

Project Name: Management of Asymptomatic Carotid Artery Stenosis
 Project ID: CRDT0510

Table 1: Invited Peer Reviewer Comments

Reviewer ¹	Section ²	Reviewer Comments	Author Response ³
1	General	Outstanding formulation of the problem and approach	Thank you
2	General	Excellent, comprehensive, well balanced summary. It is clear, easy to follow considering the amount of literature and findings that are summarized. It includes all the relevant literature. The grading of the evidence is helpful, as is the summary of professional guidelines. The only addition I suggest, is it could even more clearly contrast the evidence and the current guidelines.	We have added more to our discussion comparing the evidence with current guidelines
1	Executive Summary	Crisp, accurate	Thank you
2	Executive Summary	All as above.	Thank you
1	Introduction/Background	Thorough for the focus of key endpoints	Thank you
2	Introduction/Background	None	
1	Methods	Rigorous, systematic, appropriate approaches. Importantly includes quality of studies (A,B, and C)	Thank you
2	Methods	None	
1	Results	innovative approaches to determine effect of time and year of study on rates of stroke (coefficient of recruitment closure year). Unbiased and maintains clear equipoise in reporting results	Thank you
2	Results	None	
1	Discussion/Conclusion	Appropriate and accurate for the data without over interpretation. Quite conservative.	Thank you
2	Discussion/Conclusion	None	
1	Tables	clear, thorough	Thank you
2	Tables	None	

1	Figures	excellent and state of the art	Thank you
2	Figures	None	
1	Appendices	excellent	Thank you
2	Appendices	None	
1	References	cannot think of a missed important study	Thank you
2	References	the below references were published after the authors completed their lit review for this assessment	Thank you. We have reviewed the suggested references against our eligibility criteria. Reference 1 and 3 did not address the Key Questions. Reference 2 and 4 were editorial and narrative reviews, respectively.

¹ Peer reviewers are not listed in alphabetical order.

² If listed, page number, line number, or section refers to the draft report.

³ If listed, page number, line number, or section refers to the final report.

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Table 2: Public Review Comments

Reviewer Name ¹	Reviewer Affiliation ²	Section ³	Reviewer Comments	Author Response ⁴
Abbott, Anne L.	Baker IDI Heart and Diabetes Institute, Melbourne, Australia	General	<p>I congratulate the timing of a review of policy in relation to management of asymptomatic carotid stenosis. A lot has been published in recent years to question current best-practice guidelines and suggest a new era of improved prevention of stroke and other complications of vascular disease in patients with this lesion.</p> <p>Unfortunately, I have only just received your draft report and have only had time to read the conclusion in the executive summary. I have also read over the references lists. I have been busy preparing for the CMS review of carotid disease management at the MEDCAC meeting on the 25th Jan 2012. I will be speaking at the meeting and have been preparing policy advisory documents.</p> <p>My view of the literature concurs with a lot in the executive summary conclusion of your draft report.</p>	Thank you
Abbott, Anne L.	Baker IDI Heart and Diabetes Institute, Melbourne, Australia	General	<p>However, I would like to express a word caution about the line that attempts to identify 'subgroups of patients who benefit from medical therapy alone was unsuccessful'. This could be mis-interpreted. Perhaps better to say:</p> <p>"the over-whelming evidence is that all patients with asymptomatic carotid stenosis are likely to benefit from medical intervention (identification and non-invasive reduction in vascular disease risk using healthy life style habits and appropriate medication). We now need to identify those likely to benefit from additional invasive carotid procedures (like surgery or stenting) despite current best-practice medical intervention alone."</p>	We have incorporated most of your suggestions. In the absence of randomized evidence comparing current best medical therapy with additional carotid interventional strategies, we could not make a strong statement about medical therapy or additional invasive carotid procedures.

			<p>I would also like to draw your attention to 4 references and a press-release I have helped produce:</p> <ol style="list-style-type: none"> 1. Abbott AL., Why Medical [Non-invasive] Intervention Alone is now Best for Asymptomatic Carotid Artery Stenosis. Results of Systematic Review and Analysis. Stroke, 2009; Level 1 evidence; [impact factor 7.0] [120 citations]. This is included in your report. 2. Abbott AL: Current Medical Intervention Alone Is Superior To CEA And CAS For Asymptomatic Carotid Arterial Disease. Invited conference paper presented at the 38th Annual Vascular and Endovascular Issues, Techniques and Horizons (VEITHsymposium). New York Hilton, New York City, 2011. Available online at http://www.veithsymposium.org/pdf/vei/4587.pdf . 3. Abbott AL: Why all the landmark trials supporting surgery to prevent strokes from carotid stenosis are now obsolete: When is carotid intervention now indicated. Invited conference paper presented at the 37th Annual Vascular and Endovascular Issues, Techniques and Horizons (VEITHsymposium). New York Hilton, New York City, 2010. Available online at http://www.veithsymposium.org/pdf/vei/3766.pdf . 4. Anne Abbott, Mark Adelman, Andrei Alexandrov, Henry Barnett, Jonathan Beard, Peter Bell, Martin Björck, David Blacker, Clifford Buckley, Richard Cambria, Anthony Comerota, E. Sander Connolly, Alun Davies, Hans-Henning Eckstein, Rishad Faruqi, Gustav Fraedrich, Peter Gloviczki, Graeme Hankey, Robert Harbaugh, Eitan Heldenberg, Steven Kittner, Timothy Kleinig, Dimitri Mikhailidis, Wesley Moore, Ross Naylor, Andrew Nicolaidis, Kosmas Paraskevas, David Pelz, James Prichard, Grant Purdie, Jean-Baptiste Ricco, Thomas Riles, Peter Rothwell, Peter Sandercock, Henrik Sillesen, 	<p>Thank you for the suggested references; we have evaluated them against our eligibility criteria. Reference 1 has already been included in the report as an existing systematic review. Reference 2 and 3 were rejected because they were narrative reviews with recommendations. Reference 4 was rejected because it was an opinion piece.</p>
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			<p>J. David Spence, Francesco Spinelli, Aaron Tan, Ankur Thapar, Frank Veith, Wei Zhou. Why the United States Center for Medicare and Medicaid Services (CMS) should not extend reimbursement indications for carotid artery angioplasty/stenting. European Journal of Vascular and Endovascular Surgery, Vol 43, Copyright 2012 European Society for Vascular Surgery. Published by Elsevier Limited. All rights reserved (doi: 10.1016/j.ejvs.2011.12.006). Corrected proof available online 6th January 2012: http://www.sciencedirect.com/science/article/pii/S1078588411007866.</p> <p>to be republished in Vascular, Brain & Behavior, Angiology & International Angiology.</p>	
Abbott, Anne L.	Baker IDI Heart and Diabetes Institute, Melbourne, Australia	General	A little long and repetitive.	No comment
Abbott, Anne L.	Baker IDI Heart and Diabetes Institute, Melbourne, Australia	General	Need to more clearly define the study inclusion criteria- early and throughout all sections: Introduction, Methods, Results and Discussion. I did not know, for instance, in this review the minimum sample size for inclusion was 30 patients of patients until the end of the report. What was the degree stenosis criteria and method of determining stenosis? Was there a minimum followup period? Do not rely on an appendix. I do not think appendix C has all the criteria any way.	The degree of stenosis criteria, sample size, and duration of followup were reported in the Executive Summary and Methods section of the report. To improve clarity and visibility we have added a separate heading for sample size. With regard to determining stenosis, details are provided within the table in the main text (please see Tables 1, 6, and 7) This is indicated in the Executive Summary as "All eligible studies are described in detail in the full-text of the report."

Abbott, Anne L.	Baker IDI Heart and Diabetes Institute, Melbourne, Australia	General	Avoid distractions. Decide endpoint of most relevant for the review- eg first ipsilateral stroke, and separate from composite endpoints from trials like CREST and SAPPHIRE.	We have presented our outcomes in the following order: ipsilateral stroke as the first, followed by other outcomes for each of the Key Questions.
Abbott, Anne L.	Baker IDI Heart and Diabetes Institute, Melbourne, Australia	General	I hope this helps and please keep me informed of your publications so I can quote them.	Thank you
Abbott Laboratories	Abbott Laboratories	General	<p>To assure applicability and consistent interpretation of the results of the tech assessment, the following recommendations are made:</p> <p>1) When assessing quality and level of evidence, the definitions need to be assessed based on the analysis being performed to assure that conclusions are consistent with the definitions.</p> <p>2) Using statistical tests to determine whether populations should be pooled is necessary, but not sufficient, to determine whether it is indeed appropriate to pool such results. There may be clinically relevant differences in populations that may not be statistically significant due to limited sample sizes. In addition, adjusted and unadjusted event rates should be included.</p> <p>3) As recommended by the June 2009 MEDCAC panel, a Bayesian approach should be considered for the various meta-analyses, as well as a discussion of any important differences in findings based on statistical technique.</p> <p>4) The tech assessment authors only considered the improvements over time for medical therapy alone. The other interventions investigated appear to have improved over time as well. For completeness, such time-series analyses for CAS and CEA should be added.</p>	<p>1) We have striven to ensure that the quality and level of evidence corresponds well with our synthesis and conclusions.</p> <p>2) We have clarified the issue of limited sample size and lack of statistical significance with the following statement: "The failure to find statistically significant differences does not rule out the possibility that real differences exist between interventions." In consideration of several reviewers' comments, we have decided to plot estimates from CREST and SAPPHIRE without a formal meta-analysis. Consequently, the strength of evidence has been changed to insufficient, as these trials are not comparable because of the extreme clinical heterogeneity of the included populations.</p>

