440 ms, resting SR<50 bpm	Time to 1st symptomatic AF recurrence Azimilide 100 mg/125 mg QD vs. PC, HR: 1.58; p=0.005	N/A	2 sudden deaths in azimilide groups and 1 case of torsade de pointes	Initiated in outpatient setting
Villani R, et al., 1992 (202) 1559321	To compare the efficacy of amiodarone to disopyramide	RCT, open-label (76)	Amiodarone 200 mg/d (41) Disopyramide phosphate 500 mg/d (35)		Recurrence of AF at end of FU 57% disopyramide (13 mo) 32% amidarone (14 mo)	N/A	Disopyramide discontinued due to AE 14% <1 wk and another 14% by end of trial 8.5% developed hyperthyroidism	Amiodarone is more effective than disopyramide for prevention of recurrent AF

AAD indicates antiarrhythmic drug; ADONIS, American-Australian-African Trial With Dronedarone in Patients With Atrial Fibrillation or Atrial Flutter for the Maintenance of Sinus Rhythm; AE, adverse event; AF, atrial fibrillation; AFFIRM, Atrial Fibrillation Follow-up Investigation of Rhythm Management; ALT, alanine aminotransferase; ANDROMEDA, European Trial of Dronedarone in Moderate to Severe Congestive Heart Failure; ASAP, ASA and Plavix; ATHENA, A Trial With Dronedarone to Prevent Hospitalization or Death in Patients With Atrial Fibrillation; AV, atrioventricular; BBB, bundle-branch block; BID, twice daily; CABG, coronary artery bypass graft; CCB, calcium channel blocker; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disorder; CrCl, creatinine clearance; CTA, Canadian Trial of Atrial Fibrillation; CV, cardiovascular; DAFNE, Dronedarone Atrial Fibrillation Study after Electrical Cardioversion; DC, direct current; DCCV, direct current cardioversion; DIAMOND, Danish Investigators of Arrhythmia and Mortality on Dofetilide; DIONYSOS, Efficacy & Safety of Dronedarone Versus Amiodarone for the Maintenance of Sinus Rhythm in Patients With Atrial Fibrillation; DM, diabetes mellitus; Dx, diagnosis; FAPIS, Flecainide and Propafenone Italian Study; FU, follow-up; GEFACA, Grupo de Estudio de Fibrilacion Auricular Con Amiodarona; GI, gastrointestinal; HCL, hydrochloride; HF, heart failure; HR, hazard ratio; HTN, hypertension; Hx, history; ICD, implantable cardioverter defibrillator; K, potassium; LA, left atrial; LAD, left atrial dimension; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MSE, main safety endpoint; N/A, not applicable; NS, not significant; NYHA, New York Heart Association; OR, odds ratio; PAF, paroxysmal atrial fibrillation; PALLAS, Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy; PC, placebo; pts, patients; QD,

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once daily; QID, four times a day; QOL, quality of life; RAFT, Rythmol Atrial Fibrillation Trial; RCT, randomized controlled trial; RR, relative risk; SAFE-T, Sotalol Amiodarone Atrial Fibrillation Efficacy Trial; SAFIRE-D, Symptomatic Atrial Fibrillation Investigative Research on Dofetilide; SD, standard deviation; SOPAT, Suppression of Paroxysmal Atrial Tachyarrhythmias; SR, sinus rhythm; SVA, Supraventricular Arrhythmia Program; TIA, transient ischemic attack; TID, three times a day; Tx, therapy; UA, unstable angina; VF, ventricular fibrillation; VT, ventricular tachycardia; and WPW, Wolff-Parkinson-White.

Data Supplement 13. Outpatient Initiation of Antiarrhythmic Drug Therapy (Section 6.2.1.2)

