

## HEALTH EVIDENCE REVIEW COMMISSION (HERC)

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

**DRAFT AS POSTED FOR PUBLIC COMMENT 2/28/2013**

#### HERC COVERAGE GUIDANCE

Carotid endarterectomy is recommended for coverage in patients with 70-99% carotid stenosis without near-occlusion (*strong recommendation*).

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

Coverage of 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 Health 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

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.

Chambers BR, Donnan G. Carotid endarterectomy for asymptomatic carotid stenosis. *Cochrane Database of Systematic Reviews* 2005, 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>

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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**

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.

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 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.

### Asymptomatic Patients - Screening

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<sup>1</sup>.

#### *Benefits of Detection and Early Intervention*

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.

#### *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

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<sup>1</sup> A description of the USPSTF grades can be found in Appendix C.

the presenting event. The benefit in asymptomatic patients is small. The benefits of screening asymptomatic individuals do not outweigh the harms.

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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	Balance between desirable and undesirable effects	Quality of evidence*	Resource Allocation	Values and preferences	Expert Input	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 patients with 70-99% carotid stenosis without near-occlusion <i>Strong Recommendation</i>  Carotid endarterectomy is not recommended for coverage for patients with less than 50% carotid stenosis <i>Strong Recommendation</i>
Carotid endarterectomy in asymptomatic patients	Benefit exceeds harms for stenosis > 60% or possibly > 50% when performed in centers with complication rate of 3% or less  Subgroup analysis based on degree of stenosis found no difference between groups, but because of the small number of events, was underpowered to detect such differences	High for benefit overall, low for differential effect based on degree of stenosis	Less costly when benefit exceeds harm, more costly when harm exceeds benefit	Limited variability; most patients would opt for surgery when benefits exceed harms		Because the evidence had insufficient power to detect differences in effect based on degree of stenosis, and because it clinically seems unlikely that asymptomatic patients would derive greater benefit from surgery than symptomatic patients, coverage recommendations are similar to the symptomatic group

Indication	Balance between desirable and undesirable effects	Quality of evidence*	Resource Allocation	Values and preferences	Expert Input	Coverage Recommendation
						<p>Carotid endarterectomy is recommended for coverage in patients with 70-99% carotid stenosis without near-occlusion <i>Strong Recommendation</i></p> <p>Carotid endarterectomy is not recommended for coverage for patients with less than 50% carotid stenosis <i>Strong Recommendation</i></p>
Population screening for carotid stenosis	Benefits do not exceed harms	Moderate	Moderate costs	Moderate variability; some patients would prefer screening, others would not		<p>Screening for asymptomatic carotid artery stenosis in the general primary care population is not recommended for coverage <i>Strong Recommendation</i></p>

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

## COMMITTEE DELIBERATIONS – HTAS

## COMMITTEE DELIBERATIONS – VBBS

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.

## 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

<b>CODES</b>	<b>DESCRIPTION</b>
<b>ICD-9 Diagnosis Codes</b>	
433.1	Occlusion and stenosis of precerebral arteries; carotid
<b>ICD-9 Volume 3 (Procedure Codes)</b>	
38.02	Incision of vessel (embolectomy/ thrombectomy); other vessels of head and neck
38.12	Endarterectomy; other vessels of head and neck
<b>CPT Codes</b>	
35301	Thromboendarterectomy; carotid, vertebral, subclavian, by neck incision
<b>HCPCS Level II Codes</b>	
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. HERC Guidance Development Framework – Carotid Endarterectomy Indications

