

Stenting for Treatment of Atherosclerotic Stenosis of the Extracranial Carotid Arteries or Intracranial Arteries

Combined Comments to Draft Report

August 13, 2013

Health Technology Assessment Program (HTA)

Washington State Health Care Authority

PO Box 42712

Olympia, WA 98504-2712

(360) 725-5126

hta.hca.wa.gov

shtap@hca.wa.gov

COMBINED COMMENTS ON DRAFT REPORT

PUBLIC COMMENTS ON DRAFT REPORT1
AGENCY MEDICAL DIRECTORS' COMMENTS21
CLINICAL PEER REVIEW31

RESPONSES 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 public comments from the following parties:

Draft Report

1. David M. Topp, Director; Abbott Vascular Inc., Abbott Park, Illinois
2. Theodore A. Bass, MD, FSCAI, President; The Society for Cardiovascular Angiography and Interventions (SCAI), Washington D.C.

Specific responses pertaining to comments are included in Table 1.

	Comment	Response
David M. Topp; Abbott Vascular Inc., Abbott Park, Illinois		
1.	<p><u>Report Focus</u> The Washington State Health Care Authority Health Technology Assessment (HTA) Draft Evidence Report, dated June 28, 2013, titled “Carotid Artery Stenting” encompassed content from the Spectrum Research, Inc. report titled “Stenting for Treatment of Atherosclerotic Stenosis of the Extracranial Carotid Arteries or Intracranial Arteries”. Even though both intracranial and extracranial atherosclerotic diseases are important causes of ischemic stroke, it’s important to distinguish the differences between intracranial and extracranial carotid artery stenting, especially when carotid artery stenting is compared to carotid endarterectomy. Carotid artery stenting, when compared to carotid endarterectomy, generally refers to revascularization of the extracranial carotid arteries proximal to the petrous segment of the internal carotid artery, and does not include the intracranial vasculatures at or distal to the petrous segment. Given the differences in lesion locations, treatment modalities, U.S. Food and Drug Administration (FDA) approved labeling, and available clinical evidence on safety, efficacy, and cost-effectiveness between extracranial carotid artery stenting and intracranial artery stenting, extracranial carotid artery stenting should be evaluated independently in order to provide clear and unbiased assessment of the therapy. Information on intracranial artery stenting for treatment of atherosclerotic stenosis should be excluded from the Health Technology Assessment Draft Evidence Report so the report can focus on comparing carotid artery stenting and carotid endarterectomy as intended.</p> <p><u>Cost Comparison</u> The Washington State Utilization and Cost Data in Section 1.4 intended to provide utilization and cost comparison between carotid artery stenting and carotid endarterectomy based on data from 2009 to 2012. Since carotid endarterectomy is performed only for atherosclerotic stenosis in the extracranial vasculatures, only costs associated with extracranial carotid artery stenting should be included in this analysis for an “apple-</p>	<p>Thank you for your comments.</p> <p><u>Regarding focus:</u> The report acknowledges the distinction between extracranial and intracranial disease and their treatment in both the introduction and by evaluating intracranial disease via a separate key question.</p> <p><u>Cost comparison</u> Key Question 5 contains evaluation of full economic studies which met the inclusion criteria, including the study by Vilain.</p>

	Comment	Response
	<p>to-apple” comparison. However, the cost analysis for Carotid Artery Stenting combined Total Paid for cervical, extracranial and intracranial procedures. As noted in the report, average payment for cervical procedures were \$26,465, average payment for intracranial procedures were \$80,826 and average payment for extracranial procedures were \$34, 348. By including payment for intracranial procedures, the Total Paid and Average Paid for Carotid Artery Stenting were skewed much higher than if only payment for extracranial and cervical procedures (assuming all the cervical procedures were to treat atherosclerotic stenosis in the extracranial internal carotid arteries) were included. Intracranial procedures should be excluded from the cost analysis (and the HTA Draft Evidence Report as a whole) in order to provide an unbiased comparison between Carotid Artery Stenting and Carotid Endarterectomy. A cost-effectiveness analysis from CREST, a randomized NIH-sponsored clinical trial comparing carotid artery stenting and carotid endarterectomy in 2,502 patients, at 117 centers, with symptomatic or asymptomatic carotid atherosclerotic stenosis, concluded that the procedural and post-procedural cost differences between carotid artery stenting and carotid endarterectomy was not statistically significant.¹ This benchmark study provides great insight on the estimated costs for well-managed carotid artery stenting and carotid endarterectomy procedures.</p> <p><u>U.S. FDA Indication</u> U.S. Food and Drug Administration (FDA) labeling did not have restrictions on carotid artery stent use in high surgical risk asymptomatic patients with higher than 80% stenosis as stated on page 2 under the Introduction section and page 67 under the Indications and Contraindications section. Before 2011, U.S. FDA labeling for carotid artery stenting covered symptomatic high surgical risk patients with ≥ 50% stenosis and asymptomatic high surgical risk patients with ≥ 80% stenosis by ultrasound or angiogram. In 2011, U.S. FDA expanded the labeled indication for carotid artery stenting (only for Acculink Carotid Stent System manufactured by Abbott Vascular, Inc.) to include symptomatic standard</p>	<p>Data on cost and utilization in Washington State are provided by the Washington State Health Technology Assessment Program. The data are not used to evaluate cost-effectiveness. These administrative data reflect use of the technologies in Washington State Programs. The following clarification on these data was provided by the Program: A footnote was added to Agency Utilization Data figures 2a and 2b comparing average allowed amounts for the three procedure types. However, the state's sample size is inadequate to draw conclusions about differential cost. State utilization data for cervical, extracranial, and intracranial carotid artery procedures are included in the report to support evidence reviews for all procedure types. Endarterectomy data is included as a comparator for number of cases and adverse events, but may not be equivalent with all included CAS procedures</p>

	Comment	Response
	<p>surgical risk patients with $\geq 70\%$ stenosis by ultrasound or $\geq 50\%$ stenosis by angiogram and asymptomatic standard surgical risk patients with $\geq 70\%$ stenosis by ultrasound or $\geq 60\%$ stenosis by angiogram.² This carotid artery stenting indication expansion is based on the safety and effectiveness clinical evidence demonstrated in CREST.</p> <p>Even though there are no large-scale randomized or non-randomized comparative studies evaluating the safety and efficacy of carotid artery stenting and medical therapy versus medical therapy alone among patients with symptomatic and asymptomatic carotid stenosis to date, there is clinical evidence from numerous Investigational Device Exemption (IDE) and pre-market approval (PMA) studies over the last 10+ years, such as SAPPHIRE (2002), ARChER (2003), SECuRITY (2003), BEACH (2004), MAVeRIC (2004), CABERNET (2004), CREATE (2005), EMPIRE (2008), EPIC (2008), PROTECT (2008), ARMOUR (2009), to support U.S. FDA approval for the safe and effective use of carotid stent systems in conjunction with carotid embolic protection systems in both symptomatic and asymptomatic patients with carotid atherosclerotic stenosis. The landmark North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the Asymptomatic Carotid Atherosclerosis Study (ACAS) have established carotid endarterectomy as the standard for treating patients with symptomatic and asymptomatic carotid atherosclerotic stenosis versus medical therapy.^{3,4} CREST results demonstrated the risk of stroke, myocardial infarction, or death did not differ significantly in the CAS group and the CEA group of patients with symptomatic and asymptomatic carotid atherosclerotic stenosis.⁵ Carotid artery stenting and carotid endarterectomy are complementary, safe and effective, treatment modalities for patients with symptomatic and asymptomatic carotid atherosclerotic stenosis.</p> <p><u>Strength of Evidence</u> Since not all clinical studies are designed equal, it is important to group studies of a similar caliber for comparison purposes. In addition to the inclusion and exclusion criteria used in this draft report, it will be</p>	<p>for cost comparison.</p> <p><u>FDA Indication</u></p> <p>This has been reviewed and corrected</p>

	Comment	Response
	<p>beneficial to group and compare studies with high overall quality and low level of potential bias. Prospective, multi-center studies with large sample sizes, independent core lab assessments and tight confidence intervals are considered higher quality than retrospective single-center studies with small sample sizes, non-independent assessments, and wide confidence intervals. Simply grouping CREST and Kentucky 2004, for instance, under randomized controlled trial for evaluation creates perplexity and makes it difficult to draw conclusions and recommendations based on the assessment.</p> <p>Rating on the overall quality of the body of evidence is provided under the Summary by Key Questions – Strength of Evidence section. It is concerning that all of the outcomes provided to support this assessment report were rated “insufficient”, “low” or “moderate”, none of the outcomes were rated with “high” level of quality. In addition, reference for the outcome listed in the summary table was not provided making reviewing and commenting impossible. Adding source/citation to the outcome data will be very helpful in facilitating public comments.</p> <p><u>Additional Considerations</u> Embolic protection is an integral part of carotid artery stenting and the clinical evidence on the use of embolic protection devices (EPDs) should be included as part of this report to provide a comprehensive evaluation on the safety and effectiveness of carotid artery stenting. As noted in the report, EPD use significantly reduced the risk of thromboembolic complications. Use of embolic protection, distal or proximal, should be mandatory in carotid artery stenting procedures to ensure safety and effectiveness of the therapy.</p> <p>A large amount of clinical evidence was evaluated to support this draft assessment report, and most of the outcomes identified were rated “not statistically significant” and do not favor either carotid artery stenting or carotid endarterectomy. Do the “not statistically significant “ outcomes support offering both carotid artery stenting or carotid endarterectomy to patients with</p>	<p>Regarding listed studies: the SAPPHERE and CREST studies are included in detail in the report and appendices, together with other comparative studies which met <i>a priori</i> inclusion criteria. The other studies listed here did not meet our inclusion criteria.</p> <p><u>Strength of Evidence</u> We are fully aware that the quality of all studies is not equal and the quality of individual studies was assessed in consideration of the overall strength of evidence. The overall strength of evidence was determined for primary important outcomes as described in the methods section.</p> <p>Appendix D describes the critical appraisal and risk of bias evaluation and determination of overall</p>

	Comment	Response
	<p>atherosclerotic stenosis in the extracranial carotid arteries? It would be valuable to include conclusions and recommendations based on this assessment to provide guidance on whether the key questions were addressed and if further assessment is warranted.</p> <p><u>Other Observations</u> It is noted that the section numbering in the report does not match with the section numbering in the Table of Content, for example, BACKGROUND under section 2 in the Table of Content was labeled section 5 in the report, and can cause confusion to readers. This should be addressed in the final assessment report.</p> <p><u>References</u></p> <ol style="list-style-type: none"> Vilain KR, Magnuson EA, Li H, et al. (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. 2012:Epub ahead of print. Abbott Vascular, Inc. (2013) RX Acculink Carotid Stent System Product Instructions for Use (http://www.abbottvascular.com) North American Symptomatic Carotid Endarterectomy Trial Collaborators. (1991) Beneficial Effect of Carotid Endarterectomy in Symptomatic Patients with High Grade Carotid Stenosis N Engl J Med 1991; 325 (7):445-453. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. (1995) Endarterectomy for Asymptomatic Carotid Artery Stenosis. JAMA 1995; 273:1421-1428. Brott TG, Hobson RW, 2nd, Howard G, et al. (2010) Stenting versus endarterectomy for treatment of carotid-artery stenosis. N Engl J Med 2010; 363(1): 11-23. 	<p>strength of evidence.</p> <p>Appendix E provides detailed critical appraisal of included comparative studies based on established criteria and describing the area for potential bias for the RCTS in particular. In addition, a brief summary of study quality is found in section 3.3 of the report.</p> <p>Section 5 of the report (Summary by key question and strength of evidence) delineates factors which contributed to the down grading of evidence on specific outcomes, based on the methodologies described in Appendix D and detailed critical appraisal in Appendix E.</p> <p>Sensitivity analyses excluding older studies which did not use EPDs was done for primary outcomes.</p> <p><u>Additional considerations:</u> Comparison of EPDs was not within the scope of this report, however information on EPDs is presented throughout the report: The background provides basic information on EPDs, including data</p>

	Comment	Response
		<p>from various studies, recommendations in practice guidelines and CMS requirements for their use. Section 2.8 summarizes previous technology assessments, including reports that specifically evaluated CAS with EPD use (Blue Cross Blue Shield 2012 report) and summarizes the meta-analysis by Bersin et. al. on the use of proximal occlusion devices. For primary outcomes in our HTA report, sensitivity analyses which excluded older studies and those which did not use EPDs were conducted and the results reported.</p> <p>Regarding any recommendation for offering both CAS and CEA to patients, this is the purview of the Health Technology Clinical Committee based on their evaluation of the data and report.</p> <p><u>Other observations:</u> The formatting issues have been addressed.</p> <p><u>References:</u> The Vilain and Brott studies are included in the report. Others listed did not meet inclusion criteria.</p>

	Comment	Response
Theodore A. Bass, MD, FSCAI, President; Society for Cardiovascular Angiography and Interventions		
2.	<p>Thank you for allowing public comment on your Carotid Stenting Draft Evidence Statement which is available at: http://www.hta.hca.wa.gov/documents/cas_draft_report_062813.pdf</p> <p>At 285 pages not including appendices, it is a daunting document to review.</p> <p>The Society for Cardiovascular Angiography and Interventions (SCAI) is a professional organization representing over 4,000 invasive and interventional cardiologists. SCAI promotes excellence in cardiovascular catheterization, angiography and interventional cardiology through physician education and representation, and quality initiatives to enhance patient care. Our responses to the Key Questions follows:</p>	<p>Thank you for your comments.</p>
	<p><i>Key Question 1.</i> In symptomatic or asymptomatic persons with atherosclerotic carotid artery stenosis what is the evidence of short- and long-term comparative efficacy and effectiveness of:</p> <p>a. Extra-cranial carotid artery stenting (CAS) and medical therapy compared with medical therapy alone?</p> <p>RESPONSE: No comparisons have been made.</p> <p>a. Extra-cranial carotid artery stenting (CAS) and medical therapy compared with carotid endarterectomy (CEA) and medical therapy?</p> <p>RESPONSE: This evidence report needs to make a greater distinction between high quality randomized trials conducted in the United States and numerous weaker studies. Studies which don't include embolyic protection devices are especially weak. The meta studies in this report and developed elsewhere suffer from this flaw and should not be used in decision-making.</p> <p><i>Key Question 2.</i> In symptomatic persons with atherosclerotic stenosis of the intracranial arteries, what is</p>	<p>Please see responses above regarding critical appraisal of studies and sensitivity analyses that were conducted which considered higher quality studies and those which used EPDs.</p>

	Comment	Response
	<p>the evidence of short- and long-term comparative efficacy and effectiveness of Intracranial artery stenting and medical therapy compared with medical therapy alone?</p> <p>RESPONSE: Primary stenting has not demonstrated superiority over PTA for medically refractory intracranial stenoses, but appears to have benefit as a bailout for failed PTA or failed thrombectomy.</p> <p><i>Key Question 3.</i> What is the evidence regarding adverse events and complications, particularly during the periprocedural period and longer term, for stenting compared with alternative treatments? In persons with extracranial carotid artery stenosis, are rates of periprocedural death or stroke <3% for asymptomatic patients and <6% for symptomatic patients?</p> <p>RESPONSE: Evidence shows that CAS can and is being provided with success rates within the outcome thresholds for increased surgical risk patients and for the increased risk indications established by the AHA Council on Stroke in 1995. Additionally, the meta-analysis of CAS with POD devices demonstrated an overall 30-day MACE rate of 2.25% and no subgroup had a MACE rate of more than 2.6%, including symptomatic patients of all age subgroups (Bersin RM et al Catheterization and Cardiovascular Interventions 2012; 80:1072–1078).</p> <p><i>Key Question 4.</i> Is there evidence of differential efficacy or safety for special populations, (including consideration of age, gender, race, diabetes, atrial fibrillation or other co-morbidities, ethnicity, or disability)?</p> <p>RESPONSE: We concur with the Evidence Reports assessment that increased age is a predictor of MACE for both CAS and CEA.</p> <p><i>Key Question 5.</i> 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?</p>	<p>Data from included studies are presented in the report; In addition, Section 2.8 summarizes previous technology assessments, including reports that specifically evaluated CAS with EPD use (Blue Cross Blue Shield 2012 report) and summarizes the meta-analysis by Bersin et. al. on the use of proximal occlusion devices.</p> <p>We agree that nonrandomized studies potentially suffer from significant bias.</p>

	Comment	Response
	<p>RESPONSE: The only randomized trials in the U.S. that compared costs of CAS and CAE found little difference in costs. Non randomized studies suffer from significant bias because coverage of CAS is generally limited to the sickest patients. A strong analysis of costs would include the costs of all associated care including anesthesia (which is not separately billed or in carotid stenting) and the associated costs of employee sick leave and other ancillary costs. In comparisons of coronary stenting versus coronary surgery (CABG), the endovascular treatment has significant advantages.¹ Additionally, past costs do not necessarily predict future costs. As more devices become available in the U.S. market, it can be reasonably projected that costs for stenting will go down.</p> <p>Reference: 1. Epstein AJ et al. Impact of Minimally Invasive Surgery on Medical Spending and Employee Absenteeism. Surgery, Medical Spending, and Absenteeism. JAMA surgery. 2013. 1-7</p>	<p>Unfortunately, there are also potential biases in RCTs and potentially related to assumptions about the types of data and how they may be modeled for economic analysis. It is likely that rigorous economic evaluations which consider a broader range of important costs as well as accurate reflections of event rates may be helpful.</p> <p>Reference provided does not meet our inclusion criteria.</p>

July 30, 2013

Josh Morse, MPH
Program Director
Health Technology Assessment Program
P.O. Box 42712
Olympia, WA 98504-2712

RE: Washington State Health Care Authority, HTA Program

Dear Mr. Morse:

Abbott appreciates this opportunity to provide comments to the Washington State Health Care Authority's Health Technology Assessment program, on the Draft Evidence Report regarding carotid artery stenting (CAS). The report reviews the evidence available on the safety, efficacy, and cost-effectiveness of this technology.

