

Submitted Electronically to [MedCACpresentations@cms.hhs.gov](mailto:MedCACpresentations@cms.hhs.gov)

Ms. Maria Ellis  
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Ms. Ellis:

The undersigned groups have co-sponsored and or endorsed the *2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS Guideline on the Management of Patients With Extracranial Carotid and Vertebral Artery Disease*. We recommend our analysis and recommendations be the primary basis for determining Medicare's Coverage of treatments for carotid atherosclerosis.

The development of this guideline involved an extensive review of all available literature and writing committee members had great expertise in the various treatments for carotid atherosclerosis. The recommendations are based on a comprehensive review of the literature relevant to carotid and vertebral artery interventions through May 2010.

The document was reviewed by 55 external reviewers, including individuals nominated by each of the ASA, ACCF, AHA, AANN, AANS, ACEP, American College of Physicians, ACR, ASNR, CNS, SAIP, SCAI, SCCT, SIR, SNIS, SVM, and SVS, and by individual content reviewers, including members from the ACCF Catheterization Committee, ACCF Interventional Scientific Council, ACCF Peripheral Vascular Disease Committee, ACCF Surgeons' Scientific Council, ACCF/SCAI/SVMB/SIR/ASITN Expert Consensus Document on Carotid Stenting, ACCF/AHA Peripheral Arterial Disease Guideline Writing Committee, AHA Peripheral Vascular Disease Steering Committee, AHA Stroke Leadership Committee, and individual nominees. All information on reviewers' relationships with industry and other entities was distributed to the writing committee and is published in this document (Appendix 2).

Our guideline is the best source of information and expert consensus on this topic and we look forward to CMS's implementation of coverage policy that is consistent with our guideline.

Sincerely,

American Association of Neurological Surgeons  
American Association of Neuroscience Nurses  
American College of Cardiology  
American College of Radiology  
American Heart Association  
American Society of Neuroradiology  
American Stroke Association  
Congress of Neurological Surgeons  
Society of Atherosclerosis Imaging and Prevention  
Society for Cardiovascular Angiography and Interventions  
Society of Interventional Radiology  
Society for Vascular Medicine

December 19, 2011

Louis Jacques, M.D.  
Centers for Medicare and Medicaid Services  
7500 Security Boulevard  
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**RE: Society for Vascular Surgery Position Statement Pertaining to  
January 2012 MedCAC Meeting on Carotid Atherosclerosis**

Dear Dr. Jacques:

The Society for Vascular Surgery, representing more than 3,600 practicing vascular surgeons across the country, is the nation's oldest (founded in 1946) medical professional society devoted to the management of non-cardiac vascular disease. On a number of different occasions (September 2006-CAG-00853R, February 2007-CAG-00085R3, and March 2008-CAG-00885R6), SVS has offered position statements relating to the NCD for carotid artery stenting. In this communication, we outline briefly our current position with respect to this NCD for percutaneous transluminal angioplasty of the carotid arteries. More to the point of the MedCAC, herein we outline our responses to the seven research questions posed to the MedCAC for January 25, 2012. SVS agrees with the MedCAC that the outcomes of interest are all strokes/deaths; this indeed was the focus of our recently updated Practice Guidelines (see below). We apologize for a degree of redundancy in the direct responses to the research questions; this of course is related to the fact that several of the questions were related, but we have responded by individual question rather than group related ones.

SVS is in a unique position to comment in general in the field of carotid interventions, since our members are the only medical professionals who use all available modalities [medical therapy, surgical endarterectomy (CEA), and angioplasty and stenting (CAS)] in the management of carotid artery stenosis. Longitudinal follow-up of patients with a variety of vascular territory ailments - including carotid stenosis - is part of our core mission and routine practice. At the present time a substantial percentage of our members offer CAS, and as such, our position is predicated on offering patients the best available treatment options without prejudice or exclusivity with respect to the mode of intervention.

Although SVS may be portrayed as "protecting surgical turf," the track record of vascular surgeons in the general realm of endovascular surgery in a variety of vascular territories is well established. Over the past decade, vascular surgery practice has largely shifted from conventional open surgery to a variety of either percutaneous or hybrid endovascular procedures. A survey of our membership indicates that 51-75% of vascular surgery procedural work is endovascular in nature. SVS members have been proponents and leaders of the rapid march to endovascular therapies as the predominant mode of treatment for both aortic aneurysm disease and lower extremity occlusive disease.

Vascular surgeons continue to be not only involved in CAS (vascular surgeons performed 21% of CAS procedures in CREST with overall results equal to other specialists), but also to be national principle investigators in clinical trials investigating the worth of this modality when compared to the gold standard of CEA. [Examples include (Jon S. Matsumura, MD of Madison, WI, who serves as

national co-PI of the ACT I CAS vs. CEA trial (industry sponsored); Robert W. Hobson III, M.D. (now deceased) was national co-PI of CREST; Daniel Clair, MD of the Cleveland Clinic, was National PI of the EMPIRE (industry sponsored) trial (see Clair, D et al. Cath and CV Interventions 2011; 77; 420-29)]. SVS members and vascular surgeons at large are well positioned to embrace CAS when its safety and cost efficacy profile achieve that of CEA which has, to date, not occurred.

This approach is reflected in our recently updated Practice Guidelines referable to extracranial carotid disease (see JVS 2011;54:832). It is worth emphasis that SVS guidelines are largely concordant with four other such (international) documents published in 2011; these include the multispecialty guidelines under ACC/AHA auspices (see Circulation 2011;124:e 54-130).

In one sense, it is not at all surprising that CAS has not produced results equal to CEA since the latter is a mature procedure with a 50-year evolution and a proven track record of safety and efficacy across surgeons in a wide spectrum of practice settings. Indeed the excellent surgical results achieved in CREST (2.6% stroke/death overall) had been reported in prior studies dating back to the ACAS study (pub. 1995) and similarly reported in the SVS registry (see JVS 2009;49:71), large administrative (National Inpatient Sample) database studies (see JVS 2008;48:1442) and quality improvement databases such as NSQIP (see JVS 2009;49:331).

There are a variety of considerations which make CAS distinctly different when compared to endovascular interventions in other vascular territories. Some of these are obvious, such as the potential for stroke and even death, the traditional end points considered in assessing carotid artery interventions. SVS members have readily embraced endovascular aneurysm repair and percutaneous lower extremity arterial revascularizations because these procedures have genuine benefit for the patient when compared to open conventional vascular surgery operations. The same cannot be said of the difference between CEA and CAS where overall patient recovery is quite similar between the two procedures, and the bulk of the reported literature, including CREST, indicates a two-fold increased risk of periprocedural stroke/death for CAS vs. CEA.

Excepting our prior position statement of 3/2/2008 (re: CAG-00085R8), wherein we define anatomic high risk factors for CEA, SVS believes that no change in the current national coverage determination for CAS is indicated. We base this opinion on the best available level 1 evidence in symptomatic patients, wherein a consistent two-fold higher risk of stroke/death has been demonstrated for CAS when compared to CEA, even when CAS is performed by experts as in CREST. Furthermore, it can be anticipated that changes in the NCD would be accompanied by higher complication rates of CAS in the community setting and a substantial increase in cost when compared to CEA. Finally, while performance of CEA in appropriately selected asymptomatic patients with high-grade carotid stenosis is supported by level 1 data, SVS concurs with a variety of current practice guidelines whose consensus is that there is insufficient evidence to support CAS for the treatment of asymptomatic carotid stenosis versus best available medical therapy.

It is not SVS intent, based on communications with CMS, to outline a detailed position statement on the NCD for CAS in different patient subsets. If requested we should be pleased to do so. Our understanding is that this communication should focus on the seven research questions

posed to the MEDCAC; accordingly SVS responds in more detail to the research questions in what follows.

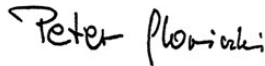
Sincerely,  
Society for Vascular Surgery



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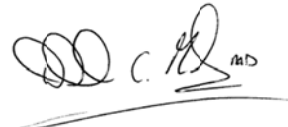
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**Q#1: Can one identify asymptomatic patients with carotid Stenosis who are at high Risk for Stroke?**

SVS HAS A HIGH (SCORE 4) LEVEL OF CONFIDENCE THAT SUCH PATIENTS CAN BE IDENTIFIED, BASED ON THE AVAILABLE NATURAL HISTORY AND CLINICAL TRIAL DATA. SUCH IDENTIFICATION AT PRESENT IS LARGELY A FUNCTION OF DEGREE OF STENOSIS, WHICH IS REASONABLE , IF IMPERFECT, SURROGATE FOR HIGH RISK. SVS AGREES THAT FURTHER RESEARCH IN THIS AREA IS SORELY NEEDED; SVS HAS IDENTIFIED THIS GENERAL TOPIC AS ITS NUMBER 1 CLINICAL RESEARCH PRIORITY AND HAS COMMITTED RESOURCES TO DEVELOPING SUCH RESEACH.

Degree of carotid bifurcation stenosis has been the most significant factor in determining whether both symptomatic and asymptomatic patients were at risk of subsequent neurological events. Stenosis was initially determined exclusively by angiography, but as non invasive techniques improved these methods supplanted angiography as the primary means for quantifying stenosis. Observational data from a number of sources have correlated the degree of stenosis and stroke risk in asymptomatic patients. In several reports on longitudinal studies of patients with asymptomatic cervical bruits, Norris et al correlated both the degree of stenosis (1) and the occurrence of plaque progression (2), with stroke risk.(1,2). Roederer et al (3) followed patients with cervical bruits and documented a high incidence of symptoms associated with plaque progression (35% at 6 months, 48% at one year). These and other observational data were subsequently confirmed by 3 prospective randomized trials. The VA trial (4), randomized 444 asymptomatic patients with hemodynamically significant stenosis by noninvasive testing and a 50% or greater angiographic stenosis to endarterectomy or medical therapy. There was a 2.5 fold reduction (8% vs. 20.6%) reduction in ipsilateral ischemic events, and a two fold reduction

in ipsilateral stroke (4.7% vs. 9.4%) over a mean 48 month follow up. The ACAS trial (5) randomized 1662 asymptomatic patients with 60% or greater carotid stenosis between surgery and medical therapy and again found a two fold reduction in stroke (5.1% vs. 11%). The largest and most recent trial, ACST (6) randomized 3120 asymptomatic patients with strikingly similar benefits for carotid endarterectomy over medical therapy (6.4% vs. 11.8%). None of these studies was able to identify an increased risk of stroke in the “severe” (80-99%) stenoses compared to “moderate” (60-79%) stenosis. These trials have shown the utility of stenosis as a predictor of increased stroke risk that can be reduced by CEA.

While stenosis has the benefit of being easily and reliably measured by several techniques, it is a relatively non specific indicator of stroke risk, since in all of these trials the annual stroke risk was modest and the majority of patients in the medical arm did not develop neurological symptoms. Efforts to characterize a group of patients, or a type of lesion, associated with an increased risk of stroke have included evaluation of plaque character, overall symptom status and evidence of silent embolization refine the definition of a “stroke prone” lesion. Moore et al (7) documented surface ulceration as an independent risk factor for stroke in asymptomatic patients. In 72 asymptomatic patients with ulcerations and <50% stenosis they reported a 12.5% annual incidence of symptoms in large or complex ulcers vs. 0.4%/yr incidence when only “minor” ulceration was present. Surface ulceration and thrombus was associated with the presence of symptoms in 241 plaques (170 asymptomatic and 71 symptomatic) taken from patients enrolled in the NASCET and ACAS trials (8). Echolucent and heterogeneous plaque seen on ultrasound (9) has been found more often in lesions that are symptomatic, as opposed to asymptomatic stenoses, and with subsequent development of symptoms in asymptomatic patients (10). Plaque features, identified on MRI such as intraplaque hemorrhage, lipid content and thin

or ruptured fibrous cap have also been correlated with subsequent development of symptoms in asymptomatic patients (11). A refined protocol of further plaque imaging, and/or TCD monitoring for microembolization may ultimately prove appropriate; further research and cost considerations will be paramount.

In a study of 821 asymptomatic patients with 60-99% carotid stenosis, Kakkos et al (12) identified asymptomatic ipsilateral cortical infarcts in 17.8%. Patients with asymptomatic ipsilateral cortical infarctions had double the annual neurological event rate (4.8 % vs 2.4%) of those without cortical lesions, irrespective of whether the stenosis was “moderate (60-79%) or “severe” (80-99%). The Asymptomatic Carotid Stenosis and Risk of Stroke (ASCERS) trial (10) followed 1121 patients with asymptomatic stenoses 50- 99% for an average of 48 months. Information on degree of stenosis, clinical conditions and plaque character were obtained at entry. Factors associated with increased risk of ipsilateral ischemic events, in addition to degree of stenosis, included: age, hypertension, smoking >10 pk/yr, renal insufficiency, contralateral TIA, plaque size and plaque character. Cerebrovascular risk scores were developed based on these data that allowed the investigators to define 4 categories of 5 year stroke risk that varied from <5% to >20%.(10). These data remain to be validated by further studies.

At present stenosis remains the sole plaque feature that can be easily, reliably and economically measured in clinical practice. It is a marker of increased stroke risk, particularly if plaque progression is seen over time. Ulceration, plaque character and plaque size, as well as evidence of ipsilateral cortical infarction are also likely factors that increase risk of neurological symptoms. However more work is needed to determine the relative importance of these factors, and whether they can be reproducibly employed as part of an algorithm to reliably identify patients who can be spared intervention. The risk stratification approach used in ASCERS is

intriguing but needs to be confirmed. At present, Level 1 data from over 5,000 patients shows that selecting patients for intervention by degree of stenosis alone, while not ideal, is sufficient to significantly reduce stroke risk by CEA. While there is no doubt that “best medical therapy” has reduced stroke risk in the last decade (13,14), it does not follow that this has obviated the additional benefit of carotid endarterectomy demonstrated by multiple controlled trials. Given the facts that one third of strokes occur without warning and ½ of TIA’s are ignored or misdiagnosed, coupled with the economic, physical and psychological impact of stroke, there remains a continued need to treat carotid stenosis in a presymptomatic state. It would be ideal to have reliable more discriminating markers of stroke risk in the future. Identification of risk factors in addition to degree of stenosis that can be widely and reliably measured would be an important part of future investigation into the proper therapy of asymptomatic carotid bifurcation disease.



## References

1. Bornstein NM, Chadwick LG, Norris JW. The value of carotid Doppler ultrasound in asymptomatic extracranial arterial disease. *Canadian J Neurological Sciences* 1988; 15: 378-83
2. Chambers BR, Norris JW. Outcome of patients with asymptomatic neck bruits. *NEJM* 1986;315:860-5
3. Roederer GO, Langlois YE, Jaeger KA et al. The natural history of carotid arterial disease in asymptomatic patients with cervical bruits. *Stroke* 1984; 15:605-613.
4. Hobson RW II, Weiss DG, Fields WS et al. Efficacy of Carotid Endarterectomy for Asymptomatic Carotid Stenosis. *NEJM* 1993; 328:221-7.
5. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. *JAMA* 1995; 273:1421-8.
6. MRC Asymptomatic Carotid Surgery Trial Collaborative Group. Prevention of disabling and fatal stroke by successful carotid endarterectomy in patients without recent neurological symptoms: randomized controlled trial. *Lancet* 2004;363:1491-1502
7. Moore WS, Boren C, Malone JM, et al. Natural History of non stenotic, asymptomatic ulcerative lesions of the carotid artery. *Archives of Surgery* 1978; 113:1352-9.
8. Fisher M, Paganini-Hill A, Martin A et al. Carotid Plaque Pathology: Thrombosis, Ulceration and Stroke Pathogenesis. *Stroke* 2005;36:253-7
9. Giannoukas AD, Sfyoeras GS, Griffen M, Slaeptsis V, Antoniou GA, Nicolaidis AN. Association of plaque echostructure and cardiovascular risk factors with symptomatic carotid artery disease. *Vasa* 2009; 38:354-67.

10. Nicolaides AN, Kakkos SK, Efthymou K et al. Asymptomatic internal carotid artery stenosis and cerebrovascular risk stratification. *J Vasc Surg* 2010; 52:1486-96
11. Takaya N, Yuan C, Chu B et al. Association between carotid plaque characteristics and subsequent cerebrovascular events. *Stroke* 2006; 37:818-23.
12. Kakkos SK, Sabetai M, Tegos T et al. Silent embolic infarcts on computed tomography brain scans and risk of ipsilateral hemispheric events in patients with asymptomatic internal carotid artery stenosis. *J Vasc. Surg.* 2009; 49:902-9.
13. Abbott AL. Medical (non surgical ) intervention alone is now best for prevention of stroke associated with asymptomatic severe carotid stenosis: results of a systematic review and analysis. *Stroke* 2009;40:e573-e583
14. Marquardt L, Geraghty OC, Mehta Z, Rothwell PM. Los risk of ipsilateral stroke in patients with asymptomatic carotid stenosis on best medical therapy. *Stroke* 2010; 41: e11-e17.

**Q#2: Is there adequate evidence to determine if patients can be identified as being at high risk for adverse events from CEA?**

SVS HAS A HIGH (SCORE 4) LEVEL OF CONFIDENCE THAT PATIENTS AT HIGH RISK FOR ADVERSE EVENTS FROM CEA CAN BE IDENTIFIED.

The prospective randomized trials comparing CEA and “best medical therapy” (1, 2, 3) did in fact exclude a number of patients often treated by CEA. In many cases reasons for lack of eligibility were based on the need to maximize follow up, or to exclude patients who might have other sources of stroke or unstable medical conditions. While it is true that the perioperative mortality was lower (0.1-0.6% vs. 1.4-1.75%) in the randomized trials than in “real world” Medicare beneficiaries (4), it is not clear that these results would have exceeded AHA recommendations (5). Therefore while it made sense to study CAS in patients in whom the benefit of CEA had not been proved by Level 1 data, it was not necessarily accurate to characterize these patients as “high risk”, in particular with respect to patient age thresholds for trial inclusion.

Definition of “high medical risk” is imprecise and not supported by robust data. Multiple single center studies demonstrated that about 1/3 of CEA patients would have been eligible for “high risk” CAS studies and that there was no difference in outcomes in these patients and those who did not have these “high risk” characteristics (6-8). Stroke and death rates in single center reports of “high risk” patients range from 1.6% to 3.6%. Outcomes from the NSQIP database were similar (9). In this study, thirty percent of 3949 CEA’s in the NSQIP database met “high risk” (as defined in the SAPPHERE trial) criterion. Overall stroke and death rates in this group were 2.2% and again there were no differences between the “high risk” and “normal risk” patients. Two factors do seem to be associated with increased complication rates after CEA:

symptomatic cardiac disease and renal failure. Every major study of CEA has demonstrated that the major non neurological source of morbidity and mortality with CEA is cardiac. Trials comparing CAS and CEA have shown that CEA is associated with increased incidence of cardiac events and a decreased risk of stroke and death as compared to CAS (10, 11).

It makes sense then that patient with severe ventricular dysfunction, active coronary ischemia and uncompensated congestive heart failure would constitute a medical high risk group. Patients, particularly those who are asymptomatic neurologically, should be evaluated for cardiac ischemia and every patient's cardiac condition should be optimally treated before intervention. In general vascular surgeons use the ACC/AHA consensus guidelines on preoperative cardiac evaluation in this regard; clinical profiling, patient functional status and the consideration of CEA as low risk surgery are all considered. Renal insufficiency is of somewhat less import, although there is evidence that it does increase the risk of both CEA and CAS (12, 13). This is therefore an important factor to consider, particularly in the neurologically asymptomatic patient. Alternatively, the large ACSRS study identified renal insufficiency as a risk factor for neurologic events in patients with asymptomatic severe carotid stenosis, thereby making the overall impact of renal disease on clinical decision making problematic (see question #1 above). Severe chronic lung disease may increase risks of general anesthesia, but this is a) uncommonly encountered in clinical practice, and b) such patients are often managed without a general anesthetic, viz. with cervical plexus block when CEA is indicated.

Definition of "anatomic high risk" is generally more straight forward. SVS in a prior position statement to CMS (March 2, 2008—CAG00085R6) favored reimbursement for CAS in circumstances of anatomic high risk as defined by SVS. These are situations in which local factors such as fibrosis or scarring of the neck would increase risks of nerve injury or wound

infection, or lesions that cannot be readily reached through a standard cervical incision. Such conditions include a “hostile neck” with extensive scarring from radiation or prior surgery, presence of a stoma in the neck, a lesion that extends above the level of the second cervical vertebra or below the clavicle (14). It is important to note however that the mere history of radiation or prior neck surgery does not constitute “anatomic high risk” and there have been multiple reports of CEA with excellent results in patients if fibrosis and scarring are not severe (15, 16, 17). Further, data suggests that the lesions in many patients associated with prior endarterectomy or radiation are fibrous in nature and are likely to remain asymptomatic for long periods of time (18). Data on the impact of contralateral carotid occlusion are mixed. While NASCET identified patients with contralateral carotid occlusion as having increased risk of stroke after intervention (19), many single center series, where operative technique and indications for shunt use are more standardized, report excellent results with CEA in the face of contralateral occlusion (20, 21, 22).

In summary, the exclusion criterion from ACAS and NASCET do not of themselves define a “high risk” group for CEA. Both single center series and the NSQIP dataset demonstrate that excellent results with CEA can be achieved in carefully selected patients despite the presence of “high risk” markers. Careful selection is particularly important in the asymptomatic patients and is likely the reason that these reported series (5-8) contrast favorably with the results of CEA in the SAPPHERE trial (23) where the combined risk of stroke and death was 7.3% despite the fact that 70 percent of patients in that trial were asymptomatic.

The major medical conditions that increase the risk of complications associated with CEA include active coronary disease, severe left ventricular dysfunction and uncompensated congestive heart failure. Neurologically symptomatic patients should have these conditions, as

well as hypertension and diabetes, optimally managed before surgery. This is almost always possible within a few days. Asymptomatic patients with these conditions should not be subjected to any intervention since long term benefit of intervention is low. Occult coronary ischemia should be identified and treated prior to surgery for asymptomatic carotid stenosis to minimize cardiac risk, and significant, untreatable coronary disease should interdict intervention for an asymptomatic carotid stenosis. Anatomic high risk patients who are neurologically symptomatic should be evaluated for CAS, while the decision between CAS and medical management for asymptomatic patients at anatomic high risk for CEA remains unresolved at present.

## References

1. North American Symptomatic Carotid Endarterectomy Trial Collaborators (NASCET): Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med* 1991;325: 445.
2. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic patients with high grade stenosis. *JAMA* 1995; 273:1421-8.
3. ACST Collaborators Group. The International Asymptomatic Carotid Surgery Trial (ACST) *Lancet* 2004; 363:1491-502.
4. Wennberg DE, Lucas FL, Birkmeyer JD, Bredenberg CE, Fisher ES. Variation in carotid endarterectomy mortality in the Medicare population: trial hospitals, volume and patient characteristics. *JAMA* 1998; 279:1278-81.
5. Biller J, Feinberg WM, Castaldo JE et al. Guidelines for carotid endarterectomy: a statement for health care professionals from a special Writing Group of the Stroke Council, American Heart Association. *Circulation* 1998; 97: 501-9.
6. Mozes G, Sullivan TM, Torres-Russotto DR, Bower TC, Hoskin TL, Sampaio SM, et al. Carotid endarterectomy in SAPHIRE-eligible high-risk patients: implications for selecting patients for carotid angioplasty and stenting. *J Vasc Surg* 2004; 39(5):958-65.
7. Gasparis AP, Ricotta L, Cuadra SA, Char DJ, Purtill WA, van Bemmelen PS, Hines GL, Giron F, Ricotta JJ: "High-Risk" Carotid Endarterectomy (CEA): Fact or Fiction. *JVS*. 37(1):40-46, 2003.
8. Illig KA, Zhang R, Tanski W, Benesch C, Sternbach Y, Green RM: Is the Rationale for Carotid Angioplasty and Stenting in Patients excluded from NASCET/ACAS or Eligible for ARChER justified?. *J Vasc Surg*. 37(3):575-81, 2003 Mar.

9. Kang JL, Chung TK, Lancaster RT, Lamuraglia GM, Conrad MF, Cambria RP. Outcomes after carotid endarterectomy: Is there a high-risk population? A National Surgical Quality Improvement Program report. *J Vasc Surg* 2009; 49(2):331-339.
10. Brott TG, Hobson RW2nd, Howard G et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. *New Eng J Med* 2010; 363:11-23.
11. Murad MH, Shahrour A, Shah ND, Montori VM, Ricotta JJ. A systematic review and meta-analysis of randomized trials of carotid endarterectomy vs. stenting. *J Vasc. Surg.* 2011; 53:792-97.
12. Hamdan AD, Pomposelli FB, Gibbons GW, Campbell DR , LoGerfo FW. Renal insufficiency and altered postoperative risk in carotid endarterectomy. *J Vasc Surg.* 1999; 29:1006-11.
13. Jackson B, English SJ, Fairman RM, Karmacharya J, Carpenter J, Woo EY. Carotid Stenting: Identification of risk factors for poor outcomes *J Vasc Surg* 2008;48:74-9.
14. Ricotta JJ, AbuRahma AF, Ascher EA, Eskandari M, Faries P. Lal, BK. Updated Guidelines for the Management of Extracranial Carotid Stenosis. *J Vasc Surg.* Volume 54, Issue 3. Pages e1-e31. Sept 2011.
15. Gagne PJ, Riles TS, Jacobowitz GR et al. Long-term follow up of patients undergoing reoperation for recurrent carotid artery disease. *J Vasc Surg* 1993; 18:999-1001.
16. Hassan-Khodja R, Sala F, Declémy S, Lagrange JL, Bouillane PJ, Batt M. Surgical management of atherosclerotic carotid artery stenosis after cervical radiation therapy. *Ann Vasc Surg* 2000;14:608-11.
17. AbuRahma AF, Jennings TG, Wulu JT, Tarakji I, Robinson PA. Redo carotid endarterectomy versus primary carotid endarterectomy. *Stroke* 2001; 32:2787-92.



18. Ricotta JJ, O'Brien MS, DeWeese JA: Natural history of recurrent and residual stenosis following carotid endarterectomy: Implications for postoperative surveillance and surgical management. *Surgery* 112:656, 1992.
19. North American Symptomatic Carotid Endarterectomy Trial. Methods, patient characteristics and progress. *Stroke* 1991;22:711-20
20. Maatz W, Kohler J, Botsios S, John V, Walterbusch G. Risk of stroke for carotid endarterectomy patients with contralateral occlusion. *Ann Vasc Surg* 2008; 22:45-51.
21. Rockman CB. Su W. Lamparello PJ. Adelman MA. Jacobowitz GR. Gagne PJ. Landis R. Riles TS. A reassessment of carotid endarterectomy in the face of contralateral carotid occlusion: surgical results in symptomatic and asymptomatic patients. *Journal of Vascular Surgery*. 2002; 36(4):668-73.
22. Mackey WC, O'Donnell TF Jr., Callow AD. Carotid Endarterectomy contralateral to an occluded carotid artery: perioperative risk and late results. *J Vasc Surg* 1990; 11:778-783.
23. Yadav JS, Wholey MH, Kuntz RE, et al. Protected carotid artery stenting versus endarterectomy in high-risk patients. *N Engl J Med* 2004; 351:1493-1501.

**Q# 3: For Persons with Symptomatic Carotid Atherosclerosis and Carotid Narrowing ( $\geq 50\%$  by angiography or  $\geq 70\%$  by ultrasound) Who are not Generally Considered at High Risk for Adverse Events from CEA**

SVS IS HIGHLY CONFIDENT (SCORE 5) THAT CEA IS THE FAVORED TREATMENT STRATEGY IN SUCH PATIENTS.

For patients with symptomatic carotid atherosclerosis and carotid stenosis ( $> 50\%$  by angiography or  $> 70\%$  by ultrasound) who are not at high risk for adverse events for carotid endarterectomy (CEA), the data conclusively supports use of CEA as the primary treatment. SVS is highly confident (score 5) in the data supporting this conclusion, and this is reflected in several practice guidelines (including that of SVS) published in 2011. The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and European Carotid Symptomatic Trial (ECST) both demonstrated the benefit of CEA in neurologically symptomatic patients with carotid stenosis greater than  $50\%$ .<sup>(1,2)</sup> There was a 7% incidence of fatal and non-fatal strokes in the surgical group in contrast to 24% in the medically treated group ( $p<0.001$ ) in patients with  $>70\%$  stenosis. This represented an absolute risk reduction of 17% in surgically treated patients over the ensuing 18 months. The mortality rate among the medically treated group was 12% in contrast to 5% for the surgically treated group ( $p<0.01$ ) with a 58% mortality risk reduction in favor of CEA. Subsequent analysis of NASCET data demonstrated the beneficial effect of CEA for patients with 50% - 69% stenosis but not for those with less than 50% stenosis.<sup>(1)</sup> Results from ECST corroborated this data even though there was a slightly different method employed for measuring degree of stenosis. ECST demonstrated that the perioperative risk of stroke and death was 7.5% which resulted in a significant reduction in subsequent stroke at the 3 year interval ( $p<.0001$ ), a 26.5% stroke risk in the medical arm and a 7% a stroke risk in the surgical group resulting in an absolute risk reduction of 14.9%.<sup>(2)</sup> The results of these early trials firmly

established CEA as the treatment of choice for patients with severe symptomatic carotid stenosis, and are now widely accepted throughout the medical community. It is to be emphasized that procedural complications of CEA in these trials were roughly 2fold increased compared to CREST. This is a grade 1 recommendation with a level of evidence B.

More recently, data from the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) and International Carotid Stenting Study (ICSS) have been further scrutinized.<sup>(3,4)</sup> In CREST at 30 days, the rate of stroke was significantly higher with stenting at 4.1% versus 2.3% with surgery, when all patients were considered, with such differences being more pronounced in symptomatic patients (CAS 6% vs CEA 3.2%). Although major stroke was not different at <1% in both groups, the periprocedural period in CEA identified fewer strokes than patients undergoing carotid artery stenting (95% confidence interval). CEA demonstrated a hazard ratio of 1.74 ipsilaterally and a ratio of 1.89 for any procedural stroke or death, favoring CEA over carotid stenting.<sup>(3)</sup> In ICSS, risk of stroke, death, or procedural myocardial infarction was higher in the stenting group than the CEA group (30 day risk 7.7% vs 4.0%,; risk ratio {RR} 1.83 (p=0.003), risk difference {RD} 3.3%.<sup>(4)</sup> These two large prospective randomized studies favored CEA for treatment of symptomatic patients.

This led neurologists, Davis and Donnan to conclude in an accompanying editorial to the CREST publication, that “from this data surgery is the treatment of choice, at least for patients with symptomatic carotid stenosis. Namely, carotid artery stenting is associated with a higher periprocedural risk of stroke or death, a difference that was still significant at 4 years.”<sup>(5)</sup> Similarly, in a commentary accompanying publication of the ICSS results in *The Lancet*, Peter M. Rothwell, MD, a noted Oxford neurologist and participant in multiple carotid

disease trials, noted an excess of acute ischemic embolic lesions on diffusion weighted magnetic resonance imaging after carotid stenting as opposed to CEA,; 46% compared to 14% ( $p < .0001$ ).<sup>(6,7)</sup> Thus, enforcing the conclusion from the ICSS manuscript that “Short term results from this randomized control trial show that CEA is safer than carotid stenting for treatment of patients with symptomatic carotid artery stenosis.”<sup>(4)</sup>

The most recent meta-analysis of all randomized trials, comparing CEA to CAS included some 7484 patients, 80% of whom were treated for symptomatic carotid stenosis. Compared with CEA, CAS was associated with an increased risk of any stroke (RR 1.40; 95% CI, 1.06-1.99).<sup>(10)</sup> When the analysis was restricted to the two most recent trials with better study methodology and more contemporary techniques, there was a significant increase in both stroke (RR 1.82; 95% CI, 1.35-2.45) and periprocedural mortality (RR 2.53; 95% CI, 1.27-5.08) for CAS vs CEA; CAS has a nonsignificant reduction in periprocedural MI. Often the European trials were criticized for using less experienced carotid interventionists as well as not universally using cerebral protection devices. (8,9) Martin M. Brown, Principal Investigator of ICSS and Warner Hacke, Principal Investigator of SPACE Trial, brought up a very interesting question when asked about EVA-3S, SPACE and ICSS, by stating that “these trials were not designed to test the very best interventionists against the very best surgeons.” Instead, they answered the question more relevant to patients and health service providers, viz. are the results equivalent for the average interventionists that treats the patient compared to the average surgeon. “The trials have convincingly shown that on average, carotid surgeons do revascularizations in symptomatic patients better than do interventionists. This does not mean that the best interventionists could not do revascularization more safely than the less good surgeon, but it does make it unlikely that the best interventionists do the procedure more safely than the best surgeon.” Despite the often

heard criticism about the level of interventionalist skill in the European trial, the data indicate that the stroke/death rate in ICSS (7.4%) for CAS is not statistically different than that for symptomatic pts treated with CAS in CREST(6.0%).

It is apparent that the data on up front stroke/death risk indicate a minimum of a 2-fold increased risk for such complication for CAS as compared to CEA. These data are intuitively logical given the nature of plaque pathology associated with symptomatic carotid stenosis; to wit such patients are likely to have intraplaque hemorrhage and other features of unstable plaque. In conclusion, even the most ardent supporter of carotid stenting has to accept from the data that for symptomatic patients, CEA is the favored treatment strategy in virtually all populations. Carotid artery stenting should be reserved as an alternative for only those patients who are anatomically unsuitable for CEA or who have significant physiologic comorbidities that make it impossible for them to undergo a CEA under cervical block anesthesia (i.e. local). Additionally, best medical treatment alone would only be a logical treatment alternative in patients with comorbid conditions expected to limit longevity to less than a year.

While SVS knows of no data to indicate that specific gender or racial/ethnic background would have a material effect on the above conclusions, a particular consideration of patient age is in order. In this consideration material discussed also in question # 4 is pertinent. An abundance of literature, including CREST (3) has associated increasing patient age with inferior outcomes of CAS compared to CEA. In virtually all CAS trials the highest complication rates were in symptomatic octogenarians, often reaching levels that most vascular surgeons would consider unacceptable. In CREST the inflection point for significantly worse outcomes for CAS occurred at about 75 years of age. There are also data available indicating unacceptable complication rates for CAS when performed within 14 days of neurologic events. Analysis of the combined

CAPTURE and EXACT registries revealed stroke/death rates for CAS approaching 10% in this setting; again this is consistent with the nature of the pathology in recently symptomatic plaques.

In older and recently symptomatic patients CEA is much preferred to CAS.

## References

1. Barnett HJ, Taylor DW, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med* 1998;339(20):1415-1425.
2. Randomized trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *The Lancet* 1998;351(9113):1379-1387.
3. Brott TG, Hobson II RWm, Howard G, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med* 2010; DOI: 10.1056/NEJMoa0912321.
4. International Carotid Stenting Study Investigators. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomized controlled trial. *Lancet* 2010;375:985-97.
5. Davis SM and Donnan GA. Carotid –artery stenting in stroke prevention. *N Engl J Med* 2010; DOI: 10.1056NEJMe1005220.
6. Rothwell PM. Carotid stenting: More Risky than endarterectomy and often no better than medical treatment alone. *Lancet* 2010;375:957-959.
7. Bonati LH, Jongen LM, Haller S, et al. New ischemic brain lesions on MRI after stenting or endarterectomy for symptomatic carotid stenosis: a sub study of the International Carotid Stenting Study (ICSS). *Lancet Neurol* 2010;DOI:10. 1016/S1474-4422(10)70057-0.
8. Space Collaborative Group. 30-day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomized non-inferiority trial. *Lancet* 2006;368:1239-1247.
9. Groschel K. Has surgery won the race against endovascular treatment for carotid stenosis? *Lancet Neurol* 2010;DOI:10. 1016/S1474-4422(10)70058-2.

10. Murad MH, Shahrour A, Shah ND, Montori VM, Ricotta JJ. A systematic review and meta-analysis of randomized trials of carotid endarterectomy vs. stenting. *J Vasc Surg* 2011;53:792-97.



**Question #4: For persons not generally considered at high risk for adverse events from CEA, what is the evidence concerning favored treatment?**

FOR PERSONS WITH ASYMPTOMATIC, SEVERE (GREATER THAN 60% BY ULTRASOUND OR OTHER IMAGING STUDIES BY NASCET CRITERIA) CAROTID STENOSIS, SVS IS HIGHLY CONFIDENT (SCORE 5) THAT THERE IS ADEQUATE EVIDENCE IN THE FORM OF LEVEL 1 DATA FROM LARGE, RANDOMIZED TRIALS SUPPORTING CAROTID ENDARTERECTOMY (CEA) AS AN EFFECTIVE TREATMENT STRATEGY (COMPARED TO THE BEST MEDICAL THERAPY) TO DECREASE STROKE OR DEATH IN THE MEDICARE POPULATION. THE SUPPORTING EVIDENCE COMES IN THE FORM OF: A) DATA FROM WELL CONDUCTED, LARGE, RANDOMIZED TRIALS; AND B) AVAILABLE NATURAL HISTORY DATA OF STROKE RISK RELATED TO HIGH-GRADE, ASYMPTOMATIC CAROTID STENOSIS.

Consistent with not only Society for Vascular Surgery updated practice guidelines (1), but also practice recommendations from at least four other international practice guidelines published during calendar year 2011 (2-5), CEA is supported as an effective stroke-reduction strategy in appropriately selected patients. Based on available trial data, the designation of an appropriate patient are those with acceptable operative risk and an anticipated life expectancy of minimum 3 to 5 years, and those with high-grade (greater than or equal to 60% NASCET criteria) stenosis, as this subgroup has been consistently identified as being at increased risk for stroke.