				<p>In addition, we could not conduct adjusted event rate analyses, as the studies do not report/present such data. We acknowledge this as a limitation.</p> <p>3) Our analyses were based on maximum likelihood meta-analysis using the exact binomial or Poisson likelihood (as appropriate) to represent within-study variability. It is well established that these analyses produce equivalent results to fully Bayesian analyses using appropriate uninformative priors, provided that the number of studies is large. Note that because we performed analyses using generalized random effects models, we are able to account for uncertainty in the estimation of between study heterogeneity (in contrast to standard inverse variance random effects meta-analysis methods that ignore estimation uncertainty for this parameter). In the meta-analyses we conducted, the number of included studies was large, generally, indicating that Bayesian and frequentist approaches would not differ substantially.</p> <p>4) For patients with</p>
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				<p>asymptomatic carotid stenosis, intensive medical management has evolved significantly over the past decade, as have endovascular approaches. While there have been evaluations of endovascular approaches in recent trials, no trials have examined the current best medical therapy against carotid endovascular procedures.</p> <p>In the absence of comparative literature for current best medical therapy (and the fact that all patients receive medical therapy for risk factors associated with carotid stenosis), it became important, and possibly the only, way to evaluate stroke reduction over time with medical therapy.</p>
Abbott Laboratories	Abbott Laboratories	General	<p>Consistency in Applying Definitions of Quality and Level of Evidence</p> <p>The tech assessment authors clearly state what constitutes Quality-A, -B and -C studies. While Quality-B studies are susceptible to some bias, it is not sufficient to invalidate the results. Quality-C studies, in contrast, have significant biases that may invalidate the study results. However, the authors include a number of registries and categorize them as Quality-B.</p> <p>Although these studies may not be biased when assessing only those patients who would be treated with medical therapy alone, they are biased when such studies are used to compare medical therapy alone to either intervention.</p> <p>The authors define a moderate level of evidence as at least two RCTs with little disagreement among studies. As noted in the Executive</p>	<p>The quality of studies is based on the assessment of risk of bias including, selection, performance, attrition, detection, and reporting biases. We do not use study design labels as a proxy for assessment of quality of studies.</p> <p>We have added the following clarifying text: "These ratings provide a shorthand description of the strength of</p>

			<p>Summary and the Results sections, CREST and SAPPHIRE agreed on a number of outcome measures, including:</p> <ul style="list-style-type: none"> ? any peri-procedural stroke; ? peri-procedural death; ? peri-procedural MI; ? peri-procedural composite outcome of any stroke, MI, or death; and ? peri-procedural cranial nerve palsy. <p>Both studies were published in leading peer reviewed journals and are considered valid. Therefore, according to widely-accepted definitions, the level of evidence should be considered moderate. In contrast, the authors indicate the level of evidence was considered low, citing considerations that were not part of their own definitions of level of evidence, such as the registry component of SAPPHIRE. The concerns noted by the authors are appropriate for a discussion of the results. Nonetheless, the level of evidence should be revised from low to moderate to be consistent with the pre-specified criteria and currently accepted standards.</p>	<p>evidence supporting the major questions we addressed. However, they by necessity may oversimplify the many complex issues involved in the appraisal of a body of evidence. Individual studies evaluated in formulating the composite rating differed in their design, reporting, and quality. The strengths and weaknesses of the individual reports, as described in detail in the text and tables, should also be taken into consideration.”</p> <p>In consideration of several reviewers’ comments, we have decided to plot estimates from CREST and SAPPHIRE without a formal meta-analysis. Consequently, the strength of evidence has been changed to insufficient, as these trials are not comparable because of the extreme clinical heterogeneity of the included populations</p>
Abbott Laboratories	Abbott Laboratories	General	<p>Assessment by Pooling across Populations</p> <p>When pooling results across multiple studies, the populations must be similar in terms of key predictors of the outcome of interest, in order for the pooled results to be reliable and interpretable. Assessing whether the populations can and should be pooled must consider both statistical and clinical perspectives. The tech assessment authors should be commended for testing for statistical heterogeneity in</p>	<p>Some heterogeneity is always expected among the included studies in a meta-analysis. The population of interest for this report is asymptomatic carotid stenosis (ranging between 50 and 99%). The heterogeneity of the</p>

		<p>populations. However, statistical significance (or lack there of) does not necessarily mean clinical significance (or lack there of).</p> <p>The authors should share exactly what the statistical test(s) could detect, as well as a clinical assessment of the differences among the populations. For example, percent diameter stenosis is one of the few agreed-upon predictors of stroke. However, there appears to be substantial heterogeneity of populations enrolled in the various medical therapy registries used to calculate the various incidence rates for this treatment. The summary incidence rates for medical therapy alone (Table 2) included studies of patients with moderate stenosis (less than 70%), as well as those with severe stenosis (greater than 70%). As a result, it is unclear what the resulting stroke rate represents.</p> <p>It likely underestimates the incidence rates for patients with severe stenosis (greater than 70%), while it likely overestimates these rates for those with moderate stenosis (less than 70%).</p> <p>In addition, when there are differences in populations that are clinically relevant, those differences should be part of the assessment of the outcomes. CREST compared CAS to CEA for standard surgical risk patients that were candidates for CEA. SAPPHIRE compared CAS to CEA for patients that were considered at higher risk for adverse outcomes from CEA but were still candidates for CEA. Therefore, one would expect there would be differences in the results for these two trials, given the differences in their respective patient populations. For example, peri-procedural death was higher in SAPPHIRE than CREST, which was to be expected given that the patient population was at higher risk in SAPPHIRE.</p> <p>SAPPHIRE and CREST provide information regarding how CAS compares to CEA in a broad range of patients, those with the lowest risk of adverse outcomes from CEA (via CREST) to those at highest risk but still treatable by CEA (via SAPPHIRE). This is not a weakness in the evidence, rather a strength, demonstrating CAS results over a</p>	<p>definitions of asymptomatic carotid stenosis has been an issue in the published literature. The heterogeneity of the definition of asymptomatic carotid stenosis is not only an issue of medical studies, but also an issue in trials of CEA and CAS, as well as trials of CEA and medical therapy. For example, among asymptomatic patients included in ACST, 36 (2%) patients that underwent CEA had <70% stenosis, and in CREST 90 patients had <70% stenosis. This accounted for 7.2% of 594 with <70% stenosis that underwent CAS and 8.2% of 587 patients with <70% stenosis that underwent CEA.</p> <p>It is for the same reasons we conducted subgroup analyses comparing moderate stenosis versus severe stenosis, whenever data was available.</p> <p>We agree that the CREST and SAPPHIRE trials addressed different populations. However, there were additional issues of reporting discrepancies in the SAPPHIRE trial. With further input from experts</p>
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			<p>range of patients.</p> <p>Finally, the authors should include both unadjusted and adjusted outcomes when divergent populations are being pooled. When comparing incidence rates for all three therapies, it is difficult to interpret the results, since the authors pooled divergent trials types with vastly different total sample sizes. The authors note that SAPPHIRE and CREST could not be pooled, yet they are pooled in the summary incidence rates for CAS. The incidence rates for CEA and medical therapy include registries, along with RCTs, with no adjustment for the differences in the populations, yet the CAS summary incidence rate only includes two RCTs. We recommend the incidence (Table 8) be revised to include adjusted and unadjusted summary incidence rates for all three therapies.</p>	<p>and methodologists, we decided to present the rates of SAPPHIRE and CREST separately, without combination into a single estimate. We have revised and presented the data in forest plots, without combining these two trials in a meta-analysis, so readers can identify the direction of effect estimates.</p> <p>Adjusted incidence rates are often not presented in primary studies. We combined any prospective comparative studies that provided long-term data.</p> <p>With further input from experts and methodologists, we decided to present the incidence rates of SAPPHIRE and CREST separately.</p>
Abbott Laboratories	Abbott Laboratories	General	<p>Challenges Associated with Meta-analyses</p> <p>Meta-analyses are challenging; there are many ways to perform these analyses and each methodology has its limitations. In this circumstance where the meta-analysis is performed across a large number of smaller studies, it is difficult to adjust for the differences in populations across the studies.</p> <p>CMS conducted a MEDCAC meeting on June 17, 2009 to gain insights into this very issue. The meeting focused on the use of Bayesian analysis techniques when assessing evidence, particularly meta-analyses. It was persuasively argued that using frequentist methods often lead to misleading results and that a Bayesian approach could be more informative. Specifically, on the voting</p>	<p>We took into consideration all the issues that you have raised here.</p> <p>Our analyses were based on maximum likelihood meta-analysis using the exact binomial or Poisson likelihood (as appropriate) to represent within-study variability. It is well established that these analyses produce equivalent results to fully Bayesian analyses using appropriate uninformative priors, provided</p>

			<p>question ? How confident are you that CMS should incorporate evidence that uses Bayesian approaches in trials or technology assessments submitted for coverage decisions?? The result was a ?highly confident? 4.33 (out of 5) for clinical trials and 4.33 for technology assessments [From the CMS website https://www.cms.gov/medicare-coverage-database/details/medcac-meeting-details.aspx?MEDCACId=49&fromdb=true].</p> <p>While CMS? advisors strongly recommended use of Bayesian methods, the authors of the current assessment do not use them, nor do they discuss their rationale for rejecting such an approach and adopting their frequentist approach.</p> <p>Given the consensus at the 2009 MEDCAC, we recommend that authors consider using Bayesian methods for the meta-analyses to assure that the results are robust. At a minimum, the authors should provide results of the meta-analyses using both statistical approaches and discuss any important differences found.</p>	<p>that the number of studies is large. Note that because we performed analyses using generalized random effects models, we were able to account for uncertainty in the estimation of between study heterogeneity (in contrast to standard inverse variance random effects meta-analysis methods that ignore estimation uncertainty for this parameter). In the meta-analyses we conducted, the number of included studies was large, generally, indicating that Bayesian and frequentist approaches would not differ substantially.</p>
Abbott Laboratories	Abbott Laboratories	General	<p>Improvements in All Three Therapies over Time</p> <p>As noted by the tech assessment authors, medical therapy for asymptomatic carotid stenosis likely has improved over time. It also may be argued that similar time-series analyses also are appropriate for the alternatives (CAS and CEA). Results presented at the FDA panel meeting indicate that CAS and CEA indeed have improved from 2000 to present [See http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM247780.pdf, Slide 62, Death or major stroke rates decrease for CAS over the period of CREST enrollment]. There was an improvement (decrease) in death and stroke over the eight-year enrollment period for CREST for those treated with</p>	<p>We agree that all therapies, including techniques, have improved over time. Even though all patients receive medical therapy for risk factors of asymptomatic carotid stenosis, the role of this therapy has not been investigated in the last decade in comparative studies or trials. In the absence of such data, the only way to address Key Question 1a was to look at cohorts and make an assessment of the possible stroke rates by comparing a recent medical cohort with a cohort from older studies. But</p>