Abbott is a global healthcare company devoted to improving life through the development of products and technologies that span the breadth of healthcare. With a portfolio of leading, science-based offerings in diagnostics, medical devices, nutritionals and branded generic pharmaceuticals, Abbott serves people in more than 150 countries and employs approximately 70,000.

Abbott is a global leader in cardiac and vascular care with market-leading products and an industry-leading pipeline. Abbott Vascular, a division of Abbott, is committed to advancing patient care by transforming the treatment of vascular disease through medical device innovations, investments in research and development, and physician training and education. We offer cutting-edge devices for coronary artery disease, peripheral vascular disease, carotid artery disease and structural heart disease, and believe it is critical that patients and providers have access to the most effective and appropriate technology and treatments. To that end, we welcome the opportunity to provide additional insight into the CAS assessment.

We look forward to working with you and the committee as you conduct your assessment. Please do not hesitate to contact me if you have any questions or if Abbott can be of any assistance.

Sincerely,

David M. Topp
Director
Abbott Laboratories
David.Topp@Abbott.com

Attachment

Carotid Artery Stenting

Submission to Washington State Health Technology Assessment Program

Comments On Draft Evidence Report

Abbott Vascular

30 July 2013

Report Focus

The Washington State Health Care Authority Health Technology Assessment (HTA) Draft Evidence Report, dated June 28, 2013, titled “Carotid Artery Stenting” encompassed content from the Spectrum Research, Inc. report titled “Stenting for Treatment of Atherosclerotic Stenosis of the Extracranial Carotid Arteries or Intracranial Arteries”. Even though both intracranial and extracranial atherosclerotic diseases are important causes of ischemic stroke, it’s important to distinguish the differences between intracranial and extracranial carotid artery stenting, especially when carotid artery stenting is compared to carotid endarterectomy. Carotid artery stenting, when compared to carotid endarterectomy, generally refers to revascularization of the extracranial carotid arteries proximal to the petrous segment of the internal carotid artery, and does not include the intracranial vasculatures at or distal to the petrous segment. Given the differences in lesion locations, treatment modalities, U.S. Food and Drug Administration (FDA) approved labeling, and available clinical evidence on safety, efficacy, and cost-effectiveness between extracranial carotid artery stenting and intracranial artery stenting, extracranial carotid artery stenting should be evaluated independently in order to provide clear and unbiased assessment of the therapy. Information on intracranial artery stenting for treatment of atherosclerotic stenosis should be excluded from the Health Technology Assessment Draft

Evidence Report so the report can focus on comparing carotid artery stenting and carotid endarterectomy as intended.

Cost Comparison

The Washington State Utilization and Cost Data in Section 1.4 intended to provide utilization and cost comparison between carotid artery stenting and carotid endarterectomy based on data from 2009 to 2012. Since carotid endarterectomy is performed only for atherosclerotic stenosis in the extracranial vasculatures, only costs associated with extracranial carotid artery stenting should be included in this analysis for an “apple-to-apple” comparison. However, the cost analysis for Carotid Artery Stenting combined Total Paid for cervical, extracranial and intracranial procedures. As noted in the report, average payment for cervical procedures were \$26,465, average payment for intracranial procedures were \$80,826 and average payment for extracranial procedures were \$34,348. By including payment for intracranial procedures, the Total Paid and Average Paid for Carotid Artery Stenting were skewed much higher than if only payment for extracranial and cervical procedures (assuming all the cervical procedures were to treat atherosclerotic stenosis in the extracranial internal carotid arteries) were included. Intracranial procedures should be excluded from the cost analysis (and the HTA Draft Evidence Report as a whole) in order to provide an unbiased comparison between Carotid Artery Stenting and Carotid Endarterectomy. A cost-effectiveness analysis from CREST, a randomized NIH-sponsored clinical trial comparing carotid artery stenting and carotid endarterectomy in 2,502 patients, at 117 centers, with symptomatic or asymptomatic carotid atherosclerotic stenosis, concluded that the procedural and post-procedural cost differences between carotid artery stenting and carotid endarterectomy was not statistically significant.¹ This benchmark study provides great insight on the estimated costs for well-managed carotid artery stenting and carotid endarterectomy procedures.

U.S. FDA Indication

U.S. Food and Drug Administration (FDA) labeling did not have restrictions on carotid artery stent use in high surgical risk asymptomatic patients with higher than 80% stenosis as stated on page 2 under the Introduction section and page 67 under the Indications and Contraindications section. Before 2011, U.S. FDA labeling for carotid artery stenting covered symptomatic high surgical risk patients with $\geq 50\%$ stenosis and asymptomatic high surgical risk patients with $\geq 80\%$ stenosis by ultrasound or angiogram. In 2011, U.S. FDA expanded the labeled indication for carotid artery stenting (only for Acculink Carotid Stent System manufactured by Abbott Vascular, Inc.) to include symptomatic standard surgical risk patients with $\geq 70\%$ stenosis by ultrasound or $\geq 50\%$ stenosis by angiogram and asymptomatic standard surgical risk patients with $\geq 70\%$ stenosis by ultrasound or $\geq 60\%$ stenosis by angiogram.² This carotid artery stenting indication expansion is based on the safety and effectiveness clinical evidence demonstrated in CREST.

Even though there are no large-scale randomized or non-randomized comparative studies evaluating the safety and efficacy of carotid artery stenting and medical therapy versus medical therapy alone among patients with symptomatic and asymptomatic carotid stenosis to date, there is clinical evidence from numerous Investigational Device Exemption (IDE) and pre-market

approval (PMA) studies over the last 10+ years, such as SAPPHIRE (2002), ARChER (2003), SECuRITY (2003), BEACH (2004), MAVeRIC (2004), CABERNET (2004), CREATE (2005), EMPIRE (2008), EPIC (2008), PROTECT (2008), ARMOUR (2009), to support U.S. FDA approval for the safe and effective use of carotid stent systems in conjunction with carotid embolic protection systems in both symptomatic and asymptomatic patients with carotid atherosclerotic stenosis. The landmark North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the Asymptomatic Carotid Atherosclerosis Study (ACAS) have established carotid endarterectomy as the standard for treating patients with symptomatic and asymptomatic carotid atherosclerotic stenosis versus medical therapy.^{3,4} CREST results demonstrated the risk of stroke, myocardial infarction, or death did not differ significantly in the CAS group and the CEA group of patients with symptomatic and asymptomatic carotid atherosclerotic stenosis.⁵ Carotid artery stenting and carotid endarterectomy are complementary, safe and effective, treatment modalities for patients with symptomatic and asymptomatic carotid atherosclerotic stenosis.

Strength of Evidence

Since not all clinical studies are designed equal, it is important to group studies of a similar caliber for comparison purposes. In addition to the inclusion and exclusion criteria used in this draft report, it will be beneficial to group and compare studies with high overall quality and low level of potential bias. Prospective, multi-center studies with large sample sizes, independent core lab assessments and tight confidence intervals are considered higher quality than retrospective single-center studies with small sample sizes, non-independent assessments, and wide confidence intervals. Simply grouping CREST and Kentucky 2004, for instance, under randomized controlled trial for evaluation creates perplexity and makes it difficult to draw conclusions and recommendations based on the assessment.

Rating on the overall quality of the body of evidence is provided under the Summary by Key Questions – Strength of Evidence section. It is concerning that all of the outcomes provided to support this assessment report were rated “insufficient”, “low” or “moderate”, none of the outcomes were rated with “high” level of quality. In addition, reference for the outcome listed in the summary table was not provided making reviewing and commenting impossible. Adding source/citation to the outcome data will be very helpful in facilitating public comments.

Additional Considerations

Embolic protection is an integral part of carotid artery stenting and the clinical evidence on the use of embolic protection devices (EPDs) should be included as part of this report to provide a comprehensive evaluation on the safety and effectiveness of carotid artery stenting. As noted in the report, EPD use significantly reduced the risk of thromboembolic complications. Use of embolic protection, distal or proximal, should be mandatory in carotid artery stenting procedures to ensure safety and effectiveness of the therapy.

A large amount of clinical evidence was evaluated to support this draft assessment report, and most of the outcomes identified were rated “not statistically significant” and do not favor either carotid artery stenting or carotid endarterectomy. Do the “not statistically significant” outcomes support offering both carotid artery stenting or carotid endarterectomy to patients with atherosclerotic stenosis in the extracranial carotid arteries? It would be valuable to include

conclusions and recommendations based on this assessment to provide guidance on whether the key questions were addressed and if further assessment is warranted.

Other Observation

It is noted that the section numbering in the report does not match with the section numbering in the Table of Content, for example, BACKGROUND under section 2 in the Table of Content was labeled section 5 in the report, and can cause confusion to readers. This should be addressed in the final assessment report.

References

1. **Vilain KR, Magnuson EA, Li H, et al.** (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*. 2012:Epub ahead of print.
2. **Abbott Vascular, Inc.** (2013) RX Acculink Carotid Stent System Product Instructions For Use (http://www.abbottvascular.com/static/cms_workspace/pdf/ifu/carotid_intervention/eIFU_RX_Acculink.pdf)
3. **North American Symptomatic Carotid Endarterectomy Trial Collaborators.** (1991) Beneficial Effect of Carotid Endarterectomy in Symptomatic Patients with High Grade Carotid Stenosis *N Engl J Med* 1991; 325 (7):445-453.
4. **Executive Committee for the Asymptomatic Carotid Atherosclerosis Study.** (1995) Endarterectomy for Asymptomatic Carotid Artery Stenosis. *JAMA* 1995; 273:1421-1428.
5. **Brott TG, Hobson RW, 2nd, Howard G, et al.** (2010) Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med* 2010; 363(1): 11-23.



The Society for Cardiovascular Angiography and Interventions Foundation

1100 17th Street NW, Suite 330, Washington, DC 20036

Main: 202.741.9854 ♦ Toll Free: 800.992.7224 ♦ Fax: 800.863.5202 ♦ E-mail: info@scai.org

Submitted Electronically to: shtap@hca.wa.gov

Officers

Theodore A. Bass, MD, FSCAI
President

Charles E. Chambers, MD, FSCAI
President-Elect

James C. Blankenship, MD, FSCAI
Vice President

J. Jeffrey Marshall, MD, FSCAI
Immediate Past President

Carl L. Tommaso, MD, FSCAI
Treasurer

David A. Cox, MD, FSCAI
Assistant Treasurer

Kenneth Rosenfield, MD, MHCDS, FSCAI
Secretary

Trustees

H. Vernon Anderson, MD, FSCAI

Robert J. Applegate, MD, FSCAI

Ralph G. Brindis, MD, MPH, FSCAI

Peter L. Duffy, MD, FSCAI

Oswaldo S. Gigliotti, MD, FSCAI

Cindy L. Grines, MD, FSCAI

Tarek A. Helmy, MD, FSCAI

Michael R. Jaff, DO, FSCAI

Dennis W. Kim, MD, PhD, FSCAI

Daniel S. Levi, MD, FSCAI

Ayman K.A. Magd, MD, PhD, FSCAI

Srihari S. Naidu, MD, FSCAI

Thach N. Nguyen, MD, FSCAI

John P. Reilly, MD, FSCAI

Kenneth Rosenfield, MD, MHCDS, FSCAI

Huay-Cheem Tan, MBBS, FSCAI

Gerald S. Werner, MD, PhD, FSCAI

Trustees for Life

Frank J. Hildner, MD, FSCAI

William C. Sheldon, MD, FSCAI

SCAI 2014 Scientific Sessions

Las Vegas, NV May 28-31, 2014

Program Chair

Morton J. Kern, MD, FSCAI

Program Co-Chairs

Michael R. Jaff, DO, FSCAI

Roxana Mehran, MD, FSCAI

Congenital Heart Disease Program Co-Chairs

Matthew J. Gillespie, MD, FSCAI

Doff B. McElhinney, MD, FSCAI

Executive Director

Norm Linsky

Dorothy Frost Teeter, MHA
Director
Washington State Health Care Authority
626 8th Avenue SE
P.O. Box 45502
Olympia, WA 98504-5502

Dear Ms. Teeter

Thank you for allowing public comment on your Carotid Stenting Draft Evidence Statement which is available at:

http://www.hta.hca.wa.gov/documents/cas_draft_report_062813.pdf. At 285 pages not including appendices, it is a daunting document to review.

The Society for Cardiovascular Angiography and Interventions (SCAI) is a professional organization representing over 4,000 invasive and interventional cardiologists. SCAI promotes excellence in cardiovascular catheterization, angiography and interventional cardiology through physician education and representation, and quality initiatives to enhance patient care. Our responses to the Key Questions follows:

Key Question 1. 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. Extra-cranial carotid artery stenting (CAS) and medical therapy compared with medical therapy alone?

RESPONSE: No comparisons have been made.

b. Extra-cranial carotid artery stenting (CAS) and medical therapy compared with carotid endarterectomy (CEA) and medical therapy?

RESPONSE: This evidence report needs to make a greater distinction between high quality randomized trials conducted in the United States and numerous weaker studies. Studies which don't include embolytic protection devices are especially weak. The meta studies in this report and developed elsewhere suffer from this flaw and should not be used in decision-making.

Key Question 2. In symptomatic persons with atherosclerotic stenosis of the intracranial arteries, what is the evidence of short- and long-term comparative efficacy and effectiveness of Intracranial artery stenting and medical therapy compared with medical therapy alone?

RESPONSE: Primary stenting has not demonstrated superiority over PTA for medically refractory intracranial stenoses, but appears to have benefit as a bailout for failed PTA or failed thrombectomy.

Key Question 3. What is the evidence regarding adverse events and complications, particularly during the periprocedural period and longer term, for stenting compared with alternative treatments? In persons with extracranial carotid artery stenosis, are rates of periprocedural death or stroke <3% for asymptomatic patients and <6% for symptomatic patients?

RESPONSE:

Evidence shows that CAS can and is being provided with success rates within the outcome thresholds for increased surgical risk patients and for the increased risk indications established by the AHA Council on Stroke in 1995. Additionally, the meta-analysis of CAS with POD devices demonstrated an overall 30-day MACE rate of 2.25% and no subgroup had a MACE rate of more than 2.6%, including symptomatic patients of all age subgroups (Bersin RM et al Catheterization and Cardiovascular Interventions 2012; 80:1072–1078).

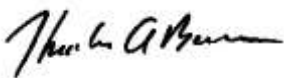
Key Question 4. Is there evidence of differential efficacy or safety for special populations, (including consideration of age, gender, race, diabetes, atrial fibrillation or other co-morbidities, ethnicity, or disability)?

RESPONSE: We concur with the Evidence Reports assessment that increased age is a predictor of MACE for both CAS and CEA.

Key Question 5. 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?

RESPONSE: The only randomized trials in the U.S. that compared costs of CAS and CAE found little difference in costs. Non randomized studies suffer from significant bias because coverage of CAS is generally limited to the sickest patients. A strong analysis of costs would include the costs of all associated care including anesthesia (which is not separately billed or in carotid stenting) and the associated costs of employee sick leave and other ancillary costs. In comparisons of coronary stenting versus coronary surgery (CABG), the endovascular treatment has significant advantages.² Additionally, past costs do not necessarily predict future costs. As more devices become available in the U.S. market, it can be reasonably projected that costs for stenting will go down.

