Washington State Health Care Authority

Health Technology Assessment

Carotid Artery Stenting:

For treatment of atherosclerotic stenosis of the intracranial arteries or extracranial carotid arteries

Final Key Questions – Public Comments

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RESPONSE TO PUBLIC COMMENTS

Spectrum Research is an independent vendor contracted to produce evidence assessment reports for the Washington HTA program. For transparency, all comments received during the public comment periods are included in this response document. Comments related to program decisions, process, or other matters not pertaining to the evidence report are acknowledged through inclusion only.

This document responds to comments from the following parties:

Key Questions

- Clif Finch; Abbott Vascular, Inc. (Letter, annotated bibliography and 13 PDFs)
- Marshall E. Hicks, MD, FSIR; Society of Interventional Radiology (Letter)
- J. Jeffrey Marshall, MD, FSCAI; Society for Cardiovascular Angiography and Interventions (Letter and Excel workbook sent by Wayne Powell)
- Mitchel Berger, MD, President , American Association of Neurological Surgeons and Ali Rezai, MD, President, Congress of Neurological Surgeons: (Joint letter)
- Kevin Walsh, MD, Physician, Yakima Valley Farm Workers Clinic, Health Technology Clinical Committee (email only)

Specific responses pertaining to comments are included in Table 1 below.

	Comment	Response
Clif Finch; Abbott Vascular, Inc.		
	Revised Key Questions presented by Abbot: 1. What is the evidence that carotid artery stenting (CAS) has periprocedural (30 day) death or stroke the rates below the established benchmarks of 3% for asymptomatic patients and 6% for symptomatic patients for: a. High risk surgical patients? b. Standard risk surgical patients? 2. In symptomatic or asymptomatic persons with atherosclerotic carotid artery stenosis what is the evidence of short- and long-term comparative efficacy and effectiveness of: a. In symptomatic high risk patients: compare CAS and medical therapy to medical therapy alone (CEA is generally not an option for such patients) b. In asymptomatic high risk patients: compare CAS and medical therapy to medical therapy alone (CEA is generally not an option for such patients) c. In symptomatic standard risk patients: compare CAS and medical therapy to CEA and medical therapy to medical therapy alone d. In asymptomatic standard risk patients: compare CAS and medical therapy to CEA and medical therapy to medical therapy alone 3. What is the evidence regarding adverse events and complications, particularly during the periprocedural period and longer term, for CAS compared with alternative treatments? a. In symptomatic high risk patients: compare CAS and medical therapy to medical therapy alone (CEA is generally not an option for such patients) b. In asymptomatic high risk patients: compare CAS and medical therapy to medical therapy alone (CEA is generally not an option for such patients) c. In symptomatic standard risk patients: compare CAS and medical therapy to CEA and medical therapy to medical therapy alone d. In asymptomatic standard risk patients: compare CAS and medical therapy to CEA and medical therapy to medical therapy alone 4. In symptomatic persons with atherosclerotic stenosis of the intracranial carotid distribution, what is the evidence of short- and long-term comparative efficacy and effectiveness of CAS and medical therapy compared with medical therapy alone? a. CAS and medical therapy compared with medical therapy alone? 5. Is there evidence of differential efficacy or safety for special populations, (including consideration of age, gender, race, diabetes, atrial fibrillation or other comorbidities, ethnicity, or disability)?	*Thank you.* *Please see responses below*