			<p>CAS. The overall event rate for death and major stroke had been reduced 77% (2.5% to 0.6%). Similarly, there has been a favorable evolution in CEA over time. Of note, death and stroke rates for asymptomatic patients have been reduced by 80% (6.9% to 1.4%) from the 1980 Cincinnati study [See Brott and Thalinger. Stroke. 1984 Nov-Dec;15(6):950-5.1980] to CREST (2010), and for symptomatic patients by 74% (12.1% to 3.2%) from these same studies.</p>	<p>the question of improvement over time was not evaluated for other techniques (CEA and CAS) because there comparative trial data exist.</p>
Abbott Laboratories	Abbott Laboratories	General	<p>General Conclusions</p> <p>The technology assessment, though comprehensive in terms of accessing available data, would be enhanced by addressing the previously discussed issues that apply to multiple analyses and conclusions. This includes first, assessing the definitions based on the analysis being performed to assure that conclusions are consistent with the definitions.</p> <p>Second, using statistical tests to determine whether populations should be pooled is necessary, but not sufficient, to determine whether it is appropriate to pool such results.</p> <p>The tech assessment authors should evaluate clinically relevant differences in the populations to be pooled, as well as provide adjusted and unadjusted event rates.</p> <p>Third, a Bayesian approach should be considered for the meta-analyses, as well as a discussion of any important differences in findings based on statistical technique.</p> <p>Finally, the tech assessment authors should consider the improvements over time for all interventions investigated, as CAS and CEA appear to have improved over time as well.</p>	<p>1) We have striven to ensure that the quality and level of evidence corresponds well with our synthesis and conclusions.</p> <p>2) We have clarified the issue of limited sample size and lack of statistical significance with the following statement: "The failure to find statistically significant differences does not rule out the possibility that real differences exist between interventions." In consideration of several reviewers' comments, we have decided to plot estimates from CREST and SAPPHIRE without a formal meta-analysis. We could not conduct adjusted event rate analyses, as the studies do not report/present such data. We acknowledge that this is a limitation.</p> <p>3) Our analyses were based on maximum likelihood meta-analysis using the exact binomial or Poisson likelihood (as appropriate) to represent</p>

				<p>within-study variability. It is well established that these analyses produce equivalent results to fully Bayesian analyses using appropriate uninformative priors, provided that the number of studies is large. Note that because we performed analyses using generalized random effects models, we are able to account for uncertainty in the estimation of between study heterogeneity (in contrast to standard inverse variance random effects meta-analysis methods that ignore estimation uncertainty for this parameter). In the meta-analyses we conducted, the number of included studies was large, generally, indicating that Bayesian and frequentist approaches would not differ substantially.</p> <p>4) For patients with asymptomatic carotid stenosis, intensive medical management has evolved significantly over the past decade, as have endovascular approaches. While there have been evaluations of endovascular approaches in recent trials, no trials have examined the current best medical therapy against</p>
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				carotid endovascular procedures. In the absence of comparative literature for current best medical therapy (and the fact that all patients receive medical therapy for risk factors associated with carotid stenosis), it became important, and possibly the only, way to evaluate stroke reduction over time with medical therapy.
Cutlip, Donald E.	Harvard Clinical Research Institute	General	The manuscript is well written and the methods are standard. The questions addressed and outcomes considered are appropriate. The search methods and studies identified are comprehensive. The draft will benefit from a careful proofread to correct several grammatical errors etc	Thank you. Our editor proofread the document.
Jaff, Michael R.	Massachusetts General Hospital	General	This is an exhaustive review of the published literature regarding management of asymptomatic carotid artery stenosis.	Thank you.
Moore, Wesley S.	David Geffen School of Medicine at UCLA	General	This is a well written, carefully organized, and clear presentation regarding the current state of knowledge concerning the management of patients with hemodynamically significant, asymptomatic carotid atherosclerosis. I have only one significant criticism and several suggestions.	Thank you.
Moore, Wesley S.	David Geffen School of Medicine at UCLA	General	Finally, the AHRQ investigators have clearly cited evidence to suggest that the medical management of the asymptomatic patient with carotid atherosclerosis has improved such that the adverse events of stroke, with medical management alone has dropped, raising the question as to whether any intervention is any longer justified. Clearly there is the need for a new, prospective randomized trial to answer this question since the prior trials, VA, ACAS, ACST, are now dated and are no longer relevant since they did not include what is considered today to be optimum medical therapy. What the AHRQ investigators failed to include in their report are the publications which suggest that there are methods to identify the "high risk" group of asymptomatic patients who may well benefit from invasive intervention in addition to receiving	Thank you. We have reviewed recent citations. Citation 3 has already been included in the report. Citations 1, 2, and 4 did not meet the inclusion criteria because they were narrative reviews. We have clarified our statement regarding difficulty in identifying the "high risk" group of asymptomatic patients who may well benefit

		<p>optimal medical therapy. I have attached several pertinent references to this report as well as copies of the publications(as pdf files) which suggest that analysis of the atherosclerotic plaque or the use of transcranial Doppler to assess emboli as detected by high intensity signals(HITS) are effective in sorting out the asymptomatic patients who are at high risk of stroke and may well benefit from intervention.</p> <p>1. J. David Spence, David Pelz and Frank J. Veith Asymptomatic Carotid Stenosis : Identifying Patients at High Enough Risk to Warrant Endarterectomy or Stenting</p> <p>ISSN: 1524-4628 Copyright © 2011 American Heart Association. All rights reserved. Print ISSN: 0039-2499. Online Stroke is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514 <i>Stroke</i> published online July 28, 2011</p> <p>2. Chrysi Bogiatzi, Myra S Cocker, Robert Beanlands & J David Spence† †University of Western Ontario, Stroke Prevention & Atherosclerosis Research Centre, Robarts Research Institute, London, Canada Identifying high-risk asymptomatic carotid stenosis Expert Opin. Med. Diagn. [Early Online]</p> <p>3. J. David Spence, MD; Arturo Tamayo, MD; Stephen P. Lownie, MD; Wai P. Ng, MD; Gary G. Ferguson, MD, PhD Absence of Microemboli on Transcranial Doppler Identifies Low-Risk Patients With Asymptomatic Carotid Stenosis (<i>Stroke</i>. 2005;36:2373-2378.)</p> <p>4. Time to rethink management strategies in asymptomatic carotid artery disease A. Ross Naylor Naylor, A. R. <i>Nat. Rev. Cardiol.</i> 9, 116–124 (2012); published online 11 October 2011; doi:10.1038/nrcardio.2011.151</p>	<p>from invasive intervention in addition to receiving optimal medical therapy.</p>
Naylor, Ross	Department of Vascular Surgery, Leicester Royal	General <p>I would like to commend the authors of this study for their very comprehensive review of data pertaining to the management of asymptomatic carotid disease. I have no major criticisms or comments except that a report of this stature should probably be a little more specific in its directions for future research. I fully agree that we need</p>	<p>Thank you. We have incorporated your suggestions in our technology assessment report.</p>

	Infirmery, Leicester		to identify a 'high risk for stroke' cohort, but it would have been helpful for the report to state that any future randomised or observational studies should include data relating to the predictive effects of the following imaging parameters: (1) silent infarction at baseline CT/MR, (2) spontaneous embolisation on transcranial Doppler, (3) computerized ultrasound plaque analysis (Gray Scale Median, juxtaluminal black area, plaque volume, discrete white areas etc), (4) evidence of intra-plaque haemorrhage on MRI, (5) biomarkers such as highly selective CRP. I am sure the authors will be aware that CREST II plans to recruit about 950 asymptomatic patients for randomization between CEA or CAS versus modern medical therapy. If there is no funding for assessing one or all of the imaging strategies (above), there is no feasible chance of identifying a higher risk cohort of patients in those randomised to medical therapy. That would be a wasted opportunity.	
White, Christopher	Society for Cardiovascular Angiography and Interventions	General	<p>Thank you for the opportunity to comment on the draft Technology Assessment Report on the Management of Asymptomatic Carotid Artery Stenosis. It is an extensive review of literature that attempts to utilize randomized controlled trials of high quality to formulate a study design and key questions. We note that important registry data from numerous carotid stent trials has been minimized or not considered in this draft report.</p> <p>The Society for Cardiovascular Angiography and Interventions (SCAI) is a professional association representing over 4,000 invasive and interventional cardiologists. SCAI promotes excellence in cardiac catheterization, angiography, and interventional cardiology through physician education and representation, and quality initiatives to enhance patient care.</p> <p>We agree that carotid artery stenosis is an important cause of ischemic stroke. In asymptomatic patients with carotid artery stenosis the optimal treatment strategy remains controversial.</p> <p>Carotid endarterectomy (CEA) is proven effective therapy for carotid artery stenosis in asymptomatic patients. Carotid artery stenting</p>	<p>We evaluated studies with a view to answer the Key Questions that were posed to us. Only medical therapy studies were evaluated as single cohorts, for the following reasons: medical therapy is prescribed to patients who are at an increased risk for carotid stenosis; and the comparative effectiveness of medical therapy has not been evaluated in studies published in the last decade.</p> <p>Thank you.</p> <p>CEA trials were conducted a decade ago. There were issues in one CAS trial</p>

			<p>(CAS) has similarly been proven in randomized controlled trials to be as effective as CEA in asymptomatic high-risk patients (SAPPHIRE) and in asymptomatic average surgical risk patients (CREST).</p> <p>Any current recommendation for the management of carotid stenosis for stroke prevention must include optimal medical therapy. Unfortunately the legacy trials that definitively showed an advantage for CEA over medical therapy in asymptomatic patients were conducted prior to the adoption of many modern medical therapies. Importantly, CEA and CAS have been proven to be equivalent in large, well-conducted randomized trials. The role of best medical therapy for stroke prevention remains controversial and should not restrict current access to revascularization strategies pending further research.</p>	<p>evaluating asymptomatic high-risk patients. The recent trial of CAS versus CEA did not evaluate medical therapy, and did not sufficiently provide information on optimal medical therapy in both groups.</p> <p>We do not make recommendations regarding treatment strategies.</p>
White, Christopher	Society for Cardiovascular Angiography and Interventions	General	<p>The fact that a clinical trial of current "best medical therapy" in this patient population has not been undertaken should not jeopardize the results of the above mentioned studies. CAS may be the most studied procedure of all time. In the last few years data on more than 10,000 CAS patients have been reported in registries designed to achieve FDA approval. There are currently seven (7) carotid stent systems that have cleared the bar and have been approved as "safe and effective" by the FDA for asymptomatic patients in various clinical categories.</p> <p>We concur that future trials of CEA and CAS should include a medical therapy arm. However this comparison cannot be done retrospectively by a review of the proposed data sources. Databases that do not include independent neurologic evaluation of clinical outcomes, such as administrative databases suffer from a significant ascertainment bias. The ascertainment bias in not having systematic neurological assessment is impossible to overcome with statistical manipulation. Any reasonable comparison of CAS must control for variables of operator specialty, operator experience, anatomic and co-morbid risk, symptom status and the use of embolic protection. It is important to standardize how adverse reactions and complications are detected and attributed. The data sources proposed do not have the ability to negate these deficiencies. We strongly recommend that the NCDR-</p>	<p>The U.S. FDA approval is based on efficacy and safety data, and not necessarily with regards to effectiveness.</p> <p>The absence of trial data should not be a reason to not evaluate a treatment strategy. In the absence of RCT data, it is important to assess the role of a treatment strategy from alternative study designs. We agree that CAS is very technique dependent, and that it has evolved over time. However, we do not agree this provides sufficient reason to disregard studies that reported data in a real-world setting.</p>