Sincerely,



Theodore A. Bass, MD, FSCAI
SCAI President, 2013-2014

² Epstein, Andrew J., et al. "Impact of Minimally Invasive Surgery on Medical Spending and Employee Absenteeism Surgery, Medical Spending, and Absenteeism." JAMA surgery (2013): 1-7.

RESPONSES TO AGENCY MEDICAL DIRECTORS

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 clinical and peer reviews from the following parties:

Draft Report

- Washington State Agency Medical Directors Workgroup

Specific responses pertaining to each comment are included in Table 1.

Table 1

	Comment	Response
Washington State Agency Medical Directors Workgroup		
	Specific comments:	
1 (major points)		
1a	<p>P15. [Regarding KQ4, differential efficacy and safety in asymptomatic patients]. <i>“Age. No RCT data were available. Data from one registry study suggested that age (< 65 versus. ≥ 65) did not modify the treatment effect of CEA versus CAS in terms of periprocedural death, stroke, or MI, or the composite outcome of periprocedural death, stroke, or MI”</i>. The description of the finding in the evidence report does not correctly reflect what the data indicate from the original study (Jim et al. 2012. <i>J Vasc Surg.</i> 55(5):1313-20). Here are the results from the study: <i>“In patients aged <65 years, the primary end point (5.23% CAS vs 3.56% CEA; P = .065) did not reach statistical significance. Subgroup analyses showed that CAS had a higher combined death/stroke/MI rate (4.44% vs 2.10%; P < .031) in asymptomatic patients but there was no difference in the symptomatic (6.00% vs 5.47%; P = .79) group. In patients aged ≥ 65 years, CEA had lower rates of death (0.91% vs 1.97%; P < .01), stroke (2.52% vs 4.89%; P < .01), and composite death/stroke/MI (4.27% vs 7.14%; P < .01). CEA in patients aged ≥ 65 years was associated with lower rates of the primary end point in symptomatic (5.27% vs 9.52%; P < .01) and asymptomatic (3.31% vs 5.27%; P < .01) subgroups. After risk adjustment, CAS patients aged ≥ 65 years were more likely to reach the primary end point”</i>. The authors of the paper concluded that compared with CEA, CAS resulted in inferior 30-day outcomes in symptomatic and asymptomatic patients aged ≥ 65 years, and these findings do not support the widespread use of CAS in patients aged ≥ 65 years.</p>	<p>We have added data tables for this study to the results section of KQ4 to provide further clarity.</p> <p>The authors of this study used subgroup analysis to conclude that age may affect treatment outcomes. However, from an epidemiological standpoint, one cannot infer that a differential subgroup effect (i.e. effect modification) is present based on separate tests of treatment effects within the two different age subgroups (ie, to compare one significant and one nonsignificant p-value). (Matthews JN, Altman DG (1996) <i>Statistics notes. Interaction 2: Compare effect sizes not P values. BMJ</i>;313(7060):808.; Kamangar F. Effect modification in epidemiology and medicine. <i>Arch Iran Med.</i> 2012; 15(9): 575 – 582.)</p> <p>In the report, KQ4 asks us to look at whether different subgroups, such as age, are differentially affected by different treatments. Put another way it is asking if a factor such as age “modifies” treatment effect. This requires evaluation of the extent to which the magnitude of estimates (relative risks, risk differences, and their corresponding 95% confidence intervals) are different</p>

	Comment	Response
Washington State Agency Medical Directors Workgroup		
		<p>from in one stratum versus the other.</p> <p>So although there were differences in each subgroup (ie, comparing one significant and one nonsignificant p-value), the confidence intervals for the RD and RR overlap, indicating that age does not modify treatment effect. This should be further researched since small numbers of events may preclude identification of modification by age.</p> <p>In terms of overall strength of evidence, this is a single registry study with moderately high risk of bias, and our reported concluded that the overall quality of evidence for this outcome based on the available study was judged to be insufficient.</p>
1b	<p>P16-17. [Regarding KQ4, differential efficacy and safety in symptomatic patients]. The description of the effect of sex on treatment outcomes and the summary data in the evidence table on p36 are confusing. It states on p16 “...data from the EVA-3S trial suggested that sex significantly modified treatment outcome in terms of ipsilateral stroke through four years: males were at greater risk of periprocedural death or stroke following CAS versus CEA, ...”. In the evidence table on p36, however, both males and females had an increased risk of periprocedural stroke following CAS vs. CEA. In addition, males were at lower risk of MI following CAS vs. CEA. Please explain, and ensure the evidence table and the description of the findings are consistent.</p>	<p>Thank you, we have corrected the text throughout (in summary statements and in KQ4 results) to address this issue.</p>
1c	<p>The CREST study (Howard et al. 2011) found that periprocedural risk of events is likely higher in women who have CAS than those who have CEA. This finding did not seem to be discussed in the evidence report.</p>	<p>This comment pertains to KQ4. In short, all data from this study was included in the evidence report (in the draft report, it was reference 92). The one outcome</p>

	Comment	Response
Washington State Agency Medical Directors Workgroup		
		<p>that this study found that sex modified treatment effect was the composite outcome of periprocedural stroke, death, or MI in symptomatic patients. We have added this conclusion to the Evidence Summary.</p> <p>In the section of asymptomatic patients, data from the Howard follow-up report of the CREST trial (for periprocedural stroke; periprocedural MI; and periprocedural stroke/death/MI were included (in KQ4, see asymptomatic patient section on sex, and the analyses from RCTs.)</p> <p>In symptomatic patients, for periprocedural death or stroke, data from the CREST trial was included in the meta-analysis (see Figure 19). Data from the Howard follow-up study (for periprocedural stroke; periprocedural MI; and periprocedural stroke/death/MI) were included and are described immediately following Figure 19. The outcome periprocedural stroke/death/MI is the outcome this comment likely refers to, however, this composite outcome was not a primary outcome for the HTA and is thus not described in the evidence tables. (The composite outcome of stroke/death/MI is not an ideal way to report results, because it lumps dissimilar outcomes together, potentially biases result to the null and doesn't allow for</p>

	Comment	Response
Washington State Agency Medical Directors Workgroup		
		evaluation of contribution of specific rates for the individual outcomes.)
1d	P10. [Regarding KQ3, safety in asymptomatic patients]. <i>“Periprocedural myocardial infarction (MI): In one RCT (CREST) there was a statistically non-significant increase in the risk of periprocedural MI for CAS compared to CEA.”</i> However, the results of the original study (Silver et al 2011) indicate that the risk was higher for CEA instead.	This has been corrected in the executive summary and report.
1e	P11. <i>“Periprocedural death”</i> . The description of the results was unclear. Increased risk was reported following CAS compared with CEA in one of the studies. The difference was statistically significant, which should be stated explicitly here.	We have clarified information in the text; information on significance is in the evidence tables as well. With regard to interpretation, consideration of statistical significance should be within the context of evaluation of effect estimate sizes, confidence interval width, sample size and study quality, in addition to consideration of findings an strength of evidence across all studies for a given outcome.
1f	P11. <i>“Periprocedural stroke or death”</i> . Similarly, a clear statement should be made here regarding the increased risk following CAS.	We have clarified this. (See comment above)
1g	P12 and 30. [Regarding KQ3, 30 days safety for extra-cranial in symptomatic patients]. <i>“Any periprocedural stroke: across six RCTs, risk of periprocedural stroke was significantly greater for CAS compared to CEA (Pooled RD: 3.39%, 95% CI .15%, 6.6%)”</i> . This statement is not consistent with the data presented in the evidence table on p30, where 4 RCTs, rather than 6 RCTs, were included and RD=2.9%.	Additional clarification has been added to the bullet. The table reflects analysis which excluded older studies (which enrolled patients prior to 2000), studies with 10 or fewer patients per arm and studies that did not use embolic protection.
1h	P13 and 30. [Regarding KQ3, 30 days safety for extra-cranial in symptomatic patients]. <i>“Periprocedural stroke or stroke: The risk of stroke or death was 7.1% for CAS and 4.1% for CEA based on pooled data across seven RCTs reporting this composite, neither of which fell below 6%”</i> . This statement is not consistent with	The estimate from the sensitivity analysis is reflected in the table. A sentence to this effect has been added. (see comment above as well)

	Comment	Response
Washington State Agency Medical Directors Workgroup		
	the data presented in the evidence table on p30, where 4 RCTs, rather than 7 RCTs, were included.	
1i	P33. The interpretation of aHR in the footnote of the table is incorrect. It also refers to CEA, which is irrelevant here.	This has been corrected.
1j	P96. [Regarding inclusion/exclusion criteria]. The studies of CAS with or without embolic protection devices were included in this evidence report. Since EPD use significantly reduces the risk of thromboembolic complications, it is important to know how many studies using CAS without EPD were included in the report, and how often is CAS without EPD still being used in current practice.	<p>Six of the 10 included RCTs used EPD and 12/17 nonrandomized studies used EPDs. For the remaining studies EPDs were not used, use was not reported or it wasn't clear if they were used. This information has been added into the report. As stated previously, sensitivity analysis for the RCT meta-analyses which excluded older, small studies and those which did not use EPDs were done for the primary outcomes.</p> <p>The Centers for Medicare and Medicaid have limited their coverage to procedures using FDA-approved CAS systems in conjunction with FDA-approved or –cleared EPDs only. FDA labeling stipulates use of EPDs(BCBS 2012).</p> <p>We found no data/references on the extent to which EPDs (regardless of type) are or are not routinely used in current clinical practice.</p>
2 (minor points)		
2a	P8. Ipsilateral stroke. "..., rates ranged from 1.5% -2.2% following CAS and 1.5% 2.4%.". Vague and incomplete sentence.	Revision made
2b	P10. [Regarding KQ3, safety for extra-cranial in asymptomatic patients] " Periprocedural cranial nerve	The evidence summary tables and assessment of overall strength of

	Comment	Response
Washington State Agency Medical Directors Workgroup		
	<i>palsy</i> : Across two RCTs, risk of periprocedural cranial nerve palsy was significantly lower for CAS compared to CEA". This finding was not included in the evidence table on p28.	evidence focus on the primary outcomes described in the report. This was a secondary outcome and therefore not included in the summary tables.
2c	P20 -39. [Regarding the evidence tables]. The total number of studies included in each table should be stated clearly somewhere in the table or in the footnote. It is good to count studies up in each outcome category, but it would be useful to know the total number of studies referred in the table to avoid any confusion or wrong impression.	A footnote with the total number of studies in each table has been added. The information can also be seen by comparing the N for each study listed for the outcome.
2d	P26. [Regarding the table]. First subtitle: "KQ1: Asymptomatic CAS vs. CEA". The data is actually regarding medical therapy and CAS, rather than CEA.	This has been corrected
2e	P27-29. [Regarding the tables]. It is not obvious to tell if the data in these tables are pertinent to extra-cranial CAS or both extra-cranial and intracranial CAS. Please specify.	Clarification has been made; All tables for KQ 3 are in patients with extracranial disease
2f	P28. Calculation error or typo in 7(58/3418) [any stroke for CEA]. The rate should be 1.7 (58/3418).	Formatting has been corrected to show the complete number.
2g	P33. Incomplete CI of the first CAS aHR (IS:70-79%).	This has been corrected
2h	P63. Line 2 and 3, "Saroo 2006] In..." . There may be a typo here.	This has been corrected
2i	P134. "Stroke or death within 30 days or ischemic stroke in the territory of the qualifying artery beyond 30 days". The discussion is under a subtitle of "Efficacy" data. It is confusing because stroke or death within 30 days is a safety outcome by definition rather than an efficacy outcome.	This was the study's primary endpoint which is a composite that included not only 30 day stroke (which is described under safety) as well as the author's estimate of longer term (1 year) probability of ischemic stroke which is was considered under efficacy.
2j	P137. "Any stroke or death within 30 days after enrollment". The total events following stenting would be 38 (33 strokes + 5 deaths), though the total number of patients who had events was 33. I understand that the five deaths in the stenting group were of a result of stroke, but death and stroke should be counted as	These are reported separately above. For the composite, so as not to double count, it is reported as 33.

	Comment	Response
Washington State Agency Medical Directors Workgroup		
	separate events.	

**Agency Medical Directors Workgroup Comments on HCA Draft Evidence Report:
Carotid Artery Stenting**

Vendor: Spectrum Research, Inc.

Report Date: June 21, 2013

1. Major points

- a. P15. [Regarding KQ4, differential efficacy and safety in asymptomatic patients]. *“Age. No RCT data were available. Data from one registry study suggested that age (< 65 versus. ≥ 65) did not modify the treatment effect of CEA versus CAS in terms of periprocedural death, stroke, or MI, or the composite outcome of periprocedural death, stroke, or MI”*. The description of the finding in the evidence report does not correctly reflect what the data indicate from the original study (Jim et al. 2012. *J Vasc Surg.* 55(5):1313-20). Here are the results from the study: *“In patients aged <65 years, the primary end point (5.23% CAS vs 3.56% CEA; P = .065) did not reach statistical significance. Subgroup analyses showed that CAS had a higher combined death/stroke/MI rate (4.44% vs 2.10%; P < .031) in asymptomatic patients but there was no difference in the symptomatic (6.00% vs 5.47%; P = .79) group. In patients aged ≥ 65 years, CEA had lower rates of death (0.91% vs 1.97%; P < .01), stroke (2.52% vs 4.89%; P < .01), and composite death/stroke/MI (4.27% vs 7.14%; P < .01). CEA in patients aged ≥ 65 years was associated with lower rates of the primary end point in symptomatic (5.27% vs 9.52%; P < .01) and asymptomatic (3.31% vs 5.27%; P < .01) subgroups. After risk adjustment, CAS patients aged ≥ 65 years were more likely to reach the primary end point”*. The authors of the paper concluded that compared with CEA, CAS resulted in inferior 30-day outcomes in symptomatic and asymptomatic patients aged ≥ 65 years, and these findings do not support the widespread use of CAS in patients aged ≥ 65 years.
- b. P16-17. [Regarding KQ4, differential efficacy and safety in symptomatic patients]. The description of the effect of sex on treatment outcomes and the summary data in the evidence table on p36 are confusing. It states on p16 *“...data from the EVA-3S trial suggested that sex significantly modified treatment outcome in terms of ipsilateral stroke through four years: males were at greater risk of periprocedural death or stroke following CAS versus CEA, ...”*. In the evidence table on p36, however, both males and females had an increased risk of periprocedural stroke following CAS vs. CEA. In addition, males were at lower risk of MI following CAS vs. CEA. Please explain, and ensure the evidence table and the description of the findings are consistent.

- c. The CREST study (Howard et al. 2011) found that periprocedural risk of events is likely higher in women who have CAS than those who have CEA. This finding did not seem to be discussed in the evidence report.
- d. P10. [Regarding KQ3, safety in asymptomatic patients]. *“Periprocedural myocardial infarction (MI): In one RCT (CREST) there was a statistically non-significant increase in the risk of periprocedural MI for CAS compared to CEA.”* However, the results of the original study (Silver et al 2011) indicate that the risk was higher for CEA instead.
- e. P11. *“Periprocedural death”*. The description of the results was unclear. Increased risk was reported following CAS compared with CEA in one of the studies. The difference was statistically significant, which should be stated explicitly here.
- f. P11. *“Periprocedural stroke or death”*. Similarly, a clear statement should be made here regarding the increased risk following CAS.
- g. P12 and 30. [Regarding KQ3, 30 days safety for extra-cranial in symptomatic patients]. *“Any periprocedural stroke: across six RCTs, risk of periprocedural stroke was significantly greater for CAS compared to CEA (Pooled RD: 3.39%, 95% CI .15%, 6.6%)”*. This statement is not consistent with the data presented in the evidence table on p30, where 4 RCTs, rather than 6 RCTs, were included and RD=2.9%.
- h. P13 and 30. [Regarding KQ3, 30 days safety for extra-cranial in symptomatic patients]. *“Periprocedural stroke or stroke: The risk of stroke or death was 7.1% for CAS and 4.1% for CEA based on pooled data across seven RCTs reporting this composite, neither of which fell below 6%”*. This statement is not consistent with the data presented in the evidence table on p30, where 4 RCTs, rather than 7 RCTs, were included.
- i. P33. The interpretation of aHR in the footnote of the table is incorrect. It also refers to CEA, which is irrelevant here.
- j. P96. [Regarding inclusion/exclusion criteria]. The studies of CAS with or without embolic protection devices were included in this evidence report. Since EPD use significantly reduces the risk of thromboembolic complications, it is important to know how many studies using CAS without EPD were included in the report, and how often is CAS without EPD still being used in current practice.