Study Name, Author, Year	Study Type	Intervention (n)	Rhythm at Time of Initiation	Place of Initiation	Patient Population	Adverse Events
Benditt D, et al., 1999 (175) 10496434	Prospective dose finding study	Sotalol 80 BID (59) Sotalol 120 BID (63) Sotalol 160 BID (62) PC (69)	SR	50 pts - outpatient 134 pts - inpatient	Structural heart disease 57% Exclusion: Hx of torsade de pointes, CHF, QT>450 ms, hypokalemia hypomagnesemia, bradycardia	No cases of VT/VF/torsade QT>520 ms in 7 pts (4 in 120 mg BID and 3 in 160 mg BID) Premature discontinuation due to AEs 25% inpatients, but 6% of outpatients (bradycardia predominantly)
Chung MK, at al., 1998 (203) 9669266	Retrospective	Sotalol	Not documented	Inpatient	120 inpatients admitted for sotalol initiation Structural heart disease (80%)	7 (5.8%) new or increased ventricular arrhythmias, 2 with torsades de pointes (d 6 in pt with pacemaker and hypokalemia and d 4 in pts with ICD) 20 (16.7%) with significant bradycardia 8 (6.7%) excessive QT prolongation
SAFE-T, Singh BN, et al., 2005 (197) 15872201	Prospective RCT	Total 665 Amiodarone 267 Sotalol 261 Placebo 137	AF	Outpatient	Initiated sotalol or amiodarone in the outpatient setting during AF Excluded CHF class III or IV, Hx of long QT, CrCl<60	1 case torsade in sotalol group (nonfatal, time of occurrence not specified) 13 deaths/267 (6 sudden) amiodarone group 15 deaths/261 (8 sudden) sotalol group 3 deaths/137 (2 sudden) PC group (no significant difference)
Zimetbaum PJ, et al., 1999 (204) 10072241	Prospective	172 Amiodarone 66 (38%) Flecainide 45 (26%) Sotalol 20 (12%) Disopyramide 16 (9%) Propafenone 11 (6%) Quinidine 8 (5%) Procainamide 6 (4%)	SR	Outpatient	Pts with AF in sinus at time of initiation started on oral antiarrhythmic medication Received 1 or 2 doses of AAD in hospital or clinic and monitored for ≤8 h and then 10 d continuous loop event recorder Exlusion: QTc>550 ms, NYHA class III or IV CHF, or pacemaker	6 symptomatic AEs (none before d 4) Class Ic 3 atrial flutter with 1:1 d 6 or 7 1 symptomatic brady d 4 Sotalol 1 symptomatic bradycardia d 7 1 QT prolongation 370-520 ms d 4

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Hauser TH, et al., 2003 (205) 12804730	Prospective	409 Amiodarone 212 (51.8%) Class Ic 127 (31.1%) Propafenone 64 (15.6%) Flecainide 63 (15.4%) Sotalol 37 (9.0%) Class IA 33 (8.1%) Quinidine 8 (2%) Disopyramide 16 (3.9%) Procainamide 9 (2.2%)	SR	Outpatient	Pts with AF in sinus at time of initiation started on oral AAD with daily 30 s recording or with Sx	Amiodarone 2 Death (sudden) d 7 and d 9 3 Bradycardia requiring pacemaker d 6, 7, and 8 9 Bradycardia requiring dose reduction Class Ic Bradycardia d 7 and d 9 dose reduction Sotalol – none Quinidine Death (sudden) d 3
CTAF, Roy D, et al., 2000 (179) 10738049	Prospective open-label RCT	403 Amiodarone 201 Sotalol 101 Propafenone 101	Sinus≈60%	Outpatient	Exclusion: QTc>480, bradycardia <50 bpm	Arrhythmic deaths – 3 amiodarone group (2 had been off the drug >1 y) and 1 in sotalol/propafenone group Cardiac arrest due to torsade – propafenone Serious bradyarrhythmias – 6 amiodarone 7 in sotalol/propafenone group Time to event after initiation not specified All events occurred beyond 2 d of drug initiation mostly bradyarrhythmias
Kochiadakis GE, et al., 2004 (187) 15589019	N/A	254 Sotalol 85 Propafenone 86 PC 83	Sinus	Inpatient	N/A	No torsades noted Sotalol - 3 bradycardia during loading phase Propafenone – 1 bradycardia, 1 QRS widening

AAD indicates antiarrhythmic drug; AE, adverse event; AF, atrial fibrillation; BID, twice daily; CHF, congestive heart failure; CrCl, creatinine clearance; CTAF, Canadian Trial of Atrial Fibrillation; Hx, history; ICD, implantable cardioverter-defibrillator; IV, intravenous; NYHA, New York Heart Association; pts, patients; RCT, randomized controlled trial; RR, relative risk; SAFE-T, Sotalol Amiodarone Atrial Fibrillation Efficacy Trial; SR, sinus rhythm; Sx, symptom; VF, ventricular fibrillation; and VT, ventricular tachycardia.

Data Supplement 14. Upsteam Therapy (Section 6.2.2)

Study Name, Author, Year	Study Aim	Study Type/ Size (N)	Intervention vs. Comparator (n)	Patient Population	Endpoints		Comments
					Primary Endpoint & Results	*Secondary Endpoint & Results*	

