HEALTH EVIDENCE REVIEW COMMISSION (HERC)

COVERAGE GUIDANCE: CAROTID ENDARTERECTOMY VS. MEDICAL MANAGEMENT AND SCREENING FOR CAROTID ARTERY STENOSIS

HERC Approved 12/5/2013; reaffirmed 1/14/2016

As a part of the coverage guidance monitoring process, HERC decided (see Appendix F) on 1/14/2016 to reaffirm the existing coverage guidance and reconsider the need to update the topic during the regular two-year review cycle.

HERC COVERAGE GUIDANCE

Carotid endarterectomy is recommended for coverage for patients who are symptomatic (recent transient ischemic attack or ischemic stroke) and who have 70-99% carotid stenosis without near-occlusion (*strong recommendation*).

For patients with 50 – 69% carotid stenosis who are symptomatic despite optimal medical management, carotid endarterectomy is recommended for coverage (*weak recommendation*).

Carotid endarterectomy is not recommended for coverage for symptomatic patients with less than 50% carotid stenosis (*strong recommendation*).

Carotid endarterectomy is recommended for coverage for patients with asymptomatic carotid stenosis of at least 60% only for those who do not tolerate (or have contraindications to) best current medical therapy (*weak recommendation*).

Screening for asymptomatic carotid artery stenosis in the general primary care population is not recommended (*strong 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.

EVIDENCE SOURCES

Chambers B.R., & Donnan, G. (2005). Carotid endarterectomy for asymptomatic carotid stenosis. *Cochrane Database of Systematic Reviews*, Issue 4. Art. No.: CD001923. DOI: 10.1002/14651858.CD001923.pub2. Retrieved July 23, 2012, from http://summaries.cochrane.org/CD001923/carotid-endarterectomy-for-asymptomatic-carotid-stenosis

> ***Publication status and date:*** *Edited (no change to conclusions), published in Issue 4, 2008.*

Grant, E.G., Benson, C.B., Moneta, G.L., Alexandrov, A.V., Baker, J.D., Bluth, E.I., et al. (2003). Carotid artery stenosis: Gray-scale and Doppler US diagnosis – Society of Radiologists in Ultrasound Consensus Conference. *Radiology, 229*(2), 340-346.

Rerkasem, K., & Rothwell, P.M. (2011). Carotid endarterectomy for symptomatic carotid stenosis. *Cochrane Database of Systematic Reviews*, Issue 4. Art. No.: CD001081. DOI: 10.1002/14651858.CD001081.pub2. Retrieved July 23, 2012, from http://summaries.cochrane.org/CD001081/carotid-endarterectomy-for-symptomatic-carotid-stenosis

U.S. Preventive Services Task Force. (2007). Screening for carotid artery stenosis: U.S. Preventive Services Task Force recommendation statement. *Annals of Internal Medicine*, *147*(12), 854-859.

Raman, G., Moorthy, D., Nadar, N, Dahabreh, I., O'Donnell, T., Thaler, D., et al. (2013). Management Strategies for Asymptomatic Carotid Stenosis. *Annals of Internal Medicine, 158*(9), 676-685.

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

SUMMARY OF EVIDENCE

Clinical Background

Stroke is the third leading cause of death and probably the most important cause of long-term disability. The case fatality rate is between 15% and 35% with the first attack and rises to 65% for subsequent strokes. The majority of recurrences occur within one year and in the same anatomic region as the first stroke. Eighty-five percent of strokes are ischemic. Carotid endarterectomy was introduced in the 1950s and increasing numbers of patients have undergone this procedure over the last three decades.

There have been five randomized controlled trials of endarterectomy in patients with a recent symptomatic carotid stenosis. The first two studies were small, performed over 30 years ago, included a high proportion of patients with non-carotid symptoms and did not stratify results by severity of stenosis. In 1991, the Veterans Affairs trial (VACSP) reported a non-significant trend in favor of surgery but this trial was stopped early when the two largest trials, the European Carotid Surgery Trial (ECST) and the North American Symptomatic Carotid Endarterectomy Trial (NASCET) reported their initial results. The final reports for ECST and NASCET were published in 1998. The European Carotid Surgery Trial reported benefit from surgery only in patients with 80% to 99% stenosis, and further limited this to 90% to 99% stenosis in women. In contrast, NASCET reported significant benefit from surgery in patients with 50% to 99% stenosis. In the previous version of this review, an attempt was made to reconcile and pool these apparently conflicting results. However, the differences between the trial results were partly due to differences in the methods of measurement of the degree of carotid stenosis on the pre-randomization catheter angiograms; the method used in ECST producing higher values than the method used in the NASCET and VACSP trials. There were also other differences, such as in the definitions of outcome events. Only by detailed re-analysis of the individual patient data and reassessment of the original angiograms can the results be properly compared or combined. In this version of the review, we have also included a pooled analysis of individual patient data from the three largest trials, in which the original angiograms were reassessed and analyses done using the same method of measurement of stenosis and the same definitions of outcomes. Neither the ECST nor the NASCET were powered to determine the effect of surgery in subgroups. Subgroup analyses of pooled individual patient data from these two trials have greater power to determine subgroup-treatment interaction reliably and therefore several such clinically important analyses have been added in this review.

Evidence Review

The three trials noted above (NASCET, VACSP and ECST) were included in this review. As the trials differed in the methods of measurement of carotid stenosis and in

the definition of stroke, a pooled analysis of individual patient data on 6092 patients (35,000 patient years of follow-up) from all three trials was completed after reassessment of the carotid angiograms and redefinition of outcomes when needed.

Presently, up to 80% of all carotid endarterectomies are performed based on the findings of Doppler ultrasound (US). To assist with the translation of US findings to angiographically defined stenosis, a chart is included in Appendix D that correlates various characteristics of the US test to degree of stenosis.

Inclusion criteria were similar for all three trials, with minor differences. All patients were symptomatic (i.e., had recent (within the last four to six months) TIA or minor ischemic stroke in the territory of the artery that was stenotic). The control group was best medical therapy, which included aspirin (79-83%), lipid-lowering medications (8-16%), antihypertensives (60%) and other antithrombotics. The exact surgical intervention was left to the discretion of the surgeon, but all surgeries were classified as endarterectomy. There were no imbalances in baseline characteristics between surgical and medical groups in the original trials.

Crossovers (patients who were randomized to one group but elected the alternate therapy) were similar for patients randomized to surgical therapy who chose medical therapy instead (0 to 3.4%) but significantly different for medical to surgical crossovers, with 22.8% of patients in the NASCET crossing over to surgery, compared to 9.2% to 9.8% in the other two trials. However, the average time to cross over to the surgical treatment was over 500 days in the two largest trials.