2. Minor points

- a. P8. Ipsilateral stroke. *“..., rates ranged from 1.5% -2.2% following CAS and 1.5% 2.4%.”*. Vague and incomplete sentence.

- b. P10. [Regarding KQ3, safety for extra-cranial in asymptomatic patients] *“Periprocedural cranial nerve palsy: Across two RCTs, risk of periprocedural cranial nerve palsy was significantly lower for CAS compared to CEA”*. This finding was not included in the evidence table on p28.
- c. P20 -39. [Regarding the evidence tables]. The total number of studies included in each table should be stated clearly somewhere in the table or in the footnote. It is good to count studies up in each outcome category, but it would be useful to know the total number of studies referred in the table to avoid any confusion or wrong impression.
- d. P26. [Regarding the table]. First subtitle: *“KQ1: Asymptomatic CAS vs. CEA”*. The data is actually regarding medical therapy and CAS, rather than CEA.
- e. P27-29. [Regarding the tables]. It is not obvious to tell if the data in these tables are pertinent to extra-cranial CAS or both extra-cranial and intracranial CAS. Please specify.
- f. P28. Calculation error or typo in $7(58/3418)$ [any stroke for CEA]. The rate should be 1.7 (58/3418).
- g. P33. Incomplete CI of the first CAS aHR (IS:70-79%).
- h. P63. Line 2 and 3, *“Saccoo 2006] In...”*. There may be a typo here.
- i. P134. *“Stroke or death within 30 days or ischemic stroke in the territory of the qualifying artery beyond 30 days”*. The discussion is under a subtitle of “Efficacy” data. It is confusing because stroke or death within 30 days is a safety outcome by definition rather than an efficacy outcome.
- j. P137. *“Any stroke or death within 30 days after enrollment”*. The total events following stenting would be 38 (33 strokes + 5 deaths), though the total number of patients who had events was 33. I understand that the five deaths in the stenting group were of a result of stroke, but death and stroke should be counted as separate events.

RESPONSES TO CLINICAL AND PEER REVIEWERS

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 section responds to clinical and peer reviews received from the following parties:

Draft Report

- Robert M. Bersin, MD, MPH; Medical Director, Endovascular Services and North End Cardiology Services, Swedish Heart and Vascular
- Stephen Monteith, MD; Swedish Cerebrovascular Center
- Rita Redberg, MD, M.Sc; Professor of Clinical Medicine, Division of Cardiology, University of California, San Francisco
- R. Eugene Zierler, MD; Professor of Surgery, Division of Vascular Surgery, University of Washington

Specific responses pertaining to comments are included in Table 1.

Table 1

	Comment	Response
<i>Robert M. Bersin, MD, MPH; Medical Director, Swedish Heart and Vascular</i>		
	Specific comments:	
KQ1 – short- and long-term comparative efficacy and effectiveness of extracranial CAS and medical therapy vs. medical therapy alone	No comparisons have been made.	No comparative studies were available.
KQ1 – short- and long-term comparative efficacy and effectiveness of extracranial CAS and medical therapy vs. CEA and medical therapy	<p>The best evidence that is also most directly relevant to the US patient population comes from prospective randomized trials performed in the United States, which were the SAPPHIRE trial for high surgical risk patients and the CREST trial for standard risk patients. The SAPPHIRE trial showed significantly better outcomes with CAS as compared to CEA at 30-days and 1-year, and equivalence at 3-years. CREST showed equivalent 4-year outcomes in standard risk patients. Periprocedural rates of individual components of the end points differed between the stenting group and the endarterectomy group for minor stroke (3.2% vs. 1.6%, P=0.01), and for myocardial infarction (1.1% vs. 2.3%, P = 0.03). Despite the slightly higher rate of periprocedural minor stroke with CAS, the health-related quality of life of CAS treated patients was better than with CEA during the early recovery period, and was equivalent at 1-year (Cohen, DJ et al J Am Coll Cardiol 2011;58:1557-1565). Neurocognitive testing also showed that the residual deficits in patients experiencing minor stroke were equivalent in the two treatment groups at 6-months as assessed by NIHSS (FDA Circulatory System Devices Advisory Panel P040012/S034 January 26, 2011). On the other hand, myocardial infarction was strong independent predictor of subsequent mortality in both treatment groups. The other prospective randomized trials comparing CAS to CEA in standard risk patients, particularly those performed in Europe, were all smaller, relatively underpowered, and generally regarded as poorly conducted in terms of CAS</p>	<p>Thank you for your comments.</p> <p>SAPPHIRE and CREST reports are included as data were available separately for asymptomatic and symptomatic patients. No pooling of data for asymptomatic patients was done. For primary outcomes in symptomatic patients in our HTA report, sensitivity analyses which excluded older studies and those which did not use EPDs were conducted and the results reported.</p> <p>SAPPHIRE, (included in KQ 4) had limited data by symptom status were available. The population was mostly asymptomatic (~70%). For the full population (symptomatic + asymptomatic combined) data from the the Yadav 2004 or the Gurm 2008 indicate that no statistical differences between CAS and CEA were found (based on intention to treat) for outcomes of death, stroke or MI at 30 days, 1 year or up to 1080 days.</p> <p>Cohen et. al. did not stratify results by</p>

	Comment	Response
	<p>technique (permitting CAS without embolic protection) and operator experience, which was very limited in most of the trials and below the standards required for CREST and US credentialing and site certification required in the US today. For this reason, I do not endorse lumping these studies together in meta-analyses to draw conclusions as was done in the Spectrum analysis and by AHRQ previously. Also, all CAS data presented in the Spectrum analysis is on patients treated with EPD filter devices rather than proximal or distal occlusion systems. A meta-analysis of proximal occlusion device (POD) published outcomes in 2,397 patients demonstrated superior outcomes as compared to outcomes reported in SAPPHIRE, CREST and other trials of patients treated with filter EPDs, and better than the outcomes with CEA reported in CREST (Bersin RM et al Catheterization and Cardiovascular Interventions 2012; 80:1072–1078). Use of a POD device is now considered the “gold standard” when treating patients with CAS, which was not considered in the Spectrum analysis but now needs to be.</p>	<p>symptom status and was thus not included.</p> <p>Comparison of EPDs was not within the scope of this report, however information on EPDs is presented throughout the report: The background provides basic information on EPDs, including data from various studies, recommendations in practice guidelines and CMS requirements for their use. Section 2.8 summarizes previous technology assessments, including reports that specifically evaluated CAS with EPD use (Blue Cross Blue Shield 2012 report) and summarizes the meta-analysis by Bersin et. al. on the use of proximal occlusion devices. For primary outcomes in our HTA report, sensitivity analyses which excluded older studies and those which did not use EPDs were conducted and the results reported.</p> <p>The analysis by Bersin, et. al. did not meet the inclusion criteria for this review and evaluated single arm CAS data. Additional information on this analysis has been put into the background for context.</p> <p>No studies comparing CAS with POD devices to CEA were identified during the search period although POD devices may now be considered the “gold standard” clinically. Reports such as this are “snapshots” and advances are not always reflected in the comparative literature at the time of report.</p>

	Comment	Response
<p>KQ2 – short- and long-term comparative efficacy and effectiveness of intracranial artery stenting and medical therapy vs. medical therapy alone</p>	<p>Primary stenting does not appear to have a clinical advantage over PTA for medically refractory intracranial stenoses, but appears to have benefit as a bailout for failed PTA or failed thrombectomy.</p>	<p>Thank you for your comments. Additional context has been added to the “Key Considerations by Clinical experts” section.</p> <p>The only comparative study found was SAMMPRIS.</p> <p>In the SAMMPRIS study population, approximately 60% of those enrolled had a history of stroke other than the qualifying event and over 60% were already receiving antithrombotic therapy. They do not report on proportion of patients with previous failed PTA or thrombectomy, however, exclusion criteria listed on clinicaltrials.gov indicates that those with previous treatment of target lesions with stent, angioplasty or other mechanical devices were excluded.</p>
<p>KQ3 – adverse events and complications for stenting compared with alternative treatments; are rates of periprocedural death or stroke <3% for asymptomatic patients and < 6% for symptomatic patients with extracranial carotid artery stenosis</p>	<p>The 3%/6% benchmarks recommended for endarterectomy were established arbitrarily in 1989 in the absence of any prospective, randomized data: " The ad hoc committee recognizes there are insufficient data to define acceptable morbidity and mortality limits for carotid endarterectomy for various indications. Nevertheless, the committee believes the upper limits of morbidity and mortality that should prompt individual peer review can be defined. These recommendations are based on current data and are likely to change." (Beebe et al Circulation 1989; 79: 472-473). The benchmarks they set in 1989 for endarterectomy were:</p> <ul style="list-style-type: none"> • Absence of symptoms <3% • Transient ischemic attack <5% • Ischemic stroke <7% • Recurrent carotid disease in the same artery after endarterectomy < 10% <p>Beebe went on to say "The risk of carotid endarterectomy should properly influence the indication for surgery. If the risk of operating on a patient is low in relation to the risk of not operating, then the benefit of carotid endarterectomy as</p>	<p>Thank you for this perspective.</p> <p>Information from the most recent clinical guidelines is included in the report regarding indications for stenting.</p> <p>“Key considerations highlighted by clinical experts” section briefly describes issues related to individual assessment of surgical risk. Some additional context has been added.</p> <p>Definitions of stroke provided in the included studies are found in Appendix H, Table H2.</p> <p>Section 3.4 provides summary information available from included</p>

	Comment	Response
	<p>a least-risk strategy may be proportionately great and worthwhile. The converse is also true. If morbidity and mortality of carotid endarterectomy are excessive in proportion to the natural history of the untreated or nonoperatively treated lesion, surgery should be avoided."</p> <p>In 1995, the AHA Council on Stroke published guidelines for endarterectomy (Stroke 1995; 26: 188-201) based on the opinions of 22 ad hoc committee members. That document references the Beebe publication as the basis for the assessment of surgical risk, even though Beebe established the benchmarks arbitrarily and not on the basis of surgical outcomes published in the literature. The ad hoc committee opinions were as follow:</p> <p>"A list of 96 potential common indications was circulated to each conference participant. This list was based on symptomatic status, percent stenosis, plaque characteristic, status of opposite carotid artery, and various levels of surgical risk. The terms used are defined below. Each participant was asked to rank each surgical indication into one of four options: proven (score=1); acceptable but not proven (score=2); uncertain (score=3); and proven inappropriate (score=4). The scores were averaged for each of the 96 indications. Finally, the indications were aggregated again to make the presentation more manageable. Since many of the indications generated a range of scores, some participants rated a given indication higher (or lower) than other participants. For this reason, an average score was selected rather than attempting to find a unanimously acceptable score.</p> <p>Definitions of Ranks for Surgical Indication for Carotid Endarterectomy</p> <p>Four choices were available for each indication as a function of surgical risk. For asymptomatic patients, the options for surgical risk for combined stroke and death as a consequence of operation were <3%, 3% to 5%, and 5% to 10%. For symptomatic patients, the surgical risk options were <6% and 6% to 10%.</p> <p>Surgical risk is based on a combined estimate of the patient's general medical fitness to undergo surgery and the individual surgeon's risk of morbidity and mortality for</p>	<p>studies on factors which may be related to surgical risk.</p>

	Comment	Response
	<p>patients with a specific surgical indication.</p> <p>A surgical indication that carries a high benefit-to-risk ratio would be acceptable in patients who were at higher surgical risk, whereas a surgical indication that had a lower benefit-to-risk ratio might be acceptable in only the best-risk patients.</p> <p><i>Proven (Score=1)</i> This designation constitutes the strongest indication for carotid endarterectomy and strongly implies that to withhold surgery in the presence of this indication would be inappropriate under normal circumstances. Indications classified as proven are generally supported by data from contemporary, prospective, randomized clinical trials.</p> <p><i>Acceptable but Not Proven (Score=2)</i> There is general agreement that this represents a good indication for surgery, with the expectation that benefits outweigh the risks. This rank is supported by promising, but not scientifically certain, data. Indications in this category may be the subject of ongoing prospective randomized trials. In that case, it is expected that patients will be offered the opportunity to participate in the trial. However, when this is not possible, either by geography or patient preference, surgery would be an acceptable alternative at the present level of knowledge.</p> <p><i>Uncertain (Score=3)</i> There are insufficient data to define the risk/benefit ratio. These potential indications should be evaluated in clinical trials.</p> <p><i>Proven Inappropriate (Score=4)</i> The current database is adequate to indicate that the stated risks of carotid endarterectomy outweigh the benefits. In general, the database includes contemporary, prospective, randomized clinical trials.</p> <p>Definitions of Stroke Categories <i>Mild Stroke</i> The residual neurological symptoms and signs of a mild stroke cause no important functional impairment.</p>	

	Comment	Response
	<p><i>Moderate Stroke</i> The residual neurological symptoms and signs of a moderate stroke result in a loss of function that may be complete in one domain (eg, arm or leg function, speech loss) and incomplete in others, but the total functional loss still allows independent existence.</p> <p><i>Severe Stroke</i> Residual neurological signs of a severe stroke are directly responsible for the patient's loss of independence.</p> <p>Current Indications for Carotid Endarterectomy</p> <p><u>Asymptomatic Patients With CAD</u></p> <p><i>For Patients With a Surgical Risk of <3%:</i></p> <ol style="list-style-type: none"> 1. <i>Proven indications:</i> none* 2. <i>Acceptable but not proven indications:</i> ipsilateral carotid endarterectomy for stenosis 75% with or without ulceration, irrespective of contralateral artery status, ranging from no disease to total occlusion* 3. <i>Uncertain indications:</i> (1) stenosis <50% with a "B" or "C" ulcer irrespective of contralateral internal carotid artery status; (2) unilateral carotid endarterectomy with CABG, coronary bypass graft required with bilateral asymptomatic stenosis >70%; (3) unilateral carotid stenosis >70%, CABG required, unilateral carotid endarterectomy with CABG 4. <i>Proven inappropriate indications:</i> none defined <p><i>For Patients With a Surgical Risk of 3% to 5%:</i></p> <ol style="list-style-type: none"> 1. <i>Proven indications:</i> none 2. <i>Acceptable but not proven indications:</i> ipsilateral carotid endarterectomy for stenosis 75% with or without ulceration but in the presence of contralateral internal carotid artery stenosis ranging from 75% to total occlusion 3. <i>Uncertain indications:</i> (1) ipsilateral carotid endarterectomy for stenosis 75% with or without 	

	Comment	Response
	<p>ulceration irrespective of contralateral artery status, ranging from no stenosis to occlusion; (2) CABG required, with bilateral asymptomatic stenosis >70%, unilateral carotid endarterectomy with CABG; (3) unilateral carotid stenosis >70%, CABG required, ipsilateral carotid endarterectomy with CABG</p> <p>4. <i>Proven inappropriate indications:</i> none defined</p> <p><i>For Patients With a Surgical Risk of 5% to 10%:</i></p> <p>1. <i>Proven indications:</i> none</p> <p>2. <i>Acceptable but not proven indications:</i> none</p> <p>3. <i>Uncertain indications:</i> (1) coronary bypass graft required with bilateral asymptomatic stenosis >70%, unilateral carotid endarterectomy with CABG; (2) unilateral carotid stenosis >70%, CABG required, ipsilateral carotid endarterectomy with CABG</p> <p>4. <i>Proven inappropriate indications:</i> (1) ipsilateral carotid endarterectomy for stenosis 75% with or without ulceration irrespective of contralateral internal carotid artery status; (2) stenosis 50% with or without ulceration irrespective of contralateral carotid artery status</p> <p><u>Symptomatic Patients With CAD</u></p> <p><i>For Patients With a Surgical Risk of <6%:</i></p> <p>1. <i>Proven indications:</i> (1) single or multiple TIAs within a 6-month interval or crescendo TIAs in the presence of a stenosis 70%, with or without ulceration, with or without antiplatelet therapy; (2) mild stroke within a 6-month interval, in the presence of a stenosis 70%, with or without ulceration, with or without antiplatelet therapy</p> <p>2. <i>Acceptable but not proven indications:</i> (1) TIA (single, multiple, or recurrent) within a 6-month interval, in the presence of a stenosis 50%, with or without ulceration, with or without antiplatelet therapy; (2) crescendo TIAs in the presence of a stenosis >50%, with or without ulceration, with or without antiplatelet therapy; (3) progressive stroke in the presence of a stenosis 70%, with or without ulceration, with or without antiplatelet</p>	