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ANTIPAF, Goette A, et al., 2012 (206) 22157519	Effect of olmesartan on AF burden in pts with paroxysmal AF and no structural heart disease	Prospective, PC-controlled RCT	Olmesartan 40 mg QD (214) PC (211)	Pts with PAF and no other indication for ACE inhibitor or ARB Tx	No difference in the 1° endpoint of AF burden (p=0.770)	No difference in QOL, time to 1st AF recurrence, time to persistent AF and hospitalizations	In pts with AF (2° prevention) but without structural disease, 1 y of ARB does not appear to decrease AF burden
GISSI-AF, 2009 (207) 20435196	N/A	Prospective, PC-controlled, RCT	Valsartan (722) PC (720)	AF and underlying CV disease, diabetes, or left atrial enlargement	Co-primary endpoints: Time to first recurrence of AF, 295 d valsartan, 271 d PC Proportion of pts who had >1 recurrence of AF>12 mo, 26.9% valsartan, 27.9% PC OR: 0.95; p=0.66	N/A	Tx with valsartan not associated with reduced AF
Healey JS, et al., 2005 (208) 15936615	Systematic review of all RCT evaluating the benefit of trials of ACE inhibitor and ARBs in prevention of AF	Meta-analysis	N/A	11 studies included with 56,308 pts	ACE inhibitor and ARB reduced incidence of AF (RR: 0.28; p=0.0002) Reduction in AF greatest in pts with HF (RR: 0.44; p=0.007) No significant reduction in pts with HTN (RR: 0.12; p=0.4) although 1 study 29% reduction in pts with LVH (RR: 0.29)	N/A	ACE inhibitor and ARBs appear to be effective in prevention of AF probably limited to pts with systolic LV dysfunction or HTN LVH
J-RHYTHM II, Yamashita T, et al., 2011 (208, 209) 21148662	N/A	Open label, RCT	Candesartan Amlodipine	Pts with PAF (2° prevention) and HTN	N/A	N/A	Tx of HTN by candesartan was not superior to amlodipine for reduction in AF frequency
Schneider MP, et al., 2010 (210) 20488299	N/A	Meta-analysis	N/A	23 studies included with 87,048 pts	N/A	N/A	N/A

1° indicates primary; 2°, secondary; ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ANTIPAF, Angiotensin II-Antagonist in Paroxysmal Atrial Fibrillation; ARB, angiotensin-receptor blockers; CV, cardiovascular; GISSI-AF, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Atrial Fibrillation; HF, heart failure; HTN, hypertension; J-RHYTHM, Japanese Rhythm Management Trial for Atrial Fibrillation; LV, left ventricular; LVH, left ventricular hypertrophy; N/A, not applicable; OR, odds ratio; PAF, paroxysmal atrial fibrillation; PC, placebo; pts, patients; QD, once daily; QOL, quality of life; RCT, randomized controlled trial; RR, relative risk; and Tx, therapy.

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Data Supplement 15. AF Catheter Ablation to Maintain Sinus Rhythm (Section 6.3)

Study Name, Author, Year	Study Aim	Study Type/ Size (N)	Intervention vs. Comparator (n)	Type of AF	Ablation Technique	Endpoints	AF Free at 1 y			Crossover Rate to RFA	Adverse Events	Study Limitations
						Primary Endpoint & Results	**Ablation**	**AAD**	**P value**			
Krittayaphong R, et al., 2003 (211) 12866763	To compare the efficacy of amiodarone to RFA for maintenance of SR	RCT (30)	RFA Amiodarone	Paroxysmal and persistent	Circumferential PVI with anatomic isolation	Freedom from AF at 12 mo	79%	40%	0.018	Not stated	1 stroke in RFA arm 46.7% AE in amiodarone arm	Small sample size, single center
RAAFT, Wazni OM, et al., 2005 (212) 15928285	To determine whether PVI is feasible as 1st line Tx for symptomatic AF	RCT (70)	RFA (33) AAD (37)	Paroxysmal	Segmental PVI with electrical isolation	Freedom from AF at 12 mo (Any recurrence of symptomatic AF or asymptomatic AF>15 s) 87% RFA 37% AAD	87%	37%	p<0.001	49%	Pulmonary vein stenosis 2 (6%) in RFA group	N/A
CACAF, Stabile G, et al., 2005 (213) 16214831	Compare RFA to AAD for prevention of AF in pts who failed AAD	RCT (137)	RFA (68) AAD – primarily amiodarone (69)	Paroxysmal and persistent	Circumferential PVI with anatomic isolation	Freedom from AF at 12 mo 55.9% RFA 8.7% AAD p<0.001	56%	9%	p<0.001	57%	4.4% major complications RFA	N/A