On re-analysis, there were no statistically significant differences between the trials in the risks of any of the main outcomes (operative risk of stroke, stroke morbidity and death) in any of the stenosis groups for either treatment group. There were likewise no statistically significant differences between trials in the effects of surgery on the relative risks of the main outcomes at five year follow up. Therefore, further analyses were performed on pooled data.

For the purposes of analysis, patients were stratified based on the degree of carotid stenosis (< 30%, 30% to 49%, 50% to 69%, 70% to 99%, near occlusion). Sub-group analysis was undertaken based on gender, age (<65, 65-74, ≥ 75) and time from most recent event to randomization (<2 weeks, 2-4 weeks, 4 to 12 weeks or > 12 weeks), type of primary event (ocular, cerebral TIA, stroke), presence of diabetes, irregular or ulcerated carotid plaque and contralateral occlusion. All of these factors had a significant effect on the risk of ipsilateral stroke in the medical group with the exception of contralateral occlusion. Male gender, older age, decreased time from ischemic event, presence of diabetes or an ulcerated plaque and those presenting with cerebral (non ocular) events all had a higher risk.

Surgery increased the five-year risk of ipsilateral ischemic stroke in patients with less than 30% stenosis (N = 1746, absolute risk reduction (ARR) -2.2%, P = 0.05), had no significant effect in patients with 30% to 49% stenosis (N = 1429, ARR 3.2%, P = 0.6), was of marginal benefit in patients with 50% to 69% stenosis (N = 1549, ARR 4.6%, P = 0.04), and was highly beneficial in patients with 70% to 99% stenosis without near-occlusion (N = 1095, ARR 16.0%, P < 0.001). However, there was no evidence of benefit (N = 262, ARR -1.7%, P = 0.9) in patients with near-occlusions (defined as > 95% stenosis). The authors note that it is possible that intention to treat analysis may have underestimated the benefit of surgery in this group because of the relatively high rate of endarterectomy in follow up in the medical treatment group. However, the rate of endarterectomy was similarly high in the 70% to 99% stenosis group, and significant benefit with surgery was seen, making this explanation less likely.

Three of the prespecified subgroup analyses showed statistically significant differences. Benefit from surgery was greatest in men (no statistically significant benefit in women) and patients aged 75 years or over, although all age categories showed some benefit from surgery. Patients who were randomized within two weeks after their last ischemic event showed the greatest benefit from surgery, and there was decreasing benefit with increasing delay, with no benefit evident if the last ischemic event was more than 12 weeks previous. Overall, there was a 7% operative risk of death or any stroke within 30 days.

[Evidence Source]

Asymptomatic Patients – Surgery

A Cochrane review last updated in 2008 evaluated carotid endarterectomy (CEA) in asymptomatic patients. Three trials with a total of 5223 patients were included. In these trials, the overall net excess of operation-related perioperative stroke or death was 2.9%. For the primary outcome of perioperative stroke or death or any subsequent stroke, patients undergoing CEA fared better than those treated medically (relative risk (RR) = 0.69, 95% confidence interval (CI) 0.57 – 0.83). Similarly, for the outcome of perioperative stroke or death or subsequent ipsilateral stroke, there was benefit for the surgical group (RR = 0.71, 95% CI 0.55 – 0.90). For the outcome of any stroke or death, there was a non-significant trend towards fewer events in the surgical group (RR = 0.92, 95% CI 0.83 – 1.02). Subgroup analyses were performed for the outcome of perioperative stroke or death or subsequent carotid stroke. CEA appeared more beneficial in men than in women and more beneficial in younger patients than in older patients although the data for age effect were inconclusive. There was no statistically significant difference between the treatment effect estimates in patients with different

grades of stenosis but the data were insufficient. Patients were randomized to surgery only if they had stenosis of 60% to 99% in two trials, or 50% to 99% in the other trial.

A technology assessment commissioned by the Agency for Healthcare Research and Quality addressed management strategies for asymptomatic carotid stenosis and was completed in 2013 (Raman 2013). This review included the same three RCTs comparing CEA to medical management as were included in the Cochrane review discussed above, as well as eight additional non-randomized studies. In addition, 26 cohort studies were included that evaluated the efficacy of medical therapy alone for asymptomatic carotid stenosis. Authors note that all patients in the RCTs were recruited before 2000 and did not receive what is currently considered best available medical therapy (primarily, statins). Meta-analysis of the three RCTs for the outcome of ipsilateral stroke found a lower risk in the CEA group (RR = 0.72 (95% CI 0.58, 0.90)[1] in long-term follow up (range of 2.7 to 10 years), although the periprocedural risk of any stroke was increased in the CEA group [RR = 5.94 (95% CI 2.06, 17.12)], as was death [RR 3.68 (95% CI 0.77, 17.72)]. There was no significant difference in the risk of any stroke or death, or death, between groups in long-term follow up.

Meta-analysis of the 26 cohort studies found an ipsilateral stroke incidence rate of 1.68% per year of follow up, and meta-regression showed that incidence was significantly lower in studies that completed recruitment between 2000 and 2010 than in those who completed recruiting prior to 2000 (1.13% vs. 2.38% per year, respectively). The authors conclude that “evidence from comparisons of CEA plus medical therapy versus medical therapy alone showed a reduction in the risk for ipsilateral stroke or any stroke with the combined approach. However, RCTs comparing CEA plus medical therapy with medical therapy alone recruited participants from the 1990s through early 2000. Medical therapy was suboptimal in these older RCTs by current standards, and findings of the RCTs may not be applicable to contemporary clinical practice.”

<u>Asymptomatic Patients - Screening</u>

The US Preventive Services Task Force issued recommendations pertaining to screening asymptomatic patients for carotid artery stenosis (CAS) in 2007. They concluded the following: The USPSTF recommends against screening for asymptomatic CAS in the general adult population. This is a grade D recommendation[2].

Benefits of Detection and Early Intervention

[1] While not presented in the publication, absolute risk reduction could be calculated, and was 1.92%, with a number needed to treat of 52.

[2] A description of the USPSTF grades can be found in Appendix C.

Good evidence indicates that in selected, high-risk trial participants with asymptomatic severe CAS, carotid endarterectomy by selected surgeons reduces the 5-year absolute incidence of all strokes or perioperative death by approximately 5%. These benefits would be less among asymptomatic people in the general population. For the general primary care population, the benefits are judged to be no greater than small**.**

The task force reached their conclusions regarding the benefits of early detection based on two of the three trials included in the reviews discussed above. They note important limitations in this evidence, including that the medical treatment group was poorly defined and did not include treatments now considered to be optimal medical management.