	Comment	Response
	<p>therapy; (4) mild stroke in the presence of a stenosis 50%, with or without ulceration, with or without antiplatelet therapy; (5) moderate stroke in the presence of a stenosis 50%, with or without ulceration, with or without antiplatelet therapy; (6) ipsilateral carotid endarterectomy combined with CABG in a patient experiencing TIAs, in the presence of unilateral or bilateral stenoses 70%, coronary bypass grafting needed</p> <p>3. <i>Uncertain indications:</i> (1) TIA (single, multiple, or recurrent) with stenosis <50% with or without ulceration, with or without antiplatelet therapy; (2) crescendo TIAs, with or without ulceration, and a stenosis <50%; (3) TIAs in a patient who requires coronary bypass grafting and has a stenosis <70%; (4) mild stroke with carotid stenosis <50%, with or without ulceration, with or without antiplatelet therapy; (4) moderate stroke with carotid stenosis <69%, with or without ulceration, with or without antiplatelet therapy; (5) evolving stroke with carotid stenosis <69%, with or without ulceration, with or without antiplatelet therapy; (6) global ischemic symptoms with ipsilateral carotid stenosis >75% but contralateral stenosis <75%, with or without ulceration, with or without antiplatelet therapy; (7) acute dissection of internal carotid artery with persistent symptoms while on heparin; (8) acute carotid occlusion, diagnosed within 6 hours, producing transient ischemic events; (9) acute carotid occlusion, diagnosed within 6 hours, producing a mild stroke</p> <p>4. <i>Proven inappropriate indications:</i> (1) moderate stroke with stenosis <50%, not on aspirin; (2) evolving stroke with stenosis <50%, not on aspirin; (3) acute internal carotid artery dissection, asymptomatic, on heparin</p> <p><i>For Patients With a Surgical Risk of 6% to 10%</i></p> <p>1. <i>Proven indications:</i> none</p> <p>2. <i>Acceptable but not proven indications:</i> (1) single or multiple TIAs within a 6-month interval, in the presence of a carotid stenosis 70%, with or without ulceration, with or without antiplatelet therapy; (2) recurrent TIAs, while on antiplatelet drugs, for a carotid stenosis 50% in the presence of ulceration, or 70% with or without ulceration; (3) crescendo TIAs with a stenosis 50%, with or without</p>	

	Comment	Response
	<p>ulceration, with or without antiplatelet therapy; (4) mild stroke in the presence of a stenosis >70%, with or without ulceration, with or without antiplatelet therapy; (5) moderate stroke with a stenosis >70%, with or without ulceration, with or without antiplatelet therapy; (6) evolving stroke in the presence of a >70% stenosis with large ulceration</p> <p>3. <i>Uncertain indications:</i> (1) single TIA with stenosis <70%, with or without ulceration, with or without antiplatelet therapy; (2) multiple TIAs within 6 months with stenosis <70%, not on antiplatelet drugs, with or without ulceration; (3) recurrent TIAs while on antiplatelet drugs with stenosis <70%, with or without ulceration; (4) crescendo TIAs for stenosis <70%, with or without ulceration, with or without antiplatelet therapy; (5) acute carotid occlusion with transient cerebral ischemia, (6) acute occlusion with mild stroke; (7) acute carotid artery dissection with continued symptoms while on heparin; (8) patient with transient cerebral ischemia secondary to a stenosis 70%, in need of CABG, with or without contralateral stenosis, use of combined operation; (9) mild stroke with stenosis <70%, with or without ulceration, with or without antiplatelet therapy; (10) moderate stroke with stenosis <70%, with or without ulceration, with or without antiplatelet therapy; (11) evolving stroke with stenosis <70%, with or without ulceration, with or without antiplatelet therapy; (12) global ischemic symptoms with an ipsilateral stenosis >75%, with or without symptoms, irrespective of contralateral artery status, with lesions up to and including contralateral occlusion</p> <p>4. <i>Proven inappropriate indications:</i> (1) single TIA, <50% stenosis, with or without ulceration, not on aspirin; (2) multiple TIAs within 6 months, stenosis <50%, not on aspirin; (3) mild stroke, stenosis <50%, not on aspirin; (4) moderate stroke, stenosis <50%, with or without ulceration, not on aspirin; (5) evolving stroke, stenosis <50%, with or without ulceration, not on aspirin; (5) global ischemic symptoms with stenosis <50%, with or without ulceration; (6) acute dissection of internal carotid artery, no symptoms while on heparin; (7) symptomatic unilateral carotid stenosis 70% in patient undergoing CABG.</p>	

	Comment	Response
	<p>As can be seen from the above, many of the recommendations for treatment in increased risk categories are exactly those for which expanded coverage was requested for carotid stenting in the anatomic high-risk patients.</p> <p>In 1998, the AHA guidelines were revised after the publication of the ACAS trial of endarterectomy in asymptomatic patients, but only for good risk patients with an operative risk of <3%. For asymptomatic good risk patients, the stroke/death rate of patients medically managed was extrapolated from Kaplan-Meier estimates to be 11% at five years with 2.7 years of follow-up in the ACAS trial in good surgical risk patients. Endarterectomy was estimated to reduce this risk to 5.1% at 5 years (a 53% reduction) in good surgical risk candidates. The guidelines were revised for good surgical risk candidates with less than a 3% operative stroke/death risk, but were not changed for higher risk patients with operative risks of >3%. "For patients with a surgical risk of 3% to 5% and for patients with a surgical risk of 5% to 10%, indications are unchanged from the original guidelines."</p> <p>The 1995 AHA guidelines for endarterectomy with a >3% risk therefore still stand today. The published literature on carotid stenting has only been in increased surgical risk patients with a >3% risk, and in this population, carotid stenting has consistently shown 30-day stroke/death rates of 4-4.5% and three year stroke/death rates of 6-7%. Carotid stenting has therefore consistently met the benchmarks established for increased surgical risk patients for the increased risk indications established by the AHA Council on Stroke in 1995. Moreover, the meta-analysis of CAS with POD devices demonstrated an overall 30-day MACE rate of 2.25% and no subgroup had a MACE rate of more than 2.6%, including symptomatic patients of all age subgroups (Bersin RM et al Catheterization and Cardiovascular Interventions 2012; 80:1072–1078).</p>	

	Comment	Response
<p>KQ4 – differential efficacy or safety for special populations</p>	<p>Age remains a predictor of MACE for both CAS and CEA, and there is a trend favoring CAS in the young, and CEA in the elderly, but the differences were not significant in the actual treatment analysis of CREST (FDA Circulatory System Devices Advisory Panel P040012/S034 January 26, 2011). The POD meta-analysis demonstrated for the first time equivalent outcomes in symptomatic vs. asymptomatic patients across all age groups suggesting that use of a POD device neutralized symptomatic status as a risk predictor, which has not been seen previously with CEA or CAS patients treated with filter EPDs. The total 30-day MACE rate never exceeded 2.6% in any subgroup, suggesting that symptomatic patients should undergo CAS with a POD device unless the anatomy is unsuitable.</p>	<p>Thank you for your comment. Regarding differential efficacy and safety based on age, we have included data from the Howard (2011) follow-up report of the CREST trial for both symptomatic and asymptomatic patients (see KQ4). We have also included patient-level data from this trial as reported in Bonati 2012 (see Figure 18 in report). Unfortunately, the data in the FDA report referred to in this comment are blacked out, making it difficult to evaluate data or interpret the report.</p>
<p>KQ5 – cost-effectiveness of CAS compared with other treatment options in the short- and long-term</p>	<p>The best evidence is from prospective randomized trials performed in the United States. The SAPPHIRE trial studied costs prospectively in high surgical risk patients and showed an incremental cost-effectiveness ratio (ICER) for stenting compared with endarterectomy of \$6,555 per quality-adjusted life year (QALY) gained (\$204,229 for symptomatic patients and \$2,667 for asymptomatic patients). Stenting was found to be much more cost effective because of superior outcomes, especially in the symptomatic population (Mahoney EM et al Cath Cardiovasc Interv 2011; 77: 463–472). CREST also had a prospective randomized cost substudy that showed total costs for the index hospitalization were similar for the CAS and CEA groups (\$15,055 versus \$14,816; mean difference, \$239/patient; 95% CI for difference, -\$297 to \$775). Neither follow-up costs after discharge nor total 1-year costs differed significantly (Vilain ER et al Stroke. 2012 Sep; 43(9):2408-2416). The highest level prospective data therefore demonstrates superior cost effectiveness for CAS in high risk patients and equal cost effectiveness in standard risk patients. Data from non-randomized registries, including Washington state utilization and cost data, suffer from significant selection bias based on differing criteria for coverage and reimbursement; ie, most CAS treatments are currently performed in high surgical risk patients and most CEA treatments are currently performed in standard risk patients. Costs of treatment in such different patient populations are expected to be quite different because of marked differences in co-morbidities, especially if costs 3 days prior and three days after the treatment are</p>	<p>Thank you for your comments.</p> <p>Key Question 5 contains evaluation of full economic studies which met the inclusion criteria, including the studies by Mahoney and Valain) and data abstracted from these studies is in the appendices. While RCTS potentially provide data with the least potential for bias on outcomes, rates, etc., the assumptions and aspects of modeling in full economic analyses are potential sources of bias and must also be considered as part of critical appraisal of such studies, which is done in section 5.</p> <p>Washington State data were provided by the Washington State Health Technology Assessment Program. The data are not used to evaluate cost-effectiveness. These administrative data reflect use of the technologies in Washington State Programs.</p>

	Comment	Response
	included in the procedural costs as was done for the Washington state utilization and cost data.	
Stephen Monteith, MD; Swedish Cerebrovascular Center		
	Specific comments	
Background	The overview of the background and relevance of the treatment of extracranial carotid atherosclerotic stenosis is well described. The disease burden and the options for treatment (medical, endarterectomy, and angioplasty/stenting) are broadly outlined appropriately. Public policy on who is appropriate for each treatment including funding sources are well discussed in the body of the review. The clinical relevance is well documented in the introductory paragraphs and is well known to the readership.	Thank you for your comments
	The most significant weakness of the introduction is the inclusion of intracranial atherosclerotic disease, and the use of angioplasty and stenting. The natural history of the treatment of intracranial atherosclerotic stenosis, indications for intervention, interventions (medical, angioplasty/stenting, surgical bypass which is controversial); are completely separate to those for extracranial atherosclerotic disease. As such inclusion of this disease entity confuses the discussion that is to follow. Whether intracranial atherosclerotic disease should be considered in the context of this review is questionable.	Thank you for your comments. The report acknowledges the distinction between extracranial and intracranial disease and their treatment's in both the introduction and by evaluating intracranial disease via a separate key question.
	The content of the literature review in terms of the background is sufficient in the context of extracranial atherosclerotic stenosis. This disease entity (including natural history, medical management) is well described in the literature and is presented well in the HTA review. The discussion of the natural history, interventions and outcomes with regards to intracranial atherosclerotic disease is less well represented. The review tends to suffer somewhat, as the discussion regarding intracranial atherosclerotic stenosis fails to adequately treat it as a distinct disease.	Evaluating intracranial disease via a separate key question acknowledges that it is considered a distinct entity.
Report Objectives and Key Questions	The key questions do a reasonable job at comparing medical therapy to the endovascular and surgical interventions. The important topics are covered, namely: intervention vs medical management, efficacy (short and long term) of	Thank you for your comments

	Comment	Response
	<p>treatments, and standardized adverse events. The intention to find differential safety data for specific populations is well laid out but the results in this category suffer from the heterogeneity of the trial data. Specifically looking for higher risk surgical candidates (prior radiation, previous radical neck dissection, tandem lesions, high carotid bifurcation, occluded collateral circulation etc.) was adequately addressed. Cost effectiveness was clearly defined.</p>	
	<p>The inclusion of intracranial atherosclerotic disease in the key questions degrades the clarity of the discussion. The vast majority of the discussion is related to extracranial disease and is of only moderate relevance to this separate disease entity.</p>	<p>Thank you for your comments. Information on intracranial stenting separate under Key Question 2.</p>
	<p>Completely separating the cases of symptomatic vs. asymptomatic disease for each of the key questions at the outset would have made the report easier to follow.</p>	<p>Thank you for your comment. This is a complex report.</p> <p>A section titled “synopsis and remaining questions” has been added to the executive summary and at the end of the report, describing primary findings by symptom status.</p>
<p>Methods</p>	<p>The methods used for identifying appropriate studies were well defined and was adequate. Using the inclusion/exclusion criteria described it is likely all the relevant recent trials were included. Certainly the universally recognized trials were well represented. LoE ratings were adequate. The relative significance of some of the more universally referenced ‘landmark’ trials was perhaps less well emphasized. For example, NASCET, ECST, ACAS, ACST, CREST, SAPPHIRE etc. The analysis of combined trials assigned weight according to number of patients contributing to the group. This unfortunately does not allow for the improved devices and skills of the operators in the case of CAS over time – Increasing the weighting of the modern trials would show the improved complication rates with CAS as techniques/operator experience have improved.</p>	<p>The following studies did not meet the inclusion criteria as they compared CEA versus medical therapy:</p> <ul style="list-style-type: none"> NASCET – CEA vs. best medical therapy; recently symptomatic patients ECST – CEA vs. best medical therapy; recently symptomatic patients ACAS – CEA vs. best medical therapy; asymptomatic patients ACAS – CEA vs. best medical therapy; asymptomatic patients CREST – included SAPPHIRE – included <p>Sensitivity analyses examined newer studies (enrollment after 2000, use of EPDs) (see above responses regarding sensitivity analyses);</p>

	Comment	Response
Results	The results are relatively well presented. The amount of detail is appropriately extensive at times however the key results are not well emphasized. Patients present to physicians with either symptomatic or asymptomatic disease. Dichotomizing from the outset would make recommendations easier to follow. In answering the key questions there is continual jumping between symptomatic and asymptomatic patients, and intermixing of the groups.	Thank you for your comments. This is a complex report and we have attempted to lay it out logically.
	It would be helpful to summarize a synthesis of the key findings in bullet form for each section. The current format (even with bullet points) is somewhat verbose in parts. The detailed explanation with discussion with the details of the relevant trials pertaining to that detail can follow in a more detailed fashion. While inclusion of this level of detail is necessary, the relevance and interpretation of this data is lost in its current presentation.	We have attempted to add clarity to various portions while retaining sufficient detail so that sections (e.g. executive summary) can stand alone.
	While the significant adverse events of CEA have been relatively stable, the complication rates of CAS have shown a trend to improve over time since SAPPHIRE. If one looks at the group of trials (SECURITY, BEACH, MAVERIC, CABERNET, EMPIRE, EPIC, PROTECT and ARMOUR) from 2002 to 2009 the overall trend is a decrease in the complication rate. The results section doesn't pick up on this and therefore some of the earlier trials with higher complication rates are not representative of the advancement in technology and improved experience of the operators that occurs during the later trials. The improvement in technique and complication rates in the later trials should be kept in mind when making recommendations to the review panel.	<p>All reports of this nature are necessarily snap shots of the best available comparative evidence and it is understood that there is continuing improvement.</p> <p>All these trials are case-series/single-arm trials of CAS and thus did not meet the inclusion criteria. Many of these case series are summarized in the 2012 Blue Cross Blue Shield Technology Evaluation Center report on CAS with EPD. While most earlier studies(2000-2003) appear to have higher 30 day death/stroke rates compared with newer studies, reported pooled estimates were 3.9% (3.3%, 4.4%) for asymptomatic patients and 7.4%(6.0%, 9.0%) for symptomatic patients.</p> <p>Spectrum does not make recommendations to the review panel.</p>