	Comment	Response
	a. In high surgical patients: compare CAS and medical therapy to medical therapy alone b. In standard surgical risk patients: compare CAS and medical therapy to CEA and medical therapy to medical therapy alone 6. What is the evidence of cost-effectiveness of CAS compared with other treatment options (medical therapy, CEA) in the short-term and the long term? e. In symptomatic high risk patients: compare CAS and medical therapy to medical therapy alone (CEA is generally not an option for such patients) f. In asymptomatic high risk patients: compare CAS and medical therapy to medical therapy alone (CEA is generally not an option for such patients) g. In symptomatic standard risk patients: compare CAS and medical therapy to CEA and medical therapy to medical therapy alone h. In asymptomatic standard risk patients: compare CAS and medical therapy to CEA and medical therapy to medical therapy alone	
1.	Comments on Key Question 1: We suggest a rearrangement of the questions to follow logical flow of going from the more general to the more specific. The first question that should be asked relates to whether there is evidence that CAS meets the current AHA/ASA benchmark standards for periprocedural death and stroke adverse event rates [i.e. 3% for asymptomatic patients and 6% for symptomatic patients].	*Thank you for your comments.* *The logical flow of the Key Questions is a matter of perspective. The flow presented reflects the overall process and questions that the Health Technology Clinical Committee uses in evaluating reports to arrive at decisions.*
2.	Comments on Key Question 2: The next step would compare therapies for carotid stenosis for efficacy and effectiveness, dividing the overall patient population by surgical risk status and symptomatic status. We recommend inclusion of the appropriate guidance to assess the efficacy and effectiveness of carotid treatments. In the landmark CREST trial, the primary composite endpoint included periprocedural (30-day) death, any stroke and MI, and ispsilateral stroke to 1 year (up to 4 years for FDA PMA analysis). The AHA/ASA guidelines rely	*Thank you for your comments* *A summary of pertinent and recent clinical guidelines (including those from AHA and other sources) will be included in the report.* *Studies reporting on outcomes related to quality of life and other pertinent patient-related outcomes will be included to the extent that they meet the predefined inclusion/exclusion criteria*

	Comment	Response
	on periprocedural stroke and death. In addition, effectiveness should look beyond clinical efficacy to what the patient's experiences. Therefore, effectiveness should include quality of life, neurological deficits, procedural complications, compliance (in terms of medical therapy), etc.	
3.	Comments on Key Question 3: As for Q2, we suggest dividing the overall patient population by surgical risk status and symptomatic status.	*Thank you for your comments* *The inclusion/exclusion criteria and patient characteristics as presented in studies selected for inclusion will be examined and, as data are available and appropriate, we will attempt to evaluate the impact of surgical risk status as part of the key question dealing with differential efficacy and safety in special populations.*
4.	Comments on Key Question 4: We propose no changes to Q4 above, other than editorial changes for consistency. Abbott Vascular does not manufacturer stents or related devices for the intracranial vasculature.	*Thank you for your comments*
5.	Comments on Key Question 5: The comparisons discussed in Q5 are revised to make them more specific. We suggest adding subquestions by patient surgical risk status. For these issues, the questions depend on the population of interest. For example, one should compare CAS and medical therapy to medical therapy alone only in patients where CEA not generally an option. In contrast, one would want to compare all three treatment options (CAS and medical therapy, CEA and medical therapy, and medical therapy alone) in a standard surgical risk population.	*Thank you for your comments* *The inclusion/exclusion criteria and patient characteristics as presented in studies selected for inclusion will be examined and, as data are available and appropriate, we will attempt to evaluate the impact of surgical risk status.*

	Comment	Response
6.	Comments on Key Question 6: As with Q2 and Q3, we recommend dividing the overall patient population by surgical risk status and symptomatic status.	*The inclusion/exclusion criteria and patient characteristics as presented in studies selected for inclusion will be examined and, as data are available and appropriate, we will attempt to evaluate the impact of surgical risk status. This most logically is part of KQ 4.*
7.	Annotated bibliography and PDFs sent.	*Thank you for your comments. We will be performing independent analyses of the highest quality evidence available to address the key questions. We will ensure that the studies listed are evaluated for inclusion. Studies that meet our predefined inclusion criteria will be included in the report.*
Marshall E. Hicks, MD, FSIR; Society of Interventional Radiology		
1.	Comments on Key Question 1 The SIR endorses the expanded indications and accompanying reimbursement for carotid artery stenting (CAS), as approved by the FDA, with additional recommendations regarding the implementation of this new policy. The 2011 Multi-Society Guideline on the Management of Patients with Extracranial Carotid and Vertebral Artery Disease, in which 14 societies reached consensus, represents an excellent review of levels of evidence. Based upon that document and the CREST data, we strongly feel that symptomatic patients, regardless of risk stratification, should be given the option of CAS [as well as carotid endarterectomy (CEA)] as treatment for carotid artery stenosis. With regard to the treatment of asymptomatic carotid artery stenoses, we believe that based upon the CREST data, if an asymptomatic patient is to be treated with carotid revascularization, that the evidence supports offering both CAS and CEA as	*Thank you for your comments* *A summary of pertinent and recent clinical guidelines (including those from AHA and other sources) will be included in the report.* *We will be performing independent analyses of the highest quality evidence available to address the key questions. If there are studies/data to describe this that meet our predefined*