Harms of Detection and Early Intervention
Good evidence indicates that both the testing strategy and the treatment with carotid endarterectomy can cause harms. A testing strategy that includes angiography will itself cause some strokes. A testing strategy that does not include angiography will cause some strokes by leading to carotid endarterectomy in people who do not have severe CAS. In excellent centers, carotid endarterectomy is associated with a 30-day stroke or mortality rate of about 3%; some areas have higher rates. These harms are judged to be no less than small.

USPSTF Assessment
The USPSTF concludes that, for individuals with asymptomatic CAS, there is moderate certainty that the benefits of screening do not outweigh the harms.

[Evidence Source]

Evidence Summary

Endarterectomy is of some benefit for 50% to 69% symptomatic stenosis and highly beneficial for 70% to 99% stenosis without near occlusion. Benefit in patients with carotid near-occlusion is uncertain. These results are generalizable only to surgically-fit patients operated on by surgeons with low complication rates (less than 7% risk of stroke and death). Benefit from endarterectomy depends not only on the degree of carotid stenosis, but also on several other factors, including the delay to surgery after the presenting event. The benefit in asymptomatic patients cannot be determined since trials were conducted before current best medical therapy was available.. The benefits of screening asymptomatic individuals do not outweigh the harms.

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	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Values and preferences	Coverage Recommendation
Carotid endarterectomy in symptomatic patients	Harms exceed benefits in stenosis < 30%, No benefit in stenosis ≥ 30% but < 50%, Small benefit exceeds harms in stenosis ≥ 50% but < 70%, and Substantial benefit in stenosis ≥ 70%	High	Less costly when benefit exceeds harm, more costly when harm exceeds benefit	Limited variability; most patients would opt for surgery when benefits exceed harms Moderate variability when stenosis ≥ 50% but < 70%	Carotid endarterectomy is recommended for coverage in symptomatic patients with 70-99% carotid stenosis without near-occlusion *Strong Recommendation* For patients with 50 – 69% carotid stenosis who are symptomatic (recent transient ischemic attack or ischemic stroke) despite optimal medical management, carotid endarterectomy is recommended for coverage. *Weak Recommendation* Carotid endarterectomy is not recommended for coverage for symptomatic patients with less than 50% carotid stenosis *Strong Recommendation*
Carotid	Unclear whether benefit exceeds	Moderate	Less costly	Moderate	Carotid endarterectomy is

Indication	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Values and preferences	Coverage Recommendation
endarterectomy in asymptomatic patients	harms for stenosis > 60% when compared to current best medical therapy	compared to prior medical therapy, insufficient compared to current best medical therapy	when benefit exceeds harm, more costly when harm exceeds benefit	variability, given lack of clear evidence of benefit	recommended for coverage for patients with asymptomatic carotid stenosis of at least 60% only for those who do not tolerate (or have contraindications to) best current medical therapy (*weak recommendation*).
Population screening for carotid stenosis	Benefits do not exceed harms	Moderate	Moderate costs	Moderate variability; some patients would prefer screening, others would not	Screening for asymptomatic carotid artery stenosis in the general primary care population is not recommended for coverage *Strong Recommendation*

Note: GRADE framework elements are described in Appendix A

POLICY LANDSCAPE

Four quality measures were identified when searching the National Quality Measures Clearinghouse. Two are measures developed by the Agency for Healthcare Research and Quality (AHRQ), one is developed by the National Committee on Quality Assurance (NCQA) and one is from an Australian entity. None are National Quality Forum endorsed. The first three are listed below:

- AHRQ: Carotid endarterectomy volume: number of carotid endarectomy discharges per hospital
- AHRQ: Carotid endartertomy mortality rate: number of deaths per total number of carotid endarterectomy discharges
- NCQA: Frequency of selected procedures - carotid endartectomy: number of carotid endarterectomy procedures per member month, per measurement year

COMMITTEE DELIBERATIONS – HTAS

HTAS confirmed a "weak recommendation" for symptomatic patients with 50-69% stenosis based on the evidence and expert opinion, consistent with the following GRADE definition: the subcommittee concludes that the desirable effects probably outweigh the undesirable effects, but is not confident.

Based on expert input, the subcommittee also elected to add Appendix D, which includes a guide for converting Doppler Ultrasound readings to various levels of stenosis, since Doppler ultrasound is the preferred diagnostic tool in current practice.

The subcommittee elected not to define indications for screening for carotid artery stenosis, as there was no trusted evidence source which adequately defined populations for whom the screening would be appropriate.

After discussion, the subcommittee elected not to define coverage criteria for asymptomatic patients with 50-69% stenosis.

COMMITTEE DELIBERATIONS – VBBS

VbBS discussed the role of screening versus diagnostic examinations. It was clarified that the USPSTF recommendation against screening in the general population applied to “adults without neurological symptoms and without a history of transient ischemic attacks (TIA) or stroke.” Given this, it was felt to be appropriate to include a screening guideline. VbBS proposed two guideline notes (for carotid artery stenosis screening and carotid endarterectomy) for the Prioritized List based on the HTAS recommendations.

HERC DELIBERATIONS

At its meeting 10/10/2013, the HERC reviewed the draft coverage guidance and requested that staff review additional evidence which provided information in the context of medical therapies which became available after the studies in the core source reports. 12/5/2013, the HERC reviewed a revised draft coverage guidance including this information and revised recommendations to encourage the use of medications over surgery where appropriate. The revised guidance recommends coverage for asymptomatic patients with 60 percent stenosis whose condition cannot appropriately be managed with medications.

During the 12/5/2013 meeting, the commission discussed whether a definition of near occlusion should be added to the coverage guidance. After discussion, the commission decided that Appendix D and the coverage guidance language provide the appropriate information. The HERC approved the revised recommendations as presented in the meeting materials and asked staff to make conforming changes to the GRADE-informed framework.

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.