			CARE registry, which includes mandatory independent neurologic assessment of outcome data, be included in this analysis.	We examined data from the NCDR-CARE registry against our eligibility criteria, and were unable to identify specific information related to asymptomatic patients.
White, Christopher	Society for Cardiovascular Angiography and Interventions	General	<p>?Real world? assessment of trial results are only valid if they compare similar groups. The proposed data appears to suffer from excess heterogeneity. In addition patient outcomes must include myocardial infarction as an endpoint, as this has been proven in the CREST to be a significant independent predictor of late mortality.</p> <p>If you are to question the applicability of the results of older trials to today?s medical treatment of carotid artery stenosis, you must question the role of CEA as well as CAS. We do not have data to support such a radical policy limiting patient treatment options. Future trials that prospectively randomize patients and include ?best medical therapy? should be conducted. Until then, we lack evidence to restrict CAS or CEA to patients who clearly benefit from revascularization therapy.</p> <p>A expanded approval for CAS and designing and conducting appropriately designed trials that include best medical therapy along with adoption of registry and quality initiatives is the only fair and rationale way to proceed.</p> <p>I would like to thank Drs. Tyrone Collins and Bryan Kluck who reviewed this report for SCAI and developed these comments.</p>	<p>We have presented data on MI if they were reported in the reviewed studies.</p> <p>We have not made recommendations to restrict any therapy. Our review evaluated the presence/absence of evidence surrounding each treatment strategy.</p> <p>We do not make any specific recommendations in our technology assessment report.</p>
Wilentz, James R.	Weill Cornell Medical College	General	This is a great effort to summarize a very heterogeneous group of research papers into a cogent analysis.	Thank you.
Anonymous Reviewer 1	NA	General	If the tact of requiring a prospective randomized comparison of CAS vs. best medical therapy is taken in order to accept CAS as a therapy for asymptomatic carotid disease is taken then a similar demand should be made upon endarterectomy rather than continued	We found insufficient data directly comparing CAS versus medical therapy. Although prior trials of CEA versus

			<p>acceptance as standard of care. The cited achievable annual rates of stroke with medical therapy only that are being used to question the role for CAS, when similarly placed against the risk of complication of CEA, stack just as favorably. Therefore any decision to not endorse use of CAS on said basis should immediately be followed by a similar decision against continued support for routine CEA until similar contemporary medical therapy vs. surgical intervention studies can be performed. Otherwise, should CEA continue to be accepted as both indicated and safe the only data of significant consideration should remain a direct comparison of safety and efficacy of CAS vs. CEA. Anything other than these two options would amount to unequal application of scrutiny.</p>	<p>medical therapy found benefit with CEA, they are no longer applicable to current practice of best medical therapy. Our review identified significant gaps comparing three important treatment strategies for the management of asymptomatic carotid stenosis.</p>
Abbott, Anne L.	Baker IDI Heart and Diabetes Institute, Melbourne, Australia	Executive Summary- Results pES-8	<p>It is an error to say there is moderate strength evidence CEA can reduce risk of stroke using the 3 best randomised trials –VACS, ACST, ACAS. Truth is these studies showed risk could be reduced by CEA using the types of patients randomised, the medical intervention given at the time and the quality of CEA given (CEA by the best available surgeons). Trouble is we have tried to generalise this to routine practice and generalise it to routine practice for decades-until the current day- assuming the RT conditions were the same across location and time. We now know such generalisation is an error. For one, conditions in routine practice are not the same as in TRs. Second, medical intervention has improved in stroke prevention efficacy. Need to differentiate what applied then and what applies now. Can no longer use these old RT results to dictate current routine practice stroke prevention. Even so, the RTs conditions may still be replicated in some parts of current routine practice: poor medical intervention and best quality surgery. However, best evidence indicates this is inefficient in stroke prevention and not cost effective compared to current medical intervention alone. It is not the best way to manage patients now.</p>	<p>The strength of evidence rating is based on the factors that include risk of bias, precision, consistency and directness. However, applicability is a different issue in evaluating these older CEA trials. We do acknowledge that there are issues in applying the findings from older trials to current clinical practice. Nonetheless, in the absence of comparative trial data comparing all three treatment strategies, we cannot make strong statements or claims about a treatment strategy. Our report did not evaluate cost-effectiveness of these three treatment strategies.</p>
Abbott, Anne L.	Baker IDI Heart and Diabetes Institute, Melbourne,	Executive Summary- Results pES-8	<p>Results pES-8: difference in stroke free survival DID change in ACST over time between immediate CEA and deferred CEA groups (average annual rate of any stroke was 1% at 5 years, only about 0.5% by 10 years).</p>	<p>We have edited these sections.</p>

	Australia			
Abbott Laboratories	Abbott Laboratories	Executive Summary	Comments in the Results section apply to the Executive Summary, to the extent that these same analyses are discussed in here. For the sake of brevity, we do not repeat these comments here.	All responses to comments have been addressed in the previous sections.
Cutlip, Donald E.	Harvard Clinical Research Institute	ES-5, next to last paragraph, line 2	Need to define the composite endpoint or change wording to say a composite endpoint including ipsilateral stroke. I think this wording is not clear	We have incorporated your suggestion into our review.
Cutlip, Donald E.	Harvard Clinical Research Institute	page ES-13, paragraph 2	Note is made of the patient-selection process in SAPPHIRE in which a substantial proportion of patients were placed in a stent registry. It is agreed this raises a concern for selection bias, although the study design indicated this group was deemed too high a surgical risk for randomization. It should be noted, however, that at least similar patient-selection issues were present in CREST, in which eligible patients were enrolled into one of several stent registries by then available, leading to a well-known prolonged enrollment period for CREST.	We agree with your comments.
Jaff, Michael R.	Massachusetts General Hospital	Executive Summary	Well written	Thank you.
Howard, Virginia	University of Alabama	Executive Summary-ES-1	Item #1. It is not clear why myocardial infarction (MI) was included in key question #1. As stated throughout the document, the goal of management of asymptomatic carotid stenosis is to decrease the risk of stroke and stroke-related death so that many studies would not be expected to have follow-up data on MI.	We agree that the goal of management of asymptomatic carotid stenosis is the reduction in ipsilateral stroke (both fatal and non-fatal). We consider MI as a patient-centered outcome, and when this outcome was reported, we reviewed it.
Howard, Virginia	University of Alabama	Executive Summary-ES-2	Search strategy indicates through February 2011 yet some references (including 81, 92) are after this cutoff. (Ref 94 has no date indicated for accessing the FDA web site)	We have updated our search and have edited search dates.
Howard, Virginia	University of Alabama	Executive Summary-ES-2	Data Analysis. Consideration should be given to indicating that actual follow-up times per each patient were not used but only the overall, median or range.	Thank you, we have clarified this point in the Executive Summary.
Howard, Virginia	University of Alabama	Executive Summary-	The statement "These RCTs showed no difference between the two treatment groups for the risk of any death, fatal stroke, or CVD death",	Thank you, we have edited this to read as: "meta-analyses

		ES-4	may not be true, based on results provided. See comments below in Results section.	of these RCTs....”
Howard, Virginia	University of Alabama	Executive Summary-ES-4	Subtitle “ <i>ipsilateral stroke</i> ” is not sufficient – should be expanded to “ <i>Any stroke within perioperative period or subsequent ipsilateral stroke</i> ” as defined in the paragraph.	We have edited these outcome headings.
Howard, Virginia	University of Alabama	Executive Summary-ES-5	Subtitle “ <i>Any stroke</i> ” is not sufficient – it should be expanded/clarified to “ <i>Perioperative death or any stroke at any time.</i> ”	We have edited these outcome headings.
Howard, Virginia	University of Alabama	Executive Summary-ES-6	It is mentioned that for SAPPHIRE, there were differences in reporting between the published paper and the unpublished data on the FDA web site. It is not clear why the unpublished data were examined as these data were not peer-reviewed. Also, was the FDA web site data for CREST examined for differences between published data and posted data?	It is important that the peer-reviewed article reported data matches well with data posted at the FDA website, since they do have access to primary data, which are usually not available to reviewers of the journal. We did review the FDA Website data for CREST, but the majority of the reanalyzed data have not been fully made available to the public.
Howard, Virginia	University of Alabama	Executive Summary-ES-8	In the statement about subgroup analysis by sex within ACAS, i.e., “ <i>men had a significantly decreased risk of ipsilateral stroke. . .</i> ” the correct wording should be “ <i>men had a significantly decreased risk of perioperative stroke or death or five-year ipsilateral stroke.</i> ” Same thing for further down on the page, in discussion about patients with prior symptoms due to contralateral stenosis or prior contralateral CEA.	We have edited these as suggested.
Howard, Virginia	University of Alabama	Executive Summary-ES-8	Statement that starts “However at the actual 2.7-year follow-up in ACAS, there were more events. . .” should be changed. The follow-up of 2.7 year is the <u>median</u> follow-up.	We have edited this as suggested.
Howard, Virginia	University of Alabama	Executive Summary-ES-9	Related to methodological quality of studies, it is because the three RCTs did have different primary outcomes that it is critically important to clearly and consistently and always define the outcomes being summarized in this report.	We have edited this sentence. The primary outcomes are described in the main body of the report and in Table 6.
Howard, Virginia	University of Alabama	Executive Summary-	Length of follow-up – there may be CREST 1-year follow-up data on the FDA web site.	We have not been able to access the 1-year data from