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	treatment options, and that they are equivalent procedures. If one does a sub-analysis of those patients who were enrolled in CREST after 2005, the stroke rate associated with CAS is equivalent or perhaps slightly better than with CEA, as a result of improved devices, technique and increased operator experience. Concerning best medical therapy (BMT) versus carotid revascularization with either CAS or CEA, one must consider not who is at "high" risk for stroke but rather in whom the risk of stroke is higher than the risks associated with carotid revascularization over the subsequent 5 years (cutoff stroke risk of ~4-6% over 5 years). There is good data from the Asymptomatic Carotid Surgery Trial (ACST) that patients younger than 75 years of age did better with CEA than with BMT. One might consider that a better cutoff would be those patients with a life expectancy of > 5yrs, which in the Medicare patient population would be those < 77 years of age, assuming a life expectancy of 82 yrs.	*inclusion/exclusion criteria for the key questions, such information will be considered. Information on operators/experience may be included for context.* *We will ensure that the studies listed are evaluated for inclusion. Studies that meet our predefined inclusion criteria will be included in the report.*
2.	Comments on Key Question 2 Recent large trials such as CREST make it clear that with adequate training, physicians can perform CAS with low complication rates. Therefore, both the expansion of indications and accompanying reimbursement should be dependent on accreditation of facilities and operators performing these procedures, based on outcomes thresholds that meet national benchmarks. One of the questions raised is the generalizability of good outcomes from CAS. In CREST, the operators were very carefully selected, with about ½ of the physicians requesting to be in CREST not approved. The ACCF multispecialty document states that CAS is a reasonable alternative to CEA when outcomes meet national benchmarks (3% S/D for asx, 6% for sx), but only through	*Thank you for your comments* *A summary of pertinent and recent clinical guidelines (including those from AHA and other sources) will be included in the report.* *We will include general information on accreditation and operators for context in the background.*

	Comment	Response
	accreditation can a facility demonstrate that these outcomes are achieved. Currently, few facilities are accredited through ICASF or ACE. Washington state may wish to consider this a precondition for treatment, as it will likely improve patient care outcomes and reduce costs.	
3.	Comments on Key Question 4 In terms of cost comparison between the two treatments, two recent studies (*based on actual data rather than models*) arrived at the same conclusion- that CEA and CAS have minor differences in overall costs and quality-adjusted life expectancy between CEA and CAS. In the March 2011 issue of *Catheterization and Cardiovascular Interventions,* Cohen, *et al* analyzed data from the SAPPHIRE trail, and found that while CAS was indeed initially more costly than CAE, CAS had a significantly shorter post procedure length of stay(1.9 days vs. 2.9) compared to CAE, resulting in total costs for CAS being only slightly higher than CEA. Similarly, Vilain, *et al*, used data from CREST which also showed that while CAS had higher initial procedural costs, post-procedure costs were less with CAS (*Stroke,*September 2012).	*Thank you for your comments.* *We will be performing independent analyses of the highest quality evidence available to address the key questions. We will ensure that the studies listed are evaluated for inclusion. Studies that meet our predefined inclusion criteria will be included in the report.*
4.	Other One issue in the asymptomatic patient group is that of the appropriate role of screening for carotid artery stenosis. The U.S. Preventive Services Task Force (USPSTF) in December 2007 recommended against screening for asymptomatic carotid artery stenosis in the general adult population, noting that this recommendation applied to adults without neurological signs or symptoms, including a history of transient ischemic attacks or stroke. The recommendations further noted that available screening and confirmatory tests (duplex ultrasonography, digital subtraction angiography, and magnetic resonance angiography) all have imperfect sensitivity and appreciable harms. We do not recommend routine screening for carotid artery	*Thank you for your comments.* *The planned report does not formally address screening. Some information may be included as context as appropriate.*