	Comment	Response
	The tables and appendices are easy to read and well put together. The implications of the major findings of the landmark trials are possibly underrepresented due to the inclusion of a large number of cohort studies and historical series. In general the data is well presented in both tabular form and discussion however the resulting implications are less well discussed.	Thank you for your comments.
Conclusions	The conclusions were valid in that for each of the key questions they were answered in detail. As a general comment the conclusions for each key question or aspect of the question should have been more succinct. The conclusion section should not introduce trials and details of the results. The detailed aspects of how the final interpretation of the answers to the key questions should have already been discussed elsewhere. The conclusion to each of the key questions should stand alone.	<p>We have attempted to add clarification.</p> <p>We were unable to identify areas in the conclusion section that introduced trials that are not represented elsewhere in the report.</p> <p>A section titled “synopsis and remaining questions” has been added to the executive summary and at the end of the report, describing primary findings by symptom status.</p>
Overall Presentation and Relevancy	The review is relatively well structured. It is certainly inclusive and a good effort has been made to rationally combine the data into digestible information. The points are well presented in the body of the HTA however the conclusion section is weakened in that it continues to introduce the details of the data which distracts from what is actually trying to be said – i.e the ‘answer’ to each of the key questions. The review doesn’t <i>succinctly</i> translate the ‘data’ into ‘information’.	<p>We have attempted to add clarification.</p> <p>A section titled “synopsis and remaining questions” has been added to the executive summary and at the end of the report, describing primary findings by symptom status.</p>
	The topic is relevant to current practice and it is crucial that the data be presented in a balanced fashion to review panels so that educated decisions regarding the future utilization of CEA/CAS are made.	
Rita Redberg		
	Specific comments	
Introduction	The introduction clearly laid out an overview of this topic, explained and documented why it is important, and defined the public policy and clinical relevance. It laid out the importance of cardiovascular disease, and stroke in particular, as well as the current therapeutic options, the	Thank you for your comments

	Comment	Response
	anatomical considerations and the key questions, methodology and criteria for rating the evidence.	
Page 2, line 10-15	This indication was revised following the SAMMPRIS trial termination in 2011 and the FDA Advisory Panel meeting of March 23, 2012. The revised Wingspan Guidelines state: "70-99 percent stenosis due to atherosclerosis of the intracranial artery related to the recurrent strokes" http://www.fda.gov/MedicalDevices/Safety/ucm314600.htm	Thank you for your comment. We have corrected this.
Page 6, line ?	Important to note that CREST included periprocedural enzyme elevations as "MI", which did not impact quality of life or lead to poor outcomes	In Appendix H, we abstracted definitions from the various studies as reported. Based on an FDA summary report, it appears that the criteria for determining MI changed during the course of the trial. We have made note of this in the report.
Page 9, line 16	"Stroke or death within 30 days or ischemic stroke in the territory of the qualifying artery beyond 30 days: This was the studies primary endpoint. Stenting was associated with a significantly higher probability of this composite outcome (20.0%) than medical therapy (12.2%), P = .009." <u>Comment:</u> The most important result of the SAMMPRIS study is the primary endpoint of stroke or death within 30 days. It is in the middle of a series of six bullets here. When summarizing study results, the study's primary endpoint should come first, followed by the other endpoints.	We have placed information on the primary endpoint first.
Background	The literature review is very well done and thorough, the methods, results and grading of the evidence were very well described and important.	Thank you for your comments
	There were issues of unrevealed conflict of interest regarding the PI of SAPPHIRE that lead to his dismissal from Cleveland Clinic in 2006 and raise some additional questions about bias and the quality of this trial.	Thank you for your comment
	The description of the previous systematic reviews and TAs was well done and helpful.	We are glad that you found this helpful
Page 65, line 1	Although it is correct that there are two devices with FDA approval for intracranial vessel stenting: NEUROLINK and Wingspan, this statement should be clarified, as it seems that NEUROLINK is a product that is no longer available. Essentially, Wingspan is the sole FDA approved device for	We have made revisions to include this information

	Comment	Response
	intracranial stenting that is currently in use.	
Page 65, line 2	Clarification - Wingspan is listed in parenthesis as being produced by Boston Scientific, which is actually produced by Stryker Neurovascular which acquired Boston Scientific Corporation in October 2010. (NYSE: BSX) today announced the execution of a definitive agreement under which Stryker Corporation will acquire Boston Scientific's Neurovascular business.	We have made revisions to include this information as appropriate.
Page 65, line 9-18	This text specifies a $\geq 50\%$ stenosis, but then references the FDA's safety communication, without specifying all of the revised guidelines, including the fact that the current indications call for stenosis of 70-99%. Should be updated to reflect the 2012 safety communication	We have updated this information
Report Objectives and Key Questions		
Page 16	<p>The subgroup analyses by age, sex, ethnicity, could be a little clearer in their explanations of the findings and adequacy of data.</p> <p>In addition, I was puzzled by the conclusion that sex did not affect outcomes, when the Howard V et al. <i>Lancet Neurology</i> 2011 paper (ref 92) found higher procedural morbidity for CAS in women. I have copied the abstract below.</p> <p>Howard 2011 title:</p> <p><i>Influence of sex on outcomes of stenting versus endarterectomy: a subgroup analysis of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST)</i></p>	<p>Thank you. We have revised the summary statements for KQ4 to increase the clarity.</p> <p>Regarding the Howard study, all data from this study was included in the evidence report (in the draft report, it was reference 92). The one outcome that this study found that sex modified treatment effect was the composite outcome of periprocedural stroke, death, or MI in symptomatic patients. We have added this conclusion to the Evidence Summary.</p> <p>In the section of asymptomatic patients, data from the Howard follow-up report of the CREST trial (for periprocedural stroke; periprocedural MI; and periprocedural stroke/death/MI were included (in KQ4, see asymptomatic patient section on sex, and the analyses from RCTs.)</p> <p>In symptomatic patients, for</p>

	Comment	Response
		periprocedural death or stroke, data from the CREST trial was included in the meta-analysis (see Figure 19). Data from the Howard follow-up study (for periprocedural stroke; periprocedural MI; and periprocedural stroke/death/MI) were included and are described immediately following Figure 19. The outcome periprocedural stroke/death/MI is the outcome this comment likely refers to, however, this composite outcome was not a primary outcome for the HTA and is thus not described in the evidence tables. (Based on advice from clinical experts, the composite outcome of stroke/death/MI is not an ideal way to report results, because it combines potentially dissimilar outcomes together.)
Methods		
Page 94, line 5-10	The listing of the trials that are currently recruiting was helpful as it lets us know what to expect in the next few years in terms of additional evidence.	
Results	I think the key questions are answered and the results clearly explained. Perhaps due to the complexity of the topic, it is a bit harder to pick out the implications of the major findings. For the most part, the gaps in the literature are well identified, although I think the current findings and limitations with regards to subgroups – age and sex – could be better highlighted, as well as the glaring deficiency of a medical treatment arm to the current RCTs, such as CREST.	Thank you. Regarding the conclusions for age and sex, we have revised the summary statements for KQ4 to increase the clarity. We have made additional notes regarding limitations of the literature.
Conclusions	None given	
Overall Presentation and Relevancy	I found the review well-structured and organized, and the main points clearly presented. This review was by necessity, fairly complicated, as it was covering two forms of carotid disease – intracranial and extracranial, in two patient populations – symptomatic and asymptomatic, and comparing carotid stents to two other forms of treatment – medical therapy and CEA.	<i>Thank you for your comments.</i> <i>We have added a brief synopsis of evidence and of gaps in evidence.</i>

	Comment	Response
	<p>It is relevant to clinical medicine, as this topic remains an area of active research and discussion, and has many areas where a clear presentation of the evidence, as has been done here, can inform clinical decision making. As CVD is common, this is important for public health and public policy.</p> <p>I found two particular conclusions from the review of this data most important, and should be highlighted more in this report: 1) no trial has compared CAS and CEA to medical therapy, which is critical, especially in asymptomatic patients and thus no conclusions on the best therapy for this group can be made at this time, 2) the use of Wingspan for intracranial stenosis is associated with increased mortality compared to medical therapy and use of this device should be halted.</p> <p>Finally, when looking at the CREST results, it is important to note that peri-operative enzymatic elevations seen in the CEA arm are not the same as full blown MIs and certainly did not have the decrement in quality of life that was seen for the strokes that were more common in the CAS arm. These two endpoints should not be considered equivalent, as they are not from a clinical or patient perspective.</p>	
R. Eugene Zierler, MD; Division of Vascular Surgery, University of Washington		
	Specific comments	Thank you for your comments
Executive Summary	The Executive Summary is well-done and very helpful, but it is quite long (for a summary), and I think that a more concise version would be useful.	
Page 5, line 1	Wherever the phrase “symptomatic and asymptomatic” is used, I suggest reversing the order to “asymptomatic and symptomatic”. This corresponds to the convention used throughout the report of listing data for asymptomatic patients first, followed by the corresponding data for symptomatic patients. This is a small point, but there is a lot for the reader to keep track of in this report, and anything that helps the reader stay oriented within the text is worth doing.	Thank you for your comments
Page 10, line ?	In the brief discussion of “Periprocedural myocardial	Thank you for your comment.

	Comment	Response
	infarction (MI)" in CREST (which occurs first here and also appears elsewhere in the report), it is stated that there is a "non-significant increase in the risk of periprocedural MI for CAS compared to CEA." My reading of the CREST reference (#14, page 42) is that the rates of periprocedural MI were 1.1% in the CAS group and 2.3% in the CEA group (P=0.03), which is a significant difference and increased in the CEA group. I recognize that this particular statement in the report refers to asymptomatic patients only, and that may account for the difference; however, this finding in CREST is well-known, and without further explanation this statement is likely to confuse some readers.	The result cited refers to analysis of the full CREST population (i.e. combined results for asymptomatic and symptomatic patients). When stratified by symptomatic/asymptomatic groups, there were non-significant increases in MI for CEA compared with CAS.
Background	Section numbering is confusing. The table of contents lists the "Background" section as 2 (2.1, 2.2, etc.), but in the text, this section is 5 (5.1, 5.2, etc.).	We have re-formatted the report.
	Otherwise content is complete and appropriate in this section.	
Report Objectives and Key Questions	Key Questions have been previously reviewed.	
Methods	Methods (Evidence) section is well-done.	
Results	As expected, the Results section contains the most detailed presentation of all the data, and it repeats much of what has already been presented in the previous sections; however, this is necessary in a comprehensive review of this type.	Thank you for your comments
Page 129, line ?	In the discussion of restenosis after CEA and CAS in RCTs, I did not see the recent paper from CREST cited. That paper is: Lal et al. <i>Lancet Neurol</i> 2012, 11:755-63. I don't think this is on the reference list, but I might have missed it.	This report was excluded as it didn't separate data for asymptomatic and symptomatic patients. They report that there were no significant differences in restenosis in symptomatic versus asymptomatic patients but do not provide data separately for these groups by treatment.
Conclusions	There is no separate "Conclusion" section. The "Strength of Evidence" section is helpful, but it is not really a "Summary".	We will revise the form for the future.
Overall Presentation and Relevancy	This report presents a huge amount of data on a number of closely related issues around the treatment of carotid artery disease, and it is a challenge for the reader to keep oriented within the text (i.e., asymptomatic vs. symptomatic, CAS vs.	Thank you for your comments. It is a complex report and we've attempted to enhance the structure and readability.

	Comment	Response
	CEA, efficacy vs. effectiveness, etc.). Therefore, structure, consistency, and liberal use of headings and subheadings are important. I have made a few comments on this elsewhere, but even for someone who is reasonably familiar with the material, it is easy to get a bit lost. At this point, I don't have any other specific suggestions, and some of this may be unavoidable given the intrinsic complexity of this particular topic.	A section titled "Synopsis and remaining questions" has been added to the Executive Summary and at the end of the report.
	The report is highly relevant to clinical medicine and should serve the intended purpose well.	
Danial K Hallam, MD, M.Sc.		
	No review received.	

Bersin-WHAT CAS Comments

1. 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. Extra-cranial carotid artery stenting (CAS) and medical therapy compared with medical therapy alone?

RESPONSE: No comparisons have been made.

b. Extra-cranial carotid artery stenting (CAS) and medical therapy compared with carotid endarterectomy (CEA) and medical therapy?

RESPONSE; The best evidence that is also most directly relevant to the US patient population comes from prospective randomized trials performed in the United States, which were the SAPPHIRE trial for high surgical risk patients and the CREST trial for standard risk patients. The SAPPHIRE trial showed significantly better outcomes with CAS as compared to CEA at 30-days and 1-year, and equivalence at 3-years. CREST showed equivalent 4-year outcomes in standard risk patients. Periprocedural rates of individual components of the end points differed between the stenting group and the endarterectomy group for minor stroke (3.2% vs. 1.6%, P=0.01), and for myocardial infarction (1.1% vs. 2.3%, P = 0.03). Despite the slightly higher rate of periprocedural minor stroke with CAS, the health-related quality of life of CAS treated patients was better than with CEA during the early recovery period, and was equivalent at 1-year (Cohen, DJ et al J Am Coll Cardiol 2011;58:1557-1565). Neurocognitive testing also showed that the residual deficits in patients experiencing minor stroke were equivalent in the two treatment groups at 6-months as assessed by NIHSS (FDA Circulatory System Devices Advisory Panel P040012/S034 January 26, 2011). On the other hand, myocardial infarction was strong independent predictor of subsequent mortality in both treatment groups. The other prospective randomized trials comparing CAS to CEA in standard risk patients, particularly those performed in Europe, were all smaller, relatively underpowered, and generally regarded as poorly conducted in terms of CAS technique (permitting CAS without embolic protection) and operator experience, which was very limited in most of the trials and below the standards required for CREST and US credentialing and site certification required in the US today. For this reason, I do not endorse lumping these studies together in meta-analyses to draw conclusions as was done in the Spectrum analysis and by AHRQ previously. Also, all CAS data presented in the Spectrum analysis is on patients treated with EPD filter devices rather than proximal or distal occlusion systems. A meta-analysis of proximal occlusion device (POD) published outcomes in 2,397 patients demonstrated superior outcomes as compared to outcomes reported in SAPPHIRE, CREST and other trials of patients treated with filter EPDs, and better than the outcomes with CEA reported in CREST (Bersin RM et al Catheterization and Cardiovascular Interventions 2012; 80:1072–1078). Use of a POD device is now considered the “gold standard” when treating patients with CAS, which was not considered in the Spectrum analysis but now needs to be.

2. In symptomatic persons with atherosclerotic stenosis of the intracranial arteries, what is the evidence of short- and long-term comparative efficacy and effectiveness of Intracranial artery stenting and medical therapy compared with medical therapy alone?

RESPONSE: Primary stenting does not appear to have a clinical advantage over PTA for medically refractory intracranial stenoses, but appears to have benefit as a bailout for failed PTA or failed thrombectomy.

3. What is the evidence regarding adverse events and complications, particularly during the periprocedural period and longer term, for stenting compared with alternative treatments? In persons with extracranial carotid artery stenosis, are rates of periprocedural death or stroke <3% for asymptomatic patients and <6% for symptomatic patients?

RESPONSE: The 3%/6% benchmarks recommended for endarterectomy were established arbitrarily in 1989 in the absence of any prospective, randomized data: "The ad hoc committee recognizes there are insufficient data to define acceptable morbidity and mortality limits for carotid endarterectomy for various indications. Nevertheless, the committee believes the upper limits of morbidity and mortality that should prompt individual peer review can be defined. These recommendations are based on current data and are likely to change." (Beebe et al *Circulation* 1989; 79: 472-473). The benchmarks they set in 1989 for endarterectomy were:

- Absence of symptoms <3%
- Transient ischemic attack <5%
- Ischemic stroke <7%
- Recurrent carotid disease in the same artery after endarterectomy < 10%

Beebe went on to say "The risk of carotid endarterectomy should properly influence the indication for surgery. If the risk of operating on a patient is low in relation to the risk of not operating, then the benefit of carotid endarterectomy as a least-risk strategy may be proportionately great and worthwhile. The converse is also true. If morbidity and mortality of carotid endarterectomy are excessive in proportion to the natural history of the untreated or nonoperatively treated lesion, surgery should be avoided."

In 1995, the AHA Council on Stroke published guidelines for endarterectomy (*Stroke* 1995; 26: 188-201) based on the opinions of 22 ad hoc committee members. That document references the Beebe publication as the basis for the assessment of surgical risk, even though Beebe established the benchmarks arbitrarily and not on the basis of surgical outcomes published in the literature. The ad hoc committee opinions were as follow:

"A list of 96 potential common indications was circulated to each conference participant. This list was based on symptomatic status, percent stenosis, plaque characteristic, status of opposite carotid artery, and various levels of surgical risk. The terms used are defined below. Each participant was asked to rank each surgical indication into one of four options: proven (score=1); acceptable but not proven (score=2); uncertain (score=3); and proven inappropriate (score=4). The scores were averaged for each of the 96 indications. Finally, the indications were aggregated again to make the presentation more manageable. Since many of the indications generated a range of scores, some participants rated a given indication higher (or lower) than other participants. For this reason, an average score was selected rather than attempting to find a unanimously acceptable score.

Definitions of Ranks for Surgical Indication for Carotid Endarterectomy

Four choices were available for each indication as a function of surgical risk. For asymptomatic patients, the options for surgical risk for combined stroke and death as a consequence of operation were <3%, 3% to 5%, and 5% to 10%. For symptomatic patients, the surgical risk options were <6% and 6% to 10%.