		ES-10		the FDA website. These have not been made fully available.
Howard, Virginia	University of Alabama	Executive Summary-ES-10	Key Question 3 (outcomes occurring within 30 days). First paragraph – neither the VA nor ACAS included MI as an outcome within 30 days, i.e. not part of the protocol and not reported. This should be deleted here and in the results section.	The VA study reported MI, both fatal and nonfatal (please see Hobson 1993, NEJM 328: 221-227; page 224—Surgical Morbidity and Mortality). ACAS reported only fatal MI (page 1424, middle column, second paragraph).
Howard, Virginia	University of Alabama	Executive Summary-ES-11	Periprocedural MI paragraph. There are no data for either the VA trial nor ACAS on periprocedural MI. This paragraph should be deleted here and in the results section. It is ok (but potentially confusing) to keep the next paragraph titled “ Periprocedural composite outcomes (stroke or death with or without MI during the periprocedural period) because it appears the authors are talking about death from MI or death from non-MI causes and those data are available but really “death during the periprocedural period” is sufficient and best.	ACAS reported only fatal MI (page 1424, middle column, second paragraph). The VA trial also reported 1.9% non-fatal MI in the post operative period (please see Hobson 1993, NEJM 328: 221-227; page 224—Surgical Morbidity and Mortality).
Howard, Virginia	University of Alabama	Executive Summary-ES-11	CAS and medical therapy versus CEA and medical therapy – Please expand on definition of “adverse events” to include also cranial nerve palsy and bleeding complications.	Thank you. We have included clinical outcomes as adverse events, and these outcomes as complications from the procedure, in the revised version.
Naylor, Ross	Department of Vascular Surgery, Leicester Royal Infirmary, Leicester	Executive Summary	My only comment would be to include an additional statement at the end about actively looking for imaging and clinical predictors of stroke in future studies (as outlined above)	Thank you. We have incorporated your comment in the Future Research section of the report.
Cutlip, Donald E.	Harvard Clinical	Introduction/ Background-	The authors state, “The most commonly used measurement method of carotid stenosis ...”. This is probably not true and doesn’t follow prior	Thank you. We have incorporated your comment

	Research Institute	Page 1, paragraph 3	discussion on non-invasive methods. Perhaps, should say in most common method used in clinical trials or most common angiographic method.	into the report.
Cutlip, Donald E.	Harvard Clinical Research Institute	Introduction/ Background- Page 2, CEA and Medical Therapy, paragraph 2	Since anti-platelet therapy differences between stenting and CEA have been controversial, perhaps the authors may want to be more specific regarding anti-platelet therapy in the CEA groups in general.	Thank you. We have incorporated your comment into the report.
Howard, Virginia	University of Alabama	Introduction/ Background- Page 1	Ref 1 (2007) is outdated. Suggest the following most current reference: Roger VL, Go AS, Lloyd-Jones DM, et al on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics—2012 Update: A Report from the American Heart Association. Circulation 2012 Jan 3;125(1):e2-e220. Epub 2011 Dec 15.	Thank you. Edited
Abbott, Anne L.	Baker IDI Heart and Diabetes Institute, Melbourne, Australia	Methods	Overall a very good analysis of the evidence. Most importantly this is a third independent meta-analysis which shows the risk of ipsilateral stroke and other complications has fallen with vascular disease medical (non-invasive) intervention alone since the randomised trials VACS, ACAS and ACST were performed. This time using study recruitment closure before and after the year 2000. This is confirmation that these randomised CEA trials are out-dated with respect to dictating current routine practice. Confirmation current guidelines advising CEA, or even CAS, for asymptomatic carotid stenosis are out-dated/ in error. This information needs to be published in prominent peer review journals giving it access to the medical and wider community.	Thank you for your comment.
Abbott, Anne L.	Baker IDI Heart and Diabetes Institute, Melbourne, Australia	Methods	Please highlight other new/consistent findings: <ul style="list-style-type: none"> i. Subgroup analyses showed statins and antiplatelet agents decreased risk of ipsilateral stroke. ii. Patients with >70% stenosis did not have a higher risk of ipsilateral stroke compared with those with (<70%, p70). This is consistent with a strong body of evidence that stroke risk using degree of stenosis within the 50-99% range, on its own, is very weak for risk stratification for 	Thank you; we have highlighted these in our discussions with the caveat that only a proportion of total eligible studies reported this information.

			asymptomatic carotid disease. However, in this analysis it was shown to be an indicator of higher risk of other any territory stroke +/- TIA) (new finding).	
Abbott, Anne L.	Baker IDI Heart and Diabetes Institute, Melbourne, Australia	Methods	Need to define/more clearly define quality A and B and C studies. Was prospective versus retrospective method considered? Apparently 40 studies met inclusion criteria. What were the criteria-plain and simple list please. What were the 40 studies? Less than 40 studies (26) are included in table 1.	Please see pages 9-10 for the definitions of A, B, and C ratings. We only included prospective studies on medical therapy. The inclusion criteria are outlined on pages 6-8. Table 1 only lists the 26 studies (from the 40 that met the inclusion criteria) that report on ipsilateral stroke. We did not restrict our inclusion criteria to only ipsilateral stroke studies.
Abbott, Anne L.	Baker IDI Heart and Diabetes Institute, Melbourne, Australia	Methods	Recognise non-perioperative stroke risk (prominent in ACST publications) is confusing and potentially misleading. It has very little clinical relevance. Must always include the 30day procedural risk when comparing outcomes with between treatment strategies.	We included periprocedural outcomes when reported in the primary studies.
Abbott, Anne L.	Baker IDI Heart and Diabetes Institute, Melbourne, Australia	Methods	Primary and secondary prevention are part of the same spectrum. Need to be a little less rigid in classification. Patients with asy carotid stenosis often are identified because of contralateral stroke symptoms or heart disease. For most aspirin, for instance, is indicated as 'secondary' prevention, even though they have an asy carotid stenosis.	Thank you for your comment. The distinction between primary and secondary prevention was only made to introduce readers to the topic. We did not use it to classify the studies.
Abbott, Anne L.	Baker IDI Heart and Diabetes Institute, Melbourne, Australia	Methods-Data analysis methods Page 10	Data analysis methods page 10 unclear. Can you give an example of your rate calculations? Did you use raw data or published Kaplan Meier derived rates? Can you convert to a rate clinicians and patients will understand- like average annual rate as mentioned late in the review Discussion.	The detailed methods are available in references 23 and 24. We used the same methods as outlined in those papers.
Cutlip, Donald E.	Harvard Clinical	Methods	Excellent and well described.	Thank you for your comment.

	Research Institute			
Jaff, Michael R.	Massachusetts General Hospital	Methods	<p>I remain very concerned about the literature cited demonstrating efficacy of medical therapy alone for asymptomatic carotid artery stenosis. As the authors know, the only true method of studying the benefits of medical therapy is to offer treatment to published goals, and to demonstrate compliance with pill counts. There are no medical therapy trials in asymptomatic carotid artery disease that provided this. In addition, in order to suggest that medical therapy alone is an effective therapy for asymptomatic carotid artery stenosis, this treatment should be studied only in patients who are candidates for carotid revascularization. For example, no one would consider revascularization in patients with asymptomatic carotid artery stenosis <70%. The studies evaluating specific medical therapies in carotid artery disease often do not even define the severity of carotid artery stenosis. For example, the SPARCL study did not require the investigator to even report if the severity of carotid artery stenosis was known, what modality was used to assess the carotid artery for stenosis. Therefore, I do not agree that this Technology Assessment has drawn an accurate conclusion regarding the efficacy of medical therapy for asymptomatic carotid artery stenosis. In my opinion, the role of comprehensive, multimodality medical therapy to reduce stroke in patients eligible for revascularization has yet to be proven. I also think that a potential major reason for the reduction in stroke rates from 2000-2010 is due to the fact that more recent studies included patients with either no reported carotid stenosis, or patients whose stenosis severity was <70%, not eligible for revascularization.</p>	<p>Thank you for your comment. The population of interest for this report is asymptomatic carotid stenosis (ranging between 50 and 99%). The heterogeneity of definition of asymptomatic carotid stenosis is not only an issue of medical studies, but also an issue in trials of CEA and CAS, as well as trials of CEA and medical therapy. For example, among asymptomatic patients included in ACST, 36 patients (2% that underwent CEA) had <70% stenosis, and in CREST 90 patients (7.6%) had <70% stenosis. It is for the same reasons we conducted subgroup analyses comparing moderate stenosis versus severe stenosis, whenever data was available (Please see Table 5, page 21).</p>
Howard, Virginia	University of Alabama	Methods-Page 6	<p>Search Strategy – some references are after February 2011. Given that these key references were included, was an additional search conducted towards the end of the year to determine if any more key papers had been published? If not, how then were these new publications or web-site postings discovered?</p>	<p>We have made the necessary edits to correct errors. In addition, we ran an updated search, and we updated the search dates to reflect this.</p>
Howard, Virginia	University of Alabama	Methods-Page 8, under heading of Outcomes	<p>First sentence states that the clinical outcome of MI was included in Key Questions 1 and 2 yet it does not appear to be included in the outline immediately following.</p>	<p>Only periprocedural MI was reported as an outcome in reviewed studies. None of the studies reported long-term data on the clinical outcome of</p>

				MI.
Howard, Virginia	University of Alabama	Methods-Page 10. Data Analysis	There does not appear to be any description of methods/justifications/limitations related to using raw counts/number of events to calculate crude percentages for each trial with long-term follow-up (e.g., Figure 4, Any stroke or perioperative death, ACAS 60/825 vs. 86/834) and disregarding differential follow-up times. While this approach is appropriate for 30-day/finite periprocedural period (Figures 14, and Figures 16-23), it is not appropriate for the post-procedural periods with differential follow-up. (See also comments below under Figures.)	We agree that this is a limitation of the reporting of the data available for synthesis. We acknowledge this as a limitation in the report. Studies failed to report adjusted hazard ratios consistently. Even when adjusted hazard ratios were reported, the outcomes were not comparable.
Moore, Wesley S.	David Geffen School of Medicine at UCLA	Methods	In my opinion, it is not appropriate to combine the SAPPHIRE TRIAL and CREST TRIAL into a meta-analysis. While it is true that these are the only prospective randomized trials that included patients with asymptomatic carotid atherosclerosis, the populations of the two trials differed markedly. The population in the SAPPHIRE trial represented patients who were considered high risk for carotid endarterectomy (CEA) while the patients entered into the CREST trial were considered to be of average risk. Furthermore, neither trial was powered to separately analyze symptomatic and asymptomatic patients. The SAPPHIRE trial demonstrated that carotid stent/angioplasty resulted in fewer primary adverse outcome events than CEA in this "high risk" group, but only when non-Q wave myocardial infarction was added. As a result of this study, CMS approved re-imburement for CAS when applied to symptomatic, high risk patients. The CREST trial, in contrast, demonstrated that CAS was associated with double the risk of stroke when compared to CEA. A sub-analysis which separated symptomatic from asymptomatic patients demonstrated fewer events in the asymptomatic category for each procedure, but maintained the same relationship; specifically, CAS had twice the stroke risk when compared to CEA. When these two studies were combined in a meta-analysis, it is not surprising that the meta-analysis showed no difference in risk between CAS and CEA since one study demonstrated benefit of CAS over CEA and the other showed benefit of CEA over CAS. The discrepancy is explained by the fact that the two studies examined different patient groups.	Thank you for your comment. After discussion with methodologists and clinical experts, we have revised the data to present it as a forest plot, without combining studies into a single estimate.