Appendix B. Applicable Codes

CODES	DESCRIPTION
ICD-9 Diagnosis Codes	
433.1	Occlusion and stenosis of precerebral arteries; carotid
ICD-9 Volume 3 (Procedure Codes)	
38.02	Incision of vessel (embolectomy/ thrombectomy); other vessels of head and neck
38.12	Endarterectomy; other vessels of head and neck
CPT Codes	
35301	Thromboendarterectomy; carotid, vertebral, subclavian, by neck incision
93880	Duplex scan of extracranial arteries; complete bilateral study
HCPCS Level II Codes	
None	

Note: Inclusion on this list does not guarantee coverage

Appendix C. What the U.S. Preventive Services Task Force Grades Mean and Suggestions for Practice

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer/provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer/provide this service.
C	C The USPSTF recommends against routinely providing the service. There may be considerations that support providing the service in an individual patient. There is moderate or high certainty that the net benefit is small.	Offer/provide this service only if other considerations support offering or providing the service in an individual patient.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the clinical considerations section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

Appendix D. Supplemental Information for Quantification of Stenosis Based on Doppler Ultrasound

Consensus Panel Gray-Scale and Doppler US Criteria for Diagnosis of ICA Stenosis

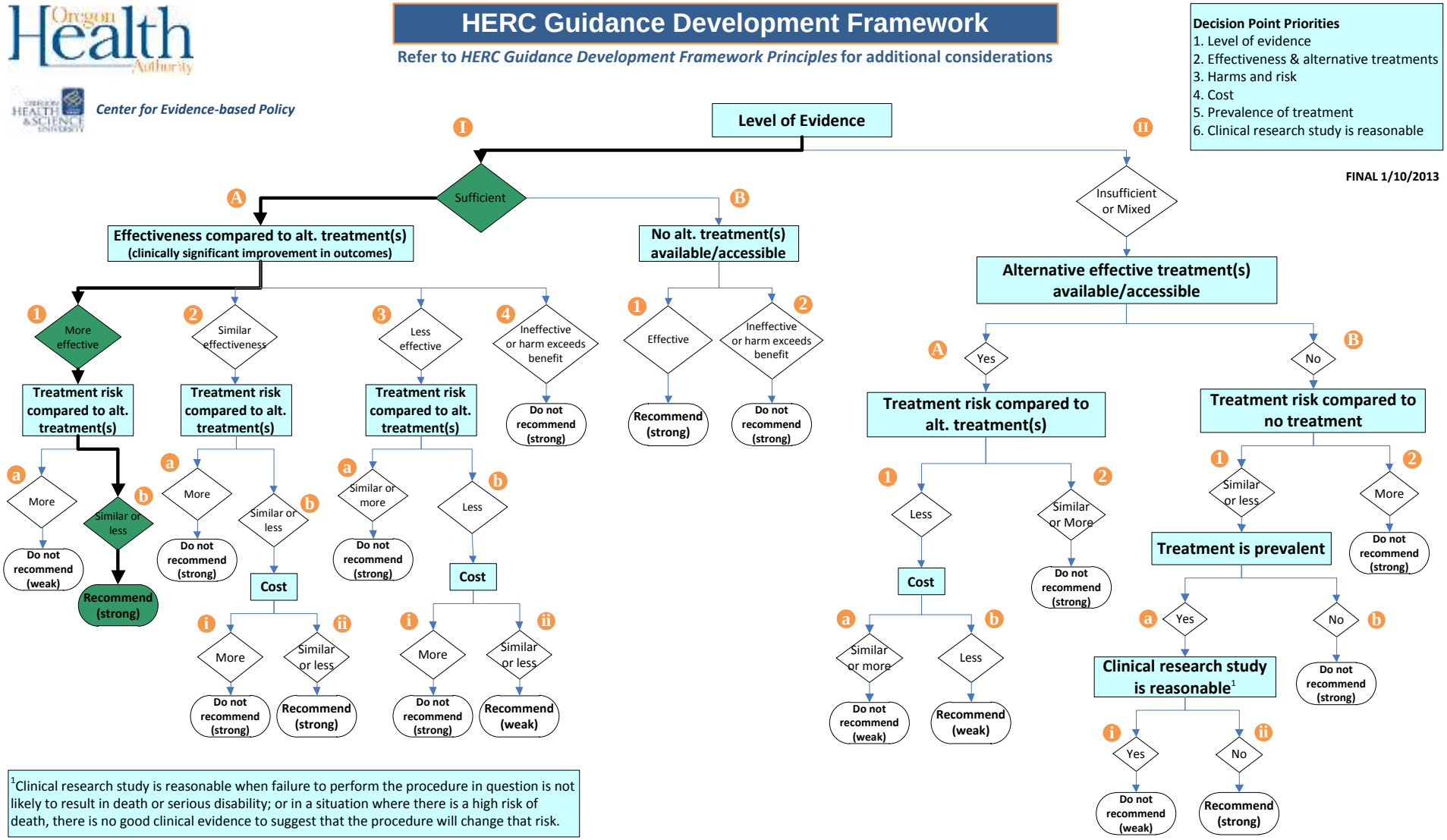
	Primary Parameters		Additional Parameters	
Degree of Stenosis (%)	**ICA PSV (cm/sec)**	**Plaque Estimate (%)***	**ICA/CCA PSV Ratio**	**ICA EDV (cm/sec)**
Normal	<125	None	<2.0	<40
<50	<125	<50	<2.0	<40
50-69	125-230	≥50	2.0-4.0	40-100
≥70 but less than near occlusion	>230	≥50	>4.0	>100
Near occlusion	High, low or undetectable	Visible	Variable	Variable
Total occlusion	Undetectable	Visible, no detectable lumen	Not applicable	Not applicable

*Plaque estimate (diameter reduction) using gray-scale and color Doppler US; ICA=internal carotid artery; CCA=common carotid artery; PSV=peak systolic velocity; EDV=end diastolic velocity

Extracted from Grant, E.G., Benson, C.B., Moneta, G.L., Alexandrov, A.V., Baker, J.D., Bluth, E.I., et al. (2003). Carotid artery stenosis: Gray-scale and Doppler US diagnosis – Society of Radiologists in Ultrasound Consensus Conference. *Radiology, 229*(2), 340-346.