DATA SUPPORTING CEA AS THE FAVORED TREATMENT STRATEGY IN THIS POPULATION

Three internationally recognized, randomized, prospective studies have addressed question #4 with consistent results supporting CEA as the optimal treatment strategy SVS.

1. The VA cooperative, asymptomatic, carotid surgery study (6): This trial was conducted in Veterans Administration hospitals and, accordingly, limited to male patients. Its criteria for entry were a greater than or equal to 50% (by angiography) asymptomatic stenosis and 444 patients were randomized to CEA versus available medical therapy, which at that point in time, was 650 mg ASA. The study was published in 1993 and the perioperative stroke/death rate after CEA was 4.3%. The primary outcome measure was combined ipsilateral neurological event (TIA and/or stroke) and death which occurred in 8% of CEA patients vs. 20.6% of the medically treated cohort (38% RR reduction  $p < 0.0002$ ). In consideration of stroke alone, the respective figures were (4.7% vs. 9.4%), insignificant related to the small study cohort. There was no survival benefit to CEA related to an overall excessive ( $>10\%/yr$ ) mortality in the entire study cohort. Despite the small sample size and inclusion of patients with moderate degree of stenosis, the data favored CEA as a more effective stroke reducing strategy.

2. The larger Asymptomatic Carotid Artery Atherosclerosis study (Published in 1995) was conducted at 39 North American community and academic centers; 117 surgeons participated (7). A total of 1662 patients with 60% (NASCET-method, angiography mandated prior to CEA) were randomized to CEA or medical therapy consisting of 325mg ASA and telephone monitored risk factor reduction counseling. Study endpoints were any stroke/death and median f/u was 2.7 years. Aggregate 5 year stroke/death occurred in 5.1% CEA patients vs. 11.0% of the medically treated cohort (relative risk reduction 53%,  $p = 0.004$ ). Favorable treatment effect of CEA was more pronounced in men. Overall perioperative stroke/death was 2.3% in CEA patients, half of which was referable to the mandated arteriography. Accordingly, the benefit of CEA would have been enhanced by elimination of catheter angiography, a reality of clinical practice over

time. One large study documented that less than 10% of CEA patients were being evaluated with invasive angiography by the year 2000. (8)

3. The most recent and largest randomized, prospective study of CEA versus optimal medical therapy was the ACST trial conducted in 30 different countries and 128 different hospitals. 3,120 patients were randomized beginning in 1993 and the final patients were enrolled in 2003. The initial publication of the actuarial five-year stroke risk showed a highly significant reduction in ipsilateral disabling, and all strokes in patients treated with CEA versus best medical therapy (relative risks 6.4% vs. 11.8% - net gain 5.4%,  $p < 0.0001$ ). (9) Important to point out with respect to the data analysis is that nearly 50% of patients actually completed five years of follow-up at that time that the study was initially published in 2004. While analysis was on an intention-to-treat basis, there was a 17% cross-over rate from the medical arm to CEA during the follow-up period. Stroke and death in the surgically treated patients was 2.8% within 30-days and, similar to many other large trials, myocardial infarction after CEA occurred in 1%. The data indicated that clinical decision making seemed appropriate, since the annual overall mortality (identical to ACAS) of study participants was 3.5% per year.

With respect to patient longevity the curves of anticipated benefit of treatment crossed at two years, which was the interval required for the medically treated group to “catch up” to the upfront morbidity of surgery. The data indicate that the annual risk of stroke in patients with optimal medical therapy was in the 2% range, essentially doubled that of the surgically treated cohort. Long-term data from the ASCT trial, out to 10 years have now been published. (10) These data indicate that the nearly 6% gain in stroke prevention of the surgically treated cohort was sustained even out to 10 years of follow-up. Net gain in the ASCT trial was equivalent for men and woman and a particular analysis of the late follow-up data in this trial has direct bearing

on the question of the adequacy of medical therapy alone. In the latter years of the trial, lipid-lowering therapy and antiplatelet therapy were used in over 80% of patients. While the proportionate gain of CEA versus medical therapy was larger in patients not on lipid-lowering therapy before stroke, the net gain at both 5 and 10 years remained highly significant for the surgically treated patients versus the medically treated cohort even on those on lipid-lowering therapy. To quote the ACST investigators...”modern statin regimens can reduce occlusive vascular events by more than a third, yet patients with tight carotid stenosis cannot have the risk from it completely abolished by medical treatment alone.”

It is unfair, in a sense, to compare the protective effect of CEA in stroke prevention to that of CAS, since the latter has not been adequately evaluated in this regard. At the moment, there is no data supporting CAS as an effective stroke-preventive strategy in asymptomatic patients. Indeed a recently published Medicare database study found overall mortality for CAS to be 1.9% amongst nearly 25,000 CAS procedures performed in Medicare beneficiaries between 2005-07 (11). SVS clinical practice guidelines (1) state that CEA is the preferred treatment in these patients (and the ACC/AHA multispecialty guidelines indicate as a Class 2B recommendation that “prophylactic CAS might be considered in highly selected patients with asymptomatic carotid stenosis, but its effectiveness compared to medical therapy alone in this situation is not well established” (level of evidence B. (2) International practice guidelines indicate that CAS should only be performed in asymptomatic patients in the context of well-conducted prospective clinical trials. (4,5). Accordingly, when intervention is appropriate in asymptomatic carotid stenosis, SVS supports CEA (score 5) as the preferred therapy.

With respect to concurrent best medical therapy in patients who are candidates for intervention for high-grade asymptomatic stenosis, current guideline with respect to processes of

care for carotid endarterectomy indicate that all patients who are either under observation for asymptomatic carotid stenosis, and especially patients who are being potentially treated with CEA should be on combined antiplatelet and statin therapy.(1) A prior Medicare database study (12), and regional quality registry (13) indicate a significant reduction in perioperative stroke/death in patients treated with antiplatelet therapy.

Other studies have documented a significant reduction in perioperative events for patients treated with statin medication (14). Furthermore, at least one report has correlated a significant reduction in the risk of restenosis after endarterectomy in patients treated with lipid-lowering therapy (15). SVS knows of no reliable data suggesting that individual racial or ethnic backgrounds have variable results with either complications from CEA or long-term stroke protection after CEA. Furthermore, the above-cited trial results are applicable to the Medicare population since < 15% of ACAS patients were under 60 years of age, and 2/3 of ACST patients were  $\geq$  65 years of age at enrollment.

A particular comment referable to patient age is appropriate. A substantial body of literature has indicated that increasing patient age is correlated with significantly increased risks of perioperative morbid events after CAS, but not CEA. The roll-in phase of CREST noted a periprocedural risk of stroke and death of 12% in octogenarians, significantly higher than the 5% in those less than 80 years of age. (16) Many other single-center reports, including those from acknowledged experts in CAS, have reported similar data. The CREST trial investigators reported a significant interaction with patient age and the differential complication rate of CAS versus endarterectomy with the inflection point at approximately 75 years of age. (17). However, the converse with respect to the patient age and anticipated complications of CEA appears disproven by best available current evidence. In a recently reported NSQIP study specifically

focused on “high-risk variables,” an overall 30-day (nurse reviewer adjudicated) stroke/death rate of 2.2% after CEA was reported. (18) In this study 19% of some 3,949 patients treated with CEA in private sector hospitals, were greater than 80 years of age, but perioperative complications were no different in octogenarians versus those less than 80 years of age.

BEST MEDICAL THERAPY ALONE FOR HIGH-GRADE ASYMPTOMATIC STENOSIS.

SVS supports the following general aspects referable to this question:

1. SVS supports the position that future large-scale prospective studies of stroke prevention strategies in patients with high-grade asymptomatic stenosis should include an optimal medical therapy treatment arm.
2. SVS supports the position that all patients, either under observation with carotid stenosis or considered for interventional therapy for carotid stenosis, should also be treated with optimal medical therapy currently consisting of antiplatelet therapy and lipid-lowering therapy. (1)
3. SVS agrees that future studies to stratify patients with asymptomatic stenosis into those at high risk for stroke are needed, but at the current time, degree of stenosis is the best available surrogate for such clinical decision making (see also response to questions #1). An abundance of literature, including the most recently conducted prospective studies in patients with asymptomatic carotid stenosis, consistently IDENTIFIES degree of stenosis as the best predictor of stroke risk. (19-21)
4. The contention that modern medical therapy is adequate treatment to control and/or prevent stroke from asymptomatic high-grade carotid stenosis, is unsubstantiated.

A comment on the flawed literature making this claim is in order. (22) In assessing stroke risk of asymptomatic carotid stenosis, most clinicians utilized data from both the NASCET study (specifically those examining the fate of a high-grade asymptomatic stenosis

contralateral to the index artery for entry into the trial) (21) the original studies of Chambers and Norris (19), and more recently, the medically treated patients in the ACST trial (10) and the ACRS prospective study of asymptomatic carotid stenosis (20).

These studies in aggregate indicated that the annual risk of unheralded stroke from high grade asymptomatic stenosis was at least 2%/year (event rate doubled if TIA included); these studies also showed that the first neurologic event was as likely (or even more likely) to be stroke as opposed to TIA. There is little doubt that modern medical therapy has had an important impact on the overall risk of stroke, but the contention that it constitutes effective stroke prevention for patients with high-grade carotid stenosis is unsubstantiated. A widely quoted 2009 meta-analysis concluded that modern Rx alone is now best prevention for stroke. (22) This meta-analysis included data from two modest-sized prospective studies (23, 24), and one large prospective study (20). This meta-analysis claimed that the annual risk of stroke of asymptomatic “severe” carotid stenosis was now in the 0.5% per year range. However, the SMART study included only 221 patients, 7% of which crossed over to surgical intervention during a nearly four-year follow-up interval and only half of the patients had high-grade stenosis (NASCET 70 to 99%), wherein prophylactic CEA would typically be offered. The Oxford vascular study (24) concluded that the risk of ipsilateral stroke was only 0.34% per year with best medical therapy, but contained only 101 patients with greater than 50% stenosis, and only 32 patients with a 70 to 99% stenosis (and three of these had a stroke). The evidence base to support the claim of medical therapy alone as adequate treatment for asymptomatic carotid stenosis is seriously flawed by inclusion of many patients with only moderate degrees of stenosis such that they would not be offered an intervention by current guidelines.

In summary, SVS is highly confident (score 5) that CEA is the favored therapy for appropriately selected asymptomatic patients. CAS is not adequately studied in this patient population and none of five Practice Guidelines published in 2011 would support CAS in this setting. The contention that modern medical therapy in this setting would provide stroke prevention equivalent to CEA is unsubstantiated.



## References

1. Ricotta JJ, AbuRahma A, Ascher E, Eskandari M, Faries P, Lal BK. Updated Society for Vascular Surgery guidelines for management of extracranial carotid disease. *J Vasc Surg*. 2011;54:e1-e31.
2. Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, Cates CU, Creager MA, Fowler SB, Friday G, Hertzberg S, McIff EB, Moore WS, Panagos PD, Riles TS, Rosenwasser RH, Taylor AJ; American College of Cardiology; American Stroke Association; American Association of Neurological Surgeons; American College of Radiology; American College of Radiology; Society of NeuroInterventional Surgery; Society for Vascular Medicine; Society for Vascular Surgery. 2011 ASA/ACCF/ AHA/AANN/AANS/ACR/ASNR/ CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease. *Circulation* 2011;124: e54-130.
3. European Stroke Organisation (ESO); Authors/Task Force Members, Tendera M, Aboyans V, Bartelink ML, Baumgartner I, Clément D, Collet JP, Cremonesi A, De Carlo M, Erbel R, Fowkes FG, Heras M, Kownator S, Minar E, Ostergren J, Poldermans D, Rimbau V, Roffi M, Röther J, Sievert H, van Sambeek M, Zeller T; ESC Committee for Practice Guidelines (CPG), Bax J, Auricchio A, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Knuuti J, Kolh P, McDonagh T, Moulin C, Poldermans D, Popescu B, Reiner Z, Sechtem U, Sirnes PA, Torbicki A, Vahanian A, Windecker S; Document Reviewers, Kolh P, Torbicki A, Agewall S, Blinc A, Bulvas M, Cosentino F, De Backer T, Gottsäter A, Gulba D, Guzik TJ, Jönsson B, Késmárky G, Kitsiou A, Kuczmik W, Larsen ML, Madaric J, Mas JL, McMurray JJ, Micari A, Mosseri M, Müller C, Naylor R, Norrving B, Oto O, Pasiński T, Plouin PF, Ribichini F, Ricco JB, Ruilope L, Schmid JP, Schwehr U, Sol BG, Sprynger M,

Tiefenbacher C, Tsioufis C, Van Damme H. ESC Guidelines on the diagnosis and treatment of peripheral artery diseases: Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries \* The Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). *Eur Heart J* 2011 Nov;32(22):2851-906. Epub 2011 Aug 26.

4. Carotid Stenting Guidelines Committee: An Intercollegiate Committee of the RACP (ANZAN, CSANZ), RACS (ANZSVS) and RANZCR. Guidelines of patient selection and performance of carotid artery stenting. *Intern Med J* 2011;41:344-347.
5. UK National Institute of Health and Clinical Excellence. Carotid artery stent placement for asymptomatic carotid artery stenosis. April 2011. Available at: <http://www.nice.org.uk/nicemedia/live/13026/54241/54241.pdf>. Accessed on October 17, 2011.
6. Hobson II W, Weiss D, Fields W, Goldstone J, Moore W, Towne J, Wright C.; Efficacy Of Carotid Endarterectomy For Asymptomatic Carotid Stenosis *N Engl J Med* 1993; 328:221-7.
7. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for Asymptomatic Carotid Artery Stenosis *JAMA* 1995;273:1421-1428.
8. LaMuraglia GM, Brewster DC, Moncure AC, Dorer DJ, Stoner MC, Trehan SK, Drummond EC, Abbott WM, Cambria RP. Carotid endarterectomy at the millennium: what interventional therapy must match. *Ann Surg.* 2004 Sep;240(3):535-44.
9. MRC asymptomatic carotid surgery trial (ACST) collaborative group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological systems: randomized controlled trial. *Lancet.* 2004; 363: 1491-502.
10. Halliday A, Harrison M, Hayter E, et.al 10 year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1) *Lancet* 2010; 376:1074-84.

11. Nallamotheu BK, Gurn HS, Ting HH, et al. Operator experience and carotid stenting outcomes in Medical beneficiaries. *JAMA* 2011;306(12):1338-1343.
12. Kresowik TF, Bratzler D, Karp HR, Hemann RA, Hendel ME, Grund SL, Brenton M, Ellerbeck EF, Nilasena DS. Multistate utilization, processes, and outcomes of carotid endarterectomy.. *J Vasc Surg.* 2001;33(2):227-34.
13. Goodney PP, Likosky DS, Cronenwett JL; Vascular Study Group of Northern New England. Factors associated with stroke or death after carotid endarterectomy in Northern New England. *J Vasc Surg.* 2008 ;48(5):1139-45.
14. McGirt MJ, Perler BA, Brooke BS, Woodworth GF, Coon A, Jain S, Buck D, Roseborough GS, Tamargo RJ, Heller J, Freischlag JA, Williams GM. 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors reduce the risk of perioperative stroke and mortality after carotid endarterectomy. *J Vasc Surg.* 2005 ;42(5):829-36.
15. LaMuraglia GM, Stoner MC, Brewster DC, Watkins MT, Juhola KL, Kwolek C, Dorer DJ, Cambria RP. Determinants of carotid endarterectomy anatomic durability: Effects of serum lipids and lipid lowering drugs. *J Vasc Surg* 2005;41:762-8.
16. Hobson RW, Howard VJ, Roubin GS et al. Carotid artery stenting is associated with increased complications in octogenarians: 30 day stroke and death in CREST lead-in phase. *J Vasc Surg* 2004;40:1106-11.
17. Brott TG, Hobson RW 2<sup>nd</sup>, Howard G, Roubin GS, Clark WM, Brooks W, Mackey A, Hill MD, Leimgruber PP, Sheffet AJ, Howard VJ, Moore WS, Voeks JH, Hopkins LN, Cutlip DE, Cohen DJ, Popma JJ, Ferguson RD, Cohen SN, Blackshear JL, Silver FL, Mohr, JP, Lal BK, Meschia JF; CREST Investigators. Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med.* 2010;363:11-23.

18. Kang JL, Chung TK, Lancaster RT, LaMuraglia GM, Conrad MF, Cambria RP. Outcomes after carotid endarterectomy: Is there a high-risk population? A National Surgical Quality Improvement Program report. *J Vasc Surg* 2009;49:331-9.
19. Chambers BR, Norris JW: Outcome in patients with asymptomatic neck bruits. *N Engl J Med* 1986; 315:860-865.
20. Nicolaides AN, Kakkos S, Griffin M, Sabetal M, Dhanjil S, Tegos T, Thomas D.J., Giannoukas A, Geroulakos G, Georgiou N, Francis S. Loannidou E, Dore C.J., For the Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) Study Group. Severity of asymptomatic carotid stenosis and risk of ipsilateral hemispheric ischaemic events: *Eur J Vasc Endovasc Surg* 2005;30: 275-284.
21. Inzitari D, Eliasziw M, Gates P, et al. The causes and risk of stroke in patients with asymptomatic internal-carotid-artery stenosis. *N Engl J Med* 2000;324:1693-700.
22. Abbott, A., PhD, MBBS, FRACP - Medical (nonsurgical) intervention alone is now best for prevention of stroke associated with asymptomatic severe carotid stenosis. *Stroke* 2009;40:e573-e583.
23. Goessens B, Visseren F, Kappelle J, Algra A, van der Graaf Y. .Asymptomatic carotid artery stenosis and the risk of new vascular events in patients with manifest arterial disease The SMART study. *Stroke* 2007; 38:1470-1475.
24. Rothwell PM, Coull AJ, Giles MF, et al. Change in stroke incidents, mortality, case – fatality, severity, and risk factors in Oxfordshire, UK from 1981-2004 (Oxford Vascular Study). *Lancet* 2004; 363:1925-1933.

**Q#5: For persons with asymptomatic carotid atherosclerosis who are not generally considered at high risk for stroke in either cerebral hemisphere:**

- a. How confident are you that there is adequate evidence to determine whether or not CAS or CEA or BMT alone is the favored treatment strategy to decrease stroke or death in the Medicare population?

**Level of Confidence:** INTERMEDIATE TO HIGH: 4

- b. If there is at least intermediate confidence (score  $\geq 2.5$  above), how confident are you that
- i. CAS is the favored treatment strategy in this population?

**Level of Confidence:** LOW: 1

- ii. CEA is the favored treatment strategy in this population?

**Level of Confidence:** INTERMEDIATE TO HIGH: 4

- iii. BMT alone is the favored treatment strategy in this population?

**Level of Confidence:** LOW TO INTERMEDIATE: 2

IMPORTANT QUALIFYING STATEMENT: THE ABOVE RESPONSES ASSUME THAT PATIENTS CONSIDERED WOULD HAVE A DEGREE OF ASYMPTOMATIC CAROTID STENOSIS WHERE CONSIDERATION FOR INTERVENTION BY CURRENT SVS GUIDELINES (IE > 60% NASCET STENOSIS) PERTAIN. SVS RECOMMENDS BEST MEDICAL THERAPY FOR ASYMPTOMATIC PATIENTS WITH LESSER DEGREES OF STENOSIS.

As discussed in detail earlier in the answer of Question 1, there continues to be a controversy over which patients should be considered high or low risk of stroke with carotid atherosclerosis. Currently Level 1 evidence supports the degree of stenosis as the most reliable indicator of increased risk of stroke in patients with asymptomatic carotid artery atherosclerosis.

Three randomized controlled trials (RCTs) [1-4] that included 5223 patients with asymptomatic carotid artery disease with a stenosis of the internal carotid artery of 50% to 99% or 60% to 99%, confirmed the degree of stenosis as a predictor of increased risk of stroke, that could be effectively decreased by carotid endarterectomy (CEA). The absolute risk reduction, however, is small and in these RCT's, performed in the years of 1983 to 2003, CEA resulted in an annual decrease of stroke risk of 0.5 to 1.0% vs. BMT alone.

While medical therapy has markedly improved in the last decade, with a meta-analysis[5] (see also question # 4 for SVS review of these data: SVS believes there the claim of the superiority of medical therapy to CEA is unsubstantiated) reporting equal or better outcomes from BMT than outcomes reported for CEA in the trials, there are those who argue that surgical results have also improved since the 1980's . Indeed, the 30 day stroke and death rate in the Asymptomatic Carotid Atherosclerotic Study (ACAS) in asymptomatic patients with  $\geq 60\%$  carotid stenosis was 2.3% (95% CI, 1.28% to 3.32%) while in CREST it was only 1.4% (95% CI, 0.79% to 4.42%). [2] In addition, preoperative contrast arteriography, that caused several strokes in the earlier trials in the surgical arm, adding a 1.2% risk of stroke rate to surgery in the ACAS trial [2]; invasive catheter angiography is rarely used before CEA today. Indeed such carotid angiography had largely disappeared from the landscape (related to its morbidity and expense), only to be resurrected for CAS.

Considering the very low risk of stroke or death due to mild asymptomatic carotid atherosclerosis (< 60% carotid stenosis), there is an Intermediate to High Level of Confidence (4) that asymptomatic patients who are not generally considered at high risk of stroke due to mild stenosis (<60%) should receive BMT and should not undergo intervention. There are no data that support CEA or CAS in asymptomatic patients with <60% carotid stenosis. The

recommendation of the SVS carotid guidelines [6] that asymptomatic patients with stenosis <60% diameter reduction should receive BMT is Strong (1) with a level of evidence that is Intermediate (B). This conservative strategy is well supported even in symptomatic patients with data of the MRC European Carotid Surgery Trial (ECST) where BMT alone was recommended for carotid stenosis of 0-29% ; results were inconclusive for stenosis between 30 to 69% with clear benefit of surgery in those with a stenosis of 70 to 99%. [7]

When one considers severe carotid atherosclerosis ( ie NASCET 60-99% stenosis), the level of evidence to define optimal treatment within this group just for those who generally are considered low risk vs. those who are at high risk is low. The issue of course in this patient group is that further risk stratification methods are neither conclusively proven of benefit, nor readily available to the practicing clinician. As discussed earlier in this document, various factors in addition to the degree of stenosis likely contribute to increased risk of stroke. The ACSRS study by Nicolaidis et al.[8] found that increasing stenosis, history of contralateral TIA and renal insufficiency were independent risk factors to predict stroke and could distinguish a high risk (4.7% per year risk of stroke ) group from a low risk (0.7%) group. Silent embolic infarcts,[9] contralateral carotid occlusion, plaque morphology, ultrasonic plaque echolucency and embolic signals on transcranial Doppler ultrasound [10, 11] have been proposed to predict a higher risk of stroke in asymptomatic patients but some of the data were inconclusive and they all have to be confirmed by other investigators. Most importantly, no RCT investigated so far the effect of CAS, CEA and BMT comparing low stroke risk vs. high stroke risk patients with severe (>60% NASCET) atherosclerosis. Although one would predict that preocclusive lesions (80 to 99%), especially those that progress during follow-up have a higher risk than those with a lesser stenosis, an observation documented by studies of Chambers and Norris,[12] none of the

RCTs could provide evidence that patients with a lesser degree of stenosis (50 – 79%) were of lower risk to develop ipsilateral stroke.

Consequently, the level of confidence to define best therapy for low risk patients with moderate to severe carotid atherosclerosis remains low. Overall, however, both low risk and high risk patients (to the extent they could be defined ) with a  $\geq 60\%$  carotid stenosis have Level 1 evidence to favor CEA vs. BMT based on historic RCTs. A recent meta-analysis by Murad et al. [13] that included data of CREST[14] and ICSS[15], that compared outcome of CAS with CEA found that stenting was associated with an increased risk of any stroke (relative risk [RR], 1.45; 95% confidence interval [CI], 1.06-1.99; I<sup>2</sup> = 40%), and nonsignificant increase in mortality (RR, 1.40; 95% CI, 0.85-2.33; I<sup>2</sup>= 5%). When analysis was restricted to contemporary data of CREST and ICSS only, the study found stenting to be associated with a significant increase in the risk of any stroke (RR, 1.82; 95% CI, 1.35-2.45) and mortality (RR, 2.53; 95% CI, 1.27-5.08). Outcome data for asymptomatic patients were insufficient in this review although the 13 trials considered included 1513 asymptomatic patients. Event rates were low, but there was a trend for increased risk of stroke after CAS vs. and increased risk of MI after CEA. These results were similar to the CREST data that in asymptomatic patients observed a stroke rate of 2.5% after CAS and 1.4% after CEA . It is the recommendation of the SVS guidelines [16] that asymptomatic patients with  $\geq 60\%$  (NASCET) diameter stenosis should be considered for CEA for reduction of long-term risk of stroke, provided the patient has a 3- to 5-year life expectancy and perioperative stroke/death rates can be  $\leq 3\%$  (GRADE 1, Level of Evidence A).



## **Discussion**

### Patient age, gender, and racial/ethnic background

The beneficial effect of CEA vs. BMT in asymptomatic patients age 80 years or younger was documented in ACAS.[2] Although men did much better than women, the difference for all events in outcome was not significant. In men, CEA reduced the 5-year event rate by 66% (95% CI, 36% to 82%); in women, the event rate was reduced by 17% (95% CI, -96% to 65%). (P=.10). However, among patients who had no perioperative event, 5-year risk was reduced by 56% for women (95% CI, -50% to 87%), compared with a reduction of 79% for men (95% CI, 52% to 91%).

The meta-analysis of Murad et al. [13] examined the effect of age and gender on outcome of patients who underwent CAS or CEA. The meta-analysis concurred with other data including an individual patient –pooled analysis,[17] CREST[18] and also the SPACE trial [19] that younger patient did better with CAS than those 70 years or older . These data support CEA as intervention in the Medicare population over CAS. The meta-analysis failed to reveal any significant treatment interactions based on gender. Howard recently reported on the influence of gender in the CREST trial that enrolled 872 women (34.9%) .[20] There was no difference in primary end-points between different genders (interaction p=0.34) . Although there was a trend to increased rate of periprocedural events in women after CAS vs, CEA, (6.8% vs. 3.8%, p=0.064), this difference was not statistically significant. In a recent review of a national database, Rockman et al found that outcome among women for perioperative stroke favored CEA over CAS, particularly in asymptomatic patients.[21]

No Level 1 data on racial and ethnic background are currently available to support any of the treatment modalities preferentially in these subgroups.

## Concurrent BMT

Results of medical therapy have greatly improved in recent years and include complex risk factor modification in addition to treatment of hyperlipidemia, statins, antihypertensive, and antiplatelet therapy. [5, 22] Both CEA and CAS adopted BMT as adjuvant treatment to CEA or CAS. In CREST CAS patients received combined antiplatelet therapy, including aspirin and clopidogrel or ticlopidin in the periprocedural period and at least 30 days afterwards. Similar antiplatelet therapy was used also for patients who underwent CEA.[23] New prospective, well designed randomized studies should include not only a treatment arm with BMT, but also BMT in addition to CEA and CAS. It is expected that results of both CEA and CAS will improve in the future when best prevention and medical treatment is used concurrent to interventions.

## References

1. Hobson, R.W., 2nd, et al., Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. The Veterans Affairs Cooperative Study Group. *N Engl J Med*, 1993. 328(4): p. 221-7.
2. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. *JAMA* 1995. 273(18): p. 1421-8.
3. Halliday, A., et al., Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet* 2004. 363: p. 1491-502.
4. Halliday, A., et al., 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomised trial. *Lancet*, 2010. 376(9746): p. 1074-84.
5. Abbott, A.L., Medical (nonsurgical) intervention alone is now best for prevention of stroke associated with asymptomatic severe carotid stenosis: results of a systematic review and analysis. *Stroke*, 2009. 40(10): p. e573-83.
6. Ricotta, J.J., et al., Updated Society for Vascular Surgery guidelines for management of extracranial carotid disease. *J Vasc Surg* 2011. 54(3): p. e1-31.
7. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. European Carotid Surgery Trialists' Collaborative Group. *Lancet*, 1991. 337: p. 1235-43.
8. Nicolaides, A.N., et al., Severity of asymptomatic carotid stenosis and risk of ipsilateral hemispheric ischaemic events: results from the ACSRS study. *Eur J Vasc Endovasc Surg*, 2005. 30(3): p. 275-84.

9. Kakkos, S.K., et al., Silent embolic infarcts on computed tomography brain scans and risk of ipsilateral hemispheric events in patients with asymptomatic internal carotid artery stenosis. *J Vasc Surg*, 2009. 49(4): p. 902-9.
10. Topakian, R., et al., Ultrasonic plaque echolucency and emboli signals predict stroke in asymptomatic carotid stenosis. *Neurology*, 2011. 77(8): p. 751-8.
11. Abbott, A.L., et al., Embolic signals and prediction of ipsilateral stroke or transient ischemic attack in asymptomatic carotid stenosis: a multicenter prospective cohort study. *Stroke*, 2005. 36(6): p. 1128-33.
12. Chambers, B.R. and J.W. Norris, Outcome in patients with asymptomatic neck bruits. *N Engl J Med*, 1986. 315(14): p. 860-5.
13. Murad, M.H., et al., A systematic review and meta-analysis of the treatments of varicose veins. *J Vasc Surg*, 2011. 53(5 Suppl): p. 49S-65S.
14. Brott, T.G., et al., Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med*, 2010. 363(1): p. 11-23.
15. Ederle, J., et al., Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. *Lancet*, 2010. 375(9719): p. 985-97.
16. Ricotta, J.J., et al., Updated Society for Vascular Surgery guidelines for management of extracranial carotid disease: executive summary. *J Vasc Surg*, 2011. 54(3): p. 832-6.
17. Bonati, L.H., et al., Short-term outcome after stenting versus endarterectomy for symptomatic carotid stenosis: a preplanned meta-analysis of individual patient data. *Lancet*, 2010. 376(9746): p. 1062-73.

18. Voeks, J.H., et al., Age and Outcomes After Carotid Stenting and Endarterectomy: The Carotid Revascularization Endarterectomy Versus Stenting Trial. *Stroke*, 2011. 42(12): p. 3484-3490.
19. Ringleb, P.A., et al., 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. *Lancet*, 2006. 368(9543): p. 1239-47.
20. Howard, V.J., et al., Influence of sex on outcomes of stenting versus endarterectomy: a subgroup analysis of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST). *Lancet Neurol*, 2011. 10(6): p. 530-7.
21. Rockman, C.B., et al., Outcome of carotid artery interventions among female patients, 2004 to 2005. *J Vasc Surg*, 2011. 53(6): p. 1457-64.
22. Abbott, A.L., Regarding "asymptomatic carotid artery stenosis-Medical therapy alone versus medical therapy plus carotid endarterectomy or stenting". *J Vasc Surg*, 2011. 53(1): p. 265; author reply 265.
23. Schneider, P.A. and A.R. Naylor, Asymptomatic carotid artery stenosis--medical therapy one versus medical therapy plus carotid endarterectomy or stenting. *J Vasc Surg*, 2010. 52(2): p. 499-507.

**Question #6a: Confidence there is adequate evidence to determine if carotid artery screening of asymptomatic persons decreases stroke or death.**

LEVEL 4

**Question #6b: If there is intermediate confidence, how confident are you that carotid artery screening of asymptomatic persons decreases stroke or death?**

LEVEL 4: SVS MAINTAINS A FAIRLY CONFIDENT POSITION THAT SCREENING AT RISK POPULATIONS IS BENEFICIAL.

### **CAROTID SCREENING**

Background:

Stroke is the third leading cause of death, and is the leading cause of disability in the United States and the western world. Eighty percent of these strokes are ischemic, and many are secondary to carotid bifurcation atherosclerosis. Unfortunately, only 15% of stroke victims have a warning TIA before stroke, and waiting until symptoms occur is neither safe nor ethical since natural history studies of asymptomatic high grade carotid stenosis indicate that the first event is as likely to be a stroke rather than a TIA. Therefore, screening (using duplex ultrasound) to detect “stroke-prone” carotid bifurcation plaque and identify a high-risk patient likely to benefit from therapy is designed to reduce stroke risk.

Stroke risk is dependent on many factors, but for patients with carotid bifurcation disease, the most important are a history of neurologic symptoms, the degree of stenosis of the carotid bifurcation plaque, and to some extent, plaque characteristics. While degree of stenosis is a convenient, generally reliable and easily obtained surrogate to identify at risk

patients, most methods of plaque characterization remain in the research realm, i.e. they are not widely available to practicing clinicians.

### **Indications for Carotid Screening in Neurologically Asymptomatic Patients**

Evaluation and treatment of patients who are asymptomatic is controversial. The benefit of carotid endarterectomy for stenosis >60%, although statistically significant in large trials, is much less than for neurologically symptomatic individuals and rests on both available natural history data and the premise that intervention (i.e. CEA) can be performed with minimal morbidity and mortality. <sup>[1, 2]</sup>

To date, there is no consensus on which patients should undergo carotid screening for detection of carotid stenosis. The American Society of Neuroimaging concluded that the efficacy of screening would be related to the prevalence of the disease in the screened populations. <sup>[3]</sup> When the prevalence of stenosis was  $\geq 20\%$ , screening reduced the risk of stroke in a cost-effective manner; with an intermediate prevalence of between 5% and 20%, screening reduced the risk of stroke in a cost-effective manner in some studies; however, the benefit was usually marginal and was lost if complications of the intervention were >5%. With a prevalence of <5%, screening has not been shown to reduce the risk of stroke in a cost-effective manner and may be harmful.

Therefore, screening of the general population is not justified. This is supported by multiple professional organizations: the Canadian Stroke Consortium, <sup>[4]</sup> the National Stroke Association, <sup>[5]</sup> and the U.S. Preventive Services Task Force. <sup>[6]</sup> The American Stroke Association/AHA Stroke Council <sup>[7]</sup> concluded that highly selected patient populations may benefit, but screening of the general population for asymptomatic carotid stenosis was unlikely to be cost-effective and might have the potential adverse effect of false-negative or false-positive

results. Recently, the American College of Cardiology Foundation, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and American Society of Interventional & Therapeutic Neuroradiology Clinical Expert Consensus Panel on Carotid Stenting recommended screening for asymptomatic patients with a carotid bruit who are potential candidates for carotid intervention and for those in whom coronary artery bypass grafting (CABG) is planned. <sup>[8]</sup>

### **Screening Patients with Asymptomatic Carotid Bruits**

Ratchford et al <sup>[9]</sup> found in a selected high-risk subgroup of asymptomatic patients that if a bruit was heard, 25% had >60% stenosis. The presence of a carotid bruit has been shown to increase the absolute risk of stroke, MI, and death. <sup>[10]</sup> In general population-based studies, the prevalence of severe stenosis is not high enough to make bruit alone an indication for carotid screening. With these facts in mind, screening should be pursued only if a bruit is associated with other risk factors for stenosis and stroke in patients who have a low operative risk and are willing to undergo carotid intervention. This is of course predicated on the knowledge from randomized trials that CEA confers superior long term protection from stroke when compared to available medical therapy. (1,2)

### **“High-Risk Stroke Patients” Who May Benefit from Screening for Asymptomatic Stenosis**

Two studies have identified specific groups of patients with a higher prevalence of significant carotid stenosis that may exceed >30%. Jacobowitz et al <sup>[11]</sup> developed a model identifying patients at high risk for >50% asymptomatic carotid stenosis. These included patients aged >60 years who had one or more of the following risk factors: CAD, history of hypertension, current smoking, and a first-degree family relative with a history of stroke. The prevalence of carotid artery stenosis was only 2% if no risk factor was present, 6% with one risk



factor, which increased to 14% for two risk factors, to 16% for three risk factors, and to 67% for four risk factors.

Qureshi et al<sup>[12]</sup> identified the following variables associated with  $\geq 60\%$  asymptomatic carotid stenosis: hypercholesterolemia (odds ratio, 1.9), current smoking (odds ratio, 2), CAD (odds ratio, 2.4), and age  $>65$  years (odds ratio, 4.1). Patients undergoing coronary revascularization are another group with an increased prevalence of carotid stenosis of 2% to 27%.<sup>[13]</sup> Overall, the prevalence of carotid artery stenosis among patients undergoing CABG is higher than the general population. In patients with symptomatic CAD and other risk factors, such as history of stroke or TIA, age  $>65$  years, diabetes mellitus, left main coronary stenosis, peripheral arterial disease (PAD), carotid bruit, and previous carotid operation; it is feasible that a subset of patients with a prevalence  $>20\%$  can be identified who might benefit from carotid screening.<sup>[14]</sup> The ACC/AHA guidelines<sup>[15]</sup> note that carotid screening before CABG is probably indicated in the following subset of patients: age  $>65$  years, left main coronary stenosis, history of smoking, history of TIA/stroke or carotid bruit, and PAD. Several studies<sup>[16]</sup> have also suggested that the prevalence of  $\geq 60\%$  carotid artery stenosis among patients with symptomatic PAD is  $>20\%$ , regardless of the patient's age.

### **Recommendation Summary for the Use of Carotid Duplex Screening**

Overall, routine screening is *not recommended* to detect clinically asymptomatic carotid stenosis in the general population or presence of a neck bruit alone without other risk factors. Screening should be considered in patients with multiple risk factors that increase the incidence of disease as long as the patients are fit for and willing to consider carotid intervention if a significant stenosis is detected: patients with evidence of clinically significant PVD, regardless of age; and patients aged  $\geq 65$  years with a history of one or more of the following risk factors:

smoking, CAD, or hypercholesterolemia. Carotid screening may be considered in patients before CABG, particularly aged >65 years and have left main disease or a history of PVD.