Surgical risk is based on a combined estimate of the patient's general medical fitness to undergo surgery and the individual surgeon's risk of morbidity and mortality for patients with a specific surgical indication.

A surgical indication that carries a high benefit-to-risk ratio would be acceptable in patients who were at higher surgical risk, whereas a surgical indication that had a lower benefit-to-risk ratio might be acceptable in only the best-risk patients.

Proven (Score=1)

This designation constitutes the strongest indication for carotid endarterectomy and strongly implies that to withhold surgery in the presence of this indication would be inappropriate under normal circumstances. Indications classified as proven are generally supported by data from contemporary, prospective, randomized clinical trials.

Acceptable but Not Proven (Score=2)

There is general agreement that this represents a good indication for surgery, with the expectation that benefits outweigh the risks. This rank is supported by promising, but not scientifically certain, data. Indications in this category may be the subject of ongoing prospective randomized trials. In that case, it is expected that patients will be offered the opportunity to participate in the trial. However, when this is not possible, either by geography or patient preference, surgery would be an acceptable alternative at the present level of knowledge.

Uncertain (Score=3)

There are insufficient data to define the risk/benefit ratio. These potential indications should be evaluated in clinical trials.

Proven Inappropriate (Score=4)

The current database is adequate to indicate that the stated risks of carotid endarterectomy outweigh the benefits. In general, the database includes contemporary, prospective, randomized clinical trials.

Definitions of Stroke Categories

Mild Stroke

The residual neurological symptoms and signs of a mild stroke cause no important functional impairment.

Moderate Stroke

The residual neurological symptoms and signs of a moderate stroke result in a loss of function that may be complete in one domain (eg, arm or leg function, speech loss) and incomplete in others, but the total functional loss still allows independent existence.

Severe Stroke

Residual neurological signs of a severe stroke are directly responsible for the patient's loss of independence.

Current Indications for Carotid Endarterectomy

Asymptomatic Patients With CAD

For Patients With a Surgical Risk of <3%

1. Proven indications: none*
2. Acceptable but not proven indications: ipsilateral carotid endarterectomy for stenosis 75% with or without ulceration, irrespective of contralateral artery status, ranging from no disease to total occlusion*
3. Uncertain indications
Stenosis <50% with a "B" or "C" ulcer irrespective of contralateral internal carotid artery status
Unilateral carotid endarterectomy with CABG, coronary bypass graft required with bilateral asymptomatic stenosis >70%
Unilateral carotid stenosis >70%, CABG required, unilateral carotid endarterectomy with CABG
4. Proven inappropriate indications: none defined

For Patients With a Surgical Risk of 3% to 5%

1. Proven indications: none
2. Acceptable but not proven indications: ipsilateral carotid endarterectomy for stenosis 75% with or without ulceration but in the presence of contralateral internal carotid artery stenosis ranging from 75% to total occlusion
3. Uncertain indications
Ipsilateral carotid endarterectomy for stenosis 75% with or without ulceration irrespective of contralateral artery status, ranging from no stenosis to occlusion
Coronary bypass graft required, with bilateral asymptomatic stenosis >70%, unilateral carotid endarterectomy with CABG
Unilateral carotid stenosis >70%, CABG required, ipsilateral carotid endarterectomy with CABG
4. Proven inappropriate indications: none defined

For Patients With a Surgical Risk of 5% to 10%

1. Proven indications: none
2. Acceptable but not proven indications: none
3. Uncertain indications
Coronary bypass graft required with bilateral asymptomatic stenosis >70%, unilateral carotid endarterectomy with CABG
Unilateral carotid stenosis >70%, CABG required, ipsilateral carotid endarterectomy with CABG
4. Proven inappropriate indications
Ipsilateral carotid endarterectomy for stenosis 75% with or without ulceration irrespective of contralateral internal carotid artery status
Stenosis 50% with or without ulceration irrespective of contralateral carotid artery status

Symptomatic Patients With CAD

For Patients With a Surgical Risk of <6%

1. Proven indications
Single or multiple TIAs within a 6-month interval or crescendo TIAs in the presence of a stenosis 70%, with or without ulceration, with or without antiplatelet therapy
Mild stroke within a 6-month interval, in the presence of a stenosis 70%, with or without ulceration, with or without antiplatelet therapy
2. Acceptable but not proven indications
TIA (single, multiple, or recurrent) within a 6-month interval, in the presence of a stenosis 50%, with or without ulceration, with or without antiplatelet therapy
Crescendo TIAs in the presence of a stenosis >50%, with or without ulceration, with or without antiplatelet therapy
Progressive stroke in the presence of a stenosis 70%, with or without ulceration, with or without antiplatelet therapy
Mild stroke in the presence of a stenosis 50%, with or without ulceration, with or without antiplatelet therapy
Moderate stroke in the presence of a stenosis 50%, with or without ulceration, with or without antiplatelet therapy
Ipsilateral carotid endarterectomy combined with CABG in a patient experiencing TIAs, in the presence of unilateral or bilateral stenoses 70%, coronary bypass grafting needed
3. Uncertain indications
TIA (single, multiple, or recurrent) with stenosis <50% with or without ulceration, with or without antiplatelet therapy

Crescendo TIAs, with or without ulceration, and a stenosis <50%

TIAs in a patient who requires coronary bypass grafting and has a stenosis <70%

Mild stroke with carotid stenosis <50%, with or without ulceration, with or without antiplatelet therapy

Moderate stroke with carotid stenosis <69%, with or without ulceration, with or without antiplatelet therapy

Evolving stroke with carotid stenosis <69%, with or without ulceration, with or without antiplatelet therapy

Global ischemic symptoms with ipsilateral carotid stenosis >75% but contralateral stenosis <75%, with or without ulceration, with or without antiplatelet therapy

Acute dissection of internal carotid artery with persistent symptoms while on heparin

Acute carotid occlusion, diagnosed within 6 hours, producing transient ischemic events

Acute carotid occlusion, diagnosed within 6 hours, producing a mild stroke

4. Proven inappropriate indications

Moderate stroke with stenosis <50%, not on aspirin

Evolving stroke with stenosis <50%, not on aspirin

Acute internal carotid artery dissection, asymptomatic, on heparin

For Patients With a Surgical Risk of 6% to 10%

1. Proven indications: none

2. Acceptable but not proven indications

Single or multiple TIAs within a 6-month interval, in the presence of a carotid stenosis 70%, with or without ulceration, with or without antiplatelet therapy

Recurrent TIAs, while on antiplatelet drugs, for a carotid stenosis 50% in the presence of ulceration, or 70% with or without ulceration

Crescendo TIAs with a stenosis 50%, with or without ulceration, with or without antiplatelet therapy

Mild stroke in the presence of a stenosis >70%, with or without ulceration, with or without antiplatelet therapy

Moderate stroke with a stenosis >70%, with or without ulceration, with or without antiplatelet therapy

Evolving stroke in the presence of a >70% stenosis with large ulceration

3. Uncertain indications

Single TIA with stenosis <70%, with or without ulceration, with or without antiplatelet therapy

Multiple TIAs within 6 months with stenosis <70%, not on antiplatelet drugs, with or without ulceration

Recurrent TIAs while on antiplatelet drugs with stenosis <70%, with or without ulceration

Crescendo TIAs for stenosis <70%, with or without ulceration, with or without antiplatelet therapy.

Acute carotid occlusion with transient cerebral ischemia

Acute occlusion with mild stroke

Acute carotid artery dissection with continued symptoms while on heparin

Patient with transient cerebral ischemia secondary to a stenosis 70%, in need of CABG, with or without contralateral stenosis, use of combined operation

Mild stroke with stenosis <70%, with or without ulceration, with or without antiplatelet therapy

Moderate stroke with stenosis <70%, with or without ulceration, with or without antiplatelet therapy

Evolving stroke with stenosis <70%, with or without ulceration, with or without antiplatelet therapy

Global ischemic symptoms with an ipsilateral stenosis >75%, with or without symptoms, irrespective of contralateral artery status, with lesions up to and including contralateral occlusion

4. Proven inappropriate indications

Single TIA, <50% stenosis, with or without ulceration, not on aspirin

Multiple TIAs within 6 months, stenosis <50%, not on aspirin

Mild stroke, stenosis <50%, not on aspirin

Moderate stroke, stenosis <50%, with or without ulceration, not on aspirin

Evolving stroke, stenosis <50%, with or without ulceration, not on aspirin

Global ischemic symptoms with stenosis <50%, with or without ulceration

Acute dissection of internal carotid artery, no symptoms while on heparin

Asymptomatic unilateral carotid stenosis 70% in patient undergoing CABG"

As can be seen from the above, many of the recommendations for treatment in increased risk categories are exactly those for which expanded coverage was requested for carotid stenting in the anatomic high-risk patients.

In 1998, the AHA guidelines were revised after the publication of the ACAS trial of endarterectomy in asymptomatic patients, but only for good risk patients with an operative risk of <3%. For asymptomatic good risk patients, the stroke/death rate of patients medically managed was extrapolated from Kaplan-Meier estimates to be 11% at five years with 2.7 years of follow-up in the ACAS trial in good surgical risk patients. Endarterectomy was estimated to reduce this risk to 5.1% at 5 years (a 53% reduction) in good surgical risk candidates. The guidelines were revised for good surgical risk candidates with less than a 3% operative stroke/death risk, but were not changed for higher risk patients with operative risks of >3%. "For patients with a surgical risk of 3% to 5% and for patients with a surgical risk of 5% to 10%,

indications are unchanged from the original guidelines."

The 1995 AHA guidelines for endarterectomy with a >3% risk therefore still stand today. The published literature on carotid stenting has only been in increased surgical risk patients with a >3% risk, and in this population, carotid stenting has consistently shown 30-day stroke/death rates of 4-4.5% and three year stroke/death rates of 6-7%. Carotid stenting has therefore consistently met the benchmarks established for increased surgical risk patients for the increased risk indications established by the AHA Council on Stroke in 1995. Moreover, the meta-analysis of CAS with POD devices demonstrated an overall 30-day MACE rate of 2.25% and no subgroup had a MACE rate of more than 2.6%, including symptomatic patients of all age subgroups (Bersin RM et al Catheterization and Cardiovascular Interventions 2012; 80:1072–1078).

4. Is there evidence of differential efficacy or safety for special populations, (including consideration of age, gender, race, diabetes, atrial fibrillation or other co-morbidities, ethnicity, or disability)?

RESPONSE: Age remains a predictor of MACE for both CAS and CEA, and there is a trend favoring CAS in the young, and CEA in the elderly, but the differences were not significant in the actual treatment analysis of CREST (FDA Circulatory System Devices Advisory Panel P040012/S034 January 26, 2011). The POD meta-analysis demonstrated for the first time equivalent outcomes in symptomatic vs. asymptomatic patients across all age groups suggesting that use of a POD device neutralized symptomatic status as a risk predictor, which has not been seen previously with CEA or CAS patients treated with filter EPDs. The total 30-day MACE rate never exceeded 2.6% in any subgroup, suggesting that symptomatic patients should undergo CAS with a POD device unless the anatomy is unsuitable.

5. 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?

RESPONSE: The best evidence is from prospective randomized trials performed in the United States. The SAPPHERE trial studied costs prospectively in high surgical risk patients and showed an incremental cost-effectiveness ratio (ICER) for stenting compared with endarterectomy of \$6,555 per quality-adjusted life year (QALY) gained (\$204,229 for symptomatic patients and \$2,667 for asymptomatic patients). Stenting was found to be much more cost effective because of superior outcomes, especially in the symptomatic population (Mahoney EM et al Cath Cardiovasc Interv 2011; 77: 463–472). CREST also had a prospective randomized cost substudy that showed total costs for the index hospitalization were similar for the CAS and CEA groups (\$15,055 versus \$14,816; mean difference, \$239/patient; 95% CI for difference, -\$297 to \$775). Neither follow-up costs after discharge nor total 1-year costs differed significantly (Vilain ER et al Stroke. 2012 Sep; 43(9):2408-2416). The highest level prospective data therefore demonstrates superior cost effectiveness for CAS in high risk patients and equal cost effectiveness in standard risk patients. Data from non-randomized registries, including Washington state utilization and cost data, suffer from significant selection bias based on differing criteria for coverage and reimbursement; ie, most CAS treatments are currently performed in high surgical risk patients and most CEA treatments are currently performed in standard risk patients. Costs of treatment in such different patient populations are expected to be quite different because of marked differences in co-morbidities, especially if costs 3 days prior and three days after the treatment are included in the procedural costs as was done for the Washington state utilization and cost data.

Reviewer Identification Information

Reviewer Name	Stephen Monteith, MD
Address	Street 550 17th Ave., Suite 110 City Seattle State WA Zip Code 98122
Phone	2063203470 206.320.3471
<i>Fax</i>	
E-mail	Stephen.monteith@swedish.org

INTRODUCTION Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Overview of topic is adequate?
- Topic of assessment is important to address?
- Public policy and clinical relevance are well defined?

The overview of the background, and relevance of the treatment of extracranial carotid atherosclerotic stenosis is well described. The disease burden and the options for treatment (medical, endarterectomy, and angioplasty/stenting) are broadly outlined appropriately. Public policy on who is appropriate for each treatment including funding sources are well discussed in the body of the review. The clinical relevance is well documented in the introductory paragraphs and is well known to the readership.

The most significant weakness of the introduction is the inclusion of intracranial atherosclerotic disease, and the use of angioplasty and stenting. The natural history of the treatment of intracranial atherosclerotic stenosis, indications for intervention, interventions (medical, angioplasty/stenting, surgical bypass which is controversial); are completely separate to those for extracranial atherosclerotic disease. As such inclusion of this disease entity confuses the discussion that is to follow. Whether intracranial atherosclerotic disease should be considered in the context of this review is questionable.

BACKGROUND Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Content of literature review/background is sufficient?

The content of the literature review in terms of the background is sufficient in the context of extracranial atherosclerotic stenosis. This disease entity (including natural history, medical management) is well described in the literature and is presented well in the HTA review. The discussion of the natural history, interventions and outcomes with

regards to intracranial atherosclerotic disease is less well represented. The review tends to suffer somewhat, as the discussion regarding intracranial atherosclerotic stenosis fails to adequately treat it as a distinct disease.

REPORT OBJECTIVES & KEY QUESTIONS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Aims/objectives clearly address relevant policy and clinical issue?
- Key questions clearly defined and adequate for achieving aims?

The key questions do a reasonable job at comparing medical therapy to the endovascular and surgical interventions. The important topics are covered, namely: intervention vs medical management, efficacy (short and long term) of treatments, and standardized adverse events. The intention to find differential safety data for specific populations is well laid out but the results in this category suffer from the heterogeneity of the trial data. Specifically looking for higher risk surgical candidates (prior radiation, previous radical neck dissection, tandem lesions, high carotid bifurcation, occluded collateral circulation etc) was adequately addressed. Cost effectiveness was clearly defined.

The inclusion of intracranial atherosclerotic disease in the key questions degrades the clarity of the discussion. The vast majority of the discussion is related to extracranial disease and is of only moderate relevance to this separate disease entity.

Completely separating the cases of symptomatic vs asymptomatic disease for each of the key questions at the outset would have made the report easier to follow.

METHODS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Method for identifying relevant studies is adequate?
- Criteria for the inclusion and exclusion of studies is appropriate?
- Method for Level of Evidence (LoE) rating is appropriate and clearly explained?
- Data abstraction and analysis/review are adequate?

The methods used for identifying appropriate studies was well defined and was adequate. Using the inclusion/exclusion criteria described it is likely all the relevant recent trials were included. Certainly the universally recognized trials were well represented. LoE ratings were adequate. The relative significance of some of the more universally referenced 'landmark' trials was perhaps less well emphasized. For example, NASCET, ECST, ACAS, ACST, CREST, SAPPHIRE etc. The analysis of combined trials assigned weight according to number of patients contributing to the group. This unfortunately does not allow for the improved devices and skills of the

operators in the case of CAS over time – Increasing the weighting of the modern trials would show the improved complication rates with CAS as techniques/operator experience have improved.

RESULTS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Amount of detail presented in the results section appropriate?
- Key questions are answered?
- Figures, tables and appendices clear and easy to read?
- Implications of the major findings clearly stated?
- Have gaps in the literature been dealt with adequately?
- Recommendations address limitations of literature?