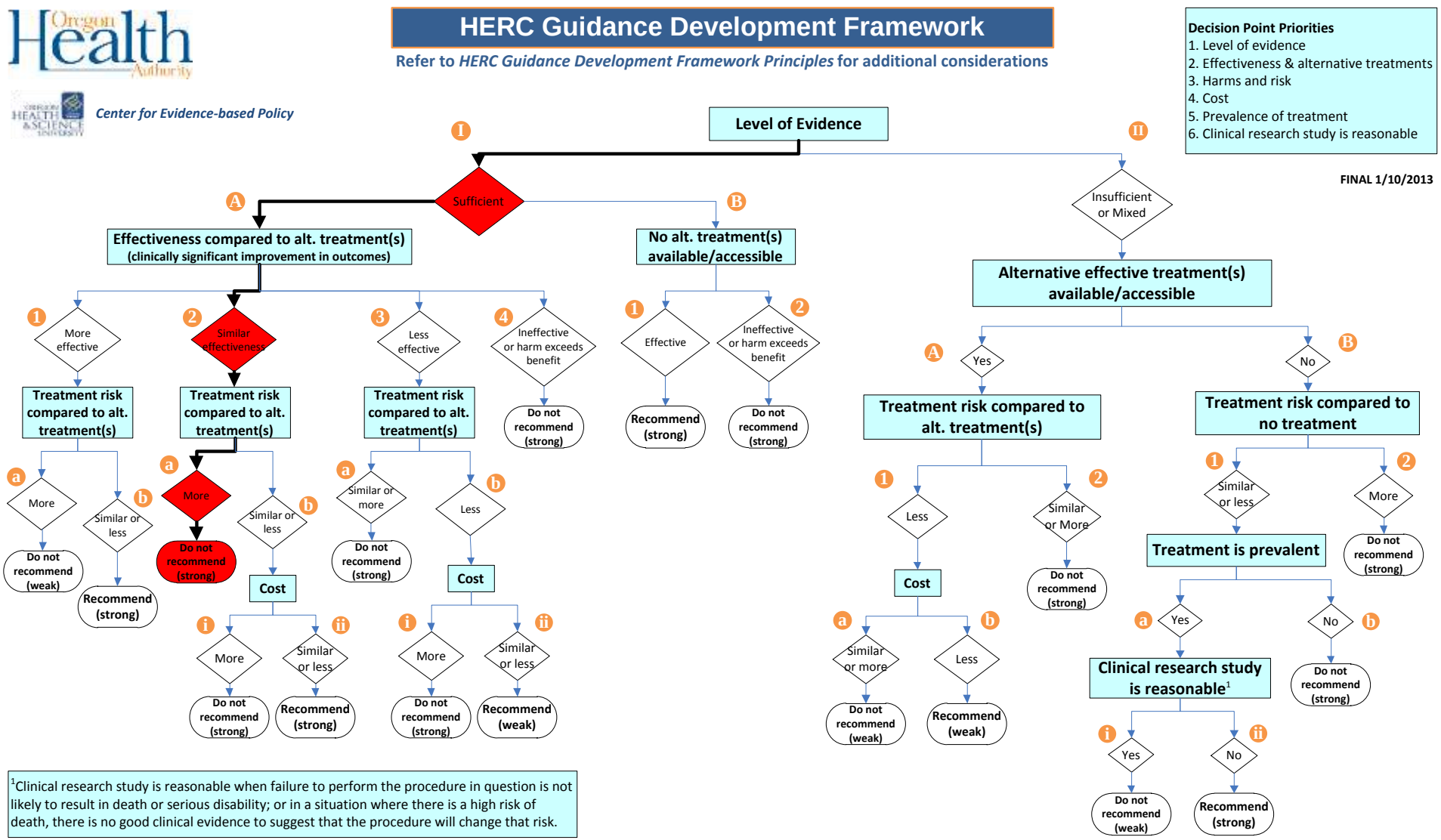
Appendix E. HERC Guidance Development Framework – Carotid Endarterectomy Indications

Carotid Endarterectomy – Stenosis ≥ 70%, Carotid Endarterectomy – 50-69% Stenosis, Symptomatic

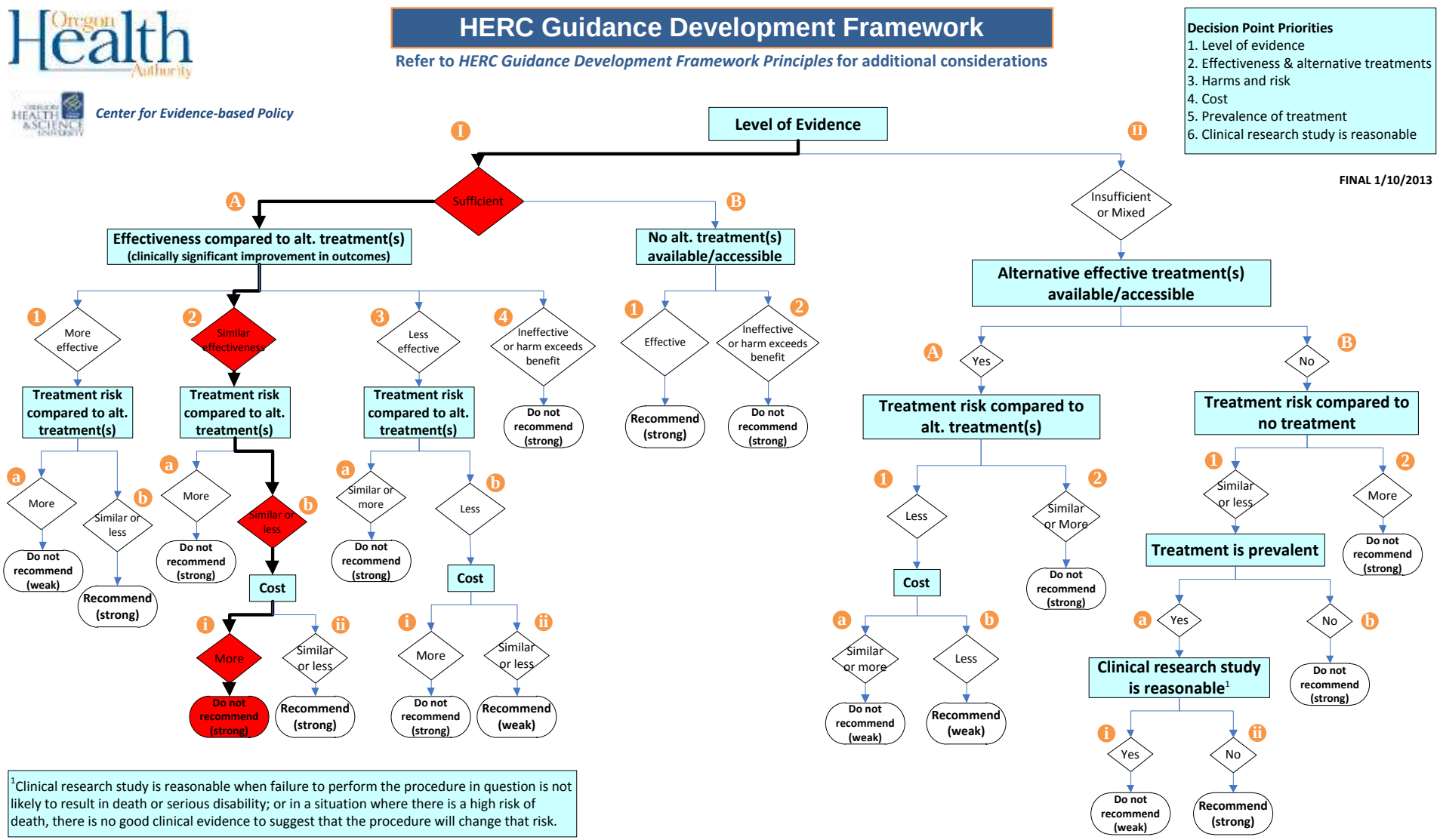


[1]Clinical research study is reasonable when failure to perform the procedure in question is not likely to result in death or serious disability; or in a situation where there is a high risk of death, there is no good clinical evidence to suggest that the procedure will change that risk.