## References

1. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. *JAMA* 1995;273:1421-8.
2. Halliday A, Mansfield A, Marro J, Peto C, Peto R, Potter J, et al. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomized controlled trial. *Lancet* 2004;363:1491-502.
3. Qureshi AI, Alexandrov AV, Tegeler CH, Hobson RW 2nd, Baker DJ, Hopkins LN, et al. Guidelines for screening of extracranial carotid artery disease: a statement for healthcare professionals from the multidisciplinary practice guidelines committee of the American Society of Neuroimaging: cosponsored by the Society of Vascular and Interventional Neurology. *J Neuroimaging* 2007;17:19-47.
4. Perry JR, Szalai JP, Norris JW. Consensus against both endarterectomy and routine screening for asymptomatic carotid artery stenosis. Canadian Stroke Consortium. *Arch Neurol* 1997;54:25-8.
5. Gorelick PB, Sacco RL, Smith DB, Alberts M, Mustone-Alexander L, Rader D, et al. Prevention of a first stroke: a review of guidelines and a multidisciplinary consensus statement from the National Stroke Association. *JAMA* 1999;281:1112-20.
6. U.S. Preventive Services Task Force. Screening for carotid artery stenosis: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2007;147:854-9.
7. Goldstein LB, Adams R, Alberts MJ, Appel LJ, Brass LM, Bushnell CD, et al. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism

8. Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: the American Academy of Neurology affirms the value of this guideline. *Stroke* 2006;37:1583-633.
9. Bates ER, Babb JD, Casey DE Jr, Cates CU, Duckwiler GR, Feldman TE, et al. ACCF/SCAI/SVMB/SIR/ASITN 2007 clinical expert consensus document on carotid stenting: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents (ACCF/SCAI/SVMB/SIR/ASITN Clinical Expert Consensus Document Committee on Carotid stenting). *J Am Coll Cardiol* 2007;49:126-70.
10. Ratchford EV, Jin Z, Di Tullio MR, Salameh MJ, Homma S, Gan R, et al. Carotid bruit for the detection of hemodynamically significant carotid stenosis: the Northern Manhattan Study. *Neurol Res* 2009;31:748-52.
11. Pickett CI, Jackson JL, Hemann BA, Atwood E. Carotid bruits as a prognostic indicator of cardiovascular death and myocardial infarction: a meta-analysis. *Lancet* 2008;371:1587-94.
12. Jacobowitz GR, Rockman CB, Gagne PJ, Adelman MA, Lamparello PJ, Landis R, et al. A model for predicting occult carotid artery stenosis: screening is justified in a selected population. *J Vasc Surg* 2003;38:705-9.
13. Qureshi AI, Janardhan V, Bennett SE, Luft AR, Hopkins LN, Guterman LR. Who should be screened for asymptomatic carotid artery stenosis? Experience from the Western New York stroke screening program. *J Neuroimaging* 2001;11:105-11.
14. Naylor AR, Mehta Z, Rothwell PM, Bell PR. Carotid artery disease and stroke after coronary artery bypass: a critical review of the literature. *Eur J Vasc Endovasc Sur* 2002;23:283-94.
15. D'Agostino RS, Svensson LG, Neumann DJ, Balkhy HH, Williamson WA, Shahian DM. Screening carotid ultrasonography and risk factors for stroke in coronary artery surgery patients. *Ann Thorac Surg* 1996;62:1714-23.

16. Eagle KA, Guyton RA, Davidoff R, Edwards FH, Ewy GA, Gardner TJ, et al. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (committee to update the 1999 guidelines for coronary artery bypass graft surgery). *Circulation* 2004;110:1168-76.
17. Marek J, Mills JL, Harvich J, Cui H, Fujitani RM. Utility of routine carotid duplex screening in patients who have claudication. *J Vasc Surg* 1996;24:572-7.

**Q#7: What unmet research needs, specific to the following issues, are important to consider and explore further?**

- a. Should future stroke prevention trials
  - i. Be powered to evaluate only symptomatic or asymptomatic patients?
  - ii. Be powered to draw conclusions regarding gender?
  - iii. Evaluate outcomes for more racially/ethnically diverse patient populations?
- b. So as to help delineate those who require carotid revascularization from those who do not, how should future trials best utilize and validate for the Medicare population the following tools to identify persons with asymptomatic carotid atherosclerosis who are at high risk for stroke?
  - i. Advanced imaging, such as 3D ultrasound, for plaque morphology
  - ii. Transcranial Doppler (TCD) for cerebral microembolization
  - iii. Pre- and post-procedure diffusion weighted MRI (DW-MRI) for silent infarcts
  - iv. Risk assessment tools and predictive stroke models

7.a.i: IT IS IMPERATIVE THAT ALL FUTURE STROKE PREVENTION TRIALS SHOULD BE POWERED TO EVALUATE SEPARATELY SYMPTOMATIC OR ASYMPTOMATIC PATIENTS.

The outcomes associated with the medical management of symptomatic and asymptomatic carotid disease as documented in all currently available clinical trials are so vastly different that pooling data from asymptomatic and symptomatic patients is highly likely to obscure important outcome differences in the symptomatic patients while exaggerating differences in asymptomatic patients. In the North American Symptomatic Carotid Endarterectomy Trial (NASCET) (symptomatic trial) medical management of 70-99% symptomatic stenosis was associated with a two year stroke risk of 26%, while the medical management of 50-69% symptomatic stenosis was associated with a five year stroke risk of 22% (1,2). In the Asymptomatic Carotid Atherosclerosis Study (ACAS) (asymptomatic trial) the medical management of asymptomatic 60% or greater stenosis was associated with a 5 year stroke risk of only 11% (3). Likewise, in the more recent Asymptomatic Carotid Surgery Trial

(ACST) (asymptomatic trial) medical management of 70% or greater asymptomatic stenosis was associated with a 5 year stroke risk of only 11.8% (4)

7.a.ii: GENDER DIFFERENCES IN TREATMENT OUTCOMES ARE REAL BUT SEEM INSUFFICIENT TO JUSTIFY POWERING STUDIES TO DETECT GENDER SPECIFIC DIFFERENCES IN RESPONSE TO TREATMENT.

While in ACAS the relative risk reduction attributable to carotid endarterectomy was 66% in men and only 17% in women, this difference failed to reach statistical significance. In ACAS, the risk of perioperative stroke or death was 3.6 % in women and 1.7% in men, but there have been many case series published since ACAS in which gender related differences in operative risk appear negligible. In fact, in the Northern New England vascular database including 3092, female gender was not associated with increased risk for adverse outcomes (5). In ACST, carotid endarterectomy was statistically significantly beneficial in both men and women, though surgical risk in women remained higher. Finally, in the European Carotid Surgery Trial (ECST) (symptomatic trial) perioperative stroke and death rates were higher in women than in men (10.4% vs 5.8%) resulting in less benefit for women and resulting in a recommendation that the threshold degree of stenosis warranting surgery be set higher for women than for men (6). In these major randomized endarterectomy versus medical management trials, gender related treatment effects were real but did not negate the benefit of intervention for symptomatic or asymptomatic disease in men or women.

As of now, there is little data indicating a gender effect on outcome in carotid stenting, at least as compared to carotid endarterectomy. In CREST the outcome difference attributable to gender

was insignificant ( $P=0.34$ ) (7). There are no data exploring gender effects in medical management versus stenting trials.

7.a.iii: THERE ARE NO DATA TO SUGGEST THAT STUDIES NEED TO BE POWERED TO DETECT OUTCOME DIFFERENCES IN MORE ETHNICALLY OR RACIALLY DIVERSE POPULATIONS.

The prevalence of carotid disease varies among racial groups, and the relative importance of carotid disease in stroke etiology varies tremendously among racial groups. However, there are no data suggesting that the ethnic or racial profile of a population affects its responses to treatment for either symptomatic or asymptomatic carotid disease.

7.b.i: PLAQUE MORPHOLOGY IS AT LEAST AS IMPORTANT AS DEGREE OF STENOSIS IN DETERMINING THE PROGNOSIS OF ASYMPTOMATIC CAROTID LESIONS.

High resolution 3D ultrasound with computer enhanced plaque analyses can detect plaque characteristics that may be more important than degree of stenosis in determining prognosis. Nicolaides' most recent work offers the most compelling data in support of plaque morphologic features as prime determinants of prognosis in asymptomatic patients (8). In this study 1121 patients with asymptomatic 50-99% carotid stenoses underwent plaque characterization using a duplex ultrasound imaging protocol and then were followed. Using this protocol severity of stenosis, gray scale median (a measure of plaque echodensity), total plaque area, and plaque heterogeneity as measured by the presence of noncalcified discrete white areas were shown to predict a wide range of clinical outcomes. Based on this work, in asymptomatic



patients we can identify a subset of patients with >80% stenosis with small, echodense, homogeneous plaques and no history of contralateral neurologic events, in whom the 5 year stroke risk is only 1.9%. Conversely, in those asymptomatic patients with >80% stenosis with moderate to large, heterogeneous echolucent plaques and a history of contralateral stroke or TIA, the 5 year risk of stroke was 70%. Similarly, in patients with 50-80% stenosis, using the same criteria, subgroups with 5 year stroke risks ranging from 1.3% to 70.4% are identified (8). These data offer compelling evidence that duplex ultrasound identifiable plaque characteristics other than stenosis are critically important determinants of plaque behavior and, therefore of prognosis in asymptomatic carotid disease patients. Furthermore, there is significant emerging evidence that plaque morphology has a significant affect on stroke risk associated with carotid artery stenting. Future clinical trials should evaluate ultrasound determined plaque morphologic characteristics apart from stenosis as reliable predictors of prognosis and of outcome under surgical, interventional, and medical management.

#### 7.b.ii: TRANSCRANIAL DOPPLER (TCD) CAN DETECT MICROEMBOLIC EVENTS AND INCREASED FREQUENCY OF THESE EVENTS IS ASSOCIATED WITH THE PRESENCE OF UNSTABLE PLAQUES.

However, these microemboli can originate from other sources (aortic arch, aortic valve). In addition, a recent study on TCD in asymptomatic carotid disease patients failed to show a statistically significant relationship between the presence of microembolic signals and neurologic outcome (9).

7.b.iii: MAGNETIC RESONANCE IMAGING SEEMS ESPECIALLY PROMISING IN THE ANALYSIS OF PLAQUE MORPHOLOGY AND IN ANALYSIS OF TREATMENT RESULTS.

In a recent prospective study of 154 asymptomatic patients presenting with 50-79% stenosis and followed for a mean of 38.2 months Takaya and colleagues noted 12 cerebrovascular events. MRI findings at study entry of thin or ruptured fibrous cap (odds ratio 17.2,  $P < .001$ ), intraplaque hemorrhage (odds ratio 5.2,  $P = .005$ ), larger area of intraplaque hemorrhage (odds ratio for  $10\text{mm}^2 = 2.6$ ,  $P = .006$ ), larger lipid rich or necrotic core (odds ratio for 10% increase = 1.6,  $P = .004$ ) and greater maximal wall thickness (odds ratio for 1 mm increase = 1.6,  $P = .008$ ) predicted clinical outcome (9). Interestingly, in this study, MRI measures of stenosis (mean luminal area and minimal luminal area) were not statistically significantly predictive of clinical events ( $P = 0.2$  and  $0.4$  respectively) (9). Also post-procedure diffusion weighted MRI detected brain infarcts can serve as endpoints in future clinical trials. Most such infarcts are clinically silent, but represent surrogate markers for treatment related microemboli.

7.b.iv: IT IS INCONCEIVABLE THAT ANY MODEL PREDICTING STROKE RISK IN PATIENTS WITH ASYMPTOMATIC CAROTID DISEASE WOULD NOT USE CAROTID DISEASE SEVERITY AS ITS MAIN RISK INDICATOR.

Therefore, we believe that research efforts should be focused on detection of plaque characteristics predictive of stroke. Predictive models incorporating other patient characteristics will develop as we develop more reliable noninvasive means for predicting plaque behavior. Perhaps the best predictive model for symptomatic patients was developed from the medical

arm of the NASCET Trial, and this model incorporated both degree of stenosis and the presence of plaque ulceration (1). Furthermore, in this study, degree of stenosis alone was a strong predictor of outcome for medically managed patients (1). It is unlikely that degree of stenosis alone will be as predictive in asymptomatic patients, but as seen in the answers to 7.b.i and 7.b.iii above it appears that other measurable plaque characteristics will be major determinants of both prognosis and response to treatment.

## References

1. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial Effect of Carotid Endarterectomy in Symptomatic Patients with High-Grade Carotid Stenosis. *NEJM* 325; 445-53; 1991.
2. Barnett HJM, Taylor DW, Eliaziw M, et al. Benefit of Carotid Endarterectomy in Patients with Symptomatic Moderate or Severe Stenosis. *NEJM* 339; 1415-25; 1998.
3. Executive Committee for Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for Asymptomatic Carotid Artery Stenosis. *JAMA* 1995; 273; 1421-8.
4. ACST Collaborators Group: The International Asymptomatic Carotid Surgery Trial (ACST). *Lancet* 363; 1491-1502, 2004.
5. Goodney PP for the Vascular Study Group of Northern New England. Factors associated with stroke or death after carotid endarterectomy in northern New England. *J. Vasc Surg.* 48; 1139-1145; 2008.
6. European Carotid Surgery Trialists' Collaborative Group. MRC European Carotid Surgery Trial: interim results for patients with severe (70-99%) or mild (0-29%) carotid stenosis. *Lancet* 337; 1235-43; 1991.
7. Brott TG, Hobson RW, Howard G, et al. Stenting versus Endarterectomy for Treatment of Carotid Artery Stenosis. *NEJM* 363; 11-23; 2010.
8. Nicolaides AN, Kakkos SK, Kyriacou E, et al. Asymptomatic internal carotid artery stenosis and cerebrovascular risk stratification. *JVS*; 2010; 52; 1486-96.
9. Abbott AL, Chambers BR, Stork JL, et al: Embolic signals and prediction of ipsilateral stroke or transient ischemic attack in asymptomatic carotid stenosis: a multicenter prospective cohort study. *Stroke* 36(6); 1128-33; 2005.

10. Takaya N, Yuan C, Chu B, Saam T, Underhill H, Cai J, Tran N, Polissar NL, Isaac C, Ferguson M, Garden GA, Cramer SC, Maravilla KR, Hashimoto B, Hatsukami TS.  
Association between carotid plaque characteristics and subsequent cerebrovascular events.  
*Stroke* 37; 818-23; 2006.



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Dear Ms. Ellis,

The American Academy of Neurology (AAN) represents 24,000 neurologists and neuroscience professionals. The body of this letter contains additional information regarding the AAN's position on the potential for expanded reimbursement for carotid artery stenting (CAS) in standard risk patients. In brief, the AAN expressly conveys the following:

1. We believe that wider reimbursement for CAS is warranted in symptomatic patients less than age 70 years that are considered standard risk (per CREST study criteria) These patients should have >50% stenosis on angiography or >70% by ultrasound; and only if facilities are required to participate in a CMS-approved risk adjusted accreditation program that documents that outcomes meet national benchmarks. Although the data are not conclusive, a sub-analysis of CREST and a meta-analysis of other studies all suggest that symptomatic patients  $\geq$  age 70 have better outcomes with CEA;
2. We do not support wider reimbursement for CAS for asymptomatic, standard risk patients since the CREST study showed an almost twofold increased risk of stroke in asymptomatic patients. Furthermore, CREST showed an age interaction with patients  $\geq$  age 70 years faring better with carotid endarterectomy (CEA) compared to CAS. The vast majority of patients that would be covered by CMS who would potentially undergo revascularization for asymptomatic stenosis are  $\geq$  70 years of age and CEA is already available for these patients.
3. Studies comparing the relative value of optimal medical therapy (OMT) alone vs. OMT + carotid revascularization are urgently needed. The CREST 2 trial applicants are applying for NIH funding for such a trial in asymptomatic patients. Expanded CAS reimbursement should not

adversely affect recruitment in trials that examine the relative value of optimal medical therapy alone vs. OMT alone plus carotid revascularization.

4. If there is expanded approval for CAS in symptomatic, standard risk patients, there should be a mandatory registry for all patients age 70 years or greater that undergo CAS for symptomatic stenosis. The 30 day rate of stroke or death should be collected and results compared with national benchmarks.

As background for these opinions, we would like to highlight several developments since the last letter of April 16, 2009. Two important randomized, multi-center studies were published in 2010 pertaining to CEA vs. CAS in standard risk patients. The International Carotid Stenting Study (ICSS) was conducted in Europe predominantly and the Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST) was done in North America<sup>1,2</sup>.

The ICSS trial enrolled patients with ipsilateral carotid territory symptoms within the previous 12 months and with at least 50% internal carotid artery (ICA) stenosis. 1713 patients were recruited from 50 academic centers. Surgeons were required to have performed at least 50 CEA operations and interventionalists were required to have done at least 50 stenting procedures, with at least 10 in the ICA.

In ICSS, within 120 days of enrollment, the risk of stroke, death and MI in the CAS group (8.5%) was significantly higher than in the surgical arm (5.2%,  $p=0.006$ ). The finding that CEA is safer than CAS is also supported by the results of an MRI substudy which showed significantly more new diffusion weighted imaging (DWI) lesions in CAS than in CEA patients. MI did not play a major role in ICSS and was confined to single cases with no significant difference but more fatal events in the CAS group.

CREST originally included only symptomatic patients with at least 50% stenosis on angiography or 70% by ultrasound. In 2005, asymptomatic patients with at least 60% stenosis by angiography or 70% by ultrasound also became eligible. 2502 patients were enrolled (including 1181 asymptomatic subjects) from 108 centers. Both surgeons and interventionalists were required to be certified as meeting performance benchmarks. Less experienced interventionalists were required to participate in a lead in phase before joining the main study.

The primary endpoint of the study was the combined rate of stroke, death, or myocardial infarction within 30 days of the procedure or ipsilateral stroke up to four years. Over a median follow-up of 2.5 years, there was no difference in the primary endpoint between the two groups (7.2% CAS vs. 6.8% CEA, hazard ratio with CAS 1.11,  $p=0.51$ ).

However, it should be recognized that the inclusion of MI as one of the components of the endpoint for standard risk patients with carotid stenosis is atypical. Table 1 delineates the primary endpoint for four contemporary studies, with CREST being the only one that includes MI in the composite endpoint. **The purpose of carotid revascularization is to prevent stroke.** Including a safety endpoint such as MI and giving it equal weight in the composite measure is problematic.

If one looks at a more “traditional endpoint” of stroke or death within 30 days plus ipsilateral stroke after 30 days, the four year rate of stroke or death was higher with CAS in the entire CREST population as well as in both subgroups of patients.

	CAS	CEA	Hazard ratio	P Value
Entire population	6.4%	4.7%	1.50	0.03
Symptomatic	8.0%	6.4%	1.37	0.14
Asymptomatic	4.5%	2.7%	1.86	0.07

The marked increase in risk of stroke or death in asymptomatic patients is particularly troublesome. The study was underpowered to look at subgroups but the higher rate of stroke or death would very likely have been significant in the asymptomatic subgroup with a few hundred more patients.

Another area of significant concern is the growing body of evidence that CAS patients  $\geq 70$  years of age fare worse with CAS compared to CEA. Even in the CREST study, which had rigorous credentialing of interventionalists, the results were notably worse in patients  $\geq 70$  years. The results are summarized as follows:

### Periprocedural Stroke and Death rates in CREST

Stroke±Death Endpoint (any stroke or death within peri-procedural period <sup>1</sup> )		Peri-procedural Period <sup>2</sup>	
		<70 rate ± SE <sup>3</sup>	70+ rate ± SE <sup>3</sup>
CAS	Asymptomatic	1.9 ± 0.8	3.2 ± 1.1
	Symptomatic	2.6 ± 0.8	9.8 ± 1.7
CEA	Asymptomatic	1.4 ± 0.7	1.4 ± 0.7
	Symptomatic	1.8 ± 0.7	4.6 ± 1.2

1. Peri-procedural period defined per protocol as 30 days post-procedure for all patients receiving assigned therapy within 30 days from randomization, or 36 days after randomization for all patients not receiving assigned treatment within 30 days
2. Because of the relatively short peri-procedural period that minimizes censoring, event rates calculated as a proportion of patients with events.

**It should be noted that, in CREST, for both symptomatic and asymptomatic patients  $\geq 70$  years, CAS failed to achieve the previous benchmarks recommended by the AHA of <6% stroke/death for symptomatic patients and <3% for asymptomatic patients.**



A meta-analysis of three European studies that enrolled patients with recently symptomatic stenosis also found worse results with CAS compared to CEA in patients  $\geq 70$  years (the median age in the three studies)<sup>3</sup>. The two procedures were comparable in patients less than age 70 years. The rates of stroke/death within 120 days of randomization were as follows:

	Age <70 years	Age $\geq 70$ years
CAS	5.8%	12.0%
CEA	5.7%	5.9%
Relative risk (CAS to CEA)	1.00	2.04 (p=0.005)

In terms of guidelines, both the American Stroke Association and a recent multispecialty document hold the view that CAS can be considered for symptomatic, standard risk patients if the periprocedure complication rate is expected to be 4-6% or less (Class IIa; Level of Evidence B)<sup>4,5</sup>. Both documents, however, give a much more guarded statement on CAS for asymptomatic patients (Class IIb; Level of Evidence B).

The American Stroke Association statement indicates that carotid revascularization should only be considered in *highly select* (italics added) patients with asymptomatic carotid stenosis. Furthermore, **both statements indicate that the value of CAS relative to medical therapy in subjects with asymptomatic stenosis is not well established**<sup>5,6</sup>.

Therefore, the AAN believes that a clinical trial such as CREST 2 should be performed to establish a scientific basis for comparing the merits of OMT alone vs. OMT + carotid revascularization in asymptomatic subjects. Given the increased risk of stroke/death in asymptomatic patients seen in CREST with CAS compared to CEA (especially for patients  $\geq 70$  years), the AAN believes that reimbursement for CAS in asymptomatic is premature scientifically. On an individual patient level, premature application of CAS in asymptomatic patients could be potentially hazardous to patients covered by CMS and compromise patient safety.

We thank CMS for consideration of our comments. If you have any questions concerning the contents of this letter, please contact Sarah Tonn at 651-695-2819 or stonn@aan.com.

Sincerely,



Bruce Sigsbee, MD, FAAN  
President, American Academy of Neurology

**Table 1**

**Key features of Multi-center carotid revascularization studies**

	SPACE	EVA 3S	ICSS	CREST
Patient population	Symptomatic only	Symptomatic only	Symptomatic only	Symptomatic and asymptomatic
Primary endpoint	Stroke/death within 30 days	Stroke/death within 30 days	Three year fatal or disabling stroke (120 day results reported)	Periprocedure stroke, death, MI plus ipsilateral stroke beyond 30 days

## REFERENCES

1. Investigators ICSS. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. *The Lancet*. 2010;375:985-997.
2. Brott TG, Hobson RW, II, Howard G, et al. Stenting versus Endarterectomy for Treatment of Carotid-Artery Stenosis. *N Engl J Med*. June 14, 2010 2010;363:11-23.
3. Carotid Stenting Trialists' Collaboration . Short-term outcome after stenting versus endarterectomy for symptomatic carotid stenosis: a preplanned meta-analysis of individual patient data. *The Lancet*. 2010;376(9746):1062-1073.
4. Furie KL, Kasner SE, Adams RJ, et al. Guidelines for the Prevention of Stroke in Patients With Stroke or Transient Ischemic Attack: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. January 1, 2011 2011;42:227-276.
5. Brott TG, Halperin JL, Abbara S, et al. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS Guideline on the Management of Patients With Extracranial Carotid and Vertebral Artery Disease: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. *Stroke*. January 31, 2011 2011:STR.0b013e3182112cc3182112.
6. Goldstein LB, Bushnell CD, Adams RJ, et al. Guidelines for the Primary Prevention of Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. February 1, 2011 2011;42:517-584.

**Medicare Evidence Development & Coverage Advisory Committee  
Management of Carotid Atherosclerosis  
January 25, 2012**

The American Heart Association (AHA) and the American Stroke Association (ASA), a division of the AHA, are pleased to provide comments to the Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) on the management of carotid atherosclerosis.

AHA/ASA is the nation's largest voluntary health organization with over 22.5 million volunteers and supporters. Since 1924, AHA/ASA has dedicated itself to building healthier lives free of cardiovascular disease and stroke – the #1 and #4 leading causes of death in the United States – through research, education, community-based programs, and advocacy.

AHA supports the efforts of the Centers for Medicare & Medicaid Services (CMS) and MEDCAC to determine the best treatment options for patients with carotid atherosclerosis. Carotid atherosclerosis places individuals at increased risk for a number of adverse cardiovascular events such as myocardial infarction, peripheral arterial disease, and the two outcomes of primary interest for this meeting – stroke and death. Carotid atherosclerosis or carotid stenosis is a significant risk factor for stroke. Carotid stenosis of 60% or more has been associated with approximately 7% of all first ischemic strokes.<sup>1</sup>

Carotid atherosclerosis affects a significant portion of the Medicare population. According to data from the Framingham Heart Study, 7% of women seniors and 9% of men seniors have carotid stenosis of more than 50%. The Cardiovascular Health Study found similar results with 5% of women and 7% of men over 65 years of age with moderate carotid stenosis between 50% and 74%, and 1.1% of women and 2.3% of men with severe stenosis of more than 75%.

Because of the serious risks associated with carotid atherosclerosis, treatment of individuals at high risk for stroke, particularly among symptomatic patients, may be recommended. Treatment options include carotid endarterectomy (CEA), carotid artery stenting (CAS), or medical therapy. AHA/ASA, in conjunction with the American College of Cardiology and the American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery, has examined these various treatment options and in 2011 issued practice guidelines for the management of patients with extracranial carotid and vertebral artery disease.<sup>2</sup>

Our comments are based on these guidelines, as well as input from experts in this field, and focus on the specific topic areas the Committee has been asked to discuss today.

## **Risk Evaluation**

***Is there adequate evidence to determine if persons in the Medicare population who are asymptomatic for carotid atherosclerosis can be identified as being at high risk for stroke in either cerebral hemisphere?***

There are a number of risk factors that contribute to an increased risk for stroke in patients with asymptomatic carotid atherosclerosis. Advanced age, for example, is a risk factor for stroke. The best risk factor, however, is the degree of carotid stenosis. In general, the more severe the stenosis, the greater the risk of stroke. For the asymptomatic population, a stenosis of more than 70% is considered to place the individual at increased risk for stroke. Other factors such as the characteristics of the plaque formation within the carotid artery may be useful in the identification of high risk individuals in the future, but these factors are not ready for widespread use. Outside of the severity of stenosis, we have not yet determined a mechanism to identify those at the highest risk for stroke.

In a related question, MEDCAC asks if there are ethical concerns to conducting randomized controlled trials of CEA, CAS, or best medical therapy in the general asymptomatic population, and if such trials would only be appropriate for individuals at high risk for stroke. AHA/ASA believes such trials pose no ethical issues; participants in the trials would be required to provide informed consent. In addition, well-designed, contemporary trials are needed to compare CEA, CAS, and medical therapy. Results from these trials would help the medical community determine the appropriate role of CEA, CAS, and medical therapy for asymptomatic patients. Expanding the trials to include both high and low risk patients may also be appropriate as the role of CEA, CAS, and medical therapy is a valid research question in both of these patient populations.

***Is there adequate evidence to determine if persons in the Medicare population, who are considering carotid revascularization, can be identified as being at high risk for adverse events from CEA?***

There are a number of co-morbidities that increase the risk of revascularization such as advanced age (> 80 years of age), New York Heart Association class III or IV heart failure, left ventricular ejection fraction < 30%, class III or IV angina pectoris, left main or multivessel coronary artery disease, the need for cardiac surgery within 30 days, a myocardial infarction within four weeks, and severe chronic lung disease. For CEA in particular, health professionals should also consider if the individual has anatomic risk factors. Unfavorable neck anatomy such as arterial stenosis distal to the second cervical vertebra or proximal (intrathoracic) arterial stenosis, previous ipsilateral CEA, contralateral vocal cord paralysis, open tracheostomy, radical surgery, and prior radiation therapy to the neck may place an individual at high risk for arterial surgery. For these patients, CAS may be a reasonable alternative to CEA when revascularization is indicated.

To identify these individuals, medical professionals should examine the individual's medical history and conduct a thorough physical exam. The individual's stroke risk, including an evaluation of cardiac function and other cerebral vessels, should also be assessed.

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<sup>1</sup> 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS Guideline on the Management of Patients with Extracranial Carotid and Vertebral Artery Disease. *Circulation* 2011, 124:e54-e130.

<sup>2</sup> Ibid. See <http://circ.ahajournals.org/content/124/4/e54.full.pdf>.

### **Favored Treatment Strategy**

***For persons with symptomatic carotid atherosclerosis and carotid narrowing ( $\geq 50\%$  by angiography or  $\geq 70\%$  by ultrasound) who are not generally considered at high risk for adverse events for CEA, is there adequate evidence to determine whether or not either CAS or CEA is the favored treatment strategy, as compared to best medical therapy alone, to decrease stroke or death in the Medicare population?***

Intervention or revascularization is the favored treatment option over best medical therapy for symptomatic patients with moderate to severe carotid stenosis who are not at high risk for CEA. Studies have shown that CEA is superior to best medical therapy in reducing the risk of stroke in these patients. While similar studies comparing CAS to best medical therapy have not been conducted, several meta-analyses of randomized trials comparing CAS to CEA found no difference in myocardial infarction, stroke, or death rates at 30 days, or in stroke or death rates at one year.<sup>3</sup> Therefore, we can reasonably conclude that because CEA and CAS are comparable, and CEA has been shown to be superior to medical therapy, both CAS and CEA are preferable to medical therapy in this patient population.

With respect to which intervention – CEA or CAS – is most appropriate for a specific patient, the multi-society practice guidelines referenced earlier recommend the following for symptomatic patients undergoing carotid revascularization:

#### Class I Recommendations:

1. Patients at average or low surgical risk who experience nondisabling ischemic stroke or transient cerebral ischemic symptoms, including hemispheric events or amaurosis fugax, within 6 months (symptomatic patients) should undergo CEA if the diameter of the lumen of the ipsilateral internal carotid artery is reduced more than 70% as documented by noninvasive imaging (*Level of Evidence: A*) or more than 50% as documented by catheter angiography (*Level of Evidence: B*) and the anticipated rate of perioperative stroke or mortality is less than 6%.
2. CAS is indicated as an alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the internal carotid artery is reduced by more than 70% as documented by noninvasive imaging or more than 50% as documented by catheter angiography and the anticipated rate of periprocedural stroke or mortality is less than 6%. (*Level of Evidence: B*)

#### Class IIa Recommendations:

1. It is reasonable to choose CEA over CAS when revascularization is indicated in older patients, particularly when arterial pathoanatomy is unfavorable for endovascular intervention. (*Level of Evidence: B*)
2. It is reasonable to choose CAS over CEA when revascularization is indicated in patients with neck anatomy unfavorable for arterial surgery. (*Level of Evidence: B*)
3. When revascularization is indicated for patients with TIA or stroke and there are no contraindications to early revascularization, intervention within 2 weeks of the index event is reasonable rather than delaying surgery. (*Level of Evidence: B*)

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<sup>3</sup> Ibid.

According to the questions posted for this meeting, MEDCAC is also interested in whether factors such as patient age, gender, and racial/ethnic background and the time to treatment affect the method of preferred method of revascularization. As noted in the Class IIa recommendation above, age is a relevant consideration. Because older patients generally have better outcomes with CEA, it is recommended that older patients undergo CEA rather than CAS. In addition, the practice guidelines also recommend that revascularization occur within two weeks of the onset of symptoms when possible.

***For persons with asymptomatic carotid atherosclerosis and carotid narrowing ( $\geq 60\%$  by angiography or  $\geq 70\%$  by ultrasound) who are not generally considered at high risk for adverse events from CEA, is there adequate evidence to determine whether or not either CAS or CEA is the favored treatment strategy as compared to best medical therapy alone, to decrease stroke or death in the Medicare population?***

The evidence comparing CEA, CAS, and best medical therapy in asymptomatic patients is lacking. Because the data are not as strong and asymptomatic patients are at lower risk for stroke, more conservative treatments are generally recommended.

For asymptomatic patients, the practice guidelines recommend:

Class IIa:

1. It is reasonable to perform CEA in asymptomatic patients who have more than 70% stenosis of the internal carotid artery if the risk of perioperative stroke, MI, and death is low. (*Level of Evidence: A*)

Class IIb:

1. Prophylactic CAS might be considered in highly selected patients with asymptomatic carotid stenosis (minimum 60% by angiography, 70% by validated Doppler ultrasound), but its effectiveness compared with medical therapy alone in this situation is not well established. (*Level of Evidence: B*)

Because the data comparing CEA, CAS, and best medical therapy in asymptomatic patients are not as robust as we would like – particularly for the use of CAS in asymptomatic patients – we would like to see additional data from randomized controlled trials that compare the three therapies. This is an area that warrants further research.

***For persons with asymptomatic carotid atherosclerosis who are not generally considered at high risk for stroke in either cerebral hemisphere, is there adequate evidence to determine whether or not CAS or CEA or best medical therapy alone is the favored treatment strategy to decrease stroke or death in the Medicare population?***

This question focuses on asymptomatic patients who are not at high risk for stroke. If, as with the first question, we use the degree of stenosis as the marker for stroke risk, this question applies to asymptomatic patients who have less than 70% stenosis.

In this patient population, there is no evidence that demonstrates that revascularization – either CEA or CAS – is better than best medical therapy.

In response to the Advisory Committee's follow-up question regarding the use of best medical therapy concurrently with CAS or CEA, we believe that all patients should receive best medical therapy either as a stand-alone treatment or in conjunction with revascularization.

### **Screening for Carotid Atherosclerosis**

***In the general Medicare population, is there adequate evidence to determine whether or not carotid artery screening of asymptomatic persons decreases stroke or death?***

Available evidence does not support the use of carotid artery screening of asymptomatic persons as a means to decrease stroke or death. In general, carotid artery screening of asymptomatic patients is not recommended. The practice guidelines consider carotid artery screening of most asymptomatic individuals to have no benefit.

#### **Class III Recommendations: No Benefit:**

1. Carotid duplex ultrasonography is not recommended for routine screening of asymptomatic patients who have no clinical manifestations of or risk factors for atherosclerosis. (*Level of Evidence: C*)
2. Carotid duplex ultrasonography is not recommended for routine evaluation of patients with neurological or psychiatric disorders unrelated to focal cerebral ischemia, such as brain tumors, familial or degenerative cerebral or motor neuron disorders, infectious and inflammatory conditions affecting the brain, psychiatric disorders, or epilepsy. (*Level of Evidence: C*)
3. Routine serial imaging of the extracranial carotid arteries is not recommended for patients who have no risk factors for development of atherosclerotic carotid disease and no disease evident on initial vascular testing. (*Level of Evidence: C*)

The guidelines, however, include a few exceptions for asymptomatic individuals who either exhibit some sign such as a carotid bruit that may be indicative of carotid stenosis or who have a number of risk factors. However, as noted below, it is still unclear if carotid artery screening of these patients, which results in a diagnosis of carotid atherosclerosis, will ultimately affect the clinical outcomes.

#### **Class IIa Recommendation:**

1. It is reasonable to perform duplex ultrasonography to detect hemodynamically significant carotid stenosis in asymptomatic patients with carotid bruit. (*Level of Evidence: C*)

#### **Class IIb Recommendations:**

1. Duplex ultrasonography to detect hemodynamically significant carotid stenosis may be considered in asymptomatic patients with symptomatic PAD, coronary artery disease (CAD), or atherosclerotic aortic aneurysm, but because such patients already have an indication for medical therapy to prevent ischemic symptoms, it is unclear whether establishing the additional diagnosis of ECVD in those without carotid bruit would justify actions that affect clinical outcomes. (*Level of Evidence: C*)
2. Duplex ultrasonography might be considered to detect carotid stenosis in asymptomatic patients without clinical evidence of atherosclerosis who have 2 or more of the following risk factors: hypertension, hyperlipidemia, tobacco smoking, a family history in a first degree relative of atherosclerosis manifested before age 60 years, or a family history of



ischemic stroke. However, it is unclear whether establishing a diagnosis of ECVD would justify actions that affect clinical outcomes. (*Level of Evidence: C*)

### **Future Research**

*What unmet research needs, specific to the following issues are important to consider and explore further?*

*Should future stroke prevention trials:*

- *Be powered to evaluate only symptomatic or asymptomatic patients?*
- *Be powered to draw conclusions regarding gender?*
- *Evaluate outcomes for more racially/ethnically diverse patient populations?*

We would like to see future research that examines stroke prevention in both symptomatic and asymptomatic patients. However, because we have less information on stroke prevention in asymptomatic patients, it is particularly important that future research focus on the asymptomatic patient population.

We would also like future research to examine the impact of gender and race/ethnicity. We are aware, however, that it is unlikely that one study will have sufficient power to evaluate all of these factors. In addition, it may be difficult for studies to evaluate certain factors such as clinical outcomes specific to females since women generally have lower event rates.

*So as to help delineate those who require carotid revascularization from those who do not, how should future trials best utilize and validate for the Medicare population the following tools to identify persons with asymptomatic carotid atherosclerosis who are at high risk for stroke?*

- *Advanced imaging, such as 3D ultrasound, for plaque morphology*
- *Transcranial Doppler (TCD) for cerebral microembolization*
- *Pre- and post-procedure diffusion weighted MRI (DW-MRI) for silent infarcts*
- *Risk assessment tools and predictive stroke models*

All of the tools listed above could be of some use in identifying asymptomatic patients who are at high risk for stroke. However, each technique would have to first be validated for its ability to reliably predict risk. We therefore recommend that these tools be incorporated into future clinical trials and evaluated to determine which mechanism(s) are appropriate for stroke risk stratification.