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Oral H, et al., 2006 (214) 16908760	Persistent AF Compare RFA to AAD for prevention of AF	RCT (146)	RFA (77) Cardioversion with short-term amiodarone (69)	Persistent	Circumferential PVI with anatomic isolation	Monthly freedom from AF off AAD 74% RFA 58% control (intention to treat) p=0.05 70% RFA 4% control (on-Tx analysis) p<0.001	70% 74%	4% (on-Tx analysis) 58% (intention to treat analysis)	p<0.001 p=0.05	77%	N/A	77% AAD crossed over to RFA
APAF Pappone C, et al., 2006 (128) 14707026	Paroxysmal AF	RCT (198)	RFA (99) AAD (99)	Paroxysmal	Circumferential PVI with anatomic isolation	Freedom from AF at: 12 mo 86% RFA 22% AAD	86%	22%	p<0.001	42%	RFA: 1 TIA, 1 pericardial effusion not requiring drainage AAD: 3 proarrhythmia flecainide, 7 thyroid disfunction amiodarone, 11 sexual dysfunction sotalol	Single center, high crossover rate (42 of 99, 42%)
A4 Jais P, et al., 2008 (215) 19029470	Compare RFA to AAD in paroxysmal AF	RCT (112)	RFA (53) AAD (59)	Paroxysmal	Circumferential PVI with electrical isolation	Freedom from AF at 12 mo	89%	23%	p<0.001	63%	RFA: (155 ablation procedures, 2 tamponade, 2 groin, hematoma) AAD: 1 hyperthyroidism	N/A
Forleo GB, et al., 2009 (216) 19443515	Compare RFA to AAD in pts with	RCT (70)	RFA (35) AAD (35)	Paroxysmal and persistent	Circumferential PVI with electrical	N/A	80%	43%	p=0.001	Not stated	N/A	N/A

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	diabetes				isolation							
Thermocool Wilber DJ, et al., 2010 (217) 20103757	Compare RFA to AAD in paroxysmal AF	RCT (167)	RFA (106) AAD (61)	Paroxysmal	Circumferential PVI with electrical isolation	Freedom from protocol-defined Tx failure (documented symptomatic AF, repeat ablation >80 d after initial, changes in drug regimen post blanking, absence of entrance block)	66%	16%	p<0.001	59%	4.9% RFA 8.8% AAD	Catheter ablation is more effective than medical Tx alone in preventing recurrent Sx of paroxysmal AF in pts who have already failed Tx with 1 AAD
STOP-AF Packer DL, et al., 2013 (218) 23500312	Assess efficacy of cryoballoon catheter ablation to AAD Tx in PAF	RCT (245)	Cryoballoon ablation (163) AAD (flecainide, propafenone, sotalol) (82)	Paroxysmal	Circumferential PVI with electrical isolation	Freedom from CTF (no detected AF, no AF interventions, no use of non-study drugs) 3-mo blanking period 69.9% cryoballoon (57.7% off drug) vs. 7.3% AAD (intention to treat) 60.1% single ablation (n=98)	70%	7.3%	p<0.001	79%	All events: cryoablation 12.3%, AAD 14.6% Procedure event rate 6.3% Phrenic nerve paralysis 11.2% (29) with 86.2% (25) resolved at 12 mo	N/A
RAAFT2 Morillo C, et al., 2014 (219)	Compare RFA to AAD as first-line therapy for pts with AF	RCT (127)	RFA (66) AAD (61)	Paroxysmal (98%%) and Persistent	Circumferential PVI with electrical isolation	AF, atrial flutter, or atrial tachycardia >30 s at 24 months	45%	28%	p=0.02	47%	9% RFA 5% AAD	>20% additional ablation
MANTRA-PAF	Compare	RCT (294)	RFA (146)	Symptomati	Circumferen	Cumulative	13%	19%	p=0.10	36%	RFA group – 1	No difference

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Cosedis Nielsen J, et al., 2012 (220) 23094720	RFA to AAD as 1st-line Tx for pts with AF		AAD (class Ic or class III) (148)	c Paroxysmal AF prior to AAD Tx	tial PVI with voltage abatement	burden of AF Per visit burden at 24 mo Freedom from AF at 24 mo	9% AF burden at 24 mo 85%	18% AF burden at 24 mo71%	p=0.007 p=0.01		death due to procedural stroke and 3 tamponade	in cumulative burden of AF endpoint and no difference in burden at 3, 6, 12 or 18 mo

A4 indicates Catheter Ablation Versus Antiarrhythmic Drugs for Atrial Fibrillation; AAD, antiarrhythmic drug; AE, adverse event; AF, atrial fibrillation; APAF, Ablate and Pace in Atrial Fibrillation; CACAF, Catheter Ablation for the Cure of Atrial Fibrillation; CTF, chronic treatment failure; N/A, not applicable; PAF, paroxysmal atrial fibrillation; Pt, patient; PVI, pulmonary vein isolation; RAAFT, Radiofrequency Ablation for Atrial Fibrillation Trial; RCT, randomized controlled trial; RFA, radiofrequency ablation; RR, relative risk; SR, sinus rhythm; STOP-AF, Sustained Treatment of Paroxysmal Atrial Fibrillation; Sx, symptom; TIA, transient ischemic attack; and Tx, therapy.