Carotid Endarterectomy – Stenosis < 50%

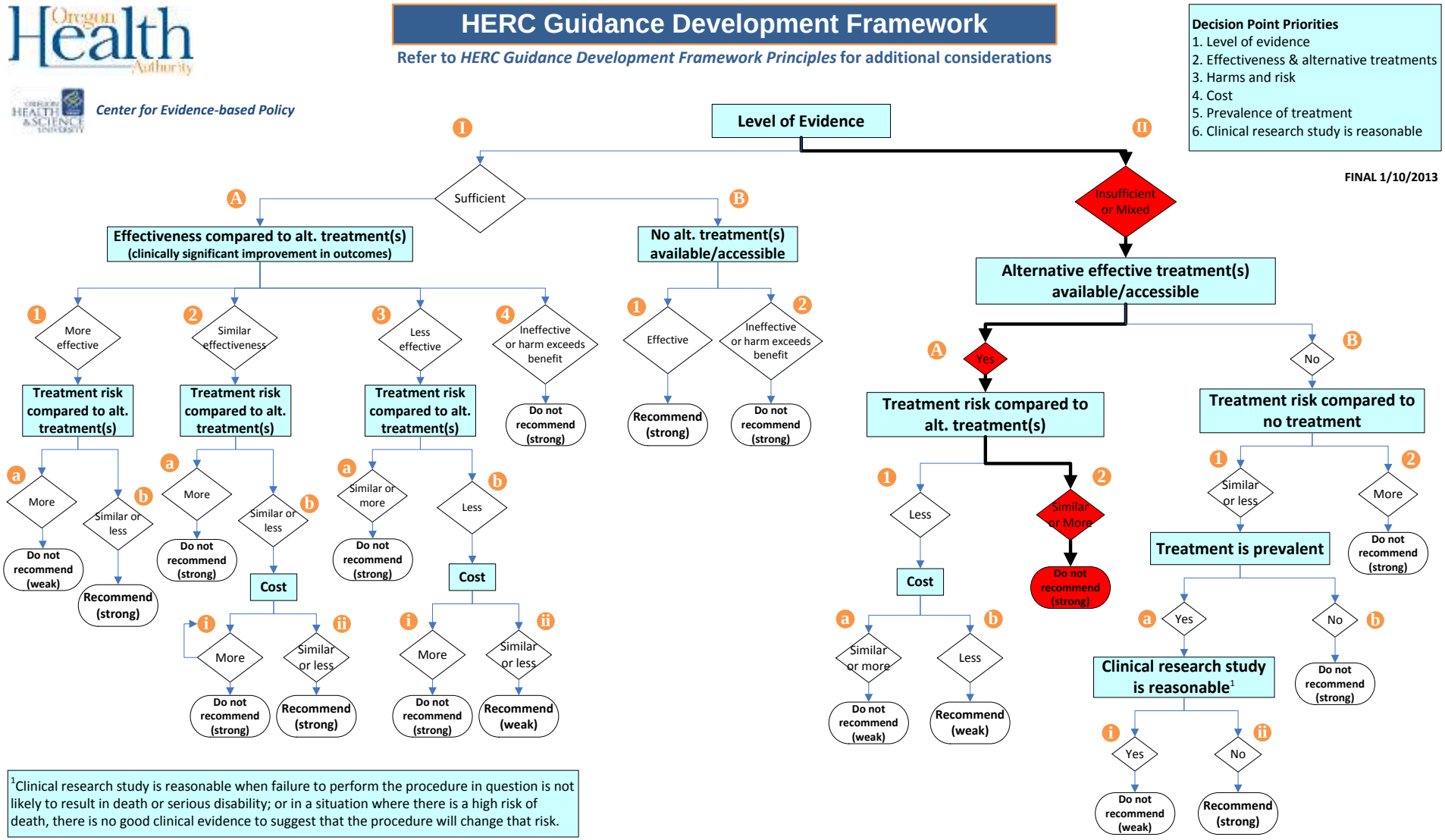


Population Screening for Carotid Stenosis



[1]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.

Asymptomatic Carotid Stenosis



[1]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 F: 2015 Rescanning Summary

HERC decision (1/14/2016): Reaffirm the existing coverage guidance and reconsider the need to update the topic during the regular two-year review cycle.

Bottom Line: There is new (but limited and contradictory) summary evidence and guidelines about the comparative effectiveness of carotid endarterectomy (CEA) vs carotid stenting or optimal medical treatment.

Scope Statement

Population description	Adults with carotid stenosis with or without recent symptoms of cerebral ischemia *Population scoping notes: None*
Intervention(s)	Carotid endarterectomy *Intervention exclusions: None*
Comparator(s)	Optimal medical therapy, carotid stenting
Outcome(s) (up to five)	**Critical:** All-cause mortality, cerebrovascular accidents **Important:** Transient ischemic attacks, development/progression of vascular dementia, quality of life *Considered but not selected for GRADE table: Need for reintervention*
Key questions	1. What is the comparative effectiveness of carotid endarterectomy for treatment of symptomatic or asymptomatic carotid stenosis? 2. What degree of carotid stenosis predicts clinical utility of carotid endarterectomy? 3. What are the harms of carotid endarterectomy? 4. Under what circumstances should carotid endarterectomy be covered for asymptomatic patients (i.e., when stenosis is found as an incidental finding)?

Scanning Results

1. Antoniou, G. A., Georgiadis, G. S., Georgakarakos, E. I., Antoniou, S. A., Bessias, N., Smyth, J. V., … Lazarides. M. K. (2013). Meta-analysis and meta-regression analysis of outcomes of carotid endarterectomy and stenting in the elderly. *Journal of the American Medical Association Surgery, 148*(12), 1140-1152. DOI: 10.1001/jamasurg.2013.4135.

Citation 1 is a large meta-analysis of 44 studies (comprising nearly 600,000 patients) of CEA or carotid stenting. It provides new information on the comparative effectiveness of CEA vs carotid stenting and suggests that the best intervention may vary depending on the age of the patient.