The results are relatively well presented. The amount of detail is appropriately extensive at times however the key results are not well emphasized. Patients present to physicians with either symptomatic or asymptomatic disease. Dichotomizing from the outset would make recommendations easier to follow. In answering the key questions there is continual jumping between symptomatic and asymptomatic patients, and intermixing of the groups.

It would be helpful to summarize a synthesis of the key findings in bullet form for each section. The current format (even with bullet points) is somewhat verbose in parts. The detailed explanation with discussion with the details of the relevant trials pertaining to that detail can follow in a more detailed fashion. While inclusion of this level of detail is necessary, the relevance and interpretation of this data is lost in its current presentation.

While the significant adverse events of CEA have been relatively stable, the complication rates of CAS have shown a trend to improve over time since SAPPHERE. If one looks at the group of trials (SECURITY, BEACH, MAVERIC, CABERNET, EMPIRE, EPIC, PROTECT and ARMOUR) from 2002 to 2009 the overall trend is a decrease in the complication rate. The results section doesn't pick up on this and therefore some of the earlier trials with higher complication rates are not representative of the advancement in technology and improved experience of the operators that occurs during the later trials. The improvement in technique and complication rates in the later trials should be kept in mind when making recommendations to the review panel.

The tables and appendices are easy to read and well put together. The implications of the major findings of the landmark trials are possibly underrepresented due to the inclusion of a large number of cohort studies and historical series. In general the data is well presented in both tabular form and discussion however the resulting implications are less well discussed.

CONCLUSIONS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Are the conclusions reached valid?

The conclusions were valid in that for each of the key questions they were answered in detail. As a general comment the conclusions for each key question or aspect of the question should have been more succinct. The conclusion section should not introduce trials and details of the results. The detailed aspects of how the final interpretation of the answers to the key questions should have already been discussed elsewhere. The conclusion to each of the key questions should stand alone.

OVERALL PRESENTATION and RELEVANCY Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Is the review well structured and organized?
- Are the main points clearly presented?
- Is it relevant to clinical medicine?
- Is it important for public policy or public health?

The review is relatively well structured. It is certainly inclusive and a good effort has been made to rationally combine the data into digestible information. The points are well presented in the body of the HTA however the conclusion section is weakened in that it continues to introduce the details of the data which distracts from what is actually trying to be said – i.e the ‘answer’ to each of the key questions. The review doesn’t *succinctly* translate the ‘data’ into ‘information’.

The topic is relevant to current practice and it is crucial that the data be presented in a balanced fashion to review panels so that educated decisions regarding the future utilization of CEA/CAS are made.

QUALITY OF REPORT

Quality Of the Report

(Click in the gray box to make your selection)

Superior

Good

Fair X

Poor

Reviewer Identification Information

Reviewer Name	Rita Redberg
Address	Street City State Zip Code
Phone	
<i>Fax</i>	
E-mail	

INTRODUCTION Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Overview of topic is adequate?
- Topic of assessment is important to address?
- Public policy and clinical relevance are well defined?

Page 6 Line

Important to note that CREST included periprocedural enzyme elevations as “MI”, which did not impact quality of life or lead to poor outcomes

The introduction clearly laid out an overview of this topic, explained and documented why it is important, and defined the public policy and clinical relevance. It laid out the importance of cardiovascular disease, and stroke in particular, as well as the current therapeutic options, the anatomical considerations and the key questions, methodology and criteria for rating the evidence.

Page 2 Line 10-15

This indication was revised following the SAMMPRIS trial termination in 2011 and the FDA Advisory Panel meeting of March 23, 2012. The revised Wingspan Guidelines state:
 “70-99 percent stenosis due to atherosclerosis of the intracranial artery related to the recurrent strokes”
<http://www.fda.gov/MedicalDevices/Safety/ucm314600.htm>

Page 9 Line 16

Stroke or death within 30 days or ischemic stroke in the territory of the qualifying artery beyond 30 days: This was the studies primary endpoint. Stenting was associated with a significantly higher probability of this composite outcome (20.0%) than medical therapy (12.2%), P = .009.”

Comment: The most important result of the SAMMPRIS study is the primary endpoint of stroke or death within 30 days. It is in the middle of a series of six bullets here. When summarizing study results, the study's primary endpoint should come first, followed by the other endpoints.

BACKGROUND Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Content of literature review/background is sufficient?
-

The literature review is very well done and thorough, the methods, results and grading of the evidence was very well described and important.

There were issues of unrevealed conflict of interest regarding the PI of SAPPHIRE that lead to his dismissal from Cleveland Clinic in 2006 and raise some additional questions about bias and the quality of this trial.

The description of the previous systematic reviews and TAs was well done and helpful.

Page 65 *Line 1*

Although it is correct that there are two devices with FDA approval for intracranial vessel stenting: NEUROLINK and Wingspan, this statement should be clarified, as it seems that NEUROLINK is a product that is no longer available. Essentially, Wingspan is the sole FDA approved device for intracranial stenting that is currently in use.

Page 65 *Line 2*

Clarification - Wingspan is listed in parenthesis as being produced by Boston Scientific, which is actually produced by Stryker Neurovascular which acquired Boston Scientific Corporation in October 2010. (NYSE: [BSX](#)) today announced the execution of a definitive agreement under which Stryker Corporation will acquire Boston Scientific's Neurovascular business.

Page 65 *Line 9-18*

This text specifies a $\geq 50\%$ stenosis, but then references the FDA's safety communication, without specifying all of the revised guidelines, including the fact that the current indications call for stenosis of 70-99%. Should be updated to reflect the 2012 safety communication.

REPORT OBJECTIVES & KEY QUESTIONS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Aims/objectives clearly address relevant policy and clinical issue?
- Key questions clearly defined and adequate for achieving aims?



Page Line

Enter Comments Here

Page 16 Line

The subgroup analyses by age, sex, ethnicity, could be a little clearer in their explanations of the findings and adequacy of data. In addition, I was puzzled by the conclusion that sex did not affect outcomes, when the Howard V et al. *Lancet Neurology* 2011 paper (ref 92) found higher procedural morbidity for CAS in women. I have copied the abstract below.

Influence of sex on outcomes of stenting versus endarterectomy: a subgroup analysis of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST)

Virginia J Howard PhD a, Prof Helmi L Lutsep MD b, Prof Ariane Mackey MD c, Prof Bart M Demaerschalk MD d, Albert D Sam MD e, Nicole R Gonzales MD f, Alice J Sheffet PhD g, Jenifer H Voeks PhD a, Prof James F Meschia MD h, Prof Thomas G Brott MD h  , for the CREST investigators

Summary**Background**

In the randomised Carotid Revascularization Endarterectomy versus Stenting Trial (CREST), the primary endpoint did not differ between carotid artery stenting and carotid endarterectomy in patients with symptomatic and asymptomatic stenosis. A prespecified secondary aim was to examine differences by sex.

Methods

Patients who were asymptomatic or had had a stroke or transient ischaemic attack within 180 days before random allocation were enrolled in CREST at 117 clinical centres in the USA and Canada. The primary outcome was the composite of stroke, myocardial infarction, or death during the periprocedural period or ipsilateral stroke within 4 years. We used standard survival methods including Kaplan-Meier survival curves and sex-by-treatment interaction term to assess the relation between patient factors and risk of reaching the primary outcome. Analyses were by intention to treat. CREST is registered with [ClinicalTrials.gov, NCT00004732](http://ClinicalTrials.gov/NCT00004732).

Findings

Between Dec 21, 2000, and July 18, 2008, 2502 patients were randomly assigned to carotid endarterectomy (n=1240) or carotid artery stenting (n=1262), 872 (34.9%) of whom were women. Rates of the primary endpoint for carotid artery stenting compared with carotid endarterectomy were 6.2% versus 6.8% in men (hazard ratio [HR] 0.99, 95% CI 0.66—1.46) and 8.9% versus 6.7% in women (1.35, 0.82—2.23). There was no significant interaction in the primary endpoint between sexes (interaction p=0.34). Periprocedural events occurred in 35 (4.3%) of 807 men assigned to carotid artery stenting compared with 40 (4.9%) of 823 assigned to carotid endarterectomy (HR 0.90, 95% CI 0.57—1.41) and 31 (6.8%) of 455 women assigned to carotid artery stenting compared with 16 (3.8%) of 417 assigned to carotid endarterectomy (1.84, 1.01—3.37; interaction p=0.064).

Interpretation

Periprocedural risk of events seems to be higher in women who have carotid artery stenting than those who have carotid endarterectomy whereas there is little difference in men. Additional data are needed to confirm whether this differential risk should be taken into account in decisions for treatment of carotid disease in women.

Page *Line*

Enter Comments Here

METHODS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Method for identifying relevant studies is adequate?
- Criteria for the inclusion and exclusion of studies is appropriate?
- Method for Level of Evidence (LoE) rating is appropriate and clearly explained?
- Data abstraction and analysis/review are adequate?

Page 94 *Line 5.10*

The listing of the trials that are currently recruiting was helpful as it lets us know what to expect in the next few years in terms of additional evidence.

Page *Line*

Enter Comments Here

Page *Line*

Enter Comments Here

RESULTS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Amount of detail presented in the results section appropriate?
- Key questions are answered?
- Figures, tables and appendices clear and easy to read?
- Implications of the major findings clearly stated?
- Have gaps in the literature been dealt with adequately?
- Recommendations address limitations of literature?

Page *Line*

I think the key questions are answered and the results clearly explained. Perhaps due to the complexity of the topic, it is a bit harder to pick out the implications of the major findings. For the most part, the gaps in the literature are well identified, although I think the current findings and limitations with regards to subgroups – age and sex – could be better highlighted, as well as the glaring deficiency of a medical treatment arm to the current RCTs, such as CREST.

Page *Line*

Enter Comments Here

Page *Line*

Enter Comments Here

CONCLUSIONS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Are the conclusions reached valid?

Page *Line*

Enter Comments Here

Page *Line*

Enter Comments Here

Page Line

Enter Comments Here

OVERALL PRESENTATION and RELEVANCY Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Is the review well structured and organized?
- Are the main points clearly presented?
- Is it relevant to clinical medicine?
- Is it important for public policy or public health?

Page Line

I found the review well structured and organized, and the main points clearly presented. This review was by necessity, fairly complicated, as it was covering two forms of carotid disease – intracranial and extracranial, in two patient populations – symptomatic and asymptomatic, and comparing carotid stents to two other forms of treatment – medical therapy and CEA. It is relevant to clinical medicine, as this topic remain an area of active research and discussion, and has many areas where a clear presentation of the evidence, as has been done here, can inform clinical decision making. As CVD is common, this is important for public health and public policy. I found two particular conclusions from the review of this data most important, and should be highlighted more in this report: 1) no trial has compared CAS and CEA to medical therapy, which is critical, especially in asymptomatic patients and thus no conclusions on the best therapy for this group can be made at this time, 2) the use of Wingspan for intracranial stenosis is associated with increased mortality compared to medical therapy and use of this device should be halted. Finally, when looking at the CREST results, it is important to note that peri-operative enzymatic elevations seen in the CEA arm are not the same as full blown MIs and certainly did not have the decrement in quality of life that was seen for the strokes, that were more common in the CAS arm. These two endpoints should not be considered equivalent, as they are not from a clinical or patient perspective.

Page Line

Enter Comments Here

Page Line

Enter Comments Here

QUALITY OF REPORT

Quality Of the Report

(Click in the gray box to make your selection)

Superior XX

Good

Fair

Poor

Page *Line*

Enter Comments Here

Page *Line*

Enter Comments Here

Page *Line*

Enter Comments Here

We would appreciate any feedback you have on the usability of this form. Please add comments in the field below.

Hard to get things to fit correctly. Otherwise fine, nice to have the questions reminder.

Reviewer Identification Information

Reviewer Name	R. Eugene Zierler, MD
Address	Street: Dept. Surgery, University of Washington Box 356410, 1959 NE Pacific Street City: Seattle State: WA Zip Code: 98195
Phone	206.598.9851
<i>Fax</i>	206.598.1466
E-mail	gzierler@uw.edu

INTRODUCTION Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Overview of topic is adequate?
- Topic of assessment is important to address?
- Public policy and clinical relevance are well defined?

The Executive Summary is well-done and very helpful, but it is quite long (for a summary), and I think that a more concise version would be useful.

Page 5 *Line 1*

Wherever the phrase “symptomatic and asymptomatic” is used, I suggest reversing the order to “asymptomatic and symptomatic”. This corresponds to the convention used throughout the report of listing data for asymptomatic patients first, followed by the corresponding data for symptomatic patients. This is a small point, but there is a lot for the reader to keep track of in this report, and anything that helps the reader stay oriented within the text is worth doing.

Page 10 *Line*

In the brief discussion of “Periprocedural myocardial infarction (MI)” in CREST (which occurs first here and also appears elsewhere in the report), it is stated that there is a “non-significant increase in the risk of periprocedural MI for CAS compared to CEA.” My reading of the CREST reference (#14, page 42) is that the rates of periprocedural MI were 1.1% in the CAS group and 2.3% in the CEA group (P=0.03), which is a significant difference and increased in the CEA group. I recognize that this particular statement in the report refers to asymptomatic patients only, and that may account for the difference; however, this finding in CREST is well-known, and without further explanation this statement is likely to confuse some readers.

BACKGROUND Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Content of literature review/background is sufficient?

Section numbering is confusing. The table of contents lists the “Background” section as 2 (2.1, 2.2, etc.), but in the text, this section is 5 (5.1, 5.2, etc.).

Otherwise content is complete and appropriate in this section.

REPORT OBJECTIVES & KEY QUESTIONS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Aims/objectives clearly address relevant policy and clinical issue?
- Key questions clearly defined and adequate for achieving aims?

Key Questions have been previously reviewed.

METHODS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Method for identifying relevant studies is adequate?
- Criteria for the inclusion and exclusion of studies are appropriate?
- Method for Level of Evidence (LoE) rating is appropriate and clearly explained?
- Data abstraction and analysis/review are adequate?

Methods (Evidence) section is well-done.

RESULTS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Amount of detail presented in the results section appropriate?
- Key questions are answered?
- Figures, tables and appendices clear and easy to read?
- Implications of the major findings clearly stated?
- Have gaps in the literature been dealt with adequately?
- Recommendations address limitations of literature?

As expected, the Results section contains the most detailed presentation of all the data, and it repeats much of what has already been presented in the previous sections; however, this is necessary in a comprehensive review of this type.

In the discussion of restenosis after CEA and CAS in RCTs, I did not see the recent paper from CREST cited. That paper is: Lal et al. *Lancet Neurol* 2012, 11:755-63. I don't think this is on the reference list, but I might have missed it.

CONCLUSIONS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Are the conclusions reached valid?

There is no separate "Conclusion" section. The "Strength of Evidence" section is helpful, but it is not really a "Summary".

OVERALL PRESENTATION and RELEVANCY Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Is the review well structured and organized?
- Are the main points clearly presented?
- Is it relevant to clinical medicine?
- Is it important for public policy or public health?

This report presents a huge amount of data on a number of closely related issues around the treatment of carotid artery disease, and it is a challenge for the reader to keep oriented within the text (i.e., asymptomatic vs. symptomatic, CAS vs. CEA, efficacy vs. effectiveness, etc.). Therefore, structure, consistency, and liberal use of headings and subheadings are important. I have made a few comments on this elsewhere, but even for someone who is reasonably familiar with the material, it is easy to get a bit lost. At this point, I don't have any other specific suggestions, and some of this may be unavoidable given the intrinsic complexity of this particular topic.

The report is highly relevant to clinical medicine and should serve the intended purpose well.

QUALITY OF REPORT

Quality Of the Report

(Click in the gray box to make your selection)

Superior

Good

Fair

Poor

This report clearly represents a tremendous amount of work, as indicated by its length and the long list of references, as well as the nature of the topic and key questions. In a reasonable amount of time (about 5 hours) I was just able to read through it, review some of the tables, look up a few references, and fill out the peer review form. I obviously did not have time to check every statement or table. Therefore, I must trust the process and assume that the data was reviewed, transcribed, and tabulated

appropriately. Based on the extent of my reading and review, I have no substantial cause for concern in this regard.

My understanding is that the primary purpose of this report is to review the relevant published data and present an evidence-based summary of the literature, and not to provide any clinical conclusions or recommendations. Therefore, no comments are necessary at this stage regarding the clinical implications of the report.

We would appreciate any feedback you have on the usability of this form. Please add comments in the field below.

The headings in this form do not correspond exactly to those on the Draft Evidence Report, making the form somewhat difficult to use. For example, there is no “Methods” section in the Report and there is no “Appraisal” section in the form. Also, if you want line numbers given on the form, you should add line numbers to each page in the Draft Report.