Data Supplement 16. Meta-Analyses and Surveys of AF Catheter Ablation (Section 6.3)

Study Name, Author, Year	Study Aim	Study Size (N)	Patient Population	Study Intervention	Endpoints	Follow-Up	Adverse Events
Bonnano C, et al., 2010 (221) 19834326	Systematic review of RCT of RFA vs. AAD	8 studies (844 pts)	N/A	N/A	98 (23.2%) of 421 pts in the Tx group and 324 (76.6%) of 423 pts in the control group had atrial tachyarrhythmia recurrence	N/A	N/A
Calkins H, et al., 2009 (222) 19808490	Systematic review of radiofrequency ablation for AF	63 studies included (8789 pts)	Mean age 55.5 y	N/A	Single-procedure success rate of ablation off AAD Tx was 57% (95% CI: 50% to 64%) Multiple procedure success rate of AAD was 71% (95% CI: 65% to 77%) Multiple procedure success rate on AAD or with unknown AAD usage was 77% (95% CI: 73% to 81%)	Major complication rate 4.9% Stroke/TIA 0.5% Mortality 0.7% Cardiac tamponade 0.8% PV stenosis 1.6% LA/esophageal fistula 0.0%	N/A
Parkash R, et al., 2011 (223) 21332861	Systematic review of RCT to assess optimal technique for RFA of AF	N/A	N/A	N/A	Freedom from AF after a single procedure RFA was found to be favorable in prevention of AF over AADs in either paroxysmal (5 studies, RR: 2.26; 95% CI: 1.74-2.94) or persistent AF (5 studies, RR: 3.20; 95% CI: 1.29-8.41)	Wide-area PVI appeared to offer the most benefit for both paroxysmal (6 studies, RR: 0.78; 95% CI: 0.63-0.97) and persistent AF (3 studies, RR: 0.64; 95% CI: 0.43-0.94)	N/A
Piccini JP, et al., 2009 (224) 20009077	Meta-analysis of all RCTs comparing PVI and medical Tx for the	N/A	N/A	N/A	Freedom from recurrent AF at 12 mo PVI was associated with markedly increased odds of freedom	N/A	Among those randomly assigned to PVI, 17% required a repeat PVI ablation before 12 mo. The

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	maintenance of sinus rhythm				from AF at 12 mo of FU (n=266/344 [77%] vs. n=102/346 [29%]; OR: 9.74; 95% CI: 3.98-23.87)		rate of major complications was 2.6% (n=9/344) in the catheter ablation group

AAD indicates antiarrhythmic drug; AF, atrial fibrillation; ; FU, follow-up; LA, left atrial; N/A, not applicable; OR, odds ratio; pts, patients; PV, pulmonary vein; PVI, pulmonary vein isolation; RCT, randomized controlled trial; RFA, radiofrequency ablation; RR, relative risk; TIA, transient ischemic attack; and Tx, therapy.

Data Supplement 17. Specific Patient Groups (Section 7)

Study	Aim of study	Study Size	Patient Population / Inclusion & Exclusion Criteria	Endpoint(s)	Statistical Analysis Reported	CI and/or P values	OR/HR/RR/ Other	Study Conclusion
Roy D, et al., 2008 (225) 18565859	To investigate maintenance of SR (rhythm control) with ventricular rate control in pts with LVEF≤35% and Sx of CHF, and a Hx of AF	1,376 (682 in rhythm-control group and 694 in rate-control group)	Inclusion criteria: LVEF≤35% (measured by nuclear imaging, echocardiography, or cardiac angiography, with testing performed ≤6 mo before enrollment); Hx of CHF (defined as symptomatic NYHA class II or IV within the previous 6 mo, asymptomatic condition that pt had been hospitalized for HF during the previous 6 mo, or LVEF≤25%; Hx of AF (with EKG documentation), defined as 1 episode lasting for ≥6 h or requiring cardioversion within the previous 6 mo or an episode lasting for ≥10 min within the previous 6 mo and previous electrical cardioversion for AF; and eligibility for long-term Tx in either of the 2 study groups Exclusion criteria: Persistent AF for ≥12 mo, a reversible cause of AF or HF, decompensated HF within 48 h prior to intended randomization, use of AADs for other arrhythmias, 2nd degree or 3rd degree AVB (bradycardia of <50 bpm), Hx of the long-QT syndrome, previous ablation of an AV node, anticipated cardiac transplantation within 6 mo, renal failure requiring dialysis, lack of birth control in women of child-bearing potential, estimated life expectancy of <1 y, and an age <18 y	1° outcome was time to death from CV causes	The 1° outcome, death from CV causes, occurred in 182 pts (27%) in the rhythm-control group and 175 pts (25%) in the rate-control group Death from any cause (32% in the rhythm-control group and 33% in the rate-control group) Ischemic or hemorrhagic stroke 3% and 4%, respectively Worsening HF (defined as HF requiring hospitalization, administration of an IV diuretic, or change in Tx strategy) Composite outcome of death from CV causes, stroke, or worsening HF	None of the 2° outcomes differed significantly between the Tx groups 95% CI: 0.86-1.30; p=0.53 95% CI: 0.80-1.17; p=0.73 95% CI: 0.40-1.35; p=0.32 95% CI: 0.72-1.06; p=0.17 95% CI: 0.77-1.06; p=0.20	HR: 1.06 HR: 0.97 HR: 0.74 HR: 0.87 HR: 0.90	The routine strategy of rhythm control does not reduce the rate of death from CV causes, as compared with a rate-control strategy in pts with AF and CHF