### **Conclusion**

In closing, thank you again for the opportunity to provide the American Heart Association's and the American Stroke Association's views on the management of carotid atherosclerosis. Carotid atherosclerosis is an important health issue for the Medicare program, affecting approximately 10% of all Medicare beneficiaries and placing them at increased risk of stroke – the number four killer of all Americans. To ensure that Medicare beneficiaries with carotid atherosclerosis receive appropriate diagnosis and treatment, we encourage CMS to implement the recommendations contained in the 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS Guideline on the Management of Patients with Extracranial Carotid and Vertebral Artery Disease.

December 19, 2011

Medicare Evidence Development & Coverage Advisory Committee  
Centers for Medicare & Medicaid services  
Coverage and Analysis Group  
S3-02-01  
7500 Security Boulevard  
Baltimore, MD 21244

Submitted electronically at: [MedCACpresentations@cms.hhs.gov](mailto:MedCACpresentations@cms.hhs.gov)

**SUBJECT: Society of Interventional Radiology comments on carotid atherosclerosis and treatment: January 25, 2012 meeting**

Dear Colleague:

The Society of Interventional Radiology (SIR) is a professional medical association that represents approximately 4,800 members who are practicing in the specialty of vascular and interventional radiology. The Society is dedicated to improving public health through pioneering advances in minimally-invasive, image-guided therapy. Our members are at the forefront of new and minimally invasive therapies to treat an array of diseases and conditions without surgery. Interventional radiology treatments have become first-line care for a wide variety of conditions and patients, including atherosclerosis treatment, osteoporosis patients with spinal fractures, peripheral arterial disease, deep vein thrombosis, uterine fibroids, cancer, and stroke patients.

The SIR endorses the expanded indications and accompanying reimbursement for carotid artery stenting (CAS), as approved by the FDA, with additional recommendations regarding the implementation of this new policy. The 2011 Multi-Society Guideline on the Management of Patients with Extracranial Carotid and Vertebral Artery Disease, in which 14 societies reached consensus, represents an excellent review of levels of evidence. Based upon that document and the CREST data, we strongly feel that symptomatic patients, regardless of risk stratification, should be given the option of CAS as treatment for carotid artery stenosis. We feel that the decision for carotid revascularization with either carotid endarterectomy (CEA) or CAS must be individualized, based upon risk factors, the clinical profile of the patient and locally available expertise. As a society, we do not endorse CAS as the treatment of choice for all carotid artery stenoses. However, based on the currently available data, we believe that if there is an indication for carotid revascularization, then both CEA and CAS should be considered, and if appropriate, the latter should be also offered to the patient as a potential treatment choice.

With regard to the treatment of asymptomatic carotid artery stenoses, we believe that based upon the CREST data, if an asymptomatic patient is to be treated with carotid revascularization, that the evidence supports offering both CAS and CEA as treatment options, and that they are equivalent procedures. If one does a sub-analysis of those patients who were enrolled in CREST after 2005, the stroke rate associated with CAS is equivalent or perhaps slightly better than with CEA, as a result of improved devices, technique and increased operator experience.

*December 19, 2011*

One issue in the asymptomatic patient group is that of the appropriate role of screening for carotid artery stenosis. The U.S. Preventive Services Task Force (USPSTF) in December 2007 recommended against screening for asymptomatic carotid artery stenosis in the general adult population, noting that this recommendation applied to adults without neurological signs or symptoms, including a history of transient ischemic attacks or stroke. The recommendations further noted that available screening and confirmatory tests (duplex ultrasonography, digital subtraction angiography, and magnetic resonance angiography) all have imperfect sensitivity and appreciable harms. Therefore, screening could lead to non-indicated surgeries that result in serious harms, including death, stroke, and myocardial infarction, in some patients. It was also stated that there may be some benefit in screening patients in whom there was a high risk of stroke, but noted that it was unclear how to identify people whose risk of stroke is high enough to justify screening, yet who do not also have a high risk for surgical complications. The major risk factors listed for carotid artery stenosis included older age, male sex, hypertension, smoking, hypercholesterolemia, and heart disease. However, there was no recommendation made as to the role of screening patients in whom a bruit was detected. This could potentially represent an "at-risk" group in which screening in the absence of symptoms might be considered. We do not recommend routine screening for carotid artery stenosis in the absence of criteria for appropriate selection of patients at high risk for carotid artery stenosis and/or stroke.

Concerning best medical therapy (BMT) versus carotid revascularization with either CAS or CEA, one must consider not who is at "high" risk for stroke but rather in whom the risk of stroke is higher than the risks associated with carotid revascularization over the subsequent 5 yrs (cutoff stroke risk of ~4-6% over 5 yrs). There is good data from the Asymptomatic Carotid Surgery Trial (ACST) that patients younger than 75 yrs of age did better with CEA than with BMT. One might consider that a better cutoff would be those patients with a life expectancy of > 5yrs, which in the Medicare patient population would be those < 77 yrs of age, assuming a life expectancy of 82 yrs. Stroke risk factors such as hypertension, smoking, peripheral artery disease, diabetes mellitus, prior stroke, etc. are well documented in the literature. We agree that the correlation between the degree of stenosis and the risk of stroke is not well proven. However, in the absence of well established criteria as to the relationship of biomarkers, plaque morphology and functional imaging to stroke risk, the currently existing criteria should be used. The society feels that there must be prospective surveillance on the outcomes of CAS performed under the expanded indications. Recent large trials such as CREST make it clear that with adequate training, physicians can perform CAS with low complication rates. Therefore, both the expansion of indications and accompanying reimbursement should be dependent on accreditation of facilities and operators performing these procedures, based on outcomes thresholds that meet national benchmarks. There are currently two programs that provide facility accreditation programs for carotid stenting procedures: the Intersocietal Commission for the Accreditation of Carotid Stenting Facilities (ICACSF), which is a multispecialty and multisociety sponsored accreditation program offered by the Intersocietal Accreditation Commission (IAC) and the Accreditation for Cardiovascular Excellence (ACE) organization, which was founded by the Society for Cardiovascular Angiography and Interventions (SCAI) and is now co-sponsored by the American College of Cardiology Foundation (ACCF). Accreditation involves mandated participation in a national registry with prospective data collection from institutions and operators performing CAS, with periodic outcomes analysis. This offers a means of assessing the impact of the expanded indications on the management of extracranial carotid artery occlusive disease. There are currently two such registries which collect data on CEA and CAS outcomes: the

*December 19, 2011*

Society for Vascular Surgery (SVS) Vascular Registry (VR) and the American College of Cardiology (ACC) National Cardiovascular Data Registry (NCDR®) CARE Registry®. SIR realizes that there are ongoing trials comparing CEA and CAS for carotid revascularization, and that data from those trials will likely further define the role of CAS in carotid revascularization. We feel that such trials must address the role of CAS in both the symptomatic and asymptomatic patient groups and should be adequately powered to do so. Additionally, it is important that future clinical trials address the issue of best medical therapy versus revascularization with CAS or CEA in asymptomatic patients. We encourage and strongly support clinical research in this area and eagerly await such data.

The SIR thanks CMS for the opportunity to present our views. If you have immediate questions, please do not hesitate to contact Tricia McClenny, SIR's Associate Executive Director at 703-691-1805, or [tricia@sirweb.org](mailto:tricia@sirweb.org). I have registered as a speaker, and look forward to presenting our Society viewpoint at the January 25<sup>th</sup> meeting. Additionally, if desired, Ms. McClenny can make available to CMS for further phone discussion the Interventional Radiologists who drafted and provided clinical input to this letter- Thomas G. Walker, MD of Massachusetts General Hospital, and James F. Benenati, MD of the Baptist Cardiac and Vascular Institute in Miami, Florida.

Sincerely,



Timothy P. Murphy, MD, FSIR  
President

CC:

Susan Sedory Holzer, Executive Director, Society of Interventional Radiology

Charles Simonton, M.D.  
Chief Medical Officer  
Divisional Vice President, Medical Affairs

Abbott Vascular  
3200 Lakeside Drive  
Santa Clara, CA 95054

December 19, 2011

Dear Members of the MEDCAC Panel:

Abbott welcomes the opportunity to provide the panel with information and data relevant to the January 25 MEDCAC meeting on Management of Carotid Atherosclerosis.

Abbott has a strong commitment to expanding the evidence base for carotid stenting and has enrolled over 20,000 patients in clinical trials over the past decade. Abbott was a co-sponsor of the NIH Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST) and received FDA marketing approval in May 2011 for the RX Acculink<sup>®</sup> Carotid Stent System for use in patients with obstructive carotid stenosis who are at standard risk for carotid endarterectomy. Abbott stents were approved for use in patients at high risk for endarterectomy in 2004 and 2005. Following the MEDCAC meeting, we plan to request that CMS reconsider the current national coverage decision for carotid stenting and expand coverage to standard surgical risk patients based on the clinical evidence.

In the attached document, we provide a brief summary of carotid artery disease and treatment options and a review of current CMS coverage for carotid stenting procedures. The majority of the document addresses each question to the MEDCAC Panel posed by CMS, based on a comprehensive review of the current evidence.

As detailed in the document, we believe the evidence demonstrates that carotid stenting and carotid endarterectomy are comparable therapies in terms of the net clinical benefit for Medicare beneficiaries. As the two therapies have different risk profiles, patients and their physicians need to determine which therapy is most appropriate for an individual. For both symptomatic patients (those who have experienced a recent stroke or other ischemic event) and asymptomatic patients (those not having experienced a recent stroke or other ischemic event) at standard risk for surgery, evidence from multiple randomized trials supports revascularization as an option for patients in addition to medical therapy.

We hope this information is helpful for the panel's deliberations and wish you a productive meeting.

Sincerely,

Charles Simonton MD, FACC, FSCAI  
Chief Medical Officer



Divisional Vice President, Medical Affairs

PRACTICE GUIDELINES

## 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/ SAIP/SCAI/SIR/SNIS/SVM/SVS Guideline on the Management of Patients With Extracranial Carotid and Vertebral Artery Disease

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery

*Developed in Collaboration With the American Academy of Neurology and Society of Cardiovascular Computed Tomography*

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The writing committee gratefully acknowledges the memory of Robert W. Hobson II, MD, who died during the development of this document but contributed immensely to our understanding of extracranial carotid and vertebral artery disease.

This document was approved by the American College of Cardiology Foundation Board of Trustees in August 2010, the American Heart Association Science Advisory and Coordinating Committee in August 2010, the Society for Vascular Surgery in December 2010, and the American Association of Neuroscience Nurses in January 2011. All other partner organizations approved the document in November 2010. The American Academy of Neurology affirms the value of this guideline.

The American College of Cardiology Foundation requests that this document be cited as follows: Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, Cates CU, Creager MA, Fowler SB, Friday G, Hertzberg VS, McIff EB, Moore WS, Panagos PD, Riles TS, Rosenwasser RH, Taylor AJ. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the

American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. *J Am Coll Cardiol* 2011;57:e16–94.

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**TABLE OF CONTENTS**

**Preamble**.....e19

**1. Introduction**.....e21

**1.1. Methodology and Evidence Review**.....e21

**1.2. Organization of the Writing Committee**.....e22

**1.3. Document Review and Approval**.....e22

**1.4. Anatomy and Definitions**.....e22

**1.5. Epidemiology of Extracranial Cerebrovascular Disease and Stroke**.....e23

**2. Atherosclerotic Disease of the Extracranial Carotid and Vertebral Arteries**.....e24

**2.1. Evaluation of Asymptomatic Patients at Risk of Extracranial Carotid Artery Disease**.....e25

        2.1.1. Recommendations for Duplex Ultrasonography to Evaluate Asymptomatic Patients With Known or Suspected Carotid Stenosis.....e25

        2.1.2. Recommendations From Other Panels.....e26

**2.2. Extracranial Cerebrovascular Disease as a Marker of Systemic Atherosclerosis**.....e26

        2.2.1. Screening for Coronary or Lower-Extremity Peripheral Arterial Disease in Patients With Atherosclerosis of the Carotid or Vertebral Arteries.....e26

**3. Clinical Presentation**.....e27

**3.1. Natural History of Atherosclerotic Carotid Artery Disease**.....e27

**3.2. Characterization of Atherosclerotic Lesions in the Extracranial Carotid Arteries**.....e27

**3.3. Symptoms and Signs of Transient Ischemic Attack and Ischemic Stroke**.....e29

        3.3.1. Public Awareness of Stroke Risk Factors and Warning Indicators.....e29

**4. Clinical Assessment of Patients With Focal Cerebral Ischemic Symptoms**.....e29

**4.1. Acute Ischemic Stroke**.....e29

**4.2. Transient Ischemic Attack**.....e29

**4.3. Amaurosis Fugax**.....e29

**4.4. Cerebral Ischemia Due to Intracranial Arterial Stenosis and Occlusion**.....e30

**4.5. Atherosclerotic Disease of the Aortic Arch as a Cause of Cerebral Ischemia**.....e30

**4.6. Atypical Clinical Presentations and Neurological Symptoms Bearing an Uncertain Relationship to Extracranial Carotid and Vertebral Artery Disease**.....e30

**5. Diagnosis and Testing**.....e30

**5.1. Recommendations for Diagnostic Testing in Patients With Symptoms or Signs of Extracranial Carotid Artery Disease**.....e30

**5.2. Carotid Duplex Ultrasonography**.....e32

**5.3. Magnetic Resonance Angiography**.....e33

**5.4. Computed Tomographic Angiography**.....e34

**5.5. Catheter-Based Contrast Angiography**.....e35

**5.6. Selection of Vascular Imaging Modalities for Individual Patients**.....e36

**6. Medical Therapy for Patients With Atherosclerotic Disease of the Extracranial Carotid or Vertebral Arteries**.....e36

**6.1. Recommendations for the Treatment of Hypertension**.....e36



<b>6.2. Cessation of Tobacco Smoking</b> .....	e37
6.2.1. Recommendation for Cessation of Tobacco Smoking .....	e37
<b>6.3. Control of Hyperlipidemia</b> .....	e37
6.3.1. Recommendations for Control of Hyperlipidemia .....	e37
<b>6.4. Management of Diabetes Mellitus</b> .....	e39
6.4.1. Recommendations for Management of Diabetes Mellitus in Patients With Atherosclerosis of the Extracranial Carotid or Vertebral Arteries .....	e39
<b>6.5. Hyperhomocysteinemia</b> .....	e39
<b>6.6. Obesity and the Metabolic Syndrome</b> .....	e40
<b>6.7. Physical Inactivity</b> .....	e40
<b>6.8. Antithrombotic Therapy</b> .....	e40
6.8.1. Recommendations for Antithrombotic Therapy in Patients With Extracranial Carotid Atherosclerotic Disease Not Undergoing Revascularization .....	e40
6.8.2. Nonsteroidal Anti-Inflammatory Drugs .....	e42

**7. Revascularization** .....

<b>7.1. Recommendations for Selection of Patients for Carotid Revascularization</b> .....	e42
<b>7.2. Carotid Endarterectomy</b> .....	e43
7.2.1. Randomized Trials of Carotid Endarterectomy .....	e43
7.2.1.1. CAROTID ENDARTERECTOMY IN SYMPTOMATIC PATIENTS .....	e43
7.2.1.2. CAROTID ENDARTERECTOMY IN ASYMPTOMATIC PATIENTS .....	e46
7.2.2. Factors Affecting the Outcome of Carotid Endarterectomy .....	e46
7.2.2.1. TECHNICAL CONSIDERATIONS .....	e46
7.2.2.2. CASE SELECTION AND OPERATOR EXPERIENCE .....	e47
7.2.2.3. DEMOGRAPHIC AND CLINICAL FACTORS .....	e47
7.2.3. Risks Associated With Carotid Endarterectomy .....	e48
7.2.4. Carotid Endarterectomy in Patients With Unfavorable Anatomy .....	e51
7.2.5. Evolution in the Safety of Carotid Surgery .....	e52
7.2.6. Evolution of Medical Therapy .....	e52
7.2.7. Recommendations for Periprocedural Management of Patients Undergoing Carotid Endarterectomy .....	e52
<b>7.3. Carotid Artery Stenting</b> .....	e53
7.3.1. Multicenter Registry Studies .....	e53
7.3.2. Risks Associated With Carotid Artery Stenting .....	e53
7.3.2.1. CARDIOVASCULAR COMPLICATIONS .....	e53
7.3.2.2. NEUROLOGICAL COMPLICATIONS .....	e54
7.3.3. Prevention of Cerebral Embolism in Patients Undergoing Catheter-Based Carotid Intervention .....	e55
7.3.4. Intravascular Ultrasound Imaging in Conjunction With Catheter-Based Carotid Intervention .....	e55
7.3.5. Management of Patients Undergoing Endovascular Carotid Artery Stenting .....	e55

7.3.5.1. RECOMMENDATIONS FOR MANAGEMENT OF PATIENTS UNDERGOING CAROTID ARTERY STENTING .....	e55
--	-----

<b>7.4. Comparative Assessment of Carotid Endarterectomy and Stenting</b> .....	e56
7.4.1. Nonrandomized Comparison of Carotid Endarterectomy With Carotid Artery Stenting .....	e56
7.4.2. Meta-Analyses Comparing Carotid Endarterectomy and Stenting .....	e57
7.4.3. Randomized Trials Comparing Carotid Endarterectomy and Carotid Artery Stenting .....	e57
7.4.3.1. HIGH-RISK PATIENTS .....	e57
7.4.3.2. CONVENTIONAL-RISK PATIENTS .....	e57
7.4.4. Selection of Carotid Endarterectomy or Carotid Artery Stenting for Individual Patients With Carotid Stenosis .....	e59
<b>7.5. Durability of Carotid Revascularization</b> .....	e60
7.5.1. Recommendations for Management of Patients Experiencing Restenosis After Carotid Endarterectomy or Stenting .....	e60
7.5.2. Clinical Durability of Carotid Surgery and Carotid Stenting .....	e60
7.5.3. Anatomic Durability of Carotid Surgery and Carotid Stenting .....	e60

**8. Vertebral Artery Disease** .....

<b>8.1. Anatomy of the Vertebrobasilar Arterial Circulation</b> .....	e61
<b>8.2. Epidemiology of Vertebral Artery Disease</b> .....	e61
<b>8.3. Clinical Presentation of Patients With Vertebrobasilar Arterial Insufficiency</b> .....	e62
<b>8.4. Evaluation of Patients With Vertebral Artery Disease</b> .....	e62
<b>8.5. Vertebral Artery Imaging</b> .....	e62
8.5.1. Recommendations for Vascular Imaging in Patients With Vertebral Artery Disease .....	e62
<b>8.6. Medical Therapy of Patients With Vertebral Artery Disease</b> .....	e62
8.6.1. Recommendations for Management of Atherosclerotic Risk Factors in Patients With Vertebral Artery Disease .....	e62
<b>8.7. Vertebral Artery Revascularization</b> .....	e63
8.7.1. Surgical Management of Vertebral Artery Disease .....	e63
8.7.2. Catheter-Based Endovascular Interventions for Vertebral Artery Disease .....	e63

**9. Diseases of the Subclavian and Brachiocephalic Arteries** .....

<b>9.1. Recommendations for the Management of Patients With Occlusive Disease of the Subclavian and Brachiocephalic Arteries</b> .....	e64
<b>9.2. Occlusive Disease of the Subclavian and Brachiocephalic Arteries</b> .....	e64
<b>9.3. Subclavian Steal Syndrome</b> .....	e64
<b>9.4. Revascularization of the Brachiocephalic and Subclavian Arteries</b> .....	e65

<b>10. Special Populations</b> .....	e66
<b>10.1. Neurological Risk Reduction in Patients With Carotid Artery Disease Undergoing Cardiac or Noncardiac Surgery</b> .....	e66
10.1.1. Recommendations for Carotid Artery Evaluation and Revascularization Before Cardiac Surgery .....	e66
10.1.2. Neurological Risk Reduction in Patients With Carotid Artery Disease Undergoing Coronary Bypass Surgery .....	e66
10.1.3. Neurological Risk Reduction in Patients Undergoing Noncoronary Cardiac or Noncardiac Surgery .....	e66
<b>11. Nonatherosclerotic Carotid and Vertebral Artery Diseases</b> .....	e66
<b>11.1. Fibromuscular Dysplasia</b> .....	e67
11.1.1. Recommendations for Management of Patients With Fibromuscular Dysplasia of the Extracranial Carotid Arteries .....	e67
<b>11.2. Cervical Artery Dissection</b> .....	e67
11.2.1. Recommendations for Management of Patients With Cervical Artery Dissection .....	e67
<b>12. Future Research</b> .....	e68
<b>References</b> .....	e70
<b>Appendix 1. Author Relationships With Industry and Other Entities</b> .....	e87
<b>Appendix 2. Reviewer Relationships With Industry and Other Entities</b> .....	e89
<b>Appendix 3. Abbreviation List</b> .....	e94

## Preamble

It is essential that the medical profession play a central role in critically evaluating the evidence related to drugs, devices, and procedures for the detection, management, or prevention of disease. Properly applied, rigorous, expert analysis of the available data documenting absolute and relative benefits and risks of these therapies and procedures can improve the effectiveness of care, optimize patient outcomes, and favorably affect the cost of care by focusing resources on the most effective strategies. One important use of such data is the production of clinical practice guidelines that, in turn, can provide a foundation for a variety of other applications such as performance measures, appropriate use criteria, clinical decision support tools, and quality improvement tools.

The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) have jointly engaged in the production of guidelines in the area of cardiovascular disease since 1980. The ACCF/AHA Task Force on Practice Guidelines (Task Force) is charged with

developing, updating, and revising practice guidelines for cardiovascular diseases and procedures, and the Task Force directs and oversees this effort. Writing committees are charged with assessing the evidence as an independent group of authors to develop, update, or revise recommendations for clinical practice.

Experts in the subject under consideration have been selected from both organizations to examine subject-specific data and write guidelines in partnership with representatives from other medical practitioner and specialty groups. Writing committees are specifically charged to perform a formal literature review; weigh the strength of evidence for or against particular tests, treatments, or procedures; and include estimates of expected health outcomes where data exist. Patient-specific modifiers, comorbidities, and issues of patient preference that may influence the choice of tests or therapies are considered. When available, information from studies on cost is considered, but data on efficacy and clinical outcomes constitute the primary basis for recommendations in these guidelines.

In analyzing the data and developing the recommendations and supporting text, the writing committee used evidence-based methodologies developed by the Task Force that are described elsewhere (1). The committee reviewed and ranked evidence supporting current recommendations with the weight of evidence ranked as Level A if the data were derived from multiple randomized clinical trials or meta-analyses. The committee ranked available evidence as Level B when data were derived from a single randomized trial or nonrandomized studies. Evidence was ranked as Level C when the primary source of the recommendation was consensus opinion, case studies, or standard of care. In the narrative portions of these guidelines, evidence is generally presented in chronological order of development. Studies are identified as observational, retrospective, prospective, or randomized when appropriate. For certain conditions for which inadequate data are available, recommendations are based on expert consensus and clinical experience and ranked as Level C. An example is the use of penicillin for pneumococcal pneumonia, for which there are no randomized trials and treatment is based on clinical experience. When recommendations at Level C are supported by historical clinical data, appropriate references (including clinical reviews) are cited if available. For issues where sparse data are available, a survey of current practice among the clinicians on the writing committee was the basis for Level C recommendations, and no references are cited. The schema for Classification of Recommendations and Level of Evidence is summarized in [Table 1](#), which also illustrates how the grading system provides an estimate of the size and the certainty of the treatment effect. A new addition to the ACCF/AHA methodology is a separation of the Class III recommendations to delineate whether the recommendation is determined to be of “no benefit” or associated with “harm” to the patient. In addition, in view of the increasing number of comparative effectiveness studies,

**Table 1. Applying Classification of Recommendations and Level of Evidence**

		SIZE OF TREATMENT EFFECT <span style="float: right;">→</span>				
		CLASS I <i>Benefit &gt;&gt;&gt; Risk</i> Procedure/Treatment <b>SHOULD</b> be performed/administered	CLASS IIa <i>Benefit &gt;&gt; Risk</i> <i>Additional studies with focused objectives needed</i> <b>IT IS REASONABLE</b> to perform procedure/administer treatment	CLASS IIb <i>Benefit ≥ Risk</i> <i>Additional studies with broad objectives needed; additional registry data would be helpful</i> Procedure/Treatment <b>MAY BE CONSIDERED</b>	CLASS III <i>No Benefit or CLASS III Harm</i>	
ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is useful/effective</li> <li>Sufficient evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation in favor of treatment or procedure being useful/effective</li> <li>Some conflicting evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation's usefulness/efficacy less well established</li> <li>Greater conflicting evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is not useful/effective and may be harmful</li> <li>Sufficient evidence from multiple randomized trials or meta-analyses</li> </ul>	
	LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is useful/effective</li> <li>Evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation in favor of treatment or procedure being useful/effective</li> <li>Some conflicting evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation's usefulness/efficacy less well established</li> <li>Greater conflicting evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is not useful/effective and may be harmful</li> <li>Evidence from single randomized trial or nonrandomized studies</li> </ul>	
	LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is useful/effective</li> <li>Only expert opinion, case studies, or standard of care</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation in favor of treatment or procedure being useful/effective</li> <li>Only diverging expert opinion, case studies, or standard of care</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation's usefulness/efficacy less well established</li> <li>Only diverging expert opinion, case studies, or standard of care</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is not useful/effective and may be harmful</li> <li>Only expert opinion, case studies, or standard of care</li> </ul>	
Suggested phrases for writing recommendations <sup>†</sup>		should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit  is not recommended is not indicated should not be done is not useful/beneficial/effective	COR III: Harm  potentially harmful causes harm associated with excess morbidity/mortality should not be done
Comparative effectiveness phrases <sup>†</sup>		treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B			

Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as gender, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use. A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Even though randomized trials are not available, there may be a very clear clinical consensus that a particular test or therapy is useful or effective. †For comparative effectiveness recommendations (Class I and IIa; Level of Evidence: A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

comparator verbs and suggested phrases for writing recommendations for the comparative effectiveness of one treatment/strategy with respect to another for Class of Recommendation I and IIa, Level of Evidence A or B only have been added.

The Task Force makes every effort to avoid actual, potential, or perceived conflicts of interest that may arise as a result of relationships with industry or other entities (RWI) among the writing committee. Specifically, all members of the writing committee, as well as peer reviewers of the document, are asked to disclose all current relationships and those 24 months before initiation of the writing effort that may be perceived as *relevant*. All guideline recommendations require a confidential vote by the writing committee and must be approved by a consensus of the members voting. Any writing committee member who develops a new RWI during his or her tenure is required to notify guideline staff in writing. These statements are reviewed by the Task

Force and all members during each conference call and/or meeting of the writing committee and are updated as changes occur. For detailed information about guideline policies and procedures, please refer to the ACCF/AHA methodology and policies manual (1). Authors' and peer reviewers' RWI pertinent to this guideline are disclosed in [Appendixes 1 and 2](#), respectively. Disclosure information for the Task Force is available online at [www.cardiosource.org/ACC/About-ACC/Leadership/Guidelines-and-Documents-Task-Forces.aspx](http://www.cardiosource.org/ACC/About-ACC/Leadership/Guidelines-and-Documents-Task-Forces.aspx). The work of the writing committee was supported exclusively by the ACCF and AHA (and the other partnering organizations) without commercial support. Writing committee members volunteered their time for this effort.

The ACCF/AHA practice guidelines address patient populations (and healthcare providers) residing in North America. As such, drugs that are currently unavailable in North America are discussed in the text without a specific class of recommen-

dition. For studies performed in large numbers of subjects outside of North America, each writing committee reviews the potential impact of different practice patterns and patient populations on the treatment effect and the relevance to the ACCF/AHA target population to determine whether the findings should inform a specific recommendation.

The ACCF/AHA practice guidelines are intended to assist healthcare providers in clinical decision making by describing a range of generally acceptable approaches for the diagnosis, management, and prevention of specific diseases or conditions. These practice guidelines represent a consensus of expert opinion after a thorough review of the available current scientific evidence and are intended to improve patient care. The guidelines attempt to define practices that meet the needs of most patients in most circumstances. The ultimate judgment regarding care of a particular patient must be made by the healthcare provider and patient in light of all the circumstances presented by that patient. Thus, there are situations in which deviations from these guidelines may be appropriate. Clinical decision making should consider the quality and availability of expertise in the area where care is provided. When these guidelines are used as the basis for regulatory or payer decisions, the goal should be improvement in quality of care. The Task Force recognizes that situations arise for which additional data are needed to better inform patient care; these areas will be identified within each respective guideline when appropriate.

Prescribed courses of treatment in accordance with these recommendations are effective only if they are followed. Because lack of patient understanding and adherence may adversely affect outcomes, physicians and other healthcare providers should make every effort to engage the patient's active participation in prescribed medical regimens and lifestyles.

The guidelines will be reviewed annually by the Task Force and considered current unless they are updated, revised, or withdrawn from distribution. The executive summary and recommendations are published in the *Journal of the American College of Cardiology*, *Circulation*, *Catheterization and Cardiovascular Interventions*, the *Journal of Cardiovascular Computed Tomography*, the *Journal of Neuro-Interventional Surgery*, *Stroke*, and *Vascular Medicine*.

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## 1. Introduction

### 1.1. Methodology and Evidence Review

The ACCF/AHA writing committee to create the 2011 Guideline on the Management of Patients With Extracranial Carotid and Vertebral Artery Disease (ECVD) con-

ducted a comprehensive review of the literature relevant to carotid and vertebral artery interventions through May 2010.

The recommendations listed in this document are, whenever possible, evidence-based. Searches were limited to studies, reviews, and other evidence conducted in human subjects and published in English. Key search words included but were not limited to *angioplasty*, *atherosclerosis*, *carotid artery disease*, *carotid endarterectomy (CEA)*, *carotid revascularization*, *carotid stenosis*, *carotid stenting*, *carotid artery stenting (CAS)*, *extracranial carotid artery stenosis*, *stroke*, *transient ischemic attack (TIA)*, and *vertebral artery disease*. Additional searches cross-referenced these topics with the following subtopics: *acetylsalicylic acid*, *antiplatelet therapy*, *carotid artery dissection*, *cerebral embolism*, *cerebral protection*, *cerebrovascular disorders*, *complications*, *comorbidities*, *extracranial atherosclerosis*, *intima-media thickness (IMT)*, *medical therapy*, *neurological examination*, *noninvasive testing*, *pharmacological therapy*, *preoperative risk*, *primary closure*, *risk factors*, and *vertebral artery dissection*. Additionally, the committee reviewed documents related to the subject matter previously published by the ACCF and AHA (and other partnering organizations). References selected and published in this document are representative and not all-inclusive.

To provide clinicians with a comprehensive set of data, whenever deemed appropriate or when published in the article, data from the clinical trials were used to calculate the absolute risk difference and number needed to treat (NNT) or harm; data related to the relative treatment effects are also provided, such as odds ratio (OR), relative risk (RR), hazard ratio (HR), or incidence rate ratio, along with confidence interval (CI) when available.

The committee used the evidence-based methodologies developed by the Task Force and acknowledges that adjudication of the evidence was complicated by the timing of the evidence when 2 different interventions were contrasted. Despite similar study designs (e.g., randomized controlled trials), research on CEA was conducted in a different era (and thus, evidence existed in the peer-reviewed literature for more time) than the more contemporary CAS trials. Because evidence is lacking in the literature to guide many aspects of the care of patients with nonatherosclerotic carotid disease and most forms of vertebral artery disease, a relatively large number of the recommendations in this document are based on consensus.

The writing committee chose to limit the scope of this document to the vascular diseases themselves and not to the management of patients with acute stroke or to the detection or prevention of disease in individuals or populations at risk, which are covered in another guideline (2). The full-text guideline is based on the presumption that readers will search the document for specific advice on the management of patients with ECVD at different phases of illness. Following the typical chronology of the clinical care of patients with ECVD, the guideline is organized in sections that address

the pathogenesis, epidemiology, diagnostic evaluation, and management of patients with ECVD, including prevention of recurrent ischemic events. The text, recommendations, and supporting evidence are intended to assist the diverse array of clinicians who provide care for patients with ECVD. In particular, they are designed to aid primary care clinicians, medical and surgical cardiovascular specialists, and trainees in the primary care and vascular specialties, as well as nurses and other healthcare personnel who seek clinical tools to promote the proper evaluation and management of patients with ECVD in both inpatient and outpatient settings. Application of the recommended diagnostic and therapeutic strategies, combined with careful clinical judgment, should improve diagnosis of each syndrome, enhance prevention, and decrease rates of stroke and related long-term disability and death. The ultimate goal of the guideline statement is to improve the duration and quality of life for people with ECVD.

### 1.2. Organization of the Writing Committee

The writing committee to develop the 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS Guideline on the Management of Patients With Extracranial Carotid and Vertebral Artery Disease was composed of experts in the areas of medicine, surgery, neurology, cardiology, radiology, vascular surgery, neurosurgery, neuroradiology, interventional radiology, noninvasive imaging, emergency medicine, vascular medicine, nursing, epidemiology, and biostatistics. The committee included representatives of the American Stroke Association (ASA), ACCF, AHA, American Academy of Neurology (AAN), American Association of Neuroscience Nurses (AANN), American Association of Neurological Surgeons (AANS), American College of Emergency Physicians (ACEP), American College of Radiology (ACR), American Society of Neuroradiology (ASNR), Congress of Neurological Surgeons (CNS), Society of Atherosclerosis Imaging and Prevention (SAIP), Society for Cardiovascular Angiography and Interventions (SCAI), Society of Cardiovascular Computed Tomography (SCCT), Society of Interventional Radiology (SIR), Society of NeuroInterventional Surgery (SNIS), Society for Vascular Medicine (SVM), and Society for Vascular Surgery (SVS).

### 1.3. Document Review and Approval

The document was reviewed by 55 external reviewers, including individuals nominated by each of the ASA, ACCF, AHA, AANN, AANS, ACEP, American College of Physicians, ACR, ASNR, CNS, SAIP, SCAI, SCCT, SIR, SNIS, SVM, and SVS, and by individual content reviewers, including members from the ACCF Catheterization Committee, ACCF Interventional Scientific Council, ACCF Peripheral Vascular Disease Committee, ACCF Surgeons' Scientific Council, ACCF/SCAI/SVMB/SIR/ASITN Expert Consensus Document on Carotid Stenting, ACCF/AHA Peripheral Arterial Disease Guideline Writing Committee, AHA Peripheral Vascular Disease Steering

Committee, AHA Stroke Leadership Committee, and individual nominees. All information on reviewers' RWI was distributed to the writing committee and is published in this document ([Appendix 2](#)).

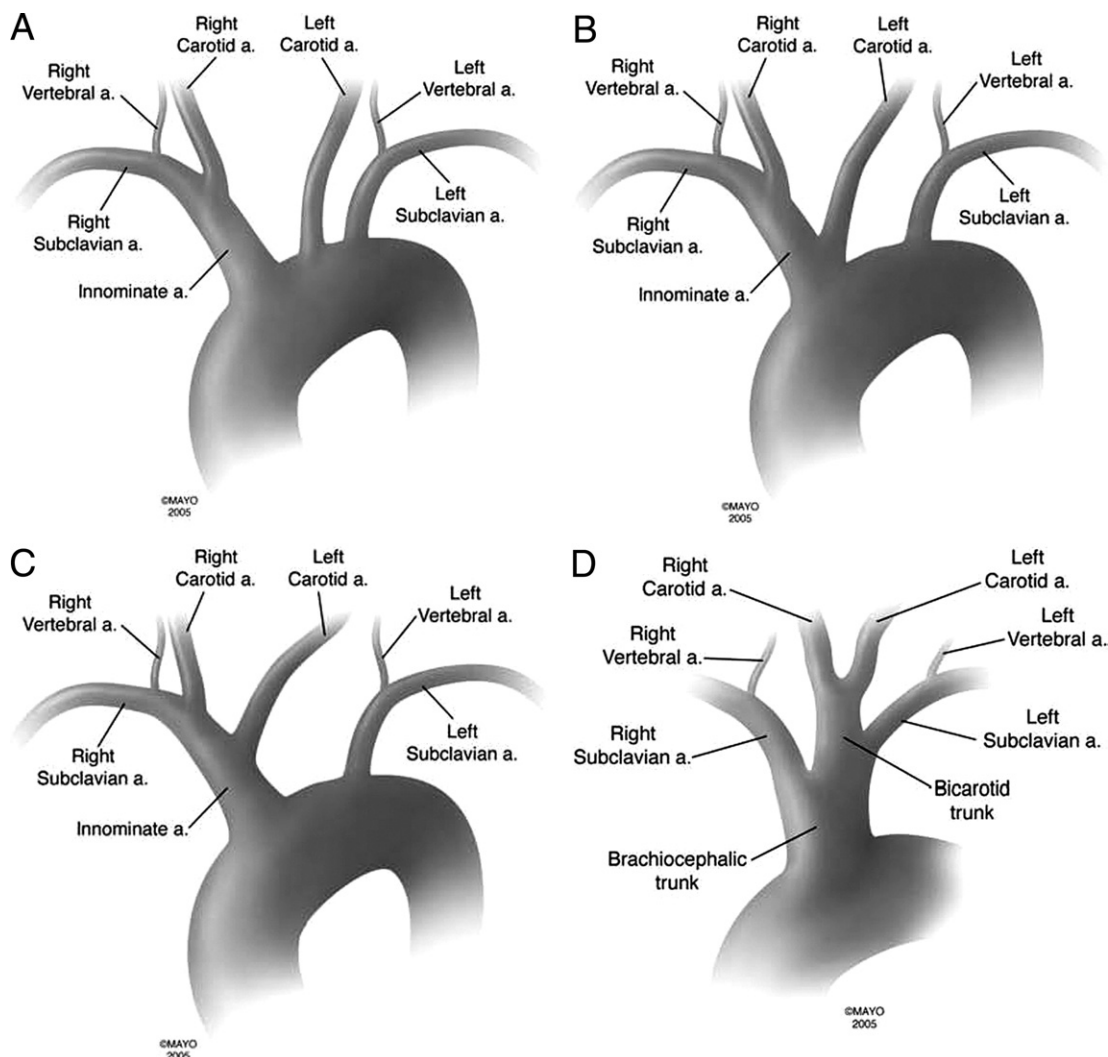
This document was reviewed and approved for publication by the governing bodies of the ASA, ACCF, and AHA and endorsed by the AANN, AANS, ACR, ASNR, CNS, SAIP, SCAI, SCCT, SIR, SNIS, SVM, and SVS. The AAN affirms the value of this guideline.