Moore, Wesley S.	David Geffen School of Medicine at UCLA	Methods	<p>The AHRQ investigators mentioned administrative data bases (observational studies), but gave them little weight. The SVS registry and the National Discharge Data base reports represented very large numbers of patients and provided the opportunity to compare the adverse event rates for CEA and CAS. These reports clearly supported the findings of CREST that the stroke/death rates for CAS were twice those of CEA in asymptomatic patients. The adverse event multiplier was even greater for symptomatic patients showing that CEA was the safer procedure.</p>	<p>There are limitations to using data from administrative databases due to the potential for ascertainment bias of evaluating neurological outcomes purely based on the codes, rather than on clinical evaluation.</p>
Abbott Laboratories	Abbott Laboratories	Results	<p>Medical Therapy Alone</p> <p>The authors should be commended for their synthesis of a number of studies conducted over many decades. Because of the diversity in the studies included in this meta-analysis of medical therapy alone, a number of issues arise, reducing confidence in the findings. Of particular concern is the use of non-randomized studies that may add significant biases.</p> <p>The authors pool data from two broadly-defined sources: 1) 3,179 medical therapy patients enrolled in RCTs comparing medical therapy to CEA and 2) 4,175 patients enrolled in studies of medical therapy alone where CEA was not part of the protocol (based on the studies listed in Table 1). These studies were designed to answer distinct questions and therefore enrolled patients at differing risks of stroke. The first group, those enrolled in RCTs involving CEA, typically had more advanced carotid disease with the majority of patients having percent diameter stenosis of greater than 70%. In contrast, the second group, those enrolled in studies focused on medical therapy alone, were less advanced with the majority of patients having percent diameter stenosis less than 70% or the diameter stenosis was not determined. Pooling data from such disparate sources makes the conclusions difficult to interpret. It is entirely plausible that the reported stroke rate for medical therapy alone is low because many, perhaps a majority of patients, had less severe stenosis, and therefore less serious carotid artery disease.</p> <p>The tech assessment notes that there is no statistically significant</p>	<p>Thank you for your comments. Patients included in the medical cohort were followed prospectively. All studies may have biases, and for this reason, we evaluated the methodological quality/risk of biases in these studies. We have also conducted subgroup analyses by categories of biases. (Quality A and B versus C).</p> <p>Please refer to the Table 5. We conducted subgroup analyses by percentage of stenosis, and we have conducted interaction tests.</p> <p>Study quality is a measure of the conduct of a study, based on the presence or absence of</p>

difference in stroke rate between those patients with moderate stenosis (less than 70%) and those with severe stenosis (greater than 70%). However, only a few of the non-randomized trials reported the proportion of patients with percent diameter stenosis greater than 70% (Appendix E). Only those studies that report the proportion of patients with percent diameter stenosis greater than 70% should be considered Quality-B. Studies where this important measure of disease severity is not reported should be considered Quality-C, as they have significant or undetermined biases that cannot be adjusted for in any analysis. Consequently, their results should be discounted or excluded.

This issue also impacts the authors' assertion that the ipsilateral stroke rates are decreasing over time. This trend is confounded by a decrease in proportion of patients with severe carotid disease in medical therapy studies.

For those few studies that did report the proportion of patients with percent diameter stenosis greater than 70%, those studies showed a decrease in the proportion of patients with severe stenosis from 100% to 40%. Until this confounding can be addressed, which could be easily done by contacting the authors of the studies, the trend could be attributed to the inclusion of patients with less severe carotid disease, rather than improves in medical therapy over time.

The meta-regression analysis that uses the last year of recruitment (recruitment closure year) as a covariate, might be strengthened by using a more traditional method, such as the time to enrollment mid-point or median.

The midpoint of study enrollment is likely more relevant to a current standard of care than the date the final patient was enrolled, particularly when some studies had extended enrollment periods. Such a move would be expected to shift one or more studies from one column to the other on Table 4, and would have impacted the results.

Given these issues, a suggested approach to performing a revised analysis of event rates for medical therapy alone should evaluate only those patients who are candidates for revascularization (as judged by

risk of biases in a study. Reporting or lack of reporting of severity of stenosis is a measure of generalizability of study findings to this particular study population.

Our reporting of evidence is based on the evaluation of available data. We contacted authors whenever the data were unclear. We have provided subgroup analyses by percentage of stenosis. We did not come across data to suggest that patients with less severe carotid disease were enrolled in these studies.

We used a liberal definition of recruitment closure year (<2000 versus ≥2000). The use of intensive medical therapy, including statins and life-style modification, began as early as the late '90s.

The population of interest for this review has been 50–99% stenosis with asymptomatic carotid disease.

Major revascularization trials have recruited asymptomatic patients with <70 percent stenosis.

			percent diameter stenosis greater than 70%). This analysis would be both clinically relevant and interpretable.	
Abbott Laboratories	Abbott Laboratories	Results	<p>CAS and medical therapy VERSUS medical therapy alone</p> <p>While the authors are correct that there are limited data and no RCTs comparing CAS to medical therapy alone, they fail to mention that when those studies were designed, it would have been considered unethical to randomize patients to medical therapy alone. ACAS and ACST established revascularization as the standard of care for asymptomatic patients with severe stenosis. Researchers today may find challenges convincing patients to be randomized to medical therapy alone, given the clear benefits demonstrated by those RCTs, and current guidelines.</p>	<p>Thank you for your comment. The standard of care was established a decade ago, but with advances in medical therapy and in surgical and intervention cardiology technology, it is important to re-examine the standard of care for asymptomatic patients. Given that the disease was asymptomatic, it is not unethical to randomize to different treatment strategies, including medical treatment.</p>
Abbott Laboratories	Abbott	Results	<p>There are several concerning issues with the analysis of the CAS versus CEA:</p> <p>(1) The definition of a moderate level of evidence is that there at least two RCTs with little disagreement among studies. As mentioned in the General comments, the results for CREST and SAPPHERE are consistent for the following endpoints:</p> <ul style="list-style-type: none"> ? any peri-procedural stroke; ? peri-procedural death; ? peri-procedural MI; ? peri-procedural composite outcome of any stroke, MI, or death; and ? peri-procedural cranial nerve palsy. <p>In addition, both studies were published in top tier peer reviewed journal and are considered valid. Therefore, according to the definition, the level of evidence should be considered moderate. In the tech assessment, the level of evidence was considered low citing considerations that were not part of the definition of level of evidence.</p>	<p>The quality of studies is determined on the basis risk of bias for the following: selection, performance, attrition, detection, and reporting biases. We do not use study design labels as a proxy for the assessment of the quality of studies.</p> <p>We have clarified with the following description: "These ratings provide a shorthand description of the strength of evidence supporting the major questions we addressed. However, they by necessity may oversimplify the many</p>

		<p>Therefore, the concerns expressed by the authors are best included in a discussion of the results but the level evidence should be changed to moderate.</p> <p>(2) The tech assessment incorrectly asserts that SAPPHIRE and CREST were designed as equivalence trials. In fact, SAPPHIRE was designed as a non-inferiority trial, as was the FDA analysis of CREST. The authors correctly state that the NIH analysis of the CREST trial was designed as a superiority trial.</p> <p>(3) The authors state that the individual components of the composite primary endpoint for CEA and CAS go in opposite directions (stroke higher for CAS than CEA and MI is higher for CEA</p>	<p>complex issues involved in the appraisal of a body of evidence. It is important to remember that the individual studies evaluated in formulating the composite rating differed in their design, reporting, and quality. The strengths and weaknesses of the individual reports, as described in detail in the text and tables, should also be taken into consideration.”</p> <p>The original text does indicate the reason for the overall rating of the strength of the evidence.</p> <p>For the SAPPHIRE study, there are inconsistencies between the journal reporting of the study design (noninferiority trial) and the FDA report (equivalence trial). Please refer to Yadav et al. 2004 (N Engl J Med 2004;351:1493-501) and the FDA site (link) for clarification.</p> <p>We assessed the direction and magnitude of the effect size from the data, and we did not</p>
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			than CAS). However, they neglect to put these results in their appropriate context. The point estimates for the stroke rates are low and within the ACC/AHA guidelines for both therapies. The differential in the MI rates, consistent in both CREST and SAPPHERE, suggests that CAS may be favored among patients at high risk of MI.	compare it with the guidelines.
Abbott, Anne L.	Baker IDI Heart and Diabetes Institute, Melbourne, Australia	Results-Page 24	ACST was a trial of immediate versus deferred CEA (about 4% of deferred patients had CEA per year (most while still asymptomatic-this is not indicated in the report). So ACST was not a study of medical intervention alone although usually cited as such. Also included patients with remote ipsilateral symptoms (12%) so not even a study of asy carotid stenosis. It is OK to point out these limitations in a report like this.	Thank you for the comment. The deferred arm did receive medical therapy, and can be considered as a medical therapy alone arm. We recognize that there is heterogeneity in the definitions of asymptomatic carotid stenosis, and our operational definition does allow for patients with remote ipsilateral symptoms.
Abbott, Anne L.	Baker IDI Heart and Diabetes Institute, Melbourne, Australia	Results-Page 25	CEA has not been shown to provide progressive stroke prevention benefit over time (survival plots in ACSA and ACST did not continue to diverge over years of followup. If we can assume medical intervention was the same in both arms of ACAS and ACST (we are told it was the same in ACST- Halliday et al 2010), longer term outcomes (at 5 or 10 years) reflect differences at randomisation. In ACST, during randomisation, statin use rose from <10% to 58% (17% among those randomised in 1993–1996, 58% in 2000–2003; figure 6, Halliday et al 2004). This is a reflection of poor medical intervention by today's standards. What has happened since randomisation is less relevant- assuming management was the same in deferred and immediate CEA groups.	Thank you for your comment. We recognize that all treatment options, including medical therapy, have been evolving over time.
Abbott, Anne L.	Baker IDI Heart and Diabetes Institute, Melbourne, Australia	Results-Page 29	how did you extract ipsilateral stroke rates from ACST data?	The data were available in the Web appendix.
Abbott, Anne L.	Baker IDI Heart and	Results	Apparently CREST included asymptomatic patients with remote ipsilateral stroke or TIA. Is that correct? I have just confirmed that the	We agree that the definition of asymptomatic carotid stenosis