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AFFIRM, Olshansky B, et al., (163) 15063430	To evaluate and compare several drug classes for long-term ventricular rate control	2027	Inclusion criteria: (All criteria must have been met). Episode of AF documented on EKG or rhythm strip within last 6 wk, ≥65 y or <65 y + ≥1 clinical risk factor for stroke (systemic HTN, DM, CHF, TIA, prior cerebral vascular accident, left atrium ≥50 mm by echocardiogram, fractional shortening <25% by echocardiogram (unless paced or LBBB present), or LVEF<0.40 by radionuclide ventriculogram, contrast angiography, or quantitative echocardiography), duration of AF episodes in last 6 mo must total ≥6 h, unless electrical and/or pharmacologic cardioversion was performed prior to 6 h, duration of continuous AF must be <6 mo, unless normal SR can be restored and maintained ≥24 h, in opinion of clinical investigator, pt (based on clinical and laboratory evaluation before randomization) must be eligible for both Tx groups, based on pt Hx, pt must be eligible for ≥2 AADs (or 2 dose levels of amiodarone) and ≥2 rate-controlling drugs Exclusion criteria: Not presented. Based on the judgment that certain therapies are contraindicated or inclusion would confound the result. Criteria included cardiac, other medical, and nonmedical	Overall rate control with various drugs (average FU 3.5±1.3 y)	Overall rate control was met in 70% of pts given beta blockers as the 1st drug (with or without digoxin), vs. 54% with CCBs (with or without digoxin), and 58% with digoxin alone Multivariate analysis revealed a significant association between 1st drug class and several clinical variables, including gender, Hx of CAD, pulmonary disease, CHF, HTN, qualifying episode being the 1st episode of AF, and baseline heart rate	N/A	N/A	In pts with AF, rate control is possible in the majority of pts. In the AFFIRM FU study, beta blockers were most effective. The authors noted frequent medication changes and drug combinations were needed

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ANDROME DA, Kober L, et al., 2008 (171) 18565860	To evaluate the efficacy of dronedarone in reducing hospitalization due to CHF in pts with symptomatic HF	627	Inclusion criteria: Pts ≥18 y hospitalized with new or worsening HF and who had ≥1 episode of SOB on minimal exertion or at rest (NYHA III or IV) or paroxysmal nocturnal dyspnea within the month before admission Exclusion criteria: LV wall motion index of >1.2 (approximating an EF of >35%), acute MI within 7 d prior to screening, a heart rate <50 bpm, PR interval >0.28 s, sinoatrial block or 2nd or 3rd degree AV block not treated with a pacemaker, Hx of Torsades de pointes, corrected QT interval >500 ms, a serum potassium level <3.5 mmol/L, use of class I or III AADs, drugs known to cause Torsades de pointes, or potent inhibitors of the P450 CYP3A4 cytochrome system, other serious disease, acute myocarditis, constrictive pericarditis, planned or recent (within the preceding mo) cardiac surgery or angioplasty, clinically significant obstructive heart disease, acute pulmonary edema within 12 h before randomization, pregnancy or lactation, expected poor compliance, or participation in another clinical trial	The 1° endpoint was the composite of death from any cause or hospitalization for HF	After inclusion of 627 pts, the trial was prematurely terminated for safety reasons. A median FU of 2-mo death occurred in 8.1% of dronedarone group and 3.8% of PC group After additional 6 mo, 42 pts in dronedarone group (13.5%) and 39 pts in PC group (12.3%) died The 1° endpoint did not differ significantly between the 2 groups; there were 53 events in the dronedarone group (17.1%) and 40 events in the PC group (12.6%)	p=0.03; 95% CI: 1.07-4.25 p=0.60; 95% CI: 0.73-1.74 p=0.12; 95% CI: 0.92-2.09	HR: 2.13 HR: 1.13 HR: 1.38	Dronedarone increased early mortality in pts recently hospitalized with symptomatic HF and depressed LV function. 96% of deaths were attributed to CV causes, predominantly progressive HF and arrhythmias