	Comment	Response
	stenosis in the absence of criteria for appropriate selection of patients at high risk for carotid artery stenosis and/or stroke.	
J. Jeffrey Marshall, MD, FSCAI; Society for Cardiovascular Angiography and Interventions		
1.	Comments on Key Question 2: In question 2, the term "intracranial carotid distribution" seems clearer if replaced by the term "intracranial carotid arteries"	*Thank you for your comments.* *Our intent is to be as accurate as possible regarding the terminology.*
2.	Other Why is only the endovascular treatment being considered while the surgical and medical treatment options are not being considered? A balanced assessment of the literature on carotid stenting has to include these other options and the federal Agency for Healthcare Quality and Research just published a Technology Assessment of all treatments for carotid stenosis on August 27, 2012. See: http://www.ahrq.gov/clinic/ta/carotidstenosis.pdf We recommend the following additional questions: • In patients who are at increased risk of CEA and who have carotid disease requiring revascularization, what is the evidence of short- and long-term comparative efficacy and effectiveness compared to CAS and medical therapy? • Is there substantial equivalence for CAS and medical therapy? (CAS has been compared to CEA directly and found to provide similar outcomes. Since CEA has been compared to medical therapy and found to be superior, CAS is presumed to provide similar comparative outcomes to medical therapy.) We also noted that any comparison of peri-procedural complications of CAS and CEA should specifically include myocardial infarction as all large clinical trials in this field have.	*Thank you for your comments.* *The intended scope of this report is to focus on comparisons of stenting (with medical therapy) versus medical therapy alone and to compare CEA (with medical therapy) versus stenting (with medical therapy). A review of medical therapy options is not within the scope of this report. The pertinent aspects of the AHRQ report and others regarding medical therapy and its comparison to CEA may be briefly summarized for context.* *Given the above, we believe that key question 1 as written encompasses the intent of the suggested additional questions – i.e. in patients with atherosclerotic carotid artery stenosis what is the evidence of short- and long-term comparative efficacy and effectiveness based on the focus described above. Data from the included studies will be compared to answer KQ 1 and the extent to which outcomes for the treatments are or are not similar will be described. The inclusion/exclusion criteria and patient characteristics as presented in studies selected for inclusion will be examined and, as data are available and appropriate, we will attempt to evaluate the impact of*

	Comment	Response
		surgical risk status as part of the key question dealing with differential efficacy and safety in special populations. *Peri-procedural outcomes will be included together will all major outcomes related to the key questions for which there are data reported in included trials.*
	An Excel Workbook containing graphs and data were also sent by Wayne Powell of SCAI.	*Thank you for providing this information.*
Mitchel Berger, MD, President , American Association of Neurological Surgeons and Ali Rezai, MD, President, Congress of Neurological Surgeons: (Joint letter)		
1.	NASCET and ECST for symptomatic disease and ACAS and ACST for asymptomatic disease established the benefits of carotid revascularization for secondary stroke prevention. The HTA may rely on these trials, including the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST), to establish the natural history of carotid disease, and then examine primary data regarding CAS safety and direct CAS comparisons with Carotid Endarterectomy (CEA)	*Thank you for your comments.* *We will ensure that the studies listed are evaluated for inclusion. Studies that meet our predefined inclusion criteria will be included in the report.*
2.	As surgeons versed in CEA and CAS, anatomical characteristics, prior surgery or neck radiation, tandem lesions, or medical comorbidities may render CEA and CAS complementary modalities in certain situations. The HTA should further explore these technical situations where CEA may be high risk and CAS favored. The draft KQ partially addresses these scenarios	*We appreciate your comments. To the extent that comparative literature is available to evaluate patients with anatomical characteristics or other factors, they will be evaluated for inclusion if they meet other inclusion criteria as well.* *The intent of the report is to include use of stenting for treatment of carotid atherosclerotic disease (de novo lesions which have not been subject to prior revascularization procedures). Patients with prior re-vascularization, post-radiation stenosis, trauma, aneurysms and other conditions are to be excluded.*