	Diabetes Institute, Melbourne, Australia		<p>CREST definition of asymptomatic included patients with symptoms of stroke or TIA in either hemisphere within the previous 180 days (3 months). See table 1 in the attached methods paper by Sheffet et al 2010 (you will need the free online version: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20088993).</p> <p>I do not know the proportion of these recently asymptomatic patients who were recruited.</p>	<p>does include recent symptomatic patients, and our inclusion criteria have clearly stated this. We acknowledge that the lack of a clear definition of asymptomatic carotid stenosis has been problematic, since many trials do include patients who have been “recently asymptomatic,” but have had some symptoms in the past.</p>
Abbott, Anne L.	Baker IDI Heart and Diabetes Institute, Melbourne, Australia	Results	<p>Myocardial infarction (MI) is a marker of poorer prognosis compared to patients without MI. But the same applies for stroke. In CREST mortality up to 4 years was 20% in patients who had 30-day periprocedural clinical or biomarker only MI and 20% for those who had 3-day periprocedural stroke. However, periprocedural stroke was twice as common as periprocedural MI. The CREST MI justification of routine practice CAS is scientifically flawed. MI is an important outcome measure. But the aim of invasive carotid procedures is to reduce risk of stroke- especially ipsilateral stroke. Stroke and death should be the primary outcomes measure of procedural trials. Further, results should be reported to allow comparison with the previous landmark procedural randomised trials, like ACAS.</p>	<p>Thank you for your comment.</p>
Cutlip, Donald E.	Harvard Clinical Research Institute	Results- Page 22, last paragraph	<p>The authors state that, “Meta-regression analyses of quality-A and -B studies showed that the incidence rates of ipsilateral stroke, ipsilateral stroke or TIA, <i>any territory stroke, and death</i> significantly decreased between 2000 and 2010 as compared with older studies (those with recruitment closure year before 2000).” I do not find where the description of results above for the subgroup based on closure year before or after 2000 report on any stroke or death, so one of these sections should be amended.</p>	<p>The last paragraph on page 22 is the summary of results. Please see the section on “Meta-regression and subgroup analyses”, page 19-20, and Figure 2 and Table 3</p>
Cutlip, Donald E.	Harvard Clinical Research Institute	Results- Page 41	<p>Study quality: The www address cited for reference #94 indicates “page not found” as a direct link. Given the non-specific criticisms indicated for the SAPPHERE trial, this is an important reference and must be corrected. I was also unable to find the reference on FDA</p>	<p>We have added the full citation. The link cited in the comment was a presentation by the device manufacturer.</p>

			<p>site, but it was available through Google docs link to FDA site (see below). Reviewing the presentation it appears the FDA presentation was based on ITT while the publication in NEJM states as treated for the asymptomatic numbers. The relative differences are minor (at 1 year NEJM publication = 9.9% vs 21.5% with negative interaction term and FDA presentation = 10.3% vs 19.2% [narrowing the difference]). The authors' repeated noting of the difference throughout the manuscript without specific details in their descriptions or an appropriate reference suggest the variance is more serious and perhaps even of more nefarious intent. It would be good if this could be cleared up before publication. It doesn't change the quality grades, since based on size of study etc SAPPIRE should be grade B. But, comments on numerous protocol deviations, suggestions of selection bias as opposed to CREST, numerous mention of the above noted differences between as treated and ITT presentations are not that useful without more details and suggest a bias on the part of the authors.</p> <p>https://docs.google.com/viewer?a=v&q=cache:bbJ8diRMTI4J:www.fda.gov/ohrms/dockets/ac/04/briefing/4033b1_04_Final%2520Cordis%2520Presentation.ppt+cordis+sapphire+carotid+fda+panel&hl=en&gl=us&pid=bl&srcid=ADGEESjBt_VOQ_TQ2GcQXNs04fykYvK68HNdTJE4opV8SYLPqwn80nNe259YZq5VfZA_q6sHQkE7dfKT83VhdYlivF2fuFN_9cly9-C_wWuw2XHdPqDtcTHptEXONM3CT9v4SfvN3gOJ&sig=AHIEtbQRE-Hfw0tG7T09y_-eux_wtEEEdHA</p>	<p>The link cited in the reference was a presentation by the lead FDA reviewer on the data. Using the full citation in the reference does not link to the document. However using the search term 4033b1_02_FDA, either in GOOGLE or on the FDA Website, does yield the PowerPoint slide presentation included in our reference.</p>
Howard, Virginia	University of Alabama	Results-Page 23. Table 6	<p>As previously mentioned, neither the VA nor the ACAS included MI as a perioperative outcome but ACST did.</p>	<p>The VA study reported fatal and nonfatal MI (please see Hobson 1993, NEJM 328: 221-227; page 224—Surgical Morbidity and Mortality).</p> <p>ACAS reported only fatal MI (page 1424, middle column, second paragraph).</p>
Howard, Virginia	University of Alabama	Results-Page 26. Top of page	<p>ACAS trial was stopped after <u>median</u> 2.7 years of follow-up.</p>	<p>Thank you. It has been changed.</p>

Howard, Virginia	University of Alabama	Results-Page 27	Ipsilateral stroke – as previously mentioned under Executive Summary comments, subtitle and definition need to be clear that this included perioperative death and it is not only ipsilateral stroke.	This has been clarified in the updated report.
Howard, Virginia	University of Alabama	Results-Page 27	Any stroke – as previously mentioned above in Executive Summary comments, subtitle and definition need to be clear that this also included perioperative death.	This has been clarified in the updated report.
Howard, Virginia	University of Alabama	Results-Page 29	Composite endpoint of ipsilateral stroke – need to expand on/clarify this to be: “Composite endpoint of ipsilateral stroke plus 30-day death and any stroke.	This has been clarified in the updated report.
Howard, Virginia	University of Alabama	Results-Page 29 Summary	needs to have “risk of ipsilateral stroke” better defined as previously mentioned.	This has been clarified in the updated report.
Howard, Virginia	University of Alabama	Results-Page 43 Key question 1d (Long-term outcomes 12 months or greater)	As noted for other sections, need to change title and text of paragraph of “ipsilateral stroke” to include any periprocedural stroke in addition to ipsilateral stroke.	This has been clarified in the updated report.
Howard, Virginia	University of Alabama	Results-Page 44	It is not clear what is meant by subheading “any stroke or MI or death” and that no RCT reported this outcome. Very confusing. I think I am confused because of the heading/subheading on the next page 45 of: “Composite endpoint of ipsilateral stroke: Any periprocedural stroke, MI, or death or postprocedural stroke.”	This composite outcome has been reported in the nonrandomized studies. We have removed the subheading for RCTs.
Howard, Virginia	University of Alabama	Results-Page 45	Not consistent in use of inclusion of statement for CREST: (adjusted for age and sex).	Please refer to Table 3 (footnote) that states all hazard ratios were adjusted. We have added adjusted for symptom status as well.
Howard, Virginia	University of Alabama	Results-Page 50 and 51	For ACAS, need to add in word “median” for 2.7 years of follow-up.	Thank you—edited.
Howard, Virginia	University of Alabama	Results-Page 53	New reference for CREST subgroup analyses by age published online Oct 6 2011, in print Dec 2011 issue. Should probably reference it for inconclusiveness. Voeks JH et al. Stroke Dec 42(12) 3484-90.	Thank you—the access to supplemental tables detailing results stratified by symptom status has not been made

				available at the journal site.
Howard, Virginia	University of Alabama	Results-Page 53	Incomplete sentence related to CREST subgroup analysis by sex.	This sentence has been corrected.
Howard, Virginia	University of Alabama	Results-Page 56	As previously mentioned in Executive Summary, definition of adverse events needs to be provided.	We have now defined it in the methods. An unfavorable event (either expected or unexpected) that occurs during the study has been classified as an adverse event. Complications were defined as therapeutic consequences or any deviation from the normal postoperative course.
Howard, Virginia	University of Alabama	Results-Page 57	“The risk of stroke or death <i>with or without MI . . .</i> ” - the phrase in italics should be deleted as it is very confusing and potentially misleading. In ACAS, there were no data provided on MIs within the periprocedural period except for MI deaths so terminology should just be deaths. I believe the same is true for the VA trial.	VA provides data for both fatal and nonfatal MI, while ACAS provides data for fatal MI.
Howard, Virginia	University of Alabama	Results-Page 58	Delete “MI” last sentence.	MI has been reported as a periprocedural outcome in the CEA trials (Page 56). , Therefore, it has been retained as an outcome in the summary.
Howard, Virginia	University of Alabama	Results-Page 60	Under heading “CAS and medical therapy versus CEA and medical therapy” “periprocedural complications” should be defined as it is not all inclusive.	It has been changed to “periprocedural adverse events,” as per the definitions now outlined in the methods
Howard, Virginia	University of Alabama	Results-Page 63	Unclear wording of the following sentence: “The strength of evidence is graded as low because of results across two trial outcomes that were in opposite directions. . . .” This reads as if it is only because the results of two separate trials – CREST and SAPPHERE – were in opposite directions, that is the reason why the evidence is graded as low. Although this is consistent with definition of strength of evidence as provided on page ES-3, this should not be the sole reason to grade the evidence as low nor does it reflect that the results of the quality-A trial should be weighed more than the two quality-B trials.	We were following the AHRQ methods guide in making assessments of the strength of evidence. (http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=318&pageaction=displayproduct).