### 1.4. Anatomy and Definitions

The normal anatomy of the aortic arch and cervical arteries that supply the brain is subject to considerable variation (3). Three aortic arch morphologies are distinguished on the basis of the relationship of the brachiocephalic (innominate) arterial trunk to the aortic arch ([Figure 1](#)). The Type I aortic arch is characterized by the origin of all 3 major vessels in the horizontal plane defined by the outer curvature of the arch. In Type II, the brachiocephalic artery originates between the horizontal planes of the outer and inner curvatures of the arch. In Type III, it originates below the horizontal plane of the inner curvature of the arch. In addition to aortic arch anatomy, the configuration of the great vessels varies. Most commonly, the brachiocephalic artery, left common carotid artery, and left subclavian artery originate separately from the aortic arch (4). The term *bovine aortic arch* refers to a frequent variant of human aortic arch branching in which the brachiocephalic and left common carotid arteries share a common origin. This anatomy is not generally found in cattle, so the term *bovine arch* is a misnomer (5,6).

The distal common carotid artery typically bifurcates into the internal and external carotid arteries at the level of the thyroid cartilage, but anomalous bifurcations may occur up to 5 cm higher or lower. The carotid bulb, a dilated portion at the origin of the internal carotid artery, usually extends superiorly for a distance of approximately 2 cm, where the diameter of the internal carotid artery becomes more uniform. The length and tortuosity of the internal carotid artery are additional sources of variation, with undulation, coiling, or kinking in up to 35% of cases, most extensively in elderly patients.

The intracranial portion of each carotid artery begins at the base of the skull, traverses the petrous bone, and enters the subarachnoid space near the level of the ophthalmic artery. There, the artery turns posteriorly and superiorly, giving rise to the posterior communicating artery, which connects through the circle of Willis with the posterior cerebral artery that arises from the vertebrobasilar circulation. The internal carotid artery then bifurcates into the anterior cerebral and middle cerebral arteries. The anterior cerebral arteries connect with the circle of Willis through the anterior communicating artery. Among the most important collateral pathways are those from the external carotid artery to the internal carotid artery (via the internal maxillary branch of the external carotid artery and the superficial temporal artery to the ophthalmic branches of the



**Figure 1. Aortic Arch Types**

**Panel A.** The most common aortic arch branching pattern found in humans has separate origins for the innominate, left common carotid, and left subclavian arteries. **Panel B.** The second most common pattern of human aortic arch branching has a common origin for the innominate and left common carotid arteries. This pattern has erroneously been referred to as a “bovine arch.” **Panel C.** In this variant of aortic arch branching, the left common carotid artery originates separately from the innominate artery. This pattern has also been erroneously referred to as a “bovine arch.” **Panel D.** The aortic arch branching pattern found in cattle has a single brachiocephalic trunk originating from the aortic arch that eventually splits into the bilateral subclavian arteries and a bicarotid trunk. a indicates artery. Reprinted with permission from Layton *et al.* (6).

internal carotid artery), from the external carotid artery to the vertebral artery (via the occipital branch of the external carotid artery), from the vertebrobasilar arterial system to the internal carotid artery (via the posterior communicating artery), and between the left and right internal carotid arteries (via the interhemispheric circulation through the anterior communicating artery). The configuration of the circle of Willis is also highly variable, with a complete circle in fewer than 50% of individuals. Variations due to tortuosity, calcification, intracranial arterial stenosis, collateral circulation, aneurysms, and arteriovenous malformation have important implications that must be considered in applying treatment recommendations to individual patients.

Extracranial cerebrovascular disease encompasses several disorders that affect the arteries that supply the brain and is an important cause of stroke and transient cerebral ischemic

attack. The most frequent cause is atherosclerosis, but other causes include fibromuscular dysplasia (FMD), cystic medial necrosis, arteritis, and dissection. Atherosclerosis is a systemic disease, and patients with ECVD typically face an escalated risk of other adverse cardiovascular events, including myocardial infarction (MI), peripheral arterial disease (PAD), and death. To improve survival, neurological and functional outcomes, and quality of life, preventive and therapeutic strategies must address both cerebral and systemic risk.

### 1.5. Epidemiology of Extracranial Cerebrovascular Disease and Stroke

When considered separately from other cardiovascular diseases, stroke is the third-leading cause of death in industrialized nations, behind heart disease and cancer, and a

leading cause of long-term disability (7). Population studies of stroke involve mainly regional populations, and the results may not be generalizable across the nation because of geographic variations. Data from the Greater Cincinnati/Northern Kentucky Stroke Study suggest an annual incidence of approximately 700,000 stroke events, of which approximately 500,000 are new and 200,000 are recurrent strokes (8). In 2003, the Centers for Disease Control and Prevention reported a higher prevalence in the “stroke belt” of 10 southeastern states (9). Among persons younger than 65 years of age, excess deaths caused by stroke occur in most racial/ethnic minority groups compared with whites (10). In NOMASS (Northern Manhattan Stroke Study), the age-adjusted incidence of first ischemic stroke per 100,000 population was 191 among blacks (95% CI 160 to 221), 149 among Hispanics (95% CI 132 to 165), and 88 (95% CI 75 to 101) among whites (11). The average annual age-adjusted overall (initial and recurrent) stroke incidence per 100,000 for those  $\geq 20$  years old was 223 for blacks, 196 for Hispanics, and 93 for whites, which represents a 2.4-fold RR for blacks and a 2-fold increase for Hispanics compared with whites (12). On a national level, however, a large number of strokes apparently go unreported. The prevalence of silent cerebral infarction between ages 55 and 64 years is approximately 11%, increasing to 22% between ages 65 and 69, 28% between ages 70 and 74, 32% between ages 75 and 79, 40% between ages 80 and 85, and 43% beyond age 85. The application of these rates to 1998 US population estimates yielded an estimated 13 million people with silent stroke (13).

Most (54%) of the 167,366 deaths attributed to stroke in 1999 were not specified by *International Classification of Disease, 9th Revision* codes for hemorrhage or infarction (14). On the basis of data from the Framingham Heart Study (15), the ARIC (Atherosclerosis Risk in Communities) study (16,17), and the Greater Cincinnati/Northern Kentucky Stroke Study (8), approximately 88% of all strokes are ischemic, 9% are intracerebral hemorrhages, and 3% are subarachnoid hemorrhages (18–22).

In the Framingham Heart Study population, the prevalence of  $>50\%$  carotid stenosis was 7% in women and 9% in men ranging in age from 66 to 93 years (23). In the Cardiovascular Health Study of subjects older than 65 years of age, 7% of men and 5% of women had moderate (50% to 74%) carotid stenosis; severe (75% to 100%) stenosis was detected in 2.3% of men and 1.1% of women (24). In NOMASS, a population-based study of people older than 40 years of age who lived in northern Manhattan, New York, 62% had carotid plaque thickness of 0.9 mm by sonography, and 39% had minimal or no (0.0 to 0.9 mm) carotid plaque (25). In those with subclinical disease, mean plaque thickness was 1.0 mm for whites, 1.7 mm for blacks, and 1.2 mm for Hispanics (25). In a population-based study of patients in Texas with TIA, 10% of those undergoing carotid ultrasonography had  $>70\%$  stenosis of at least 1 internal carotid artery (26).

Even subclinical carotid disease is associated with future stroke, as in the ARIC study, in which the IMT of the carotid artery walls of people 45 to 64 years old without ulcerated or hemodynamically significant plaque at baseline predicted stroke (16).

Carotid stenosis or occlusion as a cause of stroke has been more difficult to determine from population studies. For the NOMASS population, cerebral infarction attributed to ECVD was defined as clinical stroke with evidence of infarction on brain imaging associated with  $>60\%$  stenosis or occlusion of an extracranial carotid or vertebral artery documented by noninvasive imaging or angiography. Between 1993 and 1997, the incidence of cerebral infarction attributable to ECVD was 17 per 100,000 (95% CI 8 to 26) for blacks, 9 per 100,000 (95% CI 5 to 13) for Hispanics, and 5 per 100,000 (95% CI 2 to 8) for whites (11). Approximately 7% of all first ischemic strokes were associated with extracranial carotid stenosis of 60% or more (11). From a Mayo Clinic study of the population of Rochester, Minn, for the period 1985 to 1989, 18% of all first ischemic strokes were attributed to extracranial or intracranial large-vessel disease (27), but the report did not separately classify those with extracranial or intracranial vascular disease.

Beyond the impact on individual patients, ECVD and its consequences create a substantial social and economic burden in the United States and are increasingly recognized as a major drain on health resources worldwide. Stroke is the most frequent neurological diagnosis that requires hospitalization (21), amounting to more than half a million hospitalizations annually (18). From the 1970s to the latest figures available, the number of noninstitutionalized stroke survivors in the United States increased from an estimated 1.5 million to 6 million (19). Survivors face risks of recurrent stroke as high as 4% to 15% within a year after incident stroke and 25% by 5 years (20,28). The direct and indirect cost for acute and convalescent care for stroke victims in the United States was estimated at \$68.9 billion in 2009. The economic burden and lifetime cost vary considerably by type of stroke, averaging \$103,576 across all stroke types, with costs associated with first strokes estimated as \$228,030 for subarachnoid hemorrhage, \$123,565 for intracerebral hemorrhage, and \$90,981 for ischemic stroke (22).

## **2. Atherosclerotic Disease of the Extracranial Carotid and Vertebral Arteries**

The pathobiology of carotid and vertebral artery atherosclerosis is similar in most respects to atherosclerosis that affects other arteries. Early lesion development is initiated by intimal accumulation of lipoprotein particles. These particles undergo oxidative modification and elaborate cytokines that cause expression of adhesion molecules and chemoattractants that facilitate uptake and migration of monocytes

into the artery wall. These monocytes become lipid-laden macrophages, or foam cells, as a consequence of accumulation of modified lipoproteins and subsequently release additional cytokines, oxidants, and matrix metalloproteinases. Smooth muscle cells migrate from the media to the intima, proliferate, and elaborate extracellular matrix as extracellular lipid accumulates in a central core surrounded by a layer of connective tissue, the fibrous cap, which in many advanced plaques becomes calcified. Initially, the atherosclerotic lesion grows in an outward direction, a process designated “arterial remodeling.” As the plaque continues to grow, however, it encroaches on the lumen and causes stenosis. Plaque disruption and thrombus formation contribute to progressive narrowing of the lumen and to clinical events. The mechanisms that account for plaque disruption in the extracranial carotid and vertebral arteries are similar to those proposed for the coronary arteries (29). These include rupture of the fibrous cap, superficial erosion, and erosion of a calcium nodule. Contact of blood elements, including platelets and coagulation proteins, with constituents of the atherosclerotic plaque, such as collagen and tissue factor, promotes thrombosis. In addition, intraplaque hemorrhage caused by friable microvessels at the base of the plaque may contribute to plaque expansion.

Atherosclerotic plaques often develop at flow dividers and branch points, where there is both turbulence and shifts in shear stress. As such, there is a predilection for plaque formation at the bifurcation of the common carotid artery into the internal and external carotid arteries. Stroke and transient cerebrovascular ischemia may arise as a consequence of several mechanisms that originate in the extracranial cerebral arteries, including 1) artery-to-artery embolism of thrombus formed on an atherosclerotic plaque, 2) atheroembolism of cholesterol crystals or other atheromatous debris (e.g., Hollenhorst plaque), 3) acute thrombotic occlusion of an extracranial artery resulting from plaque rupture, 4) structural disintegration of the arterial wall resulting from dissection or subintimal hematoma, and 5) reduced cerebral perfusion resulting from critical stenosis or occlusion caused by progressive plaque growth. For neurological symptoms to result from arterial stenosis or occlusion, the intracranial collateral circulation must also be deficient, and this represents the cause of a relatively small proportion of clinical ischemic events.

## **2.1. Evaluation of Asymptomatic Patients at Risk of Extracranial Carotid Artery Disease**

### **2.1.1. Recommendations for Duplex Ultrasonography to Evaluate Asymptomatic Patients With Known or Suspected Carotid Stenosis**

#### **CLASS I**

1. In asymptomatic patients with known or suspected carotid stenosis, duplex ultrasonography, performed by a qualified technologist in a certified laboratory, is recommended as the initial diagnostic test to detect hemodynamically significant carotid stenosis. (Level of Evidence: C)

#### **CLASS IIa**

1. It is reasonable to perform duplex ultrasonography to detect hemodynamically significant carotid stenosis in asymptomatic patients with carotid bruit. (Level of Evidence: C)
2. It is reasonable to repeat duplex ultrasonography annually by a qualified technologist in a certified laboratory to assess the progression or regression of disease and response to therapeutic interventions in patients with atherosclerosis who have had stenosis greater than 50% detected previously. Once stability has been established over an extended period or the patient’s candidacy for further intervention has changed, longer intervals or termination of surveillance may be appropriate. (Level of Evidence: C)

#### **CLASS IIb**

1. Duplex ultrasonography to detect hemodynamically significant carotid stenosis may be considered in asymptomatic patients with symptomatic PAD, coronary artery disease (CAD), or atherosclerotic aortic aneurysm, but because such patients already have an indication for medical therapy to prevent ischemic symptoms, it is unclear whether establishing the additional diagnosis of ECVD in those without carotid bruit would justify actions that affect clinical outcomes. (Level of Evidence: C)
2. Duplex ultrasonography might be considered to detect carotid stenosis in asymptomatic patients without clinical evidence of atherosclerosis who have 2 or more of the following risk factors: hypertension, hyperlipidemia, tobacco smoking, a family history in a first-degree relative of atherosclerosis manifested before age 60 years, or a family history of ischemic stroke. However, it is unclear whether establishing a diagnosis of ECVD would justify actions that affect clinical outcomes. (Level of Evidence: C)

#### **CLASS III: NO BENEFIT**

1. Carotid duplex ultrasonography is not recommended for routine screening of asymptomatic patients who have no clinical manifestations of or risk factors for atherosclerosis. (Level of Evidence: C)
2. Carotid duplex ultrasonography is not recommended for routine evaluation of patients with neurological or psychiatric disorders unrelated to focal cerebral ischemia, such as brain tumors, familial or degenerative cerebral or motor neuron disorders, infectious and inflammatory conditions affecting the brain, psychiatric disorders, or epilepsy. (Level of Evidence: C)
3. Routine serial imaging of the extracranial carotid arteries is not recommended for patients who have no risk factors for development of atherosclerotic carotid disease and no disease evident on initial vascular testing. (Level of Evidence: C)

Although there is evidence from randomized trials that referred patients with asymptomatic hemodynamically significant carotid stenosis benefit from therapeutic intervention, no screening program aimed at identifying people with asymptomatic carotid stenosis has been shown to reduce their risk of stroke. Hence, there is no consensus on which patients should undergo screening tests for detection of carotid disease. Auscultation of the cervical arteries for bruits is a standard part of the physical examination of adults, but detection of a bruit correlates more closely with systemic atherosclerosis than with significant carotid stenosis (30). In the largest reported study of screening in asymptomatic patients, the prevalence of carotid stenosis >35% in those without a bruit was 6.6%, and the prevalence of >75% carotid stenosis was 1.2% (31). Because the



sensitivity of detection of a carotid bruit and the positive predictive value for hemodynamically significant carotid stenosis are relatively low, however, ultrasonography may be appropriate in some high-risk asymptomatic patients irrespective of findings on auscultation (32).

Because carotid ultrasonography is a widely available technology associated with negligible risk and discomfort, the issue becomes one of appropriate resource utilization. Lacking data from health economic studies to support mass screening of the general adult population, our recommendations are based on consensus and driven by awareness that resources are limited and as a result favor targeted screening of patients at greatest risk of developing carotid stenosis. Additional pertinent considerations are that the stroke reduction that accrues from screening asymptomatic patients and treating them with specific interventions is unknown, that the benefit is limited by the low overall prevalence of disease amenable to specific therapy in asymptomatic patients, and that revascularization procedures are associated with tangible risks.

### **2.1.2. Recommendations From Other Panels**

The AHA/ASA guideline for primary prevention of ischemic stroke recommended against screening the general population for asymptomatic carotid stenosis on the basis of concerns about lack of cost-effectiveness, the potential adverse impact of false-positive and false-negative results in the general population, and the small absolute benefit of intervention (33). In addition, the American Society of Neuroimaging recommended against the screening of unselected populations but advised the screening of adults older than 65 years of age who have 3 or more cardiovascular risk factors (34). The ACCF/SCAI/SVMB/SIR/ASITN Clinical Expert Consensus Panel on Carotid Stenting recommended the screening of asymptomatic patients with carotid bruits who are potential candidates for carotid revascularization and the screening of those in whom coronary artery bypass graft (CABG) surgery is planned (35). The US Preventive Services Task Force recommended against screening for asymptomatic carotid artery stenosis in the general adult population (36).

## **2.2. Extracranial Cerebrovascular Disease as a Marker of Systemic Atherosclerosis**

Because atherosclerosis is a systemic disease, patients with extracranial carotid or vertebral atherosclerosis frequently have atherosclerosis elsewhere, notably in the aorta, coronary arteries, and peripheral arteries (37–40). Patients with ECVD are at increased risk of MI and death attributable to cardiac disease (41–46), such that many patients with carotid stenosis face a greater risk of death caused by MI than of stroke (47,48). Coronary atherosclerosis is prevalent in patients with fatal stroke of many origins and occurs more frequently in those with carotid or vertebral artery atherosclerosis. In 803 autopsies of consecutive patients with

neurological disease (49), the prevalences of atherosclerotic coronary plaque, >50% coronary artery stenosis, and pathological evidence of MI were 72%, 38%, and 41%, respectively, among the 341 patients with a history of stroke compared with 27%, 10%, and 13%, respectively, of the 462 patients with neurological diseases other than stroke (all  $p < 0.001$ ). Two thirds of the cases of MI found at autopsy had been clinically silent. The frequency of coronary atherosclerosis and MI was similar in patients with various stroke subtypes, but the severity of coronary atherosclerosis was related to the severity of ECVD (adjusted linear  $p$  for trend  $< 0.005$ ). Risk factors associated with ECVD, such as cigarette smoking, hypercholesterolemia, diabetes, and hypertension, are the same as for atherosclerosis elsewhere, although differences exist in their relative contribution to risk in the various vascular beds. A more detailed description of risk factors and their management appears in Section 6.

The IMT of the carotid artery wall, a measurement obtained by carotid ultrasound, is also a marker of systemic atherosclerosis. Carotid IMT is a marker of risk for coronary events and stroke in patients without clinical cardiovascular disease (50,51), although in the Framingham Heart Study coefficients of correlation between carotid IMT and coronary calcification were typically  $< 0.3$  (52–55). Data from the ARIC study suggest that carotid IMT data may enhance cardiovascular risk assessment, particularly among individuals classified as being at intermediate risk by use of conventional risk factors (56,57). In epidemiological studies (58–62), IMT progresses at an average rate of  $\leq 0.03$  mm per year. Progression can be retarded by 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor drugs (statins), the combination of colestipol and niacin, and risk factor modifications (58–62). The use of IMT measurements to guide treatment based on outcomes of specific interventions for patients has not been documented.

Measurement of IMT has not yet become a routine or certified element of carotid ultrasound examinations in the United States and is not currently recognized as a screening method for atherosclerotic risk (63,64). There is no indication for measurement of IMT in patients with carotid plaque or stenosis. For specific recommendations for screening for atherosclerosis by measurement of carotid IMT in asymptomatic patients, the reader is referred to the 2010 ACCF/AHA Guidelines for Assessment of Cardiovascular Risk in Asymptomatic Adults (65).

### **2.2.1. Screening for Coronary or Lower-Extremity Peripheral Arterial Disease in Patients With Atherosclerosis of the Carotid or Vertebral Arteries**

Whether symptomatic or asymptomatic, individuals with carotid atherosclerosis are more likely to have atherosclerosis that involves other vascular beds, although the associations are quantitatively modest. Specific recommendations for screening for CAD and PAD in patients with ECVD are beyond the scope of this document, and the reader is referred to the ACC/AHA 2005 Guidelines for the Man-

agement of Patients with Peripheral Arterial Disease (66) and the AHA/ASA scientific statement on coronary risk evaluation in patients with TIA and ischemic stroke (67).

### 3. Clinical Presentation

#### 3.1. Natural History of Atherosclerotic Carotid Artery Disease

Extracranial atherosclerotic disease accounts for up to 15% to 20% of all ischemic strokes (68,69). The progression of carotid atherosclerosis may be similar to that in other arterial beds, but the relationship between plaque growth, increasing stenosis, and TIA or stroke is complex. There was a clear correlation between the degree of stenosis and the risk of stroke in the NASCET (North American Symptomatic Carotid Endarterectomy Trial) (70), but the relationship between stroke risk and severity of stenosis in asymptomatic patients was less clear in other studies. After 18 months of medical therapy without revascularization, stroke rates were 19% in those with 70% to 79% initial stenosis, 28% in those with 80% to 89% stenosis, and 33% in the 90% to 99% stenosis group, and the risk diminished with near-occlusion (70). In ACAS (Asymptomatic Carotid Atherosclerosis Study) and ACST (Asymptomatic Carotid Surgery Trial), asymptomatic patients with 60% to 80% stenosis had higher stroke rates than those with more severe stenosis (71,72). However, medical therapy in the era during which these trials were conducted was considerably limited compared with today's standards.

The natural history of asymptomatic carotid disease in patients with cervical bruits or other risk factors for stroke has been reported in case series, population-based studies, and observational arms of randomized clinical trials. In the Framingham Heart Study, the calculated age-adjusted incidence of stroke in patients with cervical bruits was 2.6 times that of those without bruits (15). A number of early natural history studies showing the incidence of stroke in asymptomatic patients with >75% stenosis are summarized in Table 2 (section on observational studies); the aggregate annual stroke rate exceeded 5% (73).

Table 2 (section on randomized trial cohorts) also summarizes event rates in randomized trial cohorts. ACAS demonstrated a rate of 11% during a 5-year period for ipsilateral stroke or death in the group managed with medical therapy, which consisted essentially of aspirin alone (neither the statin class of lipid-lowering drugs nor inhibitors of the renin-angiotensin system were conventionally used) (74). In ACST, the risk of ipsilateral stroke or death during a 5-year period in patients with  $\geq 70\%$  stenosis randomized to initial medical therapy was 4.7% (75). The difference in rates suggests that medical therapy has been associated with diminishing event rates over time and that asymptomatic disease may follow a relatively benign course in many individuals. Several other randomized trials have also documented a low rate of neurological events in

asymptomatic patients with moderate to severe internal carotid artery stenosis (76,77).

#### 3.2. Characterization of Atherosclerotic Lesions in the Extracranial Carotid Arteries

Because the correlation between severity of stenosis and ischemic events is imperfect, other characteristics have been explored as potential markers of plaque vulnerability and stroke risk. Among asymptomatic patients with carotid bruit in the Framingham Heart Study cohort, fewer than half of the stroke events affected the cerebral hemisphere ipsilateral to the bruit and carotid stenosis (15).

Investigations of the relationship between cerebral symptoms and morphological characteristics of plaque defined by ultrasound found an association of clinical cerebral ischemic events with ulceration, echolucency, intraplaque hemorrhage, and high lipid content (86,87). Molecular and cellular processes responsible for plaque composition (86–88) may be more important than the degree of stenosis in determining the risk of subsequent TIA and stroke, but the degree of carotid stenosis estimated by ultrasonography remains the main determinant of disease severity and forms the basis for most clinical decision making. Quantitative analysis of duplex ultrasound images correlates with histological findings of intraplaque hemorrhage, fibromuscular hyperplasia, calcium, and lipid composition, and the feasibility of identifying symptomatic and unstable plaques on the basis of these features has been described (87). Computer-generated measurements of carotid plaque echogenicity and surface characteristics (smooth, irregular, or ulcerated) have been performed on images obtained from patients with symptomatic or asymptomatic ipsilateral cerebral infarction, but the prognostic value of these features has not been established (89–92). Hypochoic plaques are associated with subcortical and cortical cerebral infarcts of suspected embolic origin, and hyperechoic plaques are associated with diffuse white matter infarcts of presumed hemodynamic origin (including lacunar and basal ganglia infarctions due to proximal arterial and distal intracranial vascular disease) (93).

Contrast-enhanced magnetic resonance imaging (MRI) at 1.5- and 3.0-Tesla field strengths, intravascular MRI, and computed tomography (CT) have also been used to characterize carotid atherosclerotic plaques. Thin or ruptured fibrous caps, intraplaque hemorrhage, relatively large lipid-rich or necrotic plaque cores, and overall plaque thickness have been associated with subsequent ischemic brain events in preliminary studies of asymptomatic patients with 50% to 79% carotid stenosis (94).

Metabolic activity in the vessel wall surrounding carotid plaques can be detected by positron emission tomography (PET) (95). Carotid plaques of symptomatic patients with stroke demonstrate infiltration of the fibrous cap by inflammatory cells including monocytes, macrophages, and lymphocytes (96,97). Increased uptake of  $^{18}\text{F}$ -fluorodeoxyglucose measured by PET imaging is believed to reflect inflammation (98,99).

**Table 2. Event Rates in Patients With Carotid Artery Stenosis Managed Without Revascularization**

Study (Reference)	No. of Patients	Symptom Status	Stenosis, %	Follow-Up	Medication Therapy	Endpoint	Event Rate Over Study Period (%)
<b>Observational studies</b>							
Hertzner et al. (78)	290	Asymptomatic	≥50	33–38 mo	Aspirin or dipyridamole (n=104); or anticoagulation with warfarin (n=9); or no medical treatment (n=82)	Death TIA Stroke	22.0, or 7.33 annualized 8.21, or 2.74 annualized 9.23, or 3.1 annualized
Spence et al. (79)	168	Asymptomatic	≥60	≥12 mo	Multiple, including antiplatelet, statins, exercise, Mediterranean diet, ACE inhibitors	Stroke	3.8, or 1.3 annualized
Marquardt et al. (80)	1,153	Asymptomatic	≥50	Mean 3 y	Multiple, including antiplatelet, anticoagulation, statin, antihypertensive drugs	Ipsilateral stroke	0.34 (95% CI 0.01 to 1.87) average annual event rate
Abbott et al. (81)	202	Asymptomatic	60–90	Mean 34 mo	Multiple, including antiplatelet, warfarin, antihypertensive drugs, cholesterol-lowering therapy	Ipsilateral stroke or TIA; ipsilateral carotid hemispheric stroke	Ipsilateral stroke or TIA or retinal event: 3.1 (95% CI 0.7 to 5.5) average annual rate Ipsilateral carotid hemispheric stroke: 1.0 (95% CI 0.4 to 2.4) average annual rate
Goessens et al. (82)	2,684	Asymptomatic	≥50	Mean 3.6 y (SD 2.3)	Multiple, including antiplatelet, antihypertensive drugs, lipid-lowering agents, ACE inhibitors, and/or AIIA	Ischemic stroke; death	Death: 9.0 or 2.5 annualized; ischemic stroke: 2.0 or 0.54 annualized
<b>Randomized trial cohorts</b>							
ECST (83)	3,024	Symptomatic	≥80	3 y	No surgery within 1 y or delay of surgery	Major stroke or death	26.5 over 3 y or annualized 8.83 for 1 y*
NASCET (84)	659	Symptomatic	≥70	2 y	Aspirin	Ipsilateral stroke	26.0 over 2 y or annualized 13.0 for 1 y†
VA 309 (85)	189	Symptomatic	>50	1 y	Aspirin	Ipsilateral stroke or TIA or surgical death	19.4 over 11.9 12 mo
NASCET (20)	858	Symptomatic	50–69	5 y	Antiplatelet (usually aspirin)	Ipsilateral stroke	22.2 over 5 y or annualized 4.44 for 1 y‡
NASCET (20)	1,368	Symptomatic	≤50	5 y	Antiplatelet (usually aspirin)	Ipsilateral stroke	18.7 over 5 y or annualized 3.74 for 1 y‡
ACAS (74)	1,662	Asymptomatic	>60	5 y	Aspirin	Ipsilateral stroke, surgical death	11.0 over 5 y or annualized 2.2 for 1 y§
ACST (75)	3,120	Asymptomatic	≥60	5 y	Indefinite deferral of any CEA	Any stroke	11.8 over 5 y or annualized 2.36 for 1 y§
VA (76)	444	Asymptomatic	≥50	4 y	Aspirin	Ipsilateral stroke	9.4 over 4 y or annualized 2.35 over 1 y

\*Frequency based on Kaplan-Meier. †Risk event rate based on Kaplan-Meier. ‡Failure rate based on Kaplan-Meier. §Risk rate based on Kaplan-Meier.  
 AIIA indicates angiotensin II antagonist; ACAS, Asymptomatic Carotid Atherosclerosis Study; ACE, angiotensin-converting enzyme; ACST, Asymptomatic Carotid Surgery Trial; CEA, carotid endarterectomy; CI, confidence interval; ECST, European Carotid Surgery Trial; n, number; N/A, not applicable; NASCET, North American Symptomatic Carotid Endarterectomy Trial; SD, standard deviation; TIA, transient ischemic attack; VA 309, Veterans Affairs Cooperative Studies Program 309; and VA, Veterans Affairs Cooperative Study Group.  
 Modified from Bates et al. (35).

Macrophage activity quantified by PET (100) and neovascular angiogenesis assessed by MRI have been observed in experimental models (101). Biomarkers such as C-reactive protein and certain matrix metalloproteinases with the potential to identify carotid plaque instability have also been investigated

(102–104), but the reliability of biomarkers in predicting clinical events has not been established. Several studies have shown that plaque composition is modified by treatment with statins (105–109). Despite these advances in understanding the pathophysiology of atherosclerotic plaque, the utility of mor-

phological, pathological, and biochemical features in predicting the occurrence of TIA, stroke, or other symptomatic manifestations of ECVD has not been established clearly by prospective studies.

### 3.3. Symptoms and Signs of Transient Ischemic Attack and Ischemic Stroke

TIA is conventionally defined as a syndrome of acute neurological dysfunction referable to the distribution of a single brain artery and characterized by symptoms that last <24 hours. With advances in brain imaging, many patients with symptoms briefer than 24 hours are found to have cerebral infarction. A revised definition has been developed specifying symptoms that last <1 hour, and the typical duration of symptoms is <15 minutes (110), but this change has not been accepted universally, and the 24-hour threshold is still the standard definition (111). In patients with acute ischemic stroke, symptoms and signs of neurological deficit persist longer than 24 hours.

Symptoms and signs that result from ischemia or infarction in the distribution of the right internal carotid artery or middle cerebral artery include but are not limited to left-sided weakness, left-sided paresthesia or sensory loss, left-sided neglect, abnormal visual-spatial ability, monocular blindness that affects the right eye, and right homonymous hemianopsia (visual loss that involves the right visual field). Ischemia or infarction in the distribution of the left internal carotid artery or middle cerebral artery may cause right-sided weakness, right-sided paresthesia or sensory loss, aphasia, and monocular blindness that affects the left eye or left visual field. Aphasia may be a sign of ischemia or infarction in the distribution of the right internal carotid artery in ambidextrous or left-handed individuals. Symptoms and signs that result from ischemia or infarction in the vertebrobasilar system include but are not limited to ataxia, cranial nerve deficits, visual field loss, dizziness, imbalance, and incoordination.

#### 3.3.1. Public Awareness of Stroke Risk Factors and Warning Indicators

The AHA and ASA have developed educational materials for patients that emphasize recognition of the symptoms and signs that warn of TIA and stroke and that encourage those who observe these symptoms to seek immediate medical attention, pointing out that rapid action could limit disability and prevent death.

The joint Stroke Collaborative campaign of the AAN, the ACEP, and the AHA/ASA seeks to increase stroke symptom awareness among Americans (see <http://www.giveme5forstroke.org>). A report from the region of Cincinnati, Ohio (112), found significant improvement in public knowledge of stroke warning signs as promulgated by the ASA, National Stroke Association, and the National Institute of Neurological Disorders and Stroke between 1995 and 2000 but less improvement in knowledge of stroke risk factors during the same period.

Patients with acute stroke face disease-specific causes of delay in seeking medical treatment. In 1 study, 23% had dysphasia, 77% had an upper-limb motor deficit, and 19% had an altered level of consciousness (113). In addition to clinical characteristics, demographic, cognitive, perceptual, social, emotional, and behavioral factors affect the prehospital delay in patients with ischemic stroke symptoms (114). A gender analysis of the interval from symptom onset to hospital arrival (115) found that nearly 4 times as many men and 5 times as many women exceeded the goal of <3 hours than those who did not.

## 4. Clinical Assessment of Patients With Focal Cerebral Ischemic Symptoms

### 4.1. Acute Ischemic Stroke

The immediate management of a patient presenting with a suspected acute focal neurological syndrome should follow published guidelines for emergency stroke care (2). Once the diagnosis of acute ischemic stroke is established, the patient has been stabilized, thrombolytic therapy has been administered to an eligible patient, and initial preventive therapy has been implemented, further evaluation is directed toward establishing the vascular territory involved and the cause and pathophysiology of the event (2,111,116,117). Risk stratification and secondary prevention are important for all patients.

### 4.2. Transient Ischemic Attack

TIA is an important predictor of stroke; the risk is highest in the first week, as high as 13% in the first 90 days after the initial event, and up to 30% within 5 years (26,118–124). On the basis of the conventional definition, an estimated 240,000 TIAs are diagnosed annually in the United States, and the number of undiagnosed cases is likely considerably greater (118). Early recognition of TIA, identification of patients at risk, and risk factor modification (125) are important stroke prevention measures.

In patients who display ischemic symptoms in the territory of a carotid artery that has high-grade stenosis, surgical intervention reduces the risk of major neurological events (20,75). The benefit of CEA in preventing stroke is greatly diminished beyond 2 weeks after the onset of symptoms, in large part because the risk of recurrent ischemic events is highest in this early period. After 4 weeks in women and 12 weeks in men, the benefit of surgery in these symptomatic patients is no more than that observed with surgery for asymptomatic patients, and in some cases, surgery may be harmful (126). Interventional decisions for a particular patient should be based on balancing the risks of revascularization against the risk of worsening symptoms and disability with medical therapy alone.

### 4.3. Amaurosis Fugax

Transient monocular blindness (amaurosis fugax) is caused by temporary reduction of blood flow to an eye with sudden

loss of vision, often described as a shade drawn upward or downward over the field of view (127). The most common cause is atherosclerosis of the ipsilateral internal carotid artery, but other causes have been associated with this syndrome as well. The mechanism may involve ophthalmic artery embolism, observed as fibrin, cholesterol crystals (Hollenhorst plaques), fat, or material arising from fibrocalcific degeneration of the aortic or mitral valves. Causes of transient monocular blindness follow:

- Carotid artery stenosis or occlusion
- Atherosclerosis
- Dissection
- Arteritis
- Radiation-induced arteriopathy
- Arterial embolism
- Cardiogenic embolism
- Atheroembolism
- Hypotension
- Intracranial hypertension
- Glaucoma
- Migraine
- Vasospastic or occlusive disease of the ophthalmic artery

The risk of stroke was lower among patients with transient monocular blindness than among those with hemispheric TIA in the NASCET cohort (128). The 3-year risk of stroke with medical treatment alone in patients with transient monocular blindness was related to the number of stroke risk factors (hypertension, hypercholesterolemia, diabetes, and cigarette smoking) and was specifically 1.8% in those with 0 or 1 risk factor, 12.3% in those with 2 risk factors, and 24.2% in those with 3 or 4 risk factors. In addition to the risk of stroke, permanent blindness may occur in the affected eye as a result of the initial or subsequent episodes (128–130).

#### **4.4. Cerebral Ischemia Due to Intracranial Arterial Stenosis and Occlusion**

Intracranial arterial stenosis may be caused by atherosclerosis, intimal fibroplasia, vasculitis, adventitial cysts, or vascular tumors; intracranial arterial occlusion may develop on the basis of thrombosis or embolism arising from the cardiac chambers, heart valves, aorta, proximal atheromatous disease of the carotid or vertebral arteries, or paradoxical embolism involving a defect in cardiac septation or other right-to-left circulatory shunt. The diagnosis and management of these disorders are outside the scope of this guideline, but evaluation of the intracranial vasculature may be important in some patients with ECVD to exclude high-grade tandem lesions that have implications for clinical management.

#### **4.5. Atherosclerotic Disease of the Aortic Arch as a Cause of Cerebral Ischemia**

Atheromatous disease of the aortic arch is an independent risk factor for ischemic stroke (131), but the diagnosis and management of this disorder are outside the scope of this guideline. See the 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines for the Diagnosis and Management of Patients With Thoracic Aortic Disease (132).

#### **4.6. Atypical Clinical Presentations and Neurological Symptoms Bearing an Uncertain Relationship to Extracranial Carotid and Vertebral Artery Disease**

Most studies of the natural history and treatment of TIA have included patients who experienced focal transient ischemic events. The significance of nonfocal neurological events, including transient global amnesia, acute confusion, syncope, isolated vertigo, nonrotational dizziness, bilateral weakness, or paresthesias, is less well studied. Brief, stereotyped, repetitive symptoms suggestive of transient cerebral dysfunction raise the possibility of partial seizure, and electroencephalography may be useful in such cases. When symptoms are purely sensory (numbness, pain, or paresthesia), then radiculopathy, neuropathy, microvascular cerebral or spinal pathology, or lacunar stroke should be considered. A small proportion of patients with critical (>70% and usually >90%) carotid stenosis present with memory, speech, and hearing difficulty related to hypoperfusion of the dominant cerebral hemisphere.