## Carotid Endarterectomy – Stenosis ≥ 70%

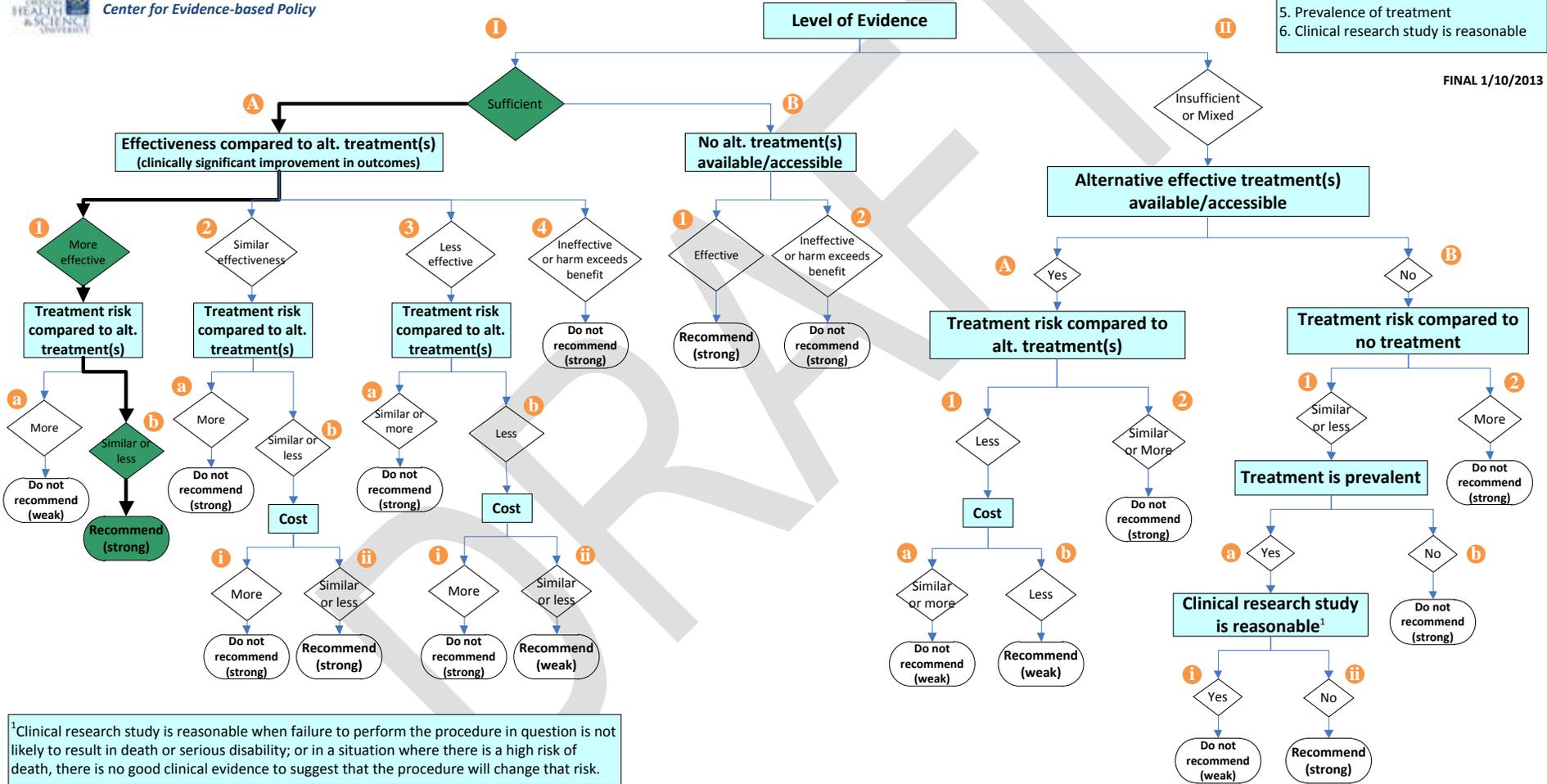


### HERC Guidance Development Framework

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

FINAL 1/10/2013



<sup>1</sup>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%

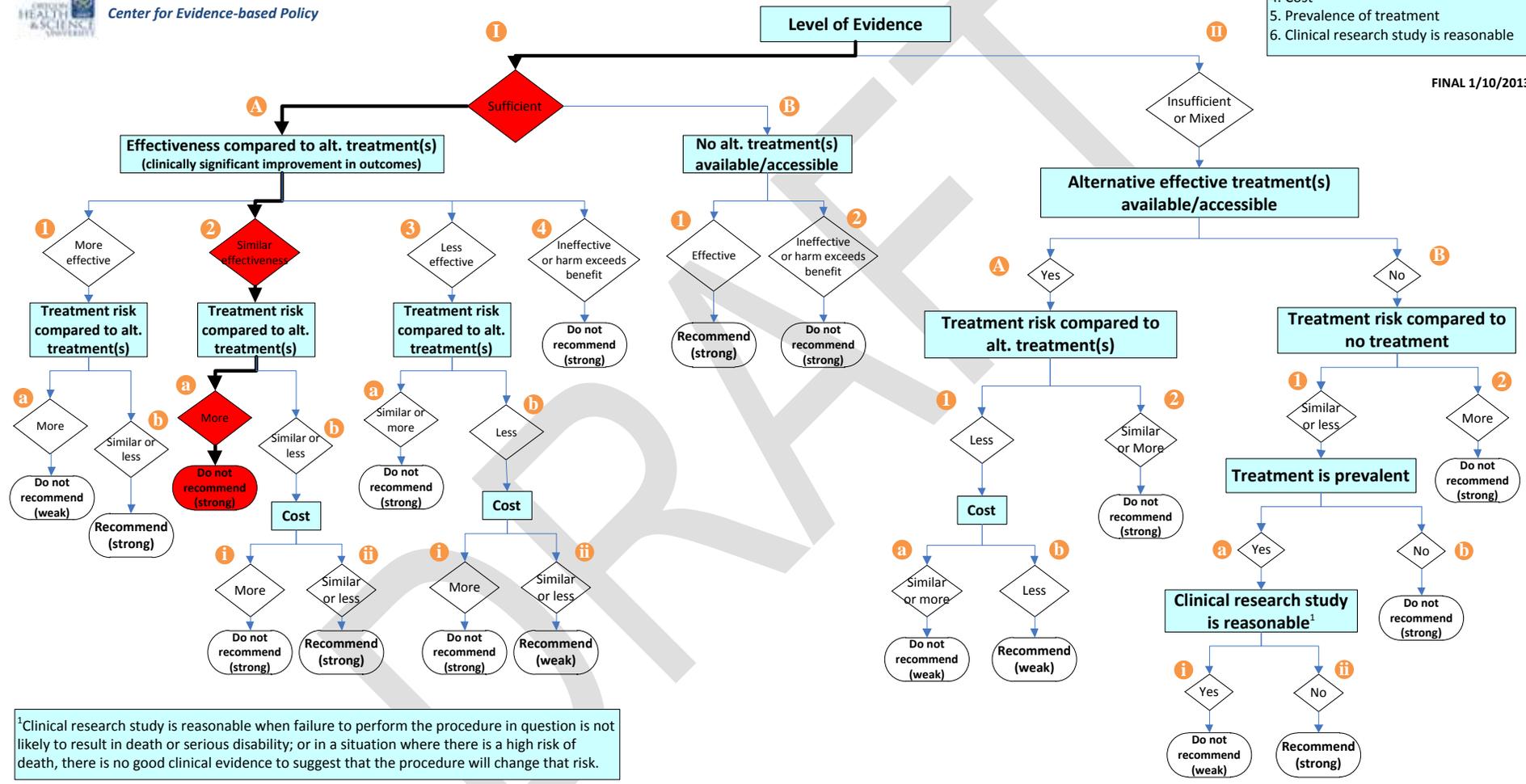


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- Decision Point Priorities**
1. Level of evidence
  2. Effectiveness & alternative treatments
  3. Harms and risk
  4. Cost
  5. Prevalence of treatment
  6. Clinical research study is reasonable

FINAL 1/10/2013



<sup>1</sup>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.

# Population Screening for Carotid Stenosis



## 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

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