2. Bekelis, K., Moses, Z., Missios, S., Desai, A., & Labropoulos, N. (2013). Indications for treatment of recurrent carotid stenosis. *British Journal of Surgery, 100*(4), 440-7. DOI: 10.1002/bjs.9027.

Citation 2 is a systematic review of 50 studies reporting on indications for CEA or carotid stenting in patients with recurrent carotid stenosis after an initial CEA. It does not provide information that would change the coverage guidance.

3. Eckstein, H. H., Kühnl, A., Dörfler, A., Kopp, I.B., Lawall, H., & Ringleb, P. A. (2013). The diagnosis, treatment and follow-up of extracranial carotid stenosis: A multidisciplinary German-Austrian guideline based on evidence and consensus. *Deutsches Ärzteblatt International, 110*(26-27), 468-76. DOI: 10.3238/arztebl.2013.0468.

Citation 3 is a systematic review and multidisciplinary evidence-based guideline from Germany and Austria. The recommendations generally comport with the existing HERC coverage guidance, although they do not require a trial of optimal medical therapy before considering CEA in asymptomatic individuals with >60% stenosis (while also acknowledging that controlled trials of various treatment options for asymptomatic patients are needed). It also offers guidance on situations in which carotid stenting may be preferable to CEA.

4. Fink, H. A., Hemmy, L. A., MacDonald, R., Carlyle, M. H., Olson, C. M., Dysken, M. W., … Wilt, T. J. (2014). Cognitive outcomes after cardiovascular procedures in older adults: A systematic review. Rockville, MD: Agency for Healthcare Research and Quality. Retrieved from http://www.cms.gov/Medicare/Coverage/DeterminationProcess/Downloads/id97ta.pdf

Citation 4 is an AHRQ review of literature on cognitive outcomes after cardiovascular procedures in older adults. It concludes that CEA and endovascular interventions for carotid revascularization result in similar intermediate-term cognitive outcomes.

5. Fokkema, M., Vrijenhoek, J. E., Den Ruijter, H. M., Groenwold, R. H., Schermerhorn, M. L., Bots, M. L., … De Borst, G. J., TREAT CARE Study Group. (2015). Stenting versus endarterectomy for restenosis following prior ipsilateral carotid endarterectomy: An individual patient data meta-analysis. *Annals of Surgery*, *261*(3), 598-604). DOI: 10.1097/SLA.0000000000000799.

Citation 5 is a meta-analysis of individual-level patient data on CEA vs carotid stenting for treatment of ipsilateral restenosis after prior CEA. The short-term outcomes of stroke, death, and restenosis were similar between the two interventions.

6. Guay, J., & Ochroch, E. A. (2012). Carotid endarterectomy plus medical therapy or medical therapy alone for carotid artery stenosis in symptomatic or asymptomatic patients: a meta-analysis. *Journal of Cardiothoracic and Vascular Anesthesia, 26*(5), 835-844. DOI: 10.1053/j.jvca.2012.01.044.

Citation 6 is a systematic review and meta-analysis of RCTs comparing CEA and medical therapy in patients with symptomatic or asymptomatic carotid stenosis. It concludes that CEA is beneficial for symptomatic patients with >50% stenosis, but offers no benefit in asymptomatic patients. The latter conclusion is potentially at odds with the current HERC coverage guidance.

7. Haedersdal, C., Sondergaard, M. P., & Olsen, T. S. (2012). Costs of secondary prevention of stroke by carotid endarterectomy. *European Neurology, 68*(1), 42-46. DOI: 10.1159/000337864.

Citation 7 is a cost-effectiveness study of CEA in the Danish National Health Service. Any conclusions are probably too indirect to influence the HERC coverage guidance.

8. Jonas, D. E., Feltner, C., Amick, H. R., Sheridan, S., Zheng, Z. J., Watford, D. J., … Harris, R. (2014). Screening for Asymptomatic Carotid Artery Stenosis: A Systematic Review and Meta-Analysis for the U.S. Preventive Services Task Force. Evidence Synthesis No. 111. AHRQ Publication No. 13-05178-EF-1. Rockville, MD: Agency for Healthcare Research and Quality. Retrieved from http://www.uspreventiveservicestaskforce.org/Home/GetFile/1/1534/cases111/pdf

9. Jonas, D. E., Feltner, C., Amick, H. R., Sheridan, S., Zheng, Z. J., Watford, D. J., … Harris, R. (2014). Screening for asymptomatic carotid artery stenosis: a systematic review and meta-analysis for the US Preventive Services Task Force. *Annals of Internal Medicine, 161*(5), 336-346. DOI: 10.7326/M14-0530.

Citations 8 and 9 comprise updated evidence and USPSTF guidelines regarding screening for carotid stenosis in asymptomatic individuals. They support the current HERC coverage guidance that does not recommend screening in asymptomatic individuals.

10. Khan, A. A., Chaudhry, S. A., Sivagnanam, K., Hassan, A. E., Suri, M. F., & Qureshi, A. I. (2012). Cost-effectiveness of carotid artery stent placement versus endarterectomy in patients with carotid artery stenosis. *Journal of Neurosurgery, 117*(1), 89-93. DOI: 10.3171/2012.3.JNS111266.

Citation 10 is an economic evaluation of carotid stenting with an embolic-prevention device vs CEA for patients at average surgical risk. Because stenting produces only marginally greater QALYs compared with CEA at greater cost, the ICER for stenting is >$200,000. It would provide new contextual information on resource use if the coverage guidance is updated.

11. LeFevre, M. L., on behalf of the U.S. Preventive Services Task Force. (2014). Screening for asymptomatic carotid artery stenosis: U.S. Preventive Services Task Force recommendation statement. *Annals of Internal Medicine, 161*(5), 356-362. DOI: 10.7326/M14-1333

Citations is updated evidence and USPSTF guidelines regarding screening for carotid stenosis in asymptomatic individuals, which supports the current HERC coverage guidance that does not recommend screening in asymptomatic individuals.

12. Liu, Z. J., Fu, W. G., Guo, Z. Y., Shen, L. G., Shi, Z. Y., & Li, J. H. (2012). Updated systematic review and meta-analysis of randomized clinical trials comparing carotid artery stenting and carotid endarterectomy in the treatment of carotid stenosis. *Annals of Vascular Surgery, 26*(4), 576-590. DOI: 10.1016/j.avsg.2011.09.009.