In a study from the Netherlands, patients with transient neurological attacks of either focal or nonfocal neurological symptoms faced an increased risk of stroke compared with those without symptoms (HR 2.14 and 1.56, respectively) (133). The pathophysiological mechanism responsible for transient global amnesia has not been elucidated, and it is not clear whether, in fact, this syndrome is related to ECVD at all (134). Vertigo (in contrast to nonrotational dizziness) was associated with a risk of subsequent stroke in a population-based study of patients 65 years of age or older, but a direct causative relationship to ECVD has not been established (135).

### **5. Diagnosis and Testing**

#### **5.1. Recommendations for Diagnostic Testing in Patients With Symptoms or Signs of Extracranial Carotid Artery Disease**

##### **CLASS I**

1. The initial evaluation of patients with transient retinal or hemispheric neurological symptoms of possible ischemic origin should include noninvasive imaging for the detection of ECVD. (*Level of Evidence: C*)
2. Duplex ultrasonography is recommended to detect carotid stenosis in patients who develop focal neurological symptoms corresponding

- to the territory supplied by the left or right internal carotid artery. (Level of Evidence: C)
3. In patients with acute, focal ischemic neurological symptoms corresponding to the territory supplied by the left or right internal carotid artery, magnetic resonance angiography (MRA) or computed tomography angiography (CTA) is indicated to detect carotid stenosis when sonography either cannot be obtained or yields equivocal or otherwise nondiagnostic results. (Level of Evidence: C)
  4. When extracranial or intracranial cerebrovascular disease is not severe enough to account for neurological symptoms of suspected ischemic origin, echocardiography should be performed to search for a source of cardiogenic embolism. (Level of Evidence: C)
  5. Correlation of findings obtained by several carotid imaging modalities should be part of a program of quality assurance in each laboratory that performs such diagnostic testing. (Level of Evidence: C)

#### **CLASS IIa**

1. When an extracranial source of ischemia is not identified in patients with transient retinal or hemispheric neurological symptoms of suspected ischemic origin, CTA, MRA, or selective cerebral angiography can be useful to search for intracranial vascular disease. (Level of Evidence: C)
2. When the results of initial noninvasive imaging are inconclusive, additional examination by use of another imaging method is reasonable. In candidates for revascularization, MRA or CTA can be useful when results of carotid duplex ultrasonography are equivocal or indeterminate. (Level of Evidence: C)
3. When intervention for significant carotid stenosis detected by carotid duplex ultrasonography is planned, MRA, CTA, or catheter-based contrast angiography can be useful to evaluate the severity of stenosis and to identify intrathoracic or intracranial vascular lesions that are not adequately assessed by duplex ultrasonography. (Level of Evidence: C)
4. When noninvasive imaging is inconclusive or not feasible because of technical limitations or contraindications in patients with transient retinal or hemispheric neurological symptoms of suspected ischemic origin, or when noninvasive imaging studies yield discordant results, it is reasonable to perform catheter-based contrast angiography to detect and characterize extracranial and/or intracranial cerebrovascular disease. (Level of Evidence: C)
5. MRA without contrast is reasonable to assess the extent of disease in patients with symptomatic carotid atherosclerosis and renal insufficiency or extensive vascular calcification. (Level of Evidence: C)
6. It is reasonable to use MRI systems capable of consistently generating high-quality images while avoiding low-field systems that do not yield diagnostically accurate results. (Level of Evidence: C)
7. CTA is reasonable for evaluation of patients with clinically suspected significant carotid atherosclerosis who are not suitable candidates for MRA because of claustrophobia, implanted pacemakers, or other incompatible devices. (Level of Evidence: C)

#### **CLASS IIb**

1. Duplex carotid ultrasonography might be considered for patients with nonspecific neurological symptoms when cerebral ischemia is a plausible cause. (Level of Evidence: C)
2. When complete carotid arterial occlusion is suggested by duplex ultrasonography, MRA, or CTA in patients with retinal or hemispheric neurological symptoms of suspected ischemic origin, catheter-based contrast angiography may be considered to determine whether the arterial lumen is sufficiently patent to permit carotid revascularization. (Level of Evidence: C)

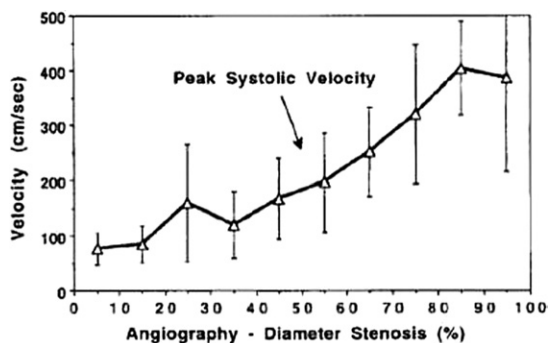
3. Catheter-based angiography may be reasonable in patients with renal dysfunction to limit the amount of radiographic contrast material required for definitive imaging for evaluation of a single vascular territory. (Level of Evidence: C)

Carotid ultrasonography, CTA, and MRA can provide the information needed to guide the choice of medical, endovascular, or surgical treatment in most cases. The severity of stenosis is defined according to angiographic criteria by the method used in NASCET (70), but it corresponds as well to assessment by sonography (136) and other accepted methods of measurement such as CTA and MRA, although the latter may overestimate the severity of stenosis. It is important to bear in mind that 75% diameter stenosis of a vessel corresponds to >90% reduction in the cross-sectional area of the lumen.

Catheter-based angiography may be necessary in some cases for definitive diagnosis or to resolve discordance between noninvasive imaging findings. These advanced imaging techniques generally do not replace carotid duplex ultrasonography for initial evaluation of suspected carotid stenosis in those with symptomatic manifestations of ischemia (or in asymptomatic individuals at risk), either as a solitary diagnostic method or as a confirmatory test to assess the severity of known stenosis. Indications for carotid duplex sonography follow (137,138):

- Cervical bruit in an asymptomatic patient
- Follow-up of known stenosis (>20%) in asymptomatic individuals
- Vascular assessment in a patient with multiple risk factors for atherosclerosis
- Stroke risk assessment in a patient with CAD or PAD
- Amaurosis fugax
- Hemispheric TIA
- Stroke in a candidate for carotid revascularization
- Follow-up after a carotid revascularization procedure
- Intraoperative assessment during CEA or stenting

Each imaging modality has strengths and weaknesses, and because the quality of images produced by each noninvasive modality differs from one institution to another, no single modality can be recommended as uniformly superior. In general, correlation of findings obtained by multiple modalities should be part of a program of quality assurance in every laboratory and institution. It is most important that data obtained in patients undergoing catheter-based angiography for evaluation of ECVD be compared with noninvasive imaging findings to assess and improve the accuracy of noninvasive vascular testing. The following discussion pertains mainly to evaluation of the cervical carotid arteries for atherosclerotic disease. There is a paucity of literature addressing evaluation of the vertebral arteries and of both the carotid and vertebral arteries for nonatherosclerotic disorders such as traumatic injury (139–141). The relative roles of noninvasive imaging and conventional angiography for these indications have not been defined.



**Figure 2. Peak Systolic Flow Velocity as a Measure of Internal Carotid Stenosis**

The relationship between peak systolic flow velocity in the internal carotid artery and the severity of stenosis as measured by contrast angiography is illustrated. Note the considerable overlap between adjacent categories of stenosis. Error bars indicate 1 standard deviation about the mean values. Reprinted with permission from Grant *et al.* (142).

Accurate assessment of the severity of arterial stenosis is essential to the selection of appropriate patients for surgical or endovascular intervention, and imaging of the extracranial carotid arteries should be performed whenever cerebral ischemia is a suspected mechanism of neurological symptoms in a viable patient. Choosing among the available vascular imaging modalities, deciding when to combine multiple modalities, and judicious application of angiography are challenging aspects of evaluation in patients with ECVD. Imaging of the aortic arch, proximal cervical arteries, and the artery distal to the site of stenosis is required before endovascular therapy to ascertain the feasibility of intervention. Less anatomic information is necessary before surgical intervention at the carotid bifurcation because the procedure entails direct exposure of the target artery.

## 5.2. Carotid Duplex Ultrasonography

Duplex ultrasound modalities combine 2-dimensional real-time imaging with Doppler flow analysis to evaluate vessels of interest (typically the cervical portions of the common, internal, and external carotid arteries) and measure blood flow velocity. The method does not directly measure the diameter of the artery or stenotic lesion. Instead, blood flow velocity is used as an indicator of the severity of stenosis (Figure 2). Several schemes have been developed for assessment of carotid stenosis by duplex ultrasound (136,143,144). The peak systolic velocity in the internal carotid artery and the ratio of the peak systolic velocity in the internal carotid artery to that in the ipsilateral common carotid artery appear to correlate best with angiographically determined arterial stenosis.

Ultrasonography is an accurate method for measuring the severity of stenosis, with the caveat that subtotal arterial occlusion may sometimes be mistaken for total occlusion. Typically, 2 categories of internal CAS severity are defined by ultrasound, one (50% to 69% stenosis) that represents the inflection point at which flow velocity accelerates above

normal because of atherosclerotic plaque and the other (70% to 99% stenosis) representing more severe nonocclusive disease, although the correlation with angiographic stenosis is approximate and varies among laboratories. According to a consensus document (136), when ultrasound is used, 50% to 69% stenosis of the internal carotid artery is associated with sonographically visible plaque and a peak systolic velocity of 125 to 230 cm/s in this vessel. Additional criteria include a ratio of internal to common carotid artery peak systolic velocities between 2 and 4 and an end-diastolic velocity of 40 to 100 cm/s in the internal carotid artery. Nonocclusive stenosis >70% in the internal carotid artery is associated with a peak systolic velocity >230 cm/s in this vessel and plaque and luminal narrowing visualized by gray-scale and color Doppler sonography. Additional criteria include a ratio of internal to common carotid artery peak systolic velocity >4 and end-diastolic velocity >100 cm/s in the internal carotid artery. The considerable overlap of velocities associated with stenosis of varying severities may make it difficult to distinguish 70% stenosis from less severe stenosis and supports the use of corroborating vascular imaging methods for more accurate assessment in equivocal or uncertain cases. The ratio of flow velocities in the internal and common carotid arteries may help distinguish between increased compensatory flow through collaterals and true contralateral internal carotid stenosis or occlusion.

Among the pitfalls in velocity-based estimation of internal carotid artery stenosis are higher velocities in women than in men and elevated velocities in the presence of contralateral carotid artery occlusion (145,146). Severe arterial tortuosity, high carotid bifurcation, obesity, and extensive vascular calcification reduce the accuracy of ultrasonography. Furthermore, *in situ* carotid stents decrease compliance of the vessel wall and can accelerate flow velocity (147). Ultrasonography may fail to differentiate between subtotal and complete arterial occlusion, although the distinction is of critical clinical importance. In such cases, intravenous administration of sonographic contrast agents may improve diagnostic accuracy (148,149), but the safety of these agents has been questioned (150). In addition to these technical factors, variability in operator expertise greatly affects the quality of examinations and reliability of results (Table 3) (151–153). Despite these limitations, ultrasonography performed by well-trained, experienced technologists provides accurate and relatively inexpensive assessment of the cervical carotid arteries (151–153,162–164). The technique is truly noninvasive and does not involve venipuncture or exposure to ionizing radiation or potentially nephrotoxic contrast material. Although results vary greatly between laboratories and operators, the sensitivity and specificity for detection or exclusion of  $\geq 70\%$  stenosis of the internal carotid artery are 85% to 90% compared with conventional angiography (Table 4) (141,165,166).

Every vascular laboratory should have a quality assurance program that compares estimates of stenosis by color Doppler ultrasound imaging with angiographic measurements.

**Table 3. Variability of Doppler Ultrasonography**

Author/Type of Study (Reference)	Study Parameters	Conclusions
<b>Variability between different centers</b>		
Perkins et al./survey (154)	Questionnaire on carotid duplex practice; 73 vascular laboratories	Diversity in diagnostic criteria; diversity in method of stenosis grading
Robless et al./survey (155)	Questionnaire on carotid duplex practice; 71 vascular laboratories	Diversity in method of stenosis grading; diversity concerning the Doppler angle used
Alexandrov et al./prospective (156)	2 Vascular laboratories in 2 hospitals; same equipment	A definite velocity criterion does not have the same validity and predictive value to grade carotid stenosis at different laboratories
Schwartz et al./prospective (157)	10 Systems, 9 hospitals	Predictive ability of different parameters to quantify stenosis was different from 1 device to another
Fillinger et al./consecutive (158)	2 Vascular laboratories, 4 systems, 360 bifurcations	Most accurate duplex criteria for a $\geq 60\%$ ICA stenosis were machine specific
Howard (151)	37 Centers, 63 Doppler devices	Performance of Doppler ultrasound was heterogeneous between devices
Howard/prospective (100)	19 Centers, 30 Doppler devices	Performance relates to the device-sonographer-reader system. Cut point for the peak systolic flow to ensure a positive predictive value of 90% in predicting a $\geq 60\%$ stenosis ranged from 151 to 390 cm/s or from 5,400 to 11,250 Hz
<b>Interequipment variability</b>		
Ranke/prospective (159)	20 ICA, 10 patients, 2 different systems, same observer	Intrastenotic peak flow velocity values were significantly higher with 1 system
Wolstenhulme/prospective (160)	2 Systems, 43 patients, same observer	Limits of agreements (within 95% of different lie) between systems: $-0.47$ to $0.45$ m/s
Daigle/in vitro (161)	6 Systems, velocity-calibrated string flow phantom	Five of 6 systems: overestimation of all peak velocities compared with the calibrated string flow phantom
<b>Interobserver and intraobserver variability</b>		
Ranke/prospective (159)	20 ICA, 11 patients, same system, 2 observers	Interobserver variation expressed as 95% CI for predicted stenosis between 2 observers was 13.6% with peak systolic velocity and 15.4% with mean velocity ratio
Wolstenhulme/prospective (160)	20 Patients, 2 systems, 1 observer	Intraobserver reproducibility coefficient for both machines was 0.48 cm/s

CI indicates confidence interval; and ICA, internal carotid artery.  
Reprinted with permission from Long et al. (167).

The use of appropriately credentialed sonographers and adherence to stringent quality assurance programs, as required for accreditation by the Intersocietal Commission for the Accreditation of Vascular Laboratories, have been associated with superior results (Standards for Accreditation in Noninvasive Vascular Testing, Part II, Vascular Laboratory Operations: Extracranial Cerebrovascular Testing; available at <http://www.icavl.org>). Characterization of plaque morphology is possible in some cases and may have therapeutic implications (181), but this is not yet widely used in practice. Future technological advances may bring about less operator-dependent 3-dimensional, high-resolution arterial imaging.

### 5.3. Magnetic Resonance Angiography

MRA can generate high-resolution noninvasive images of the cervical arteries. The radiofrequency signal characteristics of flowing blood are sufficiently distinct from surrounding soft tissue to allow imaging of the arterial lumen (182). However, there is an increasing shift to contrast-enhanced MRA to amplify the relative signal intensity of flowing

blood compared with surrounding tissues and allow more detailed evaluation of the cervical arteries (183–188). Slowly flowing blood is also better imaged with contrast-enhanced MRA, which is sensitive to both the velocity and direction of blood flow. Despite artifacts and other limitations, high-quality MRA can provide accurate anatomic imaging of the aortic arch and the cervical and cerebral arteries (167) and may be used to plan revascularization without exposure to ionizing radiation.

Technological advancements have reduced image acquisition time, decreased respiratory and other motion-based artifacts, and greatly improved the quality of MRA to rival that of conventional angiography for many applications, including evaluation of patients with ECVD. Higher-field-strength systems, such as the 3-Tesla apparatus, more powerful gradients, and sophisticated software are associated with better MRA image quality than systems with lower field strengths. Although popular with patients, low-field-strength, open MRI systems are rarely capable of producing high-quality MRA. Correlations with angiogra-



**Table 4. Sensitivity and Specificity of Duplex Ultrasonography as a Function of Degree of Carotid Stenosis**

Study, Year (Reference)	Degree of Stenosis	Carotids, n	Sensitivity, %	Specificity, %
Serfaty et al., 2000 (168)	Occlusion	46	100	90
Hood et al., 1996 (169)	Occlusion	457	100	99
White et al., 1994 (170)	Occlusion	120	80	100
Turnipseed et al., 1993 (171)	Occlusion	34	100	100
Riles et al., 1992 (172)	Occlusion	75	100	100
Riles et al., 1992 (172)	Stenosis $\geq$ 80%	75	85	80
Johnson et al., 2000 (173)	Stenosis $\geq$ 70%	76	65	95
Serfaty et al., 2000 (168)	Stenosis $\geq$ 70%	46	64	97
Huston et al., 1998 (174)	Stenosis $\geq$ 70%	100	97	75
Link et al., 1997 (175)	Stenosis $\geq$ 70%	56	87	98
Hood et al., 1996 (169)	Stenosis $\geq$ 70%	457	86	97
Bray et al., 1995 (176)	Stenosis $\geq$ 70%	128	85	96–97
Patel et al., 1995 (177)	Stenosis $\geq$ 70%	171	94	83
Turnipseed et al., 1993 (171)	Stenosis $\geq$ 70%	34	94	89
Bluth et al., 2000 (178)	Stenosis $\geq$ 60%	40	62	100
Jackson et al., 1998 (179)	Stenosis $\geq$ 60%	99	89	92
White et al., 1994 (170)	Stenosis $\geq$ 60%	120	73	88
Walters et al., 1993 (180)	Stenosis $\geq$ 60%	102	88	88
Serfaty et al., 2000 (168)	Stenosis $\geq$ 50%	46	94	83
Hood et al., 1996 (169)	Stenosis $\geq$ 50%	457	99.5	89
Bray et al., 1995 (176)	Stenosis $\geq$ 50%	128	87–95	96
Riles et al., 1992 (172)	Stenosis $\geq$ 50%	75	98	69

Modified from Long et al. (167).

phy suggest that high-quality MRA is associated with a sensitivity that ranges from 97% to 100% and a specificity that ranges from 82% to 96% (183–186,189), although these estimates may be subject to reporting bias.

Pitfalls in MRA evaluation of ECVD include overestimation of stenosis (more so with noncontrast examinations) and inability to discriminate between subtotal and complete arterial occlusion. More problematic is the inability to examine the substantial fraction of patients who have claustrophobia, extreme obesity, or incompatible implanted devices such as pacemakers or defibrillators, many of whom are at high risk for atherosclerotic ECVD. On the other hand, among the notable strengths of MRA relative to carotid ultrasound and CTA is its relative insensitivity to arterial calcification. Like sonography, MRI may be used to assess atheromatous plaque morphology (190,191), but the utility of this application in clinical practice requires further validation.

Gadolinium-based compounds used as magnetic resonance contrast agents are associated with a much lower incidence of nephrotoxicity and allergic reactions than the iodinated radiographic contrast materials used for CTA and conventional angiography. However, exposure of patients with preexisting renal dysfunction to high doses of gadolinium-based contrast agents in conjunction with MRA has been associated with nephrogenic systemic fibrosis. This poorly understood disorder causes cutaneous sclerosis, subcutaneous edema, disabling joint contractures, and injury to internal organs (192).

#### 5.4. Computed Tomographic Angiography

Multiplanar reconstructed CTA may be obtained from thin, contiguous axial images acquired after intravenous administration of radiographic contrast material. Rapid image acquisition and processing, continuous image acquisition (“spiral CT”), and multiple-detector systems have made high-resolution CTA clinically practical (193–199). Like MRA, CTA provides anatomic imaging from the aortic arch through the circle of Willis. Multiplanar reconstruction and analysis allows evaluation of even very tortuous vessels. Unlike ultrasonography or MRA, CTA provides direct imaging of the arterial lumen suitable for evaluation of stenosis. With severe stenosis, volume averaging affects the accuracy of measurement as the diameter of the residual vessel lumen approaches the resolution limit of the CT system.

Like MRA, CTA is undergoing rapid technological evolution. Increasing the number of detector rows facilitates faster, higher-resolution imaging and larger fields of view, and 16-, 32-, 64-, 256-, and 320-row detector and dual-source systems are in clinical use (200,201). Slower image acquisition by equipment with fewer detector rows allows the intravenous contrast bolus to traverse the arteries and enter the capillaries and veins before imaging is complete, degrading images by competing enhancement of these structures. Conversely, scanners with a greater number of detector rows offer faster acquisition during the arterial phase, reduce motion and respiratory artifacts, and lessen the volume of contrast required. Equipment, imaging protocols, and interpreter experience factor heavily into the

**Table 5. Sensitivity and Specificity of Computed Tomographic Angiography as a Function of Degree of Carotid Stenosis**

Study, Year (Reference)	Degree of Stenosis	Carotids, n	Sensitivity, %	Specificity, %
Anderson et al., 2000 (207)	Occlusion	80	69–100	98
Leclerc et al., 1999 (208)	Occlusion	44	100	100
Marcus et al., 1999 (209)	Occlusion	46	100	100
Verhoek et al., 1999 (210)	Occlusion	38	66–75	87–100
Magarelli et al., 1998 (211)	Occlusion	40	100	100
Link et al., 1997 (175)	Occlusion	56	100	100
Leclerc et al., 1995 (212)	Occlusion	39	100	100
Dillon et al., 1993 (213)	Occlusion	50	81–87.5	97–100
Schwartz et al., 1992 (214)	Occlusion	40	100	100
	Stenosis $\geq$ 80%	NA	NA	NA
Anderson et al., 2000 (207)	Stenosis $\geq$ 70%	80	67–77	84–92
Leclerc et al., 1999 (208)	Stenosis $\geq$ 70%	44	67–100	94–97
Marcus et al., 1999 (209)	Stenosis $\geq$ 70%	46	85–93	93–97
Verhoek et al., 1999 (210)	Stenosis $\geq$ 70%	38	80–100	95–100
Magarelli et al., 1998 (211)	Stenosis $\geq$ 70%	40	92	98.5
Link et al., 1997 (175)	Stenosis $\geq$ 70%	56	100	100
Leclerc et al., 1995 (212)	Stenosis $\geq$ 70%	39	87.5–100	96–100
Dillon et al., 1993 (213)	Stenosis $\geq$ 70%	50	81–82	94–95
Schwartz et al., 1992 (214)	Stenosis $\geq$ 70%	40	100	100
	Stenosis $\geq$ 60%	NA	NA	NA
Anderson et al., 2000 (207)	Stenosis $\geq$ 50%	80	85–90	82–91

NA indicates not available.  
 Modified from Long et al. (167).

accuracy of CTA (202–205), but in contemporary studies CTA has compared favorably with catheter angiography for evaluation of patients with ECVD, with 100% sensitivity and 63% specificity (95% CI 25% to 88%); the negative predictive value of CTA demonstrating <70% carotid artery stenosis was 100% (206) (Table 5). However, on the basis of a study that compared sonography, CTA, and MRA performed with and without administration of intravenous contrast material, the accuracy of noninvasive imaging for evaluation of cervical carotid artery stenosis may be generally overestimated in the literature (215).

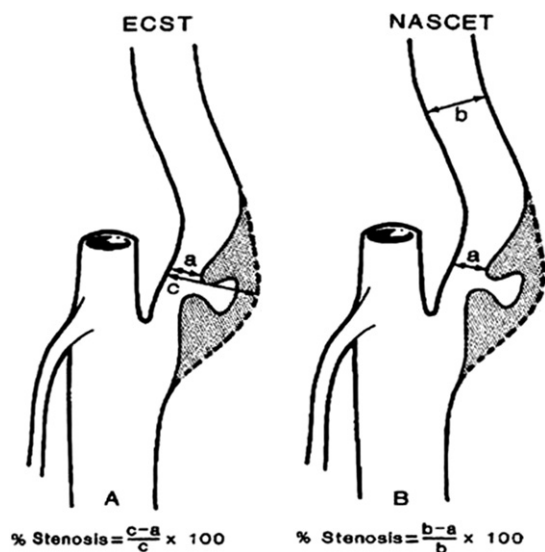
The need for relatively high volumes of iodinated contrast media restricts the application of CTA to patients with adequate renal function. Although several strategies have been evaluated, discussion of medical therapies designed to reduce the risk of contrast-induced nephropathy is beyond the scope of this document. Faster imaging acquisition and a greater number of detector rows ameliorate this problem. As with sonography, heavily calcified lesions are difficult to assess for severity of stenosis, and the differentiation of subtotal from complete arterial occlusion can be problematic (216). Metallic dental implants or surgical clips in the neck generate artifacts that may obscure the cervical arteries. Obese or uncooperative (moving) patients are difficult to scan accurately, but pacemakers and defibrillators implanted in the chest are not impediments to CTA of the cervical arteries.

Other perfusion-based CT imaging techniques can provide additional information about cerebral blood flow and help determine the hemodynamic significance of stenotic lesions in the extracranial and intracranial arteries that supply the brain.

As is the case with carotid duplex sonography, transcranial Doppler sonography, MRI, and radionuclide imaging to assess cerebral perfusion, there is no convincing evidence that available imaging methods reliably predict the risk of subsequent stroke, and there is no adequate foundation on which to recommend the broad application of these techniques for evaluation of patients with cervical arterial disease.

### 5.5. Catheter-Based Contrast Angiography

Conventional digital angiography remains the standard against which other methods of vascular imaging are compared in patients with ECVD. There are several methods for measuring stenosis in the internal carotid arteries that yield markedly different measurements in vessels with the same degree of anatomic narrowing (Figure 3), but the method used in NASCET is dominant and has been used in most modern clinical trials. It is essential to specify the methodology used both in the evaluation of individual patients with ECVD and in the assessment of the accuracy of noninvasive imaging techniques. Among the impediments to angiography as a screening modality are its costs and associated risks. The most feared complication is stroke, the incidence of which is <1% when the procedure is performed by experienced physicians (218–225). Substantially higher rates of stroke have been reported with diagnostic angiography in some series, most notably in ACAS (71), in which the incidence was 1.2% because of unusually frequent complications at a few centers. Complication rates in other studies have been substantially lower (226), and most authorities regard a stroke rate >1% with diagnostic angiography as unacceptable (227). Angiogra-



**Figure 3. Angiographic Methods for Determining Carotid Stenosis Severity**

ECST indicates European Carotid Surgery Trial; and NASCET, North American Symptomatic Carotid Endarterectomy Trial. Reprinted with permission from Osborn (217).

phy may be the preferred method for evaluation of ECVD when obesity, renal dysfunction, or indwelling ferromagnetic material renders CTA or MRA technically inadequate or impossible, and angiography is appropriate when noninvasive imaging studies produce conflicting results. In practice, however, catheter-based angiography is unnecessary for diagnostic evaluation of most patients with ECVD and is used increasingly as a therapeutic revascularization maneuver in conjunction with stent deployment.

### 5.6. Selection of Vascular Imaging Modalities for Individual Patients

Because of its widespread availability and relatively low cost, carotid duplex ultrasonography is favored for screening patients at moderate risk of disease. When this method does not suggest significant stenosis in a symptomatic patient, further anatomic assessment should be considered by use of other modalities capable of detecting more proximal or distal disease. If ultrasound imaging results are equivocal or indeterminate, MRA or CTA may be performed to confirm the extent of atherosclerotic disease and provide additional anatomic information. Conversely, patients with a high pretest probability of disease may be studied initially by MRA or CTA to more completely evaluate the cerebral vessels distal to the aortic arch, because sonographic imaging alone does not provide assessment of intrathoracic or intracranial lesions beyond the limited range of the ultrasound probe. Moreover, duplex ultrasonography may overestimate the severity of stenosis contralateral to internal carotid occlusion. This is an important consideration during the selection of asymptomatic patients for carotid revascularization, and in such cases, confirmation of the sonographic findings by another modality is recommended. Patients poorly suited to MRA because of claustrophobia, im-

planted pacemakers, or other factors may be evaluated by CTA, whereas those with extensive calcification should undergo MRA. In patients with renal insufficiency, for whom exposure to iodinated radiographic contrast stands as a relative contraindication to CTA, the relatively rare occurrence of nephrogenic systemic fibrosis has reduced the use of gadolinium contrast-enhanced MRA as well.

Because high-quality imaging potentially can be obtained by any of the recommended modalities, these are simply general suggestions. Given the variation in image quality and resource availability at one facility compared with another, other factors may govern the selection of the optimum testing modality for a particular patient. In general, though, conventional angiography is usually reserved for patients in whom adequate delineation of disease cannot be obtained by other methods, when noninvasive imaging studies have yielded discordant results, or for those with renal dysfunction in whom evaluation of a single vascular territory would limit exposure to contrast material. A patient presenting with a left hemispheric stroke or TIA, for instance, might best be evaluated by selective angiography of the left common carotid artery, which entails a small volume of contrast that is unlikely to exacerbate renal insufficiency while providing definitive images of the culprit vessel and its branches.

## 6. Medical Therapy for Patients With Atherosclerotic Disease of the Extracranial Carotid or Vertebral Arteries

### 6.1. Recommendations for the Treatment of Hypertension

#### CLASS I

1. Antihypertensive treatment is recommended for patients with hypertension and asymptomatic extracranial carotid or vertebral atherosclerosis to maintain blood pressure below 140/90 mm Hg (111,228-231). (Level of Evidence: A)

#### CLASS IIa

1. Except during the hyperacute period, antihypertensive treatment is probably indicated in patients with hypertension and symptomatic extracranial carotid or vertebral atherosclerosis, but the benefit of treatment to a specific target blood pressure (e.g., below 140/90 mm Hg) has not been established in relation to the risk of exacerbating cerebral ischemia. (Level of Evidence: C)

Hypertension increases the risk of stroke, and the relationship between blood pressure and stroke is continuous (232-234). For each 10-mm Hg increase in blood pressure, the risk of stroke increases by 30% to 45% (235). Conversely, antihypertensive therapy reduces the risk of stroke (230); meta-analysis of more than 40 trials and >188,000 patients found a 33% decreased risk of stroke for each 10-mm Hg reduction in systolic blood pressure to 115/75 mm Hg (230,231). A systematic review of 7 randomized trials found that antihypertensive therapy reduced the risk of recurrent stroke by 24% (228). The type of therapy appears less important than the response (230). For these reasons,

the AHA/ASA Guidelines for the Prevention of Stroke in Patients With Ischemic Stroke or Transient Ischemic Attack recommend antihypertensive treatment beyond the hyperacute period for patients who have experienced ischemic stroke or TIA (111).

Epidemiological studies, including the ARIC study (17), Cardiovascular Health Study (236), Framingham Heart Study (237), and MESA (Multi-Ethnic Study of Atherosclerosis) (238), among others, found an association between hypertension and the risk of developing carotid atherosclerosis (17,236,238–240). In the Framingham Heart Study, for example, there was a 2-fold greater risk of carotid stenosis >25% for each 20-mm Hg increase in systolic blood pressure (237). In SHEP (Systolic Hypertension in the Elderly Program), systolic blood pressure  $\geq$ 160 mm Hg was the strongest independent predictor of carotid stenosis (241). Meta-analysis of 17 hypertension treatment trials involving approximately 50,000 patients found a 38% reduction in risk of stroke and 40% reduction in fatal stroke with antihypertensive therapy (242). These beneficial effects were shared among whites and blacks across a wide age range (242). In patients who had experienced ischemic stroke, administration of a combination of the angiotensin-converting enzyme inhibitor perindopril and a diuretic (indapamide) significantly reduced the risk of recurrent ischemic events compared with placebo among 6105 participants randomized in the PROGRESS (Preventing Strokes by Lowering Blood Pressure in Patients With Cerebral Ischemia) trial (RR reduction 28%, 95% CI 17% to 38%;  $p < 0.0001$ ) (229). The protective value of blood pressure lowering extends even to patients without hypertension, as demonstrated in the HOPE (Heart Outcomes Protection Evaluation) trial, in which patients with systemic atherosclerosis randomized to treatment with ramipril displayed a significantly lower risk of stroke than those given a placebo (RR 0.68;  $p < 0.001$ ) (243).

In symptomatic patients with severe carotid artery stenosis, however, it is not known whether antihypertensive therapy is beneficial or confers harm by reducing cerebral perfusion. In some patients with severe carotid artery stenosis, impaired cerebrovascular reactivity may be associated with an increased risk of ipsilateral ischemic events (244). The Seventh Report of the Joint National Committee for the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) recommends blood pressure lowering for patients with ischemic heart disease or PAD but offers no specific recommendation for treatment of hypertension in patients with ECVD (245).

## 6.2. Cessation of Tobacco Smoking

### 6.2.1. Recommendation for Cessation of Tobacco Smoking

#### CLASS I

1. Patients with extracranial carotid or vertebral atherosclerosis who smoke cigarettes should be advised to quit smoking and offered

smoking cessation interventions to reduce the risks of atherosclerosis progression and stroke (246–250). (Level of Evidence: B)

Smoking increases the RR of ischemic stroke by 25% to 50% (247–253). Stroke risk decreases substantially within 5 years in those who quit smoking compared with continuing smokers (248,250). In large epidemiological studies, cigarette smoking has been associated with extracranial carotid artery IMT and the severity of carotid artery stenosis (23,254–257). In the ARIC study, current and past cigarette smoking, respectively, were associated with 50% and 25% increases in the progression of carotid IMT over 3 years compared with nonsmokers (252). In the Framingham Heart Study, extracranial carotid artery stenosis correlated with the quantity of cigarettes smoked over time (237). In the Cardiovascular Health Study, the severity of carotid artery stenosis was greater in current smokers than in former smokers, and there was a significant relationship between the severity of carotid stenosis and pack-years of exposure to tobacco (239). The RRs of finding >60% carotid stenosis were 1.5 and 3.9 among cigarette smokers with cerebral ischemia in the NOMASS and the BCID (Berlin Cerebral Ischemia Databank) studies, respectively (258).

## 6.3. Control of Hyperlipidemia

### 6.3.1. Recommendations for Control of Hyperlipidemia

#### CLASS I

1. Treatment with a statin medication is recommended for all patients with extracranial carotid or vertebral atherosclerosis to reduce low-density lipoprotein (LDL) cholesterol below 100 mg/dL (111,259,260). (Level of Evidence: B)

#### CLASS IIa

1. Treatment with a statin medication is reasonable for all patients with extracranial carotid or vertebral atherosclerosis who sustain ischemic stroke to reduce LDL-cholesterol to a level near or below 70 mg/dL (259). (Level of Evidence: B)
2. If treatment with a statin (including trials of higher-dose statins and higher-potency statins) does not achieve the goal selected for a patient, intensifying LDL-lowering drug therapy with an additional drug from among those with evidence of improving outcomes (i.e., bile acid sequestrants or niacin) can be effective (261–264). (Level of Evidence: B)
3. For patients who do not tolerate statins, LDL-lowering therapy with bile acid sequestrants and/or niacin is reasonable (261,263,265). (Level of Evidence: B)

The relationship between cholesterol and ischemic stroke is not as evident as that between cholesterol and MI, and findings from population-based studies are inconsistent. In the MR FIT (Multiple Risk Factor Intervention Trial), comprising more than 350,000 men, the RR of death increased progressively with serum cholesterol, exceeding 2.5 in those with the highest levels (266). An analysis of 45 prospective observational cohorts involving approximately 450,000 individuals, however, found no association of hypercholesterolemia with stroke (267). In the ARIC study, the relationships between lipid values and incident ischemic

stroke were weak (268). Yet in the Women's Health Study, a prospective cohort study among 27,937 U.S. women 45 years of age and older, total and LDL cholesterol levels were strongly associated with increased risk of ischemic stroke (269). The RR of a future ischemic stroke in the highest quintile of non-high-density lipoprotein (HDL) cholesterol levels compared with the lowest quintile was 2.25. In a meta-analysis of 61 prospective observational studies, most conducted in western Europe or North America, consisting of almost 900,000 adults between the ages of 40 and 89 years without previous disease and nearly 12 million person-years at risk, total cholesterol was only weakly related to ischemic stroke mortality in the general population between ages 40 and 59 years, and this was largely accounted for by the association of cholesterol with hypertension (270). Moreover, in those with below-average blood pressures, a positive relation was seen only in middle age. At older ages (70 to 89 years) and for those with systolic blood pressure >145 mm Hg, total serum cholesterol was inversely related to hemorrhagic and total stroke mortality (270). Epidemiological studies, however, have consistently found an association between cholesterol and carotid artery atherosclerosis as determined by measurement of IMT (25,255,271). In the Framingham Heart Study, the RR of carotid artery stenosis >25% was approximately 1.1 for every 10-mg/dL increase in total cholesterol (237). In the MESA study, carotid plaque lipid core detected by MRI was strongly associated with total cholesterol (272).

Lipid-lowering therapy with statins reduces the risk of stroke in patients with atherosclerosis (273). Two large meta-analyses examined the effect of statins on the risk of stroke among patients with CAD or other manifestations of atherosclerosis or at high risk for atherosclerosis (274,275). One such analysis of 26 trials comprising >90,000 patients found that statins reduced the risk of all strokes by approximately 21% (274), with stroke risk decreasing 15.6% for each 10% reduction in serum LDL cholesterol (274). Another meta-analysis of 9 trials comprising more than 65,000 patients found a 22% reduction in ischemic stroke per 1-mmol/L (40 mg/dL) reduction in serum LDL cholesterol (275). There was no effect in either meta-analysis of lowering LDL cholesterol on the risk of hemorrhagic stroke.

A randomized trial, SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels), prospectively compared the effect of atorvastatin (80 mg daily) against placebo on the risk of stroke among patients with recent stroke or TIA (259). Statin therapy reduced the absolute risk of stroke at 5 years by 2.2%, the RR of all stroke by 16%, and the RR of ischemic stroke by 22% (206).