Abbott, Anne L.	Baker IDI Heart and Diabetes Institute, Melbourne, Australia	Discussion/ Conclusion	What is your advice for current routine practice? What research do you see as most beneficial for helping improve outcome for patients with asymptomatic carotid stenosis? Should we focus still on ipsilateral stroke or widen our concern to reducing risk of other complications, like myocardial infarction, using BMT. Should we define BMT and measure the impact? Should we randomise just high risk patients? Should we concentrate on getting BMT to those who need it? Should we see if screening for asy carotid stenosis is helpful? We could compare BMT and usual care rather than screen to select for invasive carotid procedures.	The objective of the review is to evaluate the evidence comparing three treatment strategies. We do not provide clinical guideline recommendations. We have discussed the clinical implications in the discussion section.
Abbott, Anne L.	Baker IDI Heart and Diabetes Institute, Melbourne, Australia	Discussion/ Conclusion- Page 69	Can you compare the primary outcome (incidence of ips stroke) using medical intervention alone with that seen with additional CEA or CAS in the RTs?	We do not have the data to make these comparisons.
Abbott, Anne L.	Baker IDI Heart and Diabetes Institute, Melbourne, Australia	Discussion/ Conclusion- Page 69	Important to emphasise we have used one or two estimates of stroke risk with medical intervention alone (from RTs-ACAS mostly) to dictate practice for countless 100s of 1000s of patients around the world and for many years until now.	Thank you for your comment.
Abbott, Anne L.	Baker IDI Heart and Diabetes Institute, Melbourne, Australia	Discussion/ Conclusion- Page 73	Remember asy carotid stenosis is an opportunity to better prevent all complications of arterial disease, not just stroke. Complications like MI which CEA and CAS cause.	Thank you for your comment.
Abbott Laboratories	Abbott Laboratories	Discussion/ Conclusion	The conclusion section challenges the inclusion of myocardial infarction in the composite primary endpoint in the major studies comparing CAS to CEA (SAPPHIRE and CREST). While carotid interventions are designed to reduce the risk of stroke, such stroke risk reduction should not be at the cost of additional adverse events, specifically MIs. With their mission of patient safety, the FDA has appropriately required the inclusion of MI, including enzyme-elevated MI, in all the comparative carotid invention studies since 2000. Given the wealth of data regarding the long-term morbidity and mortality	We have included the use of periprocedural MI as part of a composite outcome to be the subject for future research. We have removed the rationale statement.

			associated with peri-procedural MI, the authors? questioning of the inclusion of MI in the primary composite endpoint seems misplaced. As one might expect peri-procedural stroke to be included in the primary composite endpoint of a trial evaluating a cardiac intervention, it is entirely appropriate and imperative to include MI as part of the primary composite endpoint of stroke prevention intervention trials, such as those comparing CAS to CEA.	
Cutlip, Donald E.	Harvard Clinical Research Institute	Discussion/ Conclusion	Well done. Overall a very useful review.	Thank you.
Howard, Virginia	University of Alabama	Discussion/ Conclusion- Page 69 Summary of findings	This section does not include any summary statement related to quality-A vs. B RCTS and interpretation of findings. In addition, as pointed out in methods above and also below in the Figures, some of the meta-analysis figures only use crude percentages of events and do not take into account the differential follow-up times so that meaningful comparisons across studies cannot be made.	Thank you for your comment. We have made quality rating statements consistent across the section. The presentation of survival data in each of the three trials were for different outcomes. Therefore, we had to rely on the crude rates, and could not meta-analyze survival analyses data. For CAS versus CEA, we consulted methodologists and clinical experts, and we have revised the presentation of results as forest plots without meta-analyses in our updated report.
Howard, Virginia	University of Alabama	Discussion/ Conclusion- Page 69	Ref 13 is a 2009 reference such that the most recent data from CREST was not available to be included.	We have added the most recent data from CREST to the updated report.
Howard, Virginia	University of Alabama	Discussion/ Conclusion- Page 70	Terminology of “time” in the context of the paragraphs on “no significant effect of time for any territory cerebrovascular outcomes” is not clear. Is this about results of older vs. newer studies or length of follow-up?	Yes. This is a comparison of older versus newer studies. The language has been edited to clarify this point.
Howard,	University of	Discussion/	CEA and medical therapy versus medical therapy alone – again there	This has been clarified in the

Virginia	Alabama	Conclusion- Page 70	is still some need for clarification of definitions – ACAS significant reduction was in 5-year estimated risk of ipsilateral stroke+ perioperative any stroke + death and comparison being made to ACST to 10-year risk of ipsilateral+contralateral stroke and no perioperative stroke.	updated report.
Naylor, Ross	Department of Vascular Surgery, Leicester Royal Infirmary, Leicester	Discussion/ Conclusion	See comments above about trying to identify a high risk cohort for stroke.	Thank you. We have incorporated your suggestions in our technology assessment report.
Wilentz, James R.	Weill Cornell Medical College	Discussion/ Conclusion	<p>Given the heterogeneity of the studies, and the multiple differing types of endpoints studied, it comes as no surprise that the major conclusion reached is that the incidence of stroke following diagnosis of carotid stenosis in the asymptomatic patient treated medically only has reduced significantly over the past decade with the increasing use of high-dose statin therapy as well as potent anti-platelet therapy. The failure to reach decisive conclusions as to the superiority of either method of anatomical "correction" of carotid stenosis is expected. The absence of good evidence for superiority of anatomic correction over medical therapy alone in the overall group could be due either to the absence of any salutary effect or to the failure to identify a subgroup of asymptomatic patients who might benefit. Agree with the suggestion that further study is required of the strategy of anatomic correction versus medical therapy alone whether by CAS or CEA, but would also emphasize the need for novel approaches to the identification of the segment of the asymptomatic carotid population at high risk for stroke over the years following diagnosis.</p> <p>As with the ongoing attempt to understand the "vulnerable" plaque in the coronary circulation, more effort needs to be directed to identifying those carotid plaques that have recently changed in nature either by partial thrombosis with residual high thrombotic activity or by a high metabolic state in general suggesting an active inflammatory process. Macrophage-specific PET probes have been used in laboratory animals and generalized metabolic PET probes in humans cross-registered with CTA to try to define this, and much more work needs to</p>	Thank you for your comments. The identification of high risk patients and the impact of vulnerable carotid plaque are outside the scope of this review.

			<p>be done in this arena.</p> <p>If this "vulnerable carotid" segment of the asymptomatic carotid population could be identified prospectively, the high incidence of adverse events in this group should allow clearcut delineation of a therapeutic effect of anatomic correction plus medical therapy versus medical therapy alone.</p>	
Wilentz, James R.	Weill Cornell Medical College	Discussion/ Conclusion	<p>As to the CEA/CAS conundrum for asymptomatic patients, the evidence you have summarized drawn from a much longer-tried procedure (CEA) versus a much newer procedure (CAS) with operators for CEA and centers performing CEA having much more experience over time than for those performing CAS, and the finding that it is difficult to discern a clearcut difference in outcome speak strongly to the likelihood of equivalence of outcomes. Agreed that the statistics and the quality of the studies are quite variable but, that said, and taking in the high volume of patients studied, it is compelling to view the two procedures as on par with one another. Given this, and my own experience (biased of course) as a carotid stent operator since 2000 with no major strokes in over 250 procedures, I would strongly urge approval for funding of CAS for asymptomatic patients with severe carotid stenosis. Patients with lesions of 80% or more may serve at the current time as surrogates for those with vulnerable plaques, and patients with MRI evidence of ipsilateral infarcts in non-eloquent areas of the brain (and therefore asymptomatic) should also be referred for anatomic treatment as though they were symptomatic.</p>	<p>The objective of the review is to evaluate the evidence comparing three treatment strategies. We do not provide recommendations with regard to coverage decisions, since this is not an objective of this technology assessment.</p>
Cutlip, Donald E.	Harvard Clinical Research Institute	Tables	No concerns	Thank you.
Howard, Virginia	University of Alabama	Tables- Table 6. page 23.	Remove MI from the perioperative outcome column for VA and ACAS trials.	We included MI because it was part of one of our Key Questions and data were available in these trials.
Cutlip, Donald E.	Harvard Clinical Research Institute	Figures	No concerns	Thank you.
Howard,	University of	Figures	Figures 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 should be deleted or re-analyzed	The presentation of survival

Virginia	Alabama		using event rates derived from survival analysis rather than crude percentages.	data in each of the three trials are for different outcomes. We could not make use of the survival curves from these reports. Therefore, we had to rely on the crude rates for meta-analyses. For CAS versus CEA, we consulted methodologists and clinical experts, and we have presented data as forest plots without meta-analyses in our updated report.
Howard, Virginia	University of Alabama	Figures	Figure 15 should be deleted because MI was not included as a perioperative event for these two trials.	Data for MI were available in these two CEA trials. The VA study reported deaths from MI (please see Hobson 1993, NEJM 328: 221-227; page 224—Surgical Morbidity and Mortality). ACAS page 1424, middle column, second paragraph.
Howard, Virginia	University of Alabama	Figures	In Figure 23, the reference for CREST cranial nerve palsy data should be changed to be Silver FL et al STROKE 2011 March;42(3):675-80 [Ref 80]	No change was made, since cranial nerve palsy data were available in the primary CREST paper under the “Prespecified Secondary Analyses” section.
Cutlip, Donald E.	Harvard Clinical Research Institute	Appendices	Not reviewed in detail, but no concerns on general review.	Thank you.
Cutlip, Donald E.	Harvard Clinical Research Institute	References	Except for the reference #94 noted above, no concerns.	Thank you—we have verified this reference. We have included the full Web link that leads to the FDA presentation

				(www.fda.gov/ohrms/dockets/ac/04/briefing/4033b1.htm).
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¹ Names are alphabetized by last name. Those reviewers who did not disclose their name are labeled as "Anonymous Reviewer 1", "Anonymous Reviewer 2", etc.

² Affiliation is labeled "NA" for those who did not disclose affiliation.

³ If listed, page number, line number, or section refers to the draft report.

⁴ If listed, page number, line number, or section refers to the final report.