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RACE II Van Gelder IC, et al., 2010 (167) 20231232	To investigate if lenient rate control is not inferior to strict control for preventing CV morbidity and mortality in pts with permanent AF	614	Inclusion criteria: Permanent AF up to 12 mo, age ≤80 y, mean resting heart rate >80 bpm, and current use of oral anticoagulation Tx (or ASA, if no risk factors for thromboembolic complications present) Exclusion Criteria: Paroxysmal AF; contraindications for either strict or lenient rate control (e.g., previous adverse effects on negative chronotrophic drugs); unstable HF defined as NYHA IV HF or HF necessitating hospital admission <3 mo before inclusion; cardiac surgery <3 mo; any stroke; current or foreseen pacemaker, ICD, and/or cardiac resynchronization Tx; signs of sick sinus syndrome or AV conduction disturbances (i.e., symptomatic bradycardia or asystole >3 s or escape rate <40 bpm in awake Sx-free pts; untreated hyperthyroidism or <3 mo euthyroidism; inability to walk or bike	Composite of death from CV causes, hospitalization for HF, and stroke, SE, bleeding and life-threatening arrhythmic events. FU duration 2 y, with a maximum of 3 y	1° outcome incidence at 3 y was 12.9% in the lenient-control group and 14.9% in the strict-control group. Absolute difference with respect to the lenient-control group of -2.0 percentage points More pts in the lenient-control group met the heart rate target or targets (304 [97.7%] vs. 203 [67.0%] in the strict-control group) Frequencies of Sx and AEs were similar in the 2 groups	Absolute risk difference, -2.0% Absolute risk difference, CI: -7.6-3.5; p<0.001 90% CI: 0.58-1.21; p=0.001 p<0.001	HR: 0.84	Lenient rate control is as effective as strict rate control and easier to achieve in pts with permanent AF
Gaita F, et al., 2007 (226) 17531584	Assess usefulness and safety of transcatheter ablation of AF in pts with HCM	26	Pts with HCM with paroxysmal (n=13) or permanent (n=13) AF refractory to antiarrhythmic Tx Characteristics: age 58±11 y, time from AF onset 7.3±6.2 y, left atrial volume 170±48 mL, 19±10 mo clinical FU	Pulmonary vein isolation at RFCA plus linear lesions	64% overall success rate 10 of these 16 success pts were off AAD Tx at final evaluation 77% success rate in PAF compared with 50% in the subgroup with permanent AF	NYHA FC in those achieving NSR 1.2±0.5 vs. 1.7±0.7 before the procedure, p=0.003	N/A	RFCA proved a safe and effective therapeutic option for AF, improved functional status, and was able to reduce or postpone the need for long-term pharmacologic Tx

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Kilicaslan F, et al., 2006 (227) 16500298	The purpose of this study was to report the results and outcome of PV antrum isolation in pts with AF and HOCM	27	27 pts with AF and HOCM who underwent PV antrum isolation between February 2002 and May 2004 Mean age 55±10 y Mean AF duration was 5.4±3.6 y AF was paroxysmal in 14 (52%), persistent in 9 (33%), and permanent in 4 (15%) Mean FU of 341±237 d	Maintenance of sinus rhythm after PV antrum isolation	13 pts (48%) had AF recurrence 5 of the 13 with recurrence maintained sinus rhythm with AADs, 1 of 13 remained in persistent AF, 7 of 13 underwent a second PV antrum isolation. After 2nd ablation: 5 pts remained in SR Final success rate=70% (19/27) 2 pts had recurrence after 2nd ablation; 1 maintained SR with AADs and 1 remained in persistent AF	N/A	N/A	AF recurrence after the 1st PV antrum isolation is higher in pts with HOCM. However, after repeated ablation procedures, long-term cure can be achieved in a sizable number of pts. PV antrum isolation is a feasible therapeutic option in pts with AF and HOCM
Bunch TJ, et al., 2008 (228) 18479329	Assess efficacy of RFCA for drug-refractory AF in HCM	32	Consecutive pts (25 male, age 51±11 y) with HCM underwent PV isolation (n=8) or wide area circumferential ablation with additional linear ablation (=25) for drug-refractory AF Paroxysmal AF=21 (64%) pts had paroxysmal AF Persistent/permanent AF=12 (36%) had persistent/permanent AF Duration AF=6.2±5.2 y Average EF=0.63±0.12 Average left atrial volume index was 70±24 mL/m^2 FU of 1.5±1.2 y	Survival with AF elimination and AF control	N/A	1-y survival with AF elimination was 62% (95% CI: 0.66-0.84) and with AF control was 75% (95% CI: 0.66-0.84)	N/A	AF control was less likely in pts with a persistent/chronic AF, larger left atrial volumes, and more advanced diastolic disease. Additional linear ablation may improve outcomes in pts with severe left atrial enlargement and more advanced diastolic dysfunction. 2 pts had a periprocedureal TIA, 1 PV stenosis, and 1 died after mitral valve replacement from prosthetic valve thrombosis. QOL scores improved from baseline at 3 and 12 mo