There are multiple causes of ischemic stroke, and only a limited number of studies have specifically examined the effect of statins on stroke in patients with ECVD; the available data suggest that statins are beneficial. In a secondary subgroup analysis of the trial data, there was no heterogeneity in the treatment effect for the primary end-

point (fatal and nonfatal stroke) or for secondary endpoints between patients with and without carotid stenosis (276). In those with carotid stenosis, greater benefit occurred in terms of reduction of all cerebrovascular and cardiovascular events combined, and treatment with atorvastatin was associated with a 33% reduction in the risk of any stroke (HR 0.67, 95% CI 0.47 to 0.94;  $p=0.02$ ) and a 43% reduction in risk of major coronary events (HR 0.57, 95% CI 0.32 to 1.00;  $p=0.05$ ). Subsequent carotid revascularization was reduced by 56% (HR 0.44, 95% CI 0.24 to 0.79;  $p=0.006$ ) in the group randomized to atorvastatin (276). Hence, consistent with the overall results of the trial, lipid lowering with high-dose atorvastatin reduced the risk of cerebrovascular events in particular and cardiovascular events in general in patients with and without carotid stenosis, yet those with carotid stenosis derived greater benefit (276).

Statins reduce the risk of MI by 23% and cardiovascular death by 19% in patients with CAD (275). Moreover, statin therapy reduces progression or induces regression of carotid atherosclerosis. In the Heart Protection Study, there was a 50% reduction in CEA in patients randomized to statin therapy (277). A meta-analysis of 9 trials of patients randomized to statin treatment or control found the statin effect to be closely associated with LDL cholesterol reduction. Each 10% reduction in LDL cholesterol reduced the risk of all strokes by 15.6% (95% CI 6.7 to 23.6) and of carotid IMT by 0.73% per year (95% CI 0.27 to 1.19) (274). METEOR (Measuring Effects on Intima-Media Thickness: An Evaluation of Rosuvastatin) found that compared with placebo, rosuvastatin reduced progression of carotid IMT over 2 years in patients with low Framingham risk scores and elevated serum LDL cholesterol levels (278). Two of the trials included in the meta-analysis compared greater- to lesser-intensity statin therapy. In the ARBITER (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol) trial, carotid IMT regressed after 12 months of treatment with atorvastatin (80 mg daily) but remained unchanged after treatment with pravastatin (40 mg daily) (279). The LDL cholesterol levels in the atorvastatin and pravastatin treatment groups were 76 23 and 110 30 mg/dL, respectively. In the ASAP (Atorvastatin versus Simvastatin on Atherosclerosis Progression) trial of patients with familial hypercholesterolemia, carotid IMT decreased after 2 years of treatment with 80 mg of atorvastatin daily but increased in patients randomized to 40 mg of simvastatin daily (280).

It is less clear whether lipid-modifying therapies other than high-dose statins reduce the risk of ischemic stroke or the severity of carotid artery disease. Among patients participating in the Coronary Drug Project, niacin reduced the 15-year mortality rate (9 years after study completion), primarily by decreasing the incidence of death caused by coronary disease, with a relatively small beneficial trend in the risk of death caused by cerebrovascular disease (281). In the Veterans Affairs HDL Intervention trial of men with CAD and low serum HDL cholesterol levels, gemfibrozil

reduced the risk of total strokes, which consisted mainly of ischemic strokes (282). Fenofibrate did not reduce the stroke rate in the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study of patients with diabetes mellitus (283). In the CLAS (Cholesterol Lowering Atherosclerosis) trial, the combination of colestipol and niacin reduced progression of carotid IMT (58). In the ARBITER-2 study of patients with CAD and low levels of HDL cholesterol, carotid IMT progression did not differ significantly after the addition of extended-release niacin to statin therapy compared with statin therapy alone, although there was a trend favoring the dual therapy (284). In the ENHANCE (Effect of Combination Ezetimibe and High-Dose Simvastatin vs. Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia) study, in patients with familial hypercholesterolemia, the addition of ezetimibe to simvastatin did not affect progression of carotid IMT more than the use of simvastatin alone (285).

#### 6.4. Management of Diabetes Mellitus

##### 6.4.1. Recommendations for Management of Diabetes Mellitus in Patients With Atherosclerosis of the Extracranial Carotid or Vertebral Arteries

###### CLASS IIa

1. Diet, exercise, and glucose-lowering drugs can be useful for patients with diabetes mellitus and extracranial carotid or vertebral artery atherosclerosis. The stroke prevention benefit, however, of intensive glucose-lowering therapy to a glycosylated hemoglobin A1c level less than 7.0% has not been established (286,287). (Level of Evidence: A)
2. Administration of statin-type lipid-lowering medication at a dosage sufficient to reduce LDL cholesterol to a level near or below 70 mg/dL is reasonable in patients with diabetes mellitus and extracranial carotid or vertebral artery atherosclerosis for prevention of ischemic stroke and other ischemic cardiovascular events (288). (Level of Evidence: B)

The risk of ischemic stroke in patients with diabetes mellitus is increased 2- to 5-fold (289–291) compared with patients without diabetes. The Cardiovascular Health Study investigators reported that elevated fasting and postchallenge glucose levels were associated with an increased risk of stroke (292), and diabetes was associated with carotid IMT and the severity of carotid artery stenosis (24). In the Insulin Resistance Atherosclerosis Study, diabetes and fasting glucose levels were associated with carotid IMT, and carotid IMT progressed twice as rapidly in patients with diabetes as in those without diabetes (293–295). Similarly, in the ARIC study, diabetes was associated with progression of carotid IMT (254,291,296), and in the Rotterdam study, diabetes predicted progression to severe carotid obstruction (297). In the EDIC (Epidemiology of Diabetes Interventions and Complications) study, the progression of carotid IMT was greater in patients with diabetes than in those without diabetes (298) and less in patients with diabetes treated with intensive insulin therapy than in those managed more

conventionally. In several randomized studies, pioglitazone caused less progression or induced regression of carotid IMT compared with glimepiride (299,300).

Several trials examined the effect of intensive glucose control on vascular events, with stroke included as a secondary outcome. In the United Kingdom Prospective Diabetes study, intensive treatment of blood glucose, compared with conventional management, did not affect the risk of stroke in patients with type 2 diabetes mellitus (301). In the ACCORD (Action to Control Cardiovascular Risk in Diabetes) (286) and ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) (287) trials, intensive treatment to achieve glycosylated hemoglobin levels <6.0% and <6.5%, respectively, did not reduce the risk of stroke in patients with type 2 diabetes mellitus compared with conventional treatment. In patients with type 1 diabetes mellitus, intensive insulin treatment reduced rates of nonfatal MI, stroke, or death due to cardiovascular disease by 57% during the long-term follow-up phase of the DDCT (Diabetes Control and Complications Trial)/EDIC study, but the absolute risk reduction was <1% during 17 years of follow-up. These observations suggest that it would be necessary to treat 700 patients for 17 years to prevent cardiovascular events in 19 patients; the NNT per year to prevent a single event equals 626, a relatively low return on effort for prevention of stroke (302). Effects on fatal and nonfatal strokes were not reported separately (302).

At least as important as treatment of hyperglycemia is aggressive control of other modifiable risk factors in patients with diabetes. In the UK-TIA (United Kingdom Transient Ischemic Attack) trial, treatment of hypertension was more useful than blood glucose control in reducing the rate of recurrent stroke (303). In patients with type 2 diabetes mellitus who had normal serum levels of LDL cholesterol, administration of 10 mg of atorvastatin daily was safe and effective in reducing the risk of cardiovascular events by 37% and of stroke by 48% (288). Although the severity of carotid atherosclerosis was not established in the trial cohort, the findings suggest that administration of a statin may be beneficial in patients with diabetes even when serum lipid levels are not elevated. Other agents, such as those of the fibrate class, do not appear to offer similar benefit in this situation (283,304).

#### 6.5. Hyperhomocysteinemia

Hyperhomocysteinemia increases the risk of stroke. Meta-analysis of 30 studies comprising more than 16,000 patients found a 25% difference in plasma homocysteine concentration, which corresponded to approximately 3 micromoles per liter, to be associated with a 19% difference in stroke risk (305). The risk of developing >25% extracranial carotid stenosis is increased 2-fold among elderly patients with elevated homocysteine levels (306), and plasma concentrations of folate and pyridoxal 5' phosphate are inversely associated with carotid stenosis (306). In the ARIC study,

increased carotid IMT was approximately 3-fold more likely among participants with the highest than the lowest quintile of homocysteine (307), and findings were similar in the Perth Carotid Ultrasound Disease Assessment study (308), but adjustment for renal function eliminated or attenuated the relationship between homocysteine levels and carotid IMT (309).

Stroke rates decreased and average plasma homocysteine concentrations fell after folic acid fortification of enriched grain products in the United States and Canada, but not in England and Wales, where fortification did not occur (310). Meta-analysis of 8 randomized primary prevention trials found that folic acid supplementation reduced the risk of stroke by 18% (311). Despite these observations, studies of patients with established vascular disease have not confirmed a benefit of homocysteine lowering by B-complex vitamin therapy on cardiovascular outcomes, including stroke. In the VISP (Vitamin Intervention for Stroke Prevention) study, a high-dose formulation of pyridoxine (B<sub>6</sub>), cobalamin (B<sub>12</sub>), and folic acid lowered the plasma homocysteine level 2 micromoles per liter more than a low-dose formulation of these vitamins but did not reduce the risk of recurrent ischemic stroke (312). Among patients with established vascular disease or diabetes, a combination of vitamins B<sub>6</sub>, B<sub>12</sub>, and folic acid lowered plasma homocysteine by 2.4 micromoles per liter without effects on the composite endpoint of cardiovascular death, MI, or stroke or its individual components (313). Similarly, this combination of B-complex vitamins lowered plasma homocysteine concentration by more than 2 micromoles per liter (18.5%) in women with established cardiovascular disease or 3 or more risk factors but did not alter rates of the primary composite endpoint of MI, stroke, coronary revascularization, or cardiovascular death or the secondary endpoint of stroke (314).

Given that in patients with CAD, hyperhomocysteinemia is a marker of risk but not a target for treatment and that vitamin supplementation does not appear to affect clinical outcomes, the writing committee considers the evidence insufficient to justify a recommendation for or against routine therapeutic use of vitamin supplements in patients with ECVD.

## 6.6. Obesity and the Metabolic Syndrome

The metabolic syndrome, defined by the World Health Organization and the National Cholesterol Education Program on the basis of blood glucose, hypertension, dyslipidemia, body mass index, waist/hip ratio, and urinary albumin excretion, is associated with carotid atherosclerosis after adjustment for other risk factors in men and women across several age strata and ethnic groups (315–324). This relationship to carotid atherosclerosis is strengthened in proportion to the number of components of metabolic syndrome present ( $p < 0.001$ ) (325–327). With regard to the individual components, the relationship appears strongest for hypertension (317,320,321,326,328,329), with hyper-

cholesterolemia and obesity also related to carotid atherosclerosis in several reports (317,330). Abdominal adiposity bears a graded association with the risk of stroke and TIA independent of other vascular disease risk factors (331).

## 6.7. Physical Inactivity

Physical inactivity is a well-documented, modifiable risk factor for stroke, with a prevalence of 25%, an attributable risk of 30%, and an RR of 2.7, but the risk reduction associated with treatment is unknown (33,332). Nevertheless, several meta-analyses and observational studies suggest a lower risk of stroke among individuals engaging in moderate to high levels of physical activity (333). The relationship between physical activity and carotid IMT as a marker of subclinical atherosclerosis has been inconsistent (334–337). Furthermore, it is not clear whether exercise alone is beneficial with respect to stroke risk in the absence of effects on other risk factors, such as reduction of obesity and improvements in serum lipid values and glycemic control.

## 6.8. Antithrombotic Therapy

### 6.8.1. Recommendations for Antithrombotic Therapy in Patients With Extracranial Carotid Atherosclerotic Disease Not Undergoing Revascularization

#### CLASS I

1. Antiplatelet therapy with aspirin, 75 to 325 mg daily, is recommended for patients with obstructive or nonobstructive atherosclerosis that involves the extracranial carotid and/or vertebral arteries for prevention of MI and other ischemic cardiovascular events, although the benefit has not been established for prevention of stroke in asymptomatic patients (33,260,305,338). (*Level of Evidence: A*)
2. In patients with obstructive or nonobstructive extracranial carotid or vertebral atherosclerosis who have sustained ischemic stroke or TIA, antiplatelet therapy with aspirin alone (75 to 325 mg daily), clopidogrel alone (75 mg daily), or the combination of aspirin plus extended-release dipyridamole (25 and 200 mg twice daily, respectively) is recommended (*Level of Evidence: B*) and preferred over the combination of aspirin with clopidogrel (260,305,339–342) (*Level of Evidence: B*). Selection of an antiplatelet regimen should be individualized on the basis of patient risk factor profiles, cost, tolerance, and other clinical characteristics, as well as guidance from regulatory agencies.
3. Antiplatelet agents are recommended rather than oral anticoagulation for patients with atherosclerosis of the extracranial carotid or vertebral arteries with (343,344) (*Level of Evidence: B*) or without (*Level of Evidence: C*) ischemic symptoms. (For patients with allergy or other contraindications to aspirin, see Class IIa recommendation #2, this section.)

#### CLASS IIa

1. In patients with extracranial cerebrovascular atherosclerosis who have an indication for anticoagulation, such as atrial fibrillation or a mechanical prosthetic heart valve, it can be beneficial to administer a vitamin K antagonist (such as warfarin, dose-adjusted to achieve a target international normalized ratio [INR] of 2.5 [range 2.0 to

**Table 6. American Heart Association/American Stroke Association Guidelines for Antithrombotic Therapy in Patients With Ischemic Stroke of Noncardioembolic Origin (Secondary Prevention)**

Guideline	Classification of Recommendation, Level of Evidence*
Antiplatelet agents recommended over oral anticoagulants	I, A
For initial treatment, aspirin (50–325 mg/d),† the combination of aspirin and extended-release dipyridamole, or clopidogrel	I, A
Combination of aspirin and extended-release dipyridamole recommended over aspirin alone	I, B
Clopidogrel may be considered instead of aspirin alone	IIb, B
For patients hypersensitive to aspirin, clopidogrel is a reasonable choice	IIa, B
Addition of aspirin to clopidogrel increases risk of hemorrhage	III, A

\*Recommendation: I indicates treatment is useful and effective; IIa, conflicting evidence or divergence of opinion regarding treatment usefulness and effectiveness; IIb, usefulness/efficacy of treatment is less well established; and III, treatment is not useful or effective. Level of Evidence: A indicates data from randomized clinical trials; and B, data from a single randomized clinical trial or nonrandomized studies. †Insufficient data are available to make evidence-based recommendations about antiplatelet agents other than aspirin.

Modified with permission from Sacco et al. (111).

3.0]) for prevention of thromboembolic ischemic events (345). (Level of Evidence: C)

2. For patients with atherosclerosis of the extracranial carotid or vertebral arteries in whom aspirin is contraindicated by factors other than active bleeding, including allergy, either clopidogrel (75 mg daily) or ticlopidine (250 mg twice daily) is a reasonable alternative. (Level of Evidence: C)

**CLASS III: NO BENEFIT**

1. Full-intensity parenteral anticoagulation with unfractionated heparin or low-molecular-weight heparinoids is not recommended for patients with extracranial cerebrovascular atherosclerosis who develop transient cerebral ischemia or acute ischemic stroke (2,346,347). (Level of Evidence: B)

2. Administration of clopidogrel in combination with aspirin is not recommended within 3 months after stroke or TIA (340). (Level of Evidence: B)

Although antiplatelet drugs reduce the risk of stroke compared with placebo in patients with TIA or previous stroke (305) (Table 6), no adequately powered controlled studies have demonstrated the efficacy of platelet-inhibitor drugs for prevention of stroke in asymptomatic patients with ECVD. The Asymptomatic Cervical Bruit Study compared enteric-coated aspirin, 325 mg daily, against placebo in neurologically asymptomatic patients with carotid stenosis of >50% as determined by duplex ultrasonography. On the basis of just under 2 years of follow-up, the annual rate of ischemic events and death due to any cause was 12.3% in the placebo group and 11.0% in the aspirin group (p=0.61), but the sample size of 372 patients may have been insufficient to detect a clinically meaningful difference (348). In the Veterans Affairs Cooperative Study Group (76) and ACAS

(74), the stroke rates were approximately 2% per year in groups treated with aspirin alone (74,76,349). No controlled studies of stroke have shown superior results with antiplatelet agents other than aspirin in patients with asymptomatic ECVD.

Randomized studies have compared aspirin with CEA in symptomatic patients (111). In NASCET, patients with >70% stenosis had a stroke rate of 24% after 18 months, and those with 50% to 69% stenosis had a stroke rate of 22% over 5 years with antiplatelet therapy (predominantly aspirin) and without revascularization (84). WARSS (Warfarin-Aspirin Recurrent Stroke Study) compared aspirin and warfarin for stroke prevention in patients with recent stroke (343). In the subgroup with severe large-artery stenosis or occlusion (259 patients), including ECVD, there was no benefit of warfarin over aspirin after 2 years. Patients with carotid stenosis sufficiently severe to warrant surgical intervention were excluded, which limits application of the results.

The combination of clopidogrel and aspirin did not reduce stroke risk compared with either treatment alone in the MATCH (Management of Atherothrombosis With Clopidogrel in High-Risk Patients) and CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trials (340,350). However, in ESPS-2 (Second European Stroke Prevention Study), the combination of 25 mg of aspirin twice daily plus 200 mg of extended-release dipyridamole twice daily was superior to the use of only 50 mg of aspirin daily in patients with prior TIA or stroke (341). Outcomes in a subgroup defined on the basis of ECVD have not been reported.

The PROFESS (Prevention Regimen for Effectively Avoiding Second Strokes) trial directly compared the combination of extended-release dipyridamole and aspirin versus clopidogrel (342) in 20,332 patients with prior stroke. Over a mean follow-up of 2.5 years, recurrent stroke occurred in 9% of patients in the aspirin-plus-dipyridamole group and in 8.8% of those assigned to clopidogrel (HR 1.01, 95% CI 0.92 to 1.11). Neither treatment was superior for prevention of recurrent stroke, and the risk of the composite outcome of stroke, MI, or vascular death was identical in the 2 treatment groups (13.1%). Major hemorrhagic events were more common in patients assigned to extended-release dipyridamole plus aspirin (4.1%) than in those assigned to clopidogrel (3.6%; HR 1.15, 95% CI 1.00 to 1.32), including intracranial hemorrhage (HR 1.42, 95% CI 1.11 to 1.83). The net risk of recurrent stroke or major hemorrhage was similar in the 2 groups (11.7% with aspirin plus dipyridamole versus 11.4% with clopidogrel; HR 1.03, 95% CI 0.95 to 1.11) (342). Accordingly, although clopidogrel monotherapy was associated with equal efficacy and lower risk of hemorrhage than the combination of dipyridamole plus aspirin and no less efficacy than the combination of clopidogrel plus aspirin, variations in the response to clopidogrel based on genetic factors and drug interactions make individualized treatment selection appropriate for optimum stroke prophylaxis.



Optimum therapy for patients experiencing recurrent cerebral ischemia during antiplatelet therapy has not been addressed in adequately powered randomized trials. Lacking firm evidence, physicians choose an alternative antiplatelet regimen in such cases. Aspirin or clopidogrel resistance, defined as the inability of these agents to inhibit platelet function, is one potential cause of failure in stroke prevention. There is no agreement on which platelet function test should be used to determine aspirin or clopidogrel resistance. In a study of 129 patients admitted with a diagnosis of stroke, TIA, or ECVD, no antiplatelet effect of aspirin or clopidogrel was demonstrated in 37% of cases. Aspirin resistance was more frequent in those taking 81 mg daily than in those taking 325 mg daily and was higher in those taking enteric-coated preparations of aspirin than in those taking uncoated aspirin (351). Clopidogrel resistance has also been described (352). Its effectiveness is diminished when conversion into its active form by the cytochrome P450 system, which depends primarily on the function of CYP2C19, is inhibited either because of genetic variations or owing to drugs that impede CYP2C19 activity, which adversely affects clopidogrel metabolism. Whether variation in the response to aspirin or clopidogrel is associated with a greater risk of stroke has not been established, and it is not known whether testing for or treatment of drug resistance improves outcomes.

In 2010, the U.S. Food and Drug Administration issued a boxed warning to clinicians that addressed the use of pharmacogenomic testing to identify patients with altered clopidogrel metabolism who were thus at risk of a suboptimal clinical response to clopidogrel (353,354). Variability in response to clopidogrel results from both clinical and genetic factors; genotyping and measurement of platelet inhibition may be appropriate in patients with cerebrovascular disease who have experienced ischemic events despite compliance with clopidogrel therapy or in those at high risk for such events. Genetic variability in CYP enzymes that affect platelet function has been associated with adverse outcomes. Although CYP2C19\*2 is the most common genetic variant associated with impaired response to clopidogrel, other genetic polymorphisms may also contribute to the variable responsiveness of individual patients to clopidogrel, and the specific role of individual genetic polymorphisms remains uncertain.

Information about the predictive value of pharmacogenomic testing is the focus of ongoing studies, but data on the role of genotyping in the selection of antiplatelet therapy for patients with symptomatic or asymptomatic ECVD are presently insufficient to justify specific or general recommendations. New agents such as prasugrel and ticagrelor, which are not affected by CYP2C19 genetic variants, may prove to be more effective than clopidogrel in conventional doses but have not been evaluated adequately in patients with carotid or vertebral artery disease.

Early administration of unfractionated heparin or low-molecular-weight heparin/danaparoid did not improve the outcome of patients with acute ischemic stroke (355).

## 6.8.2. Nonsteroidal Anti-Inflammatory Drugs

In a population-based stroke registry, nonsteroidal anti-inflammatory drugs (NSAIDs) were not associated with either an increased risk of hemorrhagic stroke or protection against initial ischemic stroke (357). A systematic review and meta-analysis of randomized trials involving cyclo-oxygenase type 2 inhibitors found no significant incremental risk of events compared with placebo or nonselective NSAIDs (OR 1.03, 95% CI 0.71 to 1.50 and OR 0.86, 95% CI 0.64 to 1.16, respectively) (358). Hence, in available data sets, the vascular risk associated with NSAIDs in general and cyclo-oxygenase type 2 inhibitors in particular is more apparent for MI than for stroke. The writing committee makes no recommendation for or against the use of NSAIDs because of a lack of evidence specifically pertinent to patients with ECVD, except to note the association of the use of these drugs with increased risks of both MI and gastrointestinal bleeding.

## 7. Revascularization

### 7.1. Recommendations for Selection of Patients for Carotid Revascularization\*

#### CLASS I

1. Patients at average or low surgical risk who experience nondisabling ischemic stroke<sup>†</sup> or transient cerebral ischemic symptoms, including hemispheric events or amaurosis fugax, within 6 months (symptomatic patients) should undergo CEA if the diameter of the lumen of the ipsilateral internal carotid artery is reduced more than 70%<sup>‡</sup> as documented by noninvasive imaging (20,83) (Level of Evidence: A) or more than 50% as documented by catheter angiography (20,70,83,359) (Level of Evidence: B) and the anticipated rate of perioperative stroke or mortality is less than 6%.
2. CAS is indicated as an alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the internal carotid artery is reduced by more than 70% as documented by noninvasive imaging or more than 50% as documented by catheter angiography and the anticipated rate of periprocedural stroke or mortality is less than 6% (360). (Level of Evidence: B)
3. Selection of asymptomatic patients for carotid revascularization should be guided by an assessment of comorbid conditions, life expectancy, and other individual factors and should include a thorough discussion of the risks and benefits of the procedure with an understanding of patient preferences. (Level of Evidence: C)

#### CLASS IIa

1. It is reasonable to perform CEA in asymptomatic patients who have more than 70% stenosis of the internal carotid artery if the risk of perioperative stroke, MI, and death is low (74,76,359,361–363). (Level of Evidence: A)

\*Recommendations for revascularization in this section assume that operators are experienced, having successfully performed the procedures in >20 cases with proper technique and a low complication rate based on independent neurological evaluation before and after each procedure.

<sup>†</sup>Nondisabling stroke is defined by a residual deficit associated with a score ≤2 according to the Modified Rankin Scale.

<sup>‡</sup>The degree of stenosis is based on catheter-based or noninvasive vascular imaging compared with the distal arterial lumen or velocity measurements by duplex ultrasonography. See Section 7 for details.

2. It is reasonable to choose CEA over CAS when revascularization is indicated in older patients, particularly when arterial pathoanatomy is unfavorable for endovascular intervention (360,364–368). (Level of Evidence: B)
3. It is reasonable to choose CAS over CEA when revascularization is indicated in patients with neck anatomy unfavorable for arterial surgery (369–373).<sup>§</sup> (Level of Evidence: B)
4. When revascularization is indicated for patients with TIA or stroke and there are no contraindications to early revascularization, intervention within 2 weeks of the index event is reasonable rather than delaying surgery (374). (Level of Evidence: B)

#### **CLASS IIb**

1. Prophylactic CAS might be considered in highly selected patients with asymptomatic carotid stenosis (minimum 60% by angiography, 70% by validated Doppler ultrasound), but its effectiveness compared with medical therapy alone in this situation is not well established (360). (Level of Evidence: B)
2. In symptomatic or asymptomatic patients at high risk of complications for carotid revascularization by either CEA or CAS because of comorbidities,<sup>||</sup> the effectiveness of revascularization versus medical therapy alone is not well established (35,361,362,366,369–372,375,376). (Level of Evidence: B)

#### **CLASS III: NO BENEFIT**

1. Except in extraordinary circumstances, carotid revascularization by either CEA or CAS is not recommended when atherosclerosis narrows the lumen by less than 50% (35,70,74,369,377). (Level of Evidence: A)
2. Carotid revascularization is not recommended for patients with chronic total occlusion of the targeted carotid artery. (Level of Evidence: C)
3. Carotid revascularization is not recommended for patients with severe disability<sup>¶</sup> caused by cerebral infarction that precludes preservation of useful function. (Level of Evidence: C)

## **7.2. Carotid Endarterectomy**

CEA dramatically reduces the incidence of ipsilateral stroke beyond the 30-day perioperative period, but the risk of periprocedural stroke must be considered in the assessment of overall safety and efficacy. For symptomatic patients undergoing surgical revascularization, the incidence of subsequent stroke is approximately 1.1% per year, which corresponds to stroke-free survival of approximately 93% at 5 years (Table 7). The actuarial 5-year survival in patients with carotid stenosis is approximately 75%, with CAD being the major cause of death. For asymptomatic patients, the risk of ipsilateral stroke after CEA is <0.5% per year,

§Conditions that produce unfavorable neck anatomy include but are not limited to arterial stenosis distal to the second cervical vertebra or proximal (intrathoracic) arterial stenosis, previous ipsilateral CEA, contralateral vocal cord paralysis, open tracheostomy, radical surgery, and irradiation.

||Comorbidities that increase the risk of revascularization include but are not limited to age >80 years, New York Heart Association class III or IV heart failure, left ventricular ejection fraction <30%, class III or IV angina pectoris, left main or multivessel CAD, need for cardiac surgery within 30 days, MI within 4 weeks, and severe chronic lung disease.

¶In this context, severe disability refers generally to a Modified Rankin Scale score of ≥3, but individual assessment is required, and intervention may be appropriate in selected patients with considerable disability when a worse outcome is projected with continued medical therapy alone.

but this rate may not be significantly lower than that currently associated with medical therapy alone.

### **7.2.1. Randomized Trials of Carotid Endarterectomy**

#### **7.2.1.1. CAROTID ENDARTERECTOMY IN SYMPTOMATIC PATIENTS**

The NASCET (reported in 1991) was designed to test the hypothesis that symptomatic patients with either TIA or mild stroke and 30% to 99% ipsilateral carotid stenosis would have fewer strokes after CEA and medical management than those given medical therapy (including aspirin) alone (70). Randomization was stratified according to the severity of stenosis. The high-grade stenosis category was 70% to 99% diameter reduction measured by contrast angiography by a method originally defined for an ECVD disease study in the 1960s, in which the luminal diameter at the point of greatest stenosis severity was compared with the diameter of the distal internal carotid artery (Figure 3). The lower-grade stenosis category included patients with 30% to 69% stenosis.

NASCET was stopped for the 70% to 99% stenosis group after 18 months of follow-up because a significant benefit for CEA was evident (70). In the 328 patients assigned to surgical management, the cumulative risk of ipsilateral stroke at 2 years, including perioperative events, was 9%. For the 331 patients in the high-grade stenosis category assigned to medical therapy alone, the cumulative risk of ipsilateral stroke at 2 years was 26% (absolute risk reduction 17% in favor of surgical management) (70).

Subsequently, the NASCET investigators also demonstrated a benefit of CEA for patients with 50% to 69% carotid stenosis but not for those with <50% stenosis. Among patients in the surgical group with 50% to 69% stenosis, the rate of operative mortality or stroke was 6.7% at 30 days. Over longer-term follow-up, the rate of ipsilateral stroke, including perioperative events, was 15.7% at 5 years compared with 22% for medically managed patients. In other words, approximately 15 patients would have had to undergo CEA to prevent 1 stroke over 5 years (NNT=77 patients per year) (20,70,84,381).

The ECST (European Carotid Surgery Trial), performed at about the same time as NASCET, randomized 2,518 patients over a 10-year period, yielding a mean follow-up of 3 years. Patients were stratified into 3 categories that corresponded to mild (10% to 29%), moderate (30% to 69%), and severe (70% to 99%) carotid stenosis by a different method of measurement. According to the method used in ECST, the minimal residual lumen through the zone of stenosis was compared with the estimated diameter of the carotid bulb rather than the distal internal carotid artery, which was the method used in NASCET (Figure 3, Table 8). The European study found a highly significant benefit of CEA for patients with 70% to 99% stenosis but no benefit in those with milder stenosis. When the angiograms of ECST participants were analyzed according to the method used in NASCET, no benefit for surgical treatment over medical treatment was found for those with 50% to

**Table 7. Comparative Utility of Various Management Strategies for Patients With Carotid Stenosis in Clinical Trials**

Trial, Year (Reference)	Patient Population	Intervention	Comparator	No. of Patients		Events, %		Event Used to Calculate NNT	ARR, %	NNT*
				Treatment Group	Comparator Group	Treatment Group	Comparator Group			
<b>Symptomatic CEA</b>										
NASCET (1991) (84)	Symptomatic, 70% to 99% stenosis	CEA	Medical therapy	328	321	9	26	Ipsilateral stroke	17.00	12
ECST (2003) (378)	Symptomatic, 70% to 99% stenosis	CEA	Medical therapy	Not reported	Not reported	Not reported	Not reported	Ipsilateral ischemic stroke and surgical stroke or death; ARR provided in study	18.70	27
ECST (2003) (378)	Symptomatic, 70% to 99% stenosis	CEA	Medical therapy	429	850	6.80	N/A	Stroke or surgical death; ARR provided in study	21.20	24
NASCET (1998) (20)	Symptomatic, 50% to 69% stenosis	CEA	Medical therapy	430	428	15.70	22.20	Ipsilateral stroke	6.50	77
ECST (2003) (378)	Symptomatic, 50% to 69% stenosis	CEA	Medical therapy	Not reported	Not reported	Not reported	Not reported	Ipsilateral ischemic stroke and surgical stroke or death; ARR provided in study	2.90	173
ECST (2003) (378)	Symptomatic, 50% to 69% stenosis	CEA	Medical therapy	646	850	10.00	N/A	All stroke or surgical death; ARR provided in study	5.70	88
<b>Asymptomatic CEA</b>										
ACAS (1995) (74)	Asymptomatic	CEA	Medical therapy	825	834	5.10	11	Ipsilateral stroke and periprocedural stroke or death	6	84
ACAS (1995) (74)	Asymptomatic	CEA	Medical therapy	825	834	13.40	13.60	Stroke or death	0.20	1,351
ACST (2004) (75)	Asymptomatic	Immediate CEA	Deferred CEA	1,560	1,560	3.80	3.97	Ipsilateral stroke in carotid artery territory	0.17	2,000
ACST (2004) (75)	Asymptomatic	Immediate CEA	Deferred CEA	1,560	1,560	3.80	11.00	Stroke risks	7.20	70
<b>Symptomatic</b>										
SPACE 2-y data (2008) (364)	Symptomatic	CEA	CAS	589	607	8.80	9.50	All periprocedural strokes or deaths and ipsilateral ischemic strokes up to 2 y after the procedure	0.70	286
SPACE 2-y data (2008) (364)	Symptomatic	CEA	CAS	589	607	1.90	2.20	Ipsilateral ischemic stroke within 31 d and 2 y	0.30	667
SPACE 2-y data (2008) (364)	Symptomatic	CEA	CAS	589	607	10.10	10.90	All stroke	0.80	250
EVA-3S 4-y data (2008) (379)	Symptomatic	CEA	CAS	262	265	1.50	1.50	Ipsilateral stroke	0	
EVA-3S 4-y data (2008) (379)	Symptomatic	CEA	CAS	262	265	6.20	11.10	Composite of periprocedural stroke, death, and nonprocedural ipsilateral stroke during 4 y of follow-up	4.90	82
EVA-3S 4-y data (2008) (379)	Symptomatic	CEA	CAS	262	265	3.40	9.10	All strokes	5.70	71
<b>Mixed patient populations</b>										
SAPPHIRE 1-y data (2004) (370)	Mixed population: Symptomatic, $\geq 50\%$ stenosis; Asymptomatic, $\geq 80\%$ stenosis	CEA	CAS	167	167	7.90	6.20	Stroke	1.70	58
SAPPHIRE 1-y data (2004) (370)	Mixed population: Symptomatic, $\geq 50\%$ stenosis; Asymptomatic, $\geq 80\%$ stenosis	CEA	CAS	167	167	4.80	4.20	Ipsilateral stroke	0.60	167
SAPPHIRE 1-y data (2004)† (370)	Mixed population: Symptomatic, $\geq 50\%$ stenosis; Asymptomatic, $\geq 80\%$ stenosis	CEA	CAS	167	167	20.10	12.20	Cumulative incidence of death, stroke, or MI within 30 d after the procedure or death or ipsilateral stroke between 31 d and 1 y	7.90	13
SAPPHIRE 3-y data (2008) (369)	Mixed population: Symptomatic, $\geq 50\%$ stenosis; Asymptomatic, $\geq 80\%$ stenosis	CEA	CAS	167	167	26.90	24.60	Composite of death, stroke, or MI within 30 d after the procedure; death or ipsilateral stroke between 31 d and 1,080 d; 1,080 d was converted to 3 y for normalization and NNT calculation	2.30	130

Table 7. Continued

Trial, Year (Reference)	Patient Population	Intervention	Comparator	No. of Patients		Events, %		Event Used to Calculate NNT	ARR, %	NNT*
				Treatment Group	Comparator Group	Treatment Group	Comparator Group			
SAPPHIRE 3-y data (2008) (369)	Mixed population: Symptomatic, ≥50% stenosis; Asymptomatic, ≥80% stenosis	CEA	CAS	167	167	9.00	9.00	Stroke	0	
SAPPHIRE 3-y data (2008) (369)	Mixed population: Symptomatic, ≥50% stenosis; Asymptomatic, ≥80% stenosis	CEA	CAS	167	167	5.40	6.60	Ipsilateral stroke	1.20	250
<b>Symptomatic</b>										
ICSS (2010) (380)	Symptomatic	CEA	CAS	858	855	4.10	7.70	All strokes within 120 d after randomization‡	3.60	7
ICSS (2010) (380)	Symptomatic	CEA	CAS	858	855	3.30	7.00	All strokes within 30 d after randomization‡	3.70	2
<b>CREST symptomatic</b>										
CREST 4-y data (2010) (360)	Symptomatic	CEA	CAS	653	668	8.40	8.60	All strokes, MIs, or deaths within periprocedural period and postprocedural ipsilateral strokes	0.20	2,000
CREST 4-y data (2010) (360)	Symptomatic	CEA	CAS	653	668	6.40	8.00	All periprocedural strokes or deaths or postprocedural ipsilateral strokes	1.60	250
CREST 4-y data (2010) (360)	Symptomatic	CEA	CAS	653	668	6.40	7.60	All periprocedural strokes or postprocedural ipsilateral strokes	1.20	333
<b>CREST asymptomatic</b>										
CREST 4-y data (2010) (360)	Asymptomatic	CEA	CAS	587	594	4.90	5.60	All strokes, MIs, or deaths within periprocedural period and postprocedural ipsilateral strokes	0.70	571
CREST 4-y data (2010) (360)	Asymptomatic	CEA	CAS	587	594	2.70	4.50	All periprocedural strokes or postprocedural ipsilateral strokes	1.80	223
CREST 4-y data (2010) (360)	Asymptomatic	CEA	CAS	587	594	2.70	4.50	All periprocedural strokes or deaths or postprocedural ipsilateral strokes	1.80	223
<b>CREST mixed population</b>										
CREST 4-y data (2010) (360)	Patient population not separated in table; mixed patient population	CEA	CAS	1,240	1,262	7.90	10.20	All stroke	2.30	174

\*NNT indicates number of patients needed to treat over the course of 1 year with the indicated therapy as opposed to the comparator to prevent the specified event(s). All NNT calculations have been annualized. For details of methodology, please see Suissa (381a). †The 1-year data from the SAPPHIRE trial included the primary endpoint; long-term data were used to calculate rates of the major secondary endpoint. ‡Annualized data. ††Cannot be calculated because ARR is 0.

ACAS indicates Asymptomatic Carotid Atherosclerosis Study; ACST, Asymptomatic Carotid Surgery Trial; ARR, absolute risk reduction; CAS, carotid artery stenting; CEA, carotid endarterectomy; CREST, Carotid Revascularization Endarterectomy versus Stenting Trial; ECST, European Carotid Surgery Trial; EVA-3S, Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis; ICSS, International Carotid Stenting Study; NASCET, North American Symptomatic Carotid Endarterectomy Trial; NNT, number needed to treat; N/A, not applicable; SAPPHIRE, Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy; and SPACE, Stent-Protected Angioplasty versus Carotid Endarterectomy.