	Comment	Response
3.	***Population*** • "External" should be substituted with "extracranial." • "Intracranial carotid distribution" should read "Internal carotid distribution." ***Intervention*** Per above, "external" and "intracranial" should be changed. A sample intervention statement is below: "Stenting of extracranial internal carotid artery with or without distal embolic protection, proximal protection or flow reversal adjuncts."	*Thank you for your comments. Our goal is to use accurate terminology.* *The report will make distinctions between vessels that are extracranial and those that are in the intracranial.*
4.	These outcomes appear adequate. Carotid revascularization literature does tend to distinguish between minor (< 3 NIHSS point clinical change) and major (> 3 NIHSS point clinical change) strokes. Additionally, it is worthwhile to distinguish between ipsilateral stroke and strokes in other distributions. Finally, cranial neuropathies (i.e. facial or hypoglossal palsies) should be added as these are complications of CEA that do not occur with CAS.	*To the extent that these distinctions are made in the included studies, we will report them.* *Distinctions in stroke location will be made as described in the included literature* *This will be added to the list of outcomes.*
5.	The KQs must further separate consideration of extracranial and intracranial atherosclerotic disease. Blurring carotid disease, ICAD, and materially different catheter-based treatments will ultimately limit the HCA's ability to draw meaningful conclusions from this assessment. KQ 2: This question refers to the management of ICAD that carries a completely different natural history, medication alternative (Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis [SAMMPRIS] protocol), and treatment options (intracranial angioplasty with or without intracranial stenting). These technologies are completely distinct from cervical CAS and should be treated in a separate assessment.	*Thank you for your comments.* *This key question separates out intracranial vessel stenting for ICAD from KQ 1, recognizing that there are differences. The question has been reworded for clarity.*
6.	KA4: This question begins to address the potential for population subset advantages for CAS as detailed in the introduction. It further merits mention that certain primary stroke prevention efforts (i.e. the treatment of acute carotid dissection) rely on CAS technology.	*Thank you for your comments.* *The intent of the report is to include use of stenting for treatment of atherosclerotic disease (de novo lesions which have not been subject to prior revascularization procedures) and*

	Comment	Response
		conditions such as acute carotid dissection, aneurysm, trauma, tumor, post-radiation stenosis and other conditions will be excluded.
Kevin Walsh, MD (email only)		
	Current best medical therapy for cardiovascular disease includes rigorous and compliant use of statins and antiplatelet agents, along with treatment of hypertension, cigarette smoking, and diabetes. This approach has been shown in prospective studies to decrease stroke risk for asymptomatic carotid disease as much as surgical therapy decreases it. The trials that compared CEA with medical therapy refer to a historic form of medical therapy which was antiplatelet therapy with aspirin alone. It is confusing not to have any trials which compare best medical therapy to CAS or CEA. Please search hard for anything in the literature which compares modern medical therapy to modern surgery.	*We appreciate your comments.* *We are aware that the current standard for medical therapy is different from what is represented in the primary landmark CEA studies and this will be noted in the context/background of this report. The intended scope of this report is to focus on comparisons of stenting (with medical therapy) versus medical therapy alone and to compare CEA (with medical therapy) versus stenting (with medical therapy). A comprehensive review of medical therapy options is not within the scope of this report. To the extent that included studies provide information on current standard for medical care, it will be discussed in the report.*