Citation 12 is an updated systematic review and meta-analysis of RCTs comparing CEA and carotid stenting. Its overall conclusion is that stenting is inferior to CEA with respect to stroke or death, but because of a lower incidence of myocardial infarction, stenting may be preferable in selected patients.

13. Mandavia, R., Qureshi, M. I., Dharmarajah, B., Head, K., & Davies, A. H. (2014). Safety of carotid intervention following thrombolysis in acute ischaemic stroke. *European Journal of Vascular and Endovascular Surgery, 48*(5), 505-512. DOI: 10.1016/j.ejvs.2014.08.012.

Citation 13 summarizes evidence on the appropriate use and timing of CEA after thrombolysis for acute ischemic stroke. Generally, the study supports the safety of CEA within 14 days of an acute ischemic stroke treated with thrombolysis, though the quality of evidence is low.

14. Paraskevas, K. I., Lazaridis, C., Andrews, C. M., Veith, F. J., & Giannoukas, A. D. (2014). Comparison of cognitive function after carotid artery stenting versus carotid endarterectomy. *European Journal of Vascular and Endovascular Surgery, 47*(3), 221-231. DOI: 10.1016/j.ejvs.2013.11.006.

Citation 14 is a systematic review of studies comparing cognitive function after CEA vs carotid stenting. Due to a high degree of heterogeneity among the included studies, meta-analysis was not performed and definite conclusions could not be drawn.

15. Skelly, A. C., Brodt, E. D., Hashimoto, R. E., Schenk-Kisser, J. M., Junge, M., & Holmer, H. (2013). Stenting for treatment of atherosclerotic stenosis of the extracranial carotid arteries or intracranial arteries. Olympia, WA: Washington Health Technology Assessment Program. Retrieved from http://www.hca.wa.gov/hta/documents/cas_final_report_081513.pdf

Citation 15 is a health technology assessment of carotid stenting performed for the Washington HTA. On the basis of these results, the Washington HTA has opted to cover carotid stenting for symptomatic patients with >50% stenosis or asymptomatic patients with >80% stenosis AND who are deemed to be at high operative risk for CEA. This information would potentially change HERC coverage guidance.

16. Sternbergh, W. C., Crenshaw, G. D., Bazan, H. A., & Smith, T. A. (2012). Carotid endarterectomy is more cost-effective than carotid artery stenting. *Journal of Vascular Surgery, 55*(6), 1623-1628. DOI: 10.1016/j.jvs.2011.12.045.

Citation 16 is a cost-effectiveness analysis of CEA vs carotid stenting based on a retrospective case series at a single institution. This study design is inadequate to inform HERC coverage guidance.

17. Thapar, A., Garcia Mochon, L., Epstein, D., Shalhoub, J., & Davies, A. H. (2013). Modelling the cost-effectiveness of carotid endarterectomy for asymptomatic stenosis. *British Journal of Surgery, 100*(2), 231-239. DOI: 10.1002/bjs.8960.

Citation 17 is a cost-effectiveness study of CEA for asymptomatic individuals in the British National Health Service. Any conclusions are probably too indirect to influence the HERC coverage guidance.

18. Vilain, K. R., Magnuson, E. A., Li, H., Clark, W. M., Begg, R. J., Sam, A. D., … Cohen, D. J. (2012). Costs and cost-effectiveness of carotid stenting versus endarterectomy for patients at standard surgical risk: results from the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST). *Stroke, 43*(9), 2408-2416. DOI: 10.1161/STROKEAHA.112.661355.

Citation 18 is an economic evaluation of carotid stenting vs CEA for patients at average surgical risk. It concludes that there are trivial differences in the long-term costs between the two interventions. It would provide new contextual information on resource use if the coverage guidance is updated.

19. Wang, L., Liu, X. Z., Liu, Z. L., Lan, F. M., Shi, W. C., Liu, J., & Zhang, J. N. (2013). A meta-analysis of carotid endarterectomy versus stenting in the treatment of symptomatic carotid stenosis. *Chinese Medical Journal, 126*(3), 532-535. PMID: 23422120

Citation 19 is a meta-analysis of 8 trials comparing CEA vs carotid stenting in symptomatic patients. This appears to be a low-quality systematic review and would probably not be included for review in an update of the HERC coverage guidance.

20. Yong, Y. P., Saunders, J., Abisi, S., Sprigg, N., Varadhan, K., MacSweeney, S., & Altaf, N. (2013). Safety of carotid endarterectomy following thrombolysis for acute ischemic stroke. *Journal of Vascular Surgery, 58*(6), 1671-1677. DOI: 10.1016/j.jvs.2013.05.093

Citation 20 summarizes evidence on the appropriate use and timing of CEA after thrombolysis for acute ischemic stroke. Generally, the study supports the safety of CEA within 14 days of an acute ischemic stroke treated with thrombolysis, though the quality of evidence is low.

Methods

Search Strategy
A full search of the core sources was conducted to identify systematic reviews, meta-analyses, technology assessments, and clinical practice guidelines using the terms “carotid endarterectomy” and “carotid stenosis.” Searches of core sources were limited to citations published after 2011 (the last search date of original evidence sources).

The core sources searched included:

Agency for Healthcare Research and Quality (AHRQ)
Blue Cross/Blue Shield Health Technology Assessment (HTA) program
BMJ Clinical Evidence
Canadian Agency for Drugs and Technologies in Health (CADTH)
Cochrane Library (Wiley Interscience)
Hayes, Inc.
Medicaid Evidence-based Decisions Project (MED)
National Institute for Health and Care Excellence (NICE)
Tufts Cost-effectiveness Analysis Registry
Veterans Administration Evidence-based Synthesis Program (ESP)
Washington State Health Technology Assessment Program

A MEDLINE® (Ovid) search was conducted to identify systematic reviews, meta-analyses, and technology assessments published after the search dates of original evidence sources. The search was limited to publications in English published after 2012 (last search dates of original evidence sources).

Searches for clinical practice guidelines were limited to those published since 2012 (last search date of coverage guidance). A search for relevant clinical practice guidelines was also conducted, using the following sources:

Australian Government National Health and Medical Research Council (NHMRC)
Centers for Disease Control and Prevention (CDC) – Community Preventive Services
Institute for Clinical Systems Improvement (ICSI)
National Guidelines Clearinghouse
New Zealand Guidelines Group
NICE
Scottish Intercollegiate Guidelines Network (SIGN)
United States Preventive Services Task Force (USPSTF)
Veterans Administration/Department of Defense (VA/DOD)

Inclusion/Exclusion Criteria

Studies were excluded if they were not published in English, did not address the scope statement, or were study designs other than systematic reviews, meta-analyses, technology assessment, or clinical practice guidelines.