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Di Donna P, et al., 2010 (229) 20173211	Assess the outcome of a multicentre HCM cohort following RFCA for symptomatic AF refractory to medical Tx	61	Age 54±13 y; Time from AF onset 5.7±5.5 y Paroxysmal AF=35; (57%) Recent persistent AF=15; (25%) Long-standing persistent AF=11; (18%) Ablation scheme: pulmonary vein isolation plus linear lesions 32 of 61 pts, 32 (52%) required redo procedures. Antiarrhythmic Tx was maintained in 22 (54%) FU: 29±16 mo 41 (67%) NSR at FU	N/A	In pts in NSR there was marked improvement in NYHA class (1.2±0.5 vs. 1.9±0.7 at baseline; p<0.001). In pts (33%), with AF recurrence, there was less marked, but still significant, improvement following RFCA (NYHA class 1.8±0.7 vs. 2.3±0.7 at baseline; p=0.002)	Independent predictors of AF recurrence: increased left atrium volume HR per unit increase 1.009, 95% CI: 1.001-1.018; p=0.037, and NYHA class (HR: 2.24; 95% CI: 1.16 to 4.35; p=0.016)	N/A	RFCA was successful in restoring long-term sinus rhythm and improving symptomatic status in most HCM pts with refractory AF, including the subset with proven sarcomere gene mutations, although redo procedures were often necessary. Younger HCM pts with small atrial size and mild Sx proved to be the best RFCA candidates, likely due to lesser degrees of atrial remodelling

1° indicates primary; 2, secondary; AAD, antiarrhythmic drug; AE, adverse event; AF, atrial fibrillation; AFFIRM, Atrial Fibrillation Follow-up Investigation of Rhythm Management; ANDROMEDA, European Trial of Dronedarone in Moderate to Severe Congestive Heart Failure; ASA, aspirin; AV, atrioventricular; AVB, atrioventricular block; CAD, coronary artery disease; CCB, calcium channel blocker; CHF, congestive heart failure; CV, cardiovascular; DM, diabetes mellitus; EF, ejection fraction; EKG, electrocardiogram; FU, follow up; HCM, hypertrophic cardiomyopathy; HF, heart failure; HOCM, hypertrophic obstructive cardiomyopathy; HR, hazard ratio; HTN, hypertension; Hx, history; ICD, implantable cardioverter defibrillator; IV, intravenous; LBBB, left bundle branch block; LV, left ventricular; LVEF, left ventricular ejection fraction; N/A, not applicable; NSR, normal sinus rhythm; NYHA, New York Heart Association; pts, patients; PV, pulmonary vein; QOL, quality of life; RACE, Rate Control Efficacy in Permanent Atrial Fibrillation; RFCA, radio frequency catheter ablation; RR, relative risk; SOB, shortness of breath; SR, sinus rhythm; Sx, symptom; TIA, transient ischemic attack; and Tx, therapy.

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Correction

In the article by January et al "2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society, which published online March 28, 2014, several corrections were needed. (*Circulation*. doi: 10.1161/CIR.0000000000000041).

1. On page 34, first paragraph under Section 4.2.2.2 "Newer Oral Anticoagulants," the first sentence read, "Dabigatran was the first new oral anticoagulant approved by the U.S. Food and Drug Administration (FDA) for prevention of stroke in patients with AF and is a direct thrombin inhibitor." It has been changed to read, "Dabigatran is the first new oral anticoagulant approved by the U.S. Food and Drug Administration (FDA) to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF, and is a direct thrombin inhibitor."
2. On page 35, last paragraph, the first and second sentences read, "**Rivaroxaban** is the second new oral anticoagulant approved by the FDA and is a direct factor Xa inhibitor (Figure 4). It can be administered as a single daily dose with a large meal to ensure adequate absorption." It has been changed to read, "**Rivaroxaban** is the second new oral anticoagulant approved by the FDA for reduction of risk of stroke and systemic embolism in patients with nonvalvular AF and is a direct factor Xa inhibitor (Figure 4). It should be administered as a single daily dose with the evening meal to ensure adequate absorption."
3. On page 36, second paragraph, the first sentence read, "**Apixaban** is the third new oral anticoagulant approved by the FDA and is another direct factor Xa inhibitor (Figure 4)." It has been changed to read, "**Apixaban** is the third new oral anticoagulant approved by the FDA for reduction of risk of stroke and systemic embolism with nonvalvular AF and is another direct factor Xa inhibitor (Figure 4)."
4. On page 38, in Table 8, row 2, column 4 "Rivaroxaban," the text read, "20 mg HS." It has been changed to read, "20 mg QD with the evening meal".
5. On page 38, in Table 8, row 3, column 4 "Rivaroxaban," the text read, "15 mg HS." It has been changed to read, "15 mg QD with the evening meal."
6. On page 38, in Table 8, row 4 column 4 "Rivaroxaban," the text read, "15 mg HS." It has been changed to read, "15 mg QD with the evening meal."
7. On page 39, in the Table 8 footnote, the abbreviations paragraph read, "...creatinine clearance; HS, once daily in evening with food; and INR, international normalized ratio." It has been changed to read, "...creatinine clearance; INR, international normalized ratio; and QD, once daily."

(*Circulation*. 2014;129:00-00.)
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