69% stenosis (382). For higher degrees of stenosis severity, adjusted for primary endpoints and duration of follow-up, CEA had a similar benefit for symptomatic patients across the NASCET and ECST trials for both men and women (383).

A U.S. Veterans Affairs trial of CEA, the VACS (Veterans Affairs Cooperative Study), was stopped after 189 patients with symptomatic stenosis had been randomly

allocated to surgery plus medication therapy versus medical management alone (85). At that point, with mean follow-up of 11.9 months, 7.7% of patients assigned to surgical treatment had experienced death, stroke, or TIA compared with 19.4% of those managed without surgery. Despite the small number of patients and abbreviated follow-up, this difference reached statistical significance (85), and the implications of the interim analysis were strengthened by the results of NASCET, which had become available concurrently.

Pooled analysis of the 3 largest randomized trials (VACS, NASCET, and ECST) involving more than 3,000 symptomatic patients found a 30-day stroke and death rate of 7.1% after CEA (382) (Table 7). Differences between trials in the method of measurement of carotid stenosis and definitions of outcome events confound interpretation of the meta-analysis. Analysis of individual patient-level data partially overcomes these limitations, and such an analysis

Table 8. Comparison of the Methods of Stenosis Measurement Used in ECST and NASCET

European Stenosis Scale*	North American Stenosis Scale*
65% Stenosis	30% Stenosis
70% Stenosis	40% Stenosis
90% Stenosis	80% Stenosis

\*All values are approximations.

ECST indicates European Carotid Surgery Trial; and NASCET, North American Symptomatic Carotid Endarterectomy Trial.

incorporating reassessment of carotid angiograms found the results of ECST and NASCET to be more consistent than the originally reported results suggested. The lack of benefit of CEA in patients with moderate stenosis reported by the ECST investigators (83) can be explained by differences in the method of measuring stenosis severity and definition of outcome events. With the exception of patients with chronic carotid occlusion or near-occlusion, surgery was beneficial when the degree of stenosis was >50% as measured by the technique used in NASCET (70) and VACS (85) (approximately equivalent to 65% stenosis by the method used in ECST). In patients with 50% to 69% stenosis by the method used in NASCET, the benefit was modest but increased over time. Surgery was most effective in patients with >70% carotid stenosis without occlusion or near-occlusion (382). When the combined outcome of fatal or disabling ipsilateral ischemic stroke, perioperative stroke, or death was considered, the benefit of surgery was evident only in patients with 80% to 99% stenosis. Surgery offered little or no long-term benefit to patients with near-occlusion of a carotid artery, in whom the risk of stroke was lower among medically treated patients than in those with lesser degrees of severe stenosis, perhaps as a result of collateral blood flow (384,385).

#### 7.2.1.2. CAROTID ENDARTERECTOMY IN ASYMPTOMATIC PATIENTS

The first major trial of CEA in asymptomatic patients was conducted in 10 U.S. Veterans Affairs medical centers to test the hypothesis that surgery in combination with aspirin and risk factor modification would result in fewer TIAs, strokes, and deaths than medical management alone (76). Among 444 patients randomized over a 54-month period, 211 CEA procedures were performed and 233 patients were treated medically. The 30-day mortality rate was 1.9% in patients assigned to undergo surgery, and the incidence of stroke was 2.4%, for a combined rate of 4.3%. By 5 years, the differences in outcomes reached statistical significance, with a 10% overall rate of adverse events in the surgical group compared with 20% in the group given medical therapy alone. Inclusion of TIA in the primary composite endpoint was a source of controversy, because the study was not powered to detect a difference in the composite endpoint of death and stroke without TIA (76,386,387).

The hypothesis that CEA plus aspirin and risk factor control (albeit limited by modern standards) would reduce the rate of TIA, stroke, and death compared with aspirin and risk factor control without surgery was evaluated in ACAS (74). In response to criticism of the VACS design, the primary endpoint did not include TIA, which raised the requisite recruitment. The trial was stopped before completion after randomization of 1,662 patients when an advantage to CEA became apparent among patients with lesions producing >60% stenosis as measured by the method used in NASCET. After a mean follow-up of 2.7 years, the projected 5-year rates of ipsilateral stroke, perioperative stroke, and death were 5.1% for surgical patients and 11%

for patients treated medically. The 30-day perioperative death and stroke rate for patients undergoing CEA was 2.3%, but some patients assigned to the surgical group experienced stroke during contrast angiography and did not undergo surgery (74,388–391).

The ACST, sponsored by the Medical Research Council of Great Britain, randomized 3,120 asymptomatic patients with hemodynamically significant carotid artery stenosis to immediate CEA versus delayed surgery on the basis of the onset of symptoms (72). The 30-day risk of stroke or death in either group, including the perioperative period, was 3.1%. Five-year rates, including perioperative events, were 6.4% for the early-surgery group versus 11.7% for the group initially managed medically. The primary endpoint in ACST differed from that in ACAS by inclusion of strokes contralateral to the index carotid lesion. As with ACAS, during the conduct of ACST (1993 to 2003), medical therapy was scant by modern standards (see Section 7.2.6).

A summary of outcomes of randomized trials of CEA in asymptomatic patients is given in Table 7, as well as an analysis of the benefit of revascularization in terms of the NNT to prevent stroke over a period of 1 year. It is important to emphasize that selection of asymptomatic patients for carotid revascularization should include careful consideration of life expectancy, age, sex, and comorbidities. The benefit of surgery may now be less than anticipated on the basis of earlier randomized trials, and the cited 3% complication rate should be interpreted in the context of interim advances in medical therapy. Even when the data from ACAS and ACST are combined to increase the statistical power of the estimate of benefit, it remains unclear whether women benefit as much as men from CEA (363).

#### 7.2.2. Factors Affecting the Outcome of Carotid Endarterectomy

A wide range of patient- and operator-related factors, some more tangible than others, can substantially influence both the immediate- and long-term outcomes of CEA.

##### 7.2.2.1. TECHNICAL CONSIDERATIONS

In the more than 50 years that CEA has been performed, there has been considerable variation in surgical technique. Initially, local anesthesia was advocated instead of general anesthesia to permit observation of the patient's level of consciousness and motor function during temporary clamping of the carotid artery. Because only 10% of patients undergoing CEA develop cerebral dysfunction during arterial clamping, other techniques have been developed, including electroencephalographic or other types of monitoring, to assess cerebral function under anesthesia (392,393). Advocates of local anesthesia maintain that adverse cardiac events occur less frequently than during CEA under general anesthesia, but retrospective analyses and data from surgical trials have failed to demonstrate a significant difference in outcomes based on the type of anesthesia used.

A key reason to monitor cerebral function dynamically during surgery, including measurement of residual collateral perfusion pressure (394) or internal carotid artery back pressure, is to select patients who may benefit from shunting during the period of arterial clamping. Arguments for selective as opposed to routine shunting are related to the complications that occasionally occur during shunting, including embolism of atheromatous debris or air through the shunt, mechanical injury to the distal internal carotid artery during shunt placement, and obscuring of the arterial anatomy at the distal zone of CEA. To date, however, no study has shown a difference in 30-day morbidity and mortality with routine versus selective shunting during CEA.

Variations in the technique of arterial repair after CEA depend mainly on the length of the arteriotomy. The advantage of primary closure is speed, but disadvantages include higher incidences of residual and recurrent stenosis. The advantage of patch closure is visual confirmation of complete plaque removal, but the disadvantage is the greater length of time required for closure. Multiple comparative reviews have failed to demonstrate a consistent difference in outcomes with either technique compared with the other (395–405). One report involved a single experienced surgeon and a series of patients who required staged bilateral CEA in whom 1 side was randomly allocated to primary closure and the other side to patch angioplasty (406). Patch angioplasty was associated with lower 30-day surgical morbidity and mortality and fewer cases of residual or recurrent stenosis as assessed by periodic duplex scanning for up to 1 year postoperatively. On the basis of these observations and a Cochrane meta-analysis of case series (407), patch angioplasty after open CEA is now favored by most surgeons.

Eversion CEA is a major variation in operative technique designed in part to avoid patch angioplasty closure and to relocate the proximal internal carotid artery when the artery becomes redundant after CEA. The avoidance of a longitudinal arteriotomy reduces the likelihood of stricture and the need for patching, but the technique is difficult in patients with high carotid bifurcations or long lesions. Furthermore, the eversion technique makes internal shunting more difficult. Randomized trials comparing the eversion and direct arteriotomy techniques have found no difference in morbidity, mortality, or rates of restenosis (408,409).

#### 7.2.2.2. CASE SELECTION AND OPERATOR EXPERIENCE

The relationships of perioperative mortality, neurological morbidity, and other adverse events after CEA to surgeon and hospital volume are complex. Hospitals in which fewer than 100 CEA operations are performed annually typically have poorer results than those in which larger numbers are performed (410–421). However, the threshold criteria for patient selection for CEA can also influence outcomes. Perioperative results are best for asymptomatic patients, who are more numerous than symptomatic patients. Sur-

geons with higher volumes are likely to operate on more asymptomatic cases and have better results. Surgeons who favor selection of symptomatic patients typically have higher 30-day rates of stroke and death. In ACAS, surgeons were selected for participation on the basis of individual experience, morbidity and mortality, and a minimum annual caseload of 12, with the expectation that the average would be closer to 20 operations per year. With this process, the 30-day surgical morbidity and mortality rate for CEA in ACAS was 1.5% (389,391,415,416,422,423), but case volume did not influence results. Extrapolation of the results of this and other carotid revascularization trials to clinical decision making requires consideration of patient selection and procedural results.

#### 7.2.2.3. DEMOGRAPHIC AND CLINICAL FACTORS

The influence of patient age on surgical risk is unclear, but advanced age does not preclude elective CEA in appropriately selected patients, and several case series report neurological morbidity and mortality rates in octogenarians comparable to those in younger patients (424,425). Patients older than 80 years of age were excluded from participation in both NASCET (prior to 1991) (70) and ACAS (74), although in NASCET, the greatest benefit of surgery compared with medical management was observed in older patients (up to the age of 80 years) (70). In the randomized ACST study, no benefit accrued from CEA in patients 80 years of age or older (72). More recent results from the SPACE (Stent-Protected Angioplasty versus Carotid Endarterectomy) trial showed a 5.9% combined rate of stroke and death after CEA for symptomatic patients younger than 75 years of age with carotid stenosis. The rate among those older than 75 years of age was lower than reported for symptomatic patients in NASCET and ECST, which indicates either that surgical therapy has become safer with time or that the inherent risks of these cohorts differed in important ways. Several reports point to higher risks of complications among older patients undergoing CEA (426,427), but others suggest that patients 75 years of age or older with few cardiovascular risk factors face risks of perioperative stroke and death comparable to younger patients (428).

Women undergoing CEA face higher operative risk than men (10.4% versus 5.8% for men in ECST) (83,429–431). In the ACAS and NASCET studies, women had less favorable outcomes than men in terms of surgical mortality, neurological morbidity, and recurrent carotid stenosis and gained little or no benefit from surgery (70,74). The reasons for these sex-based differences are complex, and several studies have found that patch angioplasty closure in women materially improves results (432,433). Because the number of minorities enrolled in randomized trials has been insufficient to permit meaningful statistical analysis, it is difficult to evaluate differences in the results of CEA on the basis of race beyond general observations. For example, although Chinese populations appear to develop atherosclerosis at the

carotid bifurcations at different frequencies than white populations (434), the immediate and long-term results of CEA appear comparable. Black patients develop intracranial disease more frequently than ECVD and may undergo CEA less often than members of other racial groups. Among the uncertainties is how much the perceived differences reflect biological factors as opposed to inequities in access to diagnosis and treatment (435,436).

### 7.2.3. Risks Associated With Carotid Endarterectomy

The risks associated with CEA involve neurological and nonneurological complications, including hypertension or hypotension, hemorrhage, acute arterial occlusion, stroke, MI, venous thromboembolism, cranial nerve palsy, infection, arterial restenosis, and death (437). The risk of stroke or death is related mainly to the patient's preoperative clinical status. Symptomatic patients have a higher risk than asymptomatic patients (OR 1.62;  $p < 0.0001$ ), as do those with hemispheric versus retinal symptoms (OR 2.31;  $p < 0.001$ ), urgent versus nonurgent operation (OR 4.9;  $p < 0.001$ ), and reoperation versus primary surgery (OR 1.95;  $p < 0.018$ ) (438–440). A report of external case-by-case reviews by nonsurgeons of a total of 1972 CEA procedures in asymptomatic patients performed by 64 surgeons at 6 hospitals in 1997 and 1998 reported rates of 7.11% for stroke or death, 2.28% for stroke, and 2.93% for TIA (441). Patients with high-risk anatomic criteria, such as restenosis after CEA and contralateral carotid arterial occlusion, face much higher perioperative stroke/death rates than observed in the NASCET or ACAS patient cohorts (74,437). Reports of perioperative stroke and death rates of 19.9% have been documented in patients undergoing reoperative CEA procedures (442). In NASCET, the stroke and death rate at 30 days was 14.3% among patients with contralateral carotid occlusion (443). The more recent literature documents considerably lower complication rates (444–451), although outcomes of CEA in patients at high surgical risk are still relatively unfavorable, with the combined rate of stroke, death, or MI at 7.4% for high-risk patients compared with 2.9% among low-risk patients in 1 series (452) that did not separately report rates of stroke and death without MI. Other rate and relative risk data for perioperative stroke or death after CEA are listed in Table 9.

In a meta-analysis of nearly 16,000 symptomatic patients undergoing CEA, the 30-day risk of stroke or death was 7.7% when a neurologist evaluated the patient and 2.3% when a vascular surgeon performed the evaluation (359). These data suggest a 3-fold increase in reported events when independent adjudication is used and support a policy of evaluation by a neurologist for patients undergoing CEA. Clinical neurological assessment is crucial to the application of recommendations for selection of patients for CEA, which includes estimation of perioperative stroke risk. Recent trials of CEA that included rigorous independent neurological examination before and after CEA confirmed low rates of perioperative stroke (1.4% in previously asymp-

tomatic patients and 3.2% in symptomatic patients in CREST [Carotid Revascularization Endarterectomy versus Stenting Trial] [360] and 3.3% among symptomatic patients in ICSS [International Carotid Stenting Study] [368] based on 30-day per-protocol analysis).

Other than stroke, neurological complications include intracerebral hemorrhage, which may occur as a consequence of the hyperperfusion syndrome despite control of blood pressure. This syndrome occurs in fewer than 1% of patients when blood pressure has been stable preoperatively and well managed perioperatively (461–464). Cranial nerve injury has been reported in as many as 7% of patients undergoing CEA but was not disabling in most studies, resulting in permanent injury in fewer than 1% of cases (382,465,466). In ECST, in which patients underwent extensive preoperative and postoperative neurological assessments, the incidence of cranial neuropathy was 5.1% (465). The neuropathy that appeared early in the postoperative period resolved in one fourth of the cases by the time of discharge, leaving 3.7% of patients with residual cranial nerve deficits. In decreasing order of frequency, these deficits involved palsies of the hypoglossal, marginal mandibular, recurrent laryngeal, and spinal accessory nerves and Horner syndrome (437,451,465,467,468). The only clinical factor linked to cranial nerve dysfunction was duration of the surgical procedure longer than 2 hours.

Cardiovascular instability has been reported in 20% of patients undergoing CEA, with hypertension in 20%, hypotension in 5%, and perioperative MI in 1%. The use of local anesthesia or cervical block in selected patients may lessen the likelihood of these complications (469). Because atherosclerosis of the carotid bifurcation is commonly associated with coronary atherosclerosis, myocardial ischemia is a major cause of perioperative complications, including nonfatal MI, and late mortality in patients undergoing CEA. The risk of cardiopulmonary complications is related to advanced age, New York Heart Association class III or IV heart failure, active angina pectoris, left main or multivessel coronary disease, urgent cardiac surgery in the preceding 30 days, left ventricular ejection fraction  $\leq 30\%$ , MI within 30 days, severe chronic lung disease, and severe renal insufficiency (470–472). In NASCET, 10% of patients experienced a complication in the perioperative period. The majority of these were cardiovascular (8.1%) or pulmonary (0.8%). In NASCET (70) and ECST (83), the incidence of perioperative MI was 0.3% and 0.2%, respectively. Venous thromboembolism is rare among patients undergoing CEA (473–475); in ECST, the rate was 0.1%, and no cases were reported in NASCET (377,382, 437,473–478).

Wound complications are related primarily to infection (incidence  $\leq 1\%$ ) (479,480) and hematoma ( $\leq 5\%$ ), depending in part on perioperative antiplatelet therapy (481), duration of surgery, perioperative use of heparin and protamine, and other factors. Prior ipsilateral CEA, contralateral laryngeal nerve palsy, and permanent tracheostomy may complicate wound management (465).

**Table 9. Randomized Trials Comparing Endarterectomy With Stenting in Symptomatic Patients With Carotid Stenosis**

Trial, Year (Reference)	No. of Patients	Key Features	Death or Any Stroke	OR (95% CI)	Comments
Leicester, 1998 (453)	Seventeen had received their allocated treatment before trial suspension	Single center; patients with symptomatic carotid stenosis >70%.	CEA: 0/10 (0%)* CAS: 5/7 (71.4%)*	p=0.0034; OR not reported	Terminated prematurely because of safety concerns.
CAVATAS-CEA, 2001 (454)	504	Multicenter; patients of any age with symptomatic or asymptomatic carotid stenosis suitable for CEA or CAS.	CEA: 25/253 (9.9%) CAS: 25/251 (10.0%)	p=NS in original article; OR not reported	Follow-up to 3 y; relatively low stent use (26%) in CAS group.
Kentucky, 2001 (455)	104	Single center; patients with symptomatic carotid stenosis >70% (events within 3 mo of evaluation).	CEA: 1/51 (2.0%) CAS: 0/53 (0%)	0.31 (0.01 to 7.90)	
SAPPHIRE, 2004 (370)	334	Multicenter randomized trial of patients with ≥80% asymptomatic carotid stenosis (70%) and ≥50% symptomatic carotid stenosis (30%).	CEA: 9.3% symptomatic patients‡* CAS: 2.1% symptomatic patients‡	p=0.18†	Terminated prematurely because of a drop in randomization.
EVA-3S, 2006 (456)	527	Multicenter; patients with symptomatic carotid stenosis >60% within 120 d before enrollment suitable for CEA or CAS.	CEA: 10/259 (3.9%) CAS: 25/261 (9.6%)	RR 2.5 (1.2 to 5.1), p=0.01	Study terminated prematurely because of safety and fertility issues; concerns about operator inexperience in the CAS arm and nonuniform use of embolism protection devices.
SPACE, 2006 (457)	1,183	Multicenter; patients >50 y old with symptomatic carotid stenosis >70% in the 180 d before enrollment.	Primary endpoint of ipsilateral ischemic stroke or death from time of randomization to 300 d after the procedure: CEA: 37/584 (6.3%) CAS: 41/599 (6.8%)	1.19 (0.75 to 1.92)	Study terminated prematurely after fertility analysis; concerns about operator inexperience in the CAS arm and nonuniform use of embolism protection devices.
EVA-3S 4-y follow-up, 2008 (379)	527	Multicenter, randomized, open, assessor-blinded, noninferiority trial. Compared outcome after CAS with outcome after CEA in 527 patients who had carotid stenosis of at least 60% that had recently become symptomatic.	Major outcome events up to 4 y for any periprocedural stroke or death: CEA: 6.2% CAS: 11.1%	HR for any stroke or periprocedural death 1.77 (1.03 to 3.02); p=0.04 HR for any stroke or death 1.39 (0.96 to 2.00); p=0.08 HR for CAS versus CEA 1.97 (1.06 to 3.67); p=0.03	A hazard function analysis showed 4-y differences in cumulative probabilities of outcomes between CAS and CEA were largely accounted for by the higher periprocedural (within 30 d of the procedure) risk of stenting compared with endarterectomy. After the periprocedural period, the risk of ipsilateral stroke was low and similar in the 2 treatment groups.



**Table 9. Continued**

Trial, Year (Reference)	No. of Patients	Key Features	Death or Any Stroke	OR (95% CI)	Comments
SPACE 2-y follow-up, 2008 (364)	1,214	Patients with symptomatic, severe ( $\geq 70\%$ ) carotid artery stenosis were recruited to this noninferiority trial and randomly assigned with a block randomization design to undergo CAS or CEA.	<p>Intention-to-treat population: Ipsilateral ischemic strokes within 2 y, including any periprocedural strokes or deaths:</p> <p>CAS: 56 (9.5%)                      CEA: 50 (8.8%)</p> <p>Any deaths between randomization and 2 y:</p> <p>CAS: 32 (6.3%)                      CEA: 28 (5.0%)</p> <p>Any strokes between randomization and 2 y:</p> <p>CAS: 64 (10.9%)                      CEA: 57 (10.1%)</p> <p>Ipsilateral ischemic stroke within 31 d and 2 y:</p> <p>CAS: 12 (2.2%)                      CEA: 10 (1.9%)</p> <p>Per-protocol population: Ipsilateral ischemic strokes within 2 y, including any periprocedural strokes or deaths:</p> <p>CAS: 53 (9.4%)                      CEA: 43 (7.8%)</p> <p>Any deaths between randomization and 2 y:</p> <p>CAS: 29 (6.2%)                      CEA: 25 (4.9%)</p> <p>Any strokes between randomization and 2 y:</p> <p>CAS: 61 (11.5%)                      CEA: 51 (9.8%)</p> <p>Ipsilateral ischemic stroke within 31 d and 2 y:</p> <p>CAS: 12 (2.3%)                      CEA: 10 (2.0%)</p>	<p>Intention-to-treat population: Ipsilateral ischemic strokes within 2 y, including any periprocedural strokes or deaths:</p> <p>HR 1.10 (0.75 to 1.61)</p> <p>Any deaths between randomization and 2 y:</p> <p>HR 1.11 (0.67 to 1.85)</p> <p>Any strokes between randomization and 2 y:</p> <p>HR 1.10 (0.77 to 1.57)</p> <p>Ipsilateral ischemic stroke within 31 d and 2 y:</p> <p>HR 1.17 (0.51 to 2.70)</p> <p>Per-protocol population: Ipsilateral ischemic strokes within 2 y, including any periprocedural strokes or deaths:</p> <p>HR 1.23 (0.82 to 1.83)</p> <p>Any deaths between randomization and 2 y:</p> <p>HR 1.14 (0.67 to 1.94)</p> <p>Any strokes between randomization and 2 y:</p> <p>HR 1.19 (0.83 to 1.73)</p> <p>Ipsilateral ischemic stroke within 31 d and 2 y:</p> <p>HR 1.18 (0.51 to 2.73)</p>	<p>In both the intention-to-treat and per-protocol populations, recurrent stenosis of <math>\geq 70\%</math> was significantly more frequent in the CAS group than the CEA group, with a life-table estimate of 10.7% versus 4.6% (<math>p=0.0009</math>) and 11.1% versus 4.6% (<math>p=0.0007</math>), respectively.</p>
SAPPHIRE 3-y follow-up, 2008 (369)	260	Long-term data were collected for 260 individuals; included symptomatic carotid artery stenosis of at least 50% of the luminal diameter or an asymptomatic stenosis of at least 80%.	<p>Stroke:</p> <p>CAS: 15 (9.0%)                      CEA: 15 (9.0%)</p> <p>Ipsilateral stroke:</p> <p>CAS: 11 (7.0%)                      CEA: 9 (5.4%)</p> <p>Death:</p> <p>CAS: 31 (18.6%)                      CEA: 35 (21%)</p> <p>Note: data were calculated using <math>n=167</math> for both groups because breakdowns of CAS and CEA for <math>N=260</math> were not given.</p>	<p>Stroke:</p> <p><math>p=0.99</math> (–6.1 to 6.1)</p> <p>Death:</p> <p><math>p=0.68</math> (–10.9 to 6.1)</p>	
Wallstent, 2005 (458)	219	Included symptomatic angiographic carotid stenosis $>70\%$ .	<p>CAS: 13 (12.2%)                      CEA: 5 (4.5%)</p>	N/A	Premature termination based on futility analysis.

**Table 9. Continued**

Trial, Year (Reference)	No. of Patients	Key Features	Death or Any Stroke	OR (95% CI)	Comments
SAPPHIRE (symptomatic data), 2008 (459)	96	Included patients with $\geq 50\%$ carotid stenosis.	CEA: 3 (6.5%) CAS: 0	N/A	Premature termination secondary to declining enrollment.
ICSS, 2010 (368)	1,713	Multicenter study. In the study, the degree of carotid stenosis was 70% to 99% in 89% of stent patients and in 91% of endarterectomy patients. Study patients had $>50\%$ carotid artery stenosis measured by the NASCET criteria.	120-d follow-up data available only: CAS: 72/853 (8.5%) CEA: 40/857 (4.7%)	OR not available; HR 1.86 (1.26 to 2.74) p=0.001	Primary outcome was 3-y rate of fatal or disabling stroke in any territory; interim results have been provided for 120-d rate of stroke, death, or procedural MI.
CREST, 2010 (360)	2,502	The study included 1,321 symptomatic patients and 1,181 asymptomatic patients. Symptomatic patients in the study had $\geq 50\%$ carotid stenosis by angiography, $\geq 70\%$ by ultrasound or $\geq 70\%$ by CTA or MRA. Asymptomatic patients had carotid stenosis (patients with symptoms beyond 180 d were considered asymptomatic) $\geq 60\%$ by angiography, $\geq 70\%$ by ultrasound, or $\geq 80\%$ by CTA or MRA.	Any periprocedural stroke or postprocedural ipsilateral stroke: Symptomatic: CAS: 37 (5.5 0.9 SE) CEA: 21 (3.2 0.7 SE) Any periprocedural stroke or death or postprocedural ipsilateral stroke: Symptomatic: CAS: 40 (6.0 0.9 SE) CEA: 21 (3.2 0.7 SE)	Any periprocedural stroke or postprocedural ipsilateral stroke: Symptomatic: p=0.04 Any periprocedural stroke or death or postprocedural ipsilateral stroke: Symptomatic: p=0.02	The risk of composite primary outcome of stroke, MI, or death did not differ significantly among symptomatic and asymptomatic patients between CAS and CEA.

\*Death and ipsilateral stroke. †Combined asymptomatic and symptomatic patients for death, any stroke. ‡Death, stroke, and MI.  
CAS indicates carotid artery stent; CAVATAS, Carotid And Vertebral Artery Transluminal Angioplasty Study; CEA, carotid endarterectomy; CI, confidence interval; CREST, Carotid Revascularization Endarterectomy versus Stenting Trial; CTA, computed tomography angiography; EVA-3S, Endarterectomy Versus Angioplasty in patients with Symptomatic Severe carotid Stenosis; HR, hazard ratio; ICSS, International Carotid Stenting Study; MI, myocardial infarction; MRA, magnetic resonance angiography; N/A, not available; NASCET, North American Symptomatic Carotid Endarterectomy Trial; NS, not significant; OR, odds ratio; RR, risk reduction; SAPPHIRE, Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy; SE, standard error; and SPACE, Stent-Protected Angioplasty versus Carotid Endarterectomy.  
Modified from Ederle et al. (460).

Other medical comorbidities contribute to the risk associated with CEA (444,452,482). Patients with pulmonary disease, particularly those requiring supplemental oxygen, are at risk of complications including ventilator dependence and pneumonia (483). Renal insufficiency is an independent risk factor for adverse outcomes of pulmonary complications and cardiac events after CEA (484). Additionally, in a retrospective analysis of data collected at 123 Veterans Affairs Medical Centers as part of the National Surgical Quality Improvement Program (n=20,899), patients with severe chronic renal insufficiency (glomerular filtration rate  $<30$  mL/min) had significantly higher mortality rates by both univariate and multivariate analyses. Patients with impaired renal function, including those who required dialysis, faced higher risks of mortality and stroke-related morbidity in some reports, whereas in others the results appeared to be independent of renal function (485). A study of more than 1,000 CEA operations in nearly 900 patients found a higher perioperative mortality rate among those with chronic renal insufficiency and a significant association

between chronic renal insufficiency and 30-day mortality (486). In a series of 184 patients, the mortality rate was 3% among patients with chronic renal insufficiency compared with no deaths in a control group without renal insufficiency. Among the 23 patients with serum creatinine levels 3 mg/dL or higher, the mortality rate was 17% (p<0.001) (487).

#### 7.2.4. Carotid Endarterectomy in Patients With Unfavorable Anatomy

A high carotid bifurcation or an atheromatous lesion that extends into the internal carotid artery beyond the exposed surgical field represents a technical challenge during CEA, and carotid lesions located at or above the level of the second cervical vertebra are particularly problematic. High cervical exposure increases the risk of cranial nerve injury. Similarly, lesions below the clavicle, prior radical neck surgery or radiation, and contralateral carotid occlusion are each associated with higher risk (488,489). Several maneuvers are available to improve arterial exposure under these

circumstances, and in the hands of experienced surgeons, these maneuvers yield satisfactory outcomes.

Among the challenges of reoperative CEA for recurrent stenosis is the accumulation of scar tissue after ipsilateral CEA. Contralateral laryngeal nerve palsy is a relative contraindication to CEA, because bilateral nerve palsies could compromise the airway (465). Patients who have undergone radical neck surgery or tracheostomy pose surgical challenges because of the difficulty of exposing the artery and the relatively high risk of perioperative infection. The risk of cranial nerve injury is higher in these situations, but the overall risks of mortality and stroke are comparable.

Patients who have undergone cervical radiation therapy face an increased incidence of disease at the carotid bifurcation. Modern radiation therapy has been designed specifically to avoid severe fibrotic tissue reactions. Several series indicate that CEA can be performed successfully after neck radiation (490), although the procedure is technically challenging. In this situation, CAS may be safer to perform, but the rate of restenosis after CAS is high, ranging from 18% to 80% over 3 years (373,491,492).

### 7.2.5. Evolution in the Safety of Carotid Surgery

Complication rates associated with CEA have improved steadily over 2 generations. The 30-day stroke and mortality rates of 2.3% among asymptomatic patients in ACAS (1994) and 5.0% for symptomatic patients in the first part of the NASCET (1999) are often cited as benchmarks against which other forms of interventional therapy are compared. More recent reports, however, suggest considerably lower risks than reported in those early trials. Surgical training and case volume are important determinants of clinical outcomes with CEA. The experiences of individual surgeons include a series of 442 consecutive CEAs in 391 patients with a 0.45% cumulative 30-day rate of stroke and death (493). A population-based study of 14,095 CEA procedures in the state of Virginia between 1997 and 2001 reported cumulative stroke and mortality rates of 1.0% and 0.5%, respectively, and a progressive decline in these rates each year (494). For 23,237 CEA procedures performed in Maryland between 1994 and 2003, the cumulative stroke rate was 0.73%. The stroke rate was 2.12% in 1994, 1.47% in 1995, and from 0.29% to 0.65% between 1996 and 2003, with a more pronounced reduction in perioperative stroke among symptomatic patients than among asymptomatic patients (412). Similar findings were noted in California, where 51,231 CEA procedures performed between 1999 and 2003 were associated with a cumulative in-hospital stroke rate of 0.54%. Methodologies varied with rates of perioperative stroke and were generally higher when documented by a neurologist. Mortality rates in both states remained relatively stable over the reported periods, 0.33% to 0.58% in Maryland and 0.78% to 0.91% in California (412), and trends were similar in other states (495) and countries including, Australia (496), Italy (497), and Sweden (498).

### 7.2.6. Evolution of Medical Therapy

Trials of carotid revascularization must be interpreted in the context of the evolution of medical therapy for patients with atherosclerotic disease. Although pharmacotherapy aimed at risk reduction was incorporated in most trials, guidelines and strategies have changed, and more effective measures have enhanced the therapeutic armamentarium. The outcomes of trials that use modern atherosclerotic risk factor treatment may differ from those reported, which reduces the generalizability of the results to contemporary practice.

Concurrently, surgical outcomes have improved with advances in training, increased hospital and operator volumes, and better perioperative medical management, including control of blood pressure with beta blockers and angiotensin inhibitors and the widespread use of statins (415,422,423,499). A 1991 report indicated that 55% of participants in NASCET were treated with antihypertensive drugs. Treatment with lipid-lowering agents was used infrequently in NASCET (20), and medical therapy was not described in the primary report of ACAS. The evolution of medical therapy, with which patients typically gain benefit whether or not surgery is performed, is pertinent to the interpretation of the results of randomized trials, most of which were performed more than a decade ago. The ACST investigators reported changes in medical therapies over time for the 10-year period that began in 1993. By the last follow-up in 2002 to 2003, 81% of patients were taking antihypertensive medication and 70% were undergoing lipid-lowering treatment, but the outcomes of CEA were reported for only the first 5 years (ending in 1998), during which concurrent use of such medical therapy was considerably less frequent (60% of participants had systolic blood pressure >160 mm Hg; 33% had total serum cholesterol >250 mg/dL; management of diabetes [20% prevalence] was not detailed; and the proportion of participants who were active tobacco smokers was not reported). As typically occurs in patient care, advances that result in a decline in adverse event rates over time must be considered in interpreting the safety and efficacy of interventions, and caution is necessary with regard to assumptions about the constancy of the response to medical therapy alone over time.

### 7.2.7. Recommendations for Perioperative Management of Patients Undergoing Carotid Endarterectomy

#### CLASS I

1. Aspirin (81 to 325 mg daily) is recommended before CEA and may be continued indefinitely postoperatively (338,500). (Level of Evidence: A)
2. Beyond the first month after CEA, aspirin (75 to 325 mg daily), clopidogrel (75 mg daily), or the combination of low-dose aspirin plus extended-release dipyridamole (25 and 200 mg twice daily, respectively) should be administered for long-term prophylaxis against ischemic cardiovascular events (339,343,350). (Level of Evidence: B)

3. Administration of antihypertensive medication is recommended as needed to control blood pressure before and after CEA. (Level of Evidence: C)
4. The findings on clinical neurological examination should be documented within 24 hours before and after CEA. (Level of Evidence: C)

**CLASS IIa**

1. Patch angioplasty can be beneficial for closure of the arteriotomy after CEA (406,407). (Level of Evidence: B)
2. Administration of statin lipid-lowering medication for prevention of ischemic events is reasonable for patients who have undergone CEA irrespective of serum lipid levels, although the optimum agent and dose and the efficacy for prevention of restenosis have not been established (501). (Level of Evidence: B)
3. Noninvasive imaging of the extracranial carotid arteries is reasonable 1 month, 6 months, and annually after CEA to assess patency and exclude the development of new or contralateral lesions (364,502). Once stability has been established over an extended period, surveillance at longer intervals may be appropriate. Termination of surveillance is reasonable when the patient is no longer a candidate for intervention. (Level of Evidence: C)

In the ACE (Acetylsalicylic Acid and Carotid Endarterectomy) study, a randomized trial involving 2849 patients and 4 different daily aspirin-dose regimens, the risk of stroke, MI, and death within 30 days and 3 months of CEA was lower for patients assigned to the lower-dose aspirin groups (81 mg or 325 mg daily) than for those taking 650 mg or 1300 mg of aspirin (RR 1.31 [95% CI 0.98 to 1.75], 5.4% versus 7.0% at 30 days [ $p=0.07$ ] and RR 1.34 [95% CI 1.03 to 1.75], 6.2% versus 8.4% at 3 months [ $p=0.03$ ], respectively) (500). The optimum duration of antithrombotic therapy after CEA has not been established, but beyond the first month postoperatively, it appears reasonable to use antithrombotic therapy as recommended for long-term prevention of ischemic events in patients with atherosclerosis.

A retrospective review of 1,566 patients undergoing CEA by 13 surgeons at a single center between 1994 and 2004 (42% symptomatic; 8% in combination with myocardial revascularization surgery) found lower rates of perioperative stroke (1.2% versus 4.5%;  $p<0.01$ ), TIA (1.5% versus 3.6%;  $p<0.01$ ), all-cause mortality (0.3% versus 2.1%;  $p<0.01$ ), and length of hospital stay (2 [interquartile range 2 to 5] versus 3 [2 to 7] days;  $p<0.05$ ) among the 42% of patients who received statin medication for at least 1 week before surgery than among those who did not (503). By multivariate analysis adjusted for demographics and comorbidities, statin use was associated with a 3-fold reduction in the risk of stroke (OR 0.35, 95% CI 0.15 to 0.85;  $p<0.05$ ) and a 5-fold reduction in the risk of death (OR 0.20, 95% CI 0.04 to 0.99;  $p<0.05$ ).

### 7.3. Carotid Artery Stenting

The results of randomized trials have not shown consistent outcome differences between CAS and CEA. CAS may be superior to CEA in certain patient groups, such as those exposed to previous neck surgery or radiation injury. A summary of stroke and mortality outcomes among symp-

tomatic and asymptomatic patients enrolled in major randomized trials and registries is provided in Tables 9 and 10.

Although 30-day morbidity and mortality rates are important benchmarks for determining the benefit of a procedure in a population with a known event rate, the confidence bounds that surround estimates of event rates with CEA and CAS often overlap. When performed in conjunction with an embolic protection device (EPD), the risks associated with CAS may be lower than those associated with CEA in patients at elevated risk of surgical complications. On the other hand, in a nationwide U.S. sample of 226,111 CEA procedures during 2003 and 2004, the mortality rate was 0.44% and the rate of stroke was 0.95%, whereas the in-hospital stroke rate for asymptomatic patients undergoing CAS was 2-fold higher than that after CEA (504). The risks of stroke among octogenarians were 1% for CEA and 3% for CAS, whereas the mortality rates were similar and low for both procedures. These data have been criticized, however, because severity of illness may not have been comparable in the 2 cohorts and because the primary outcome measures were self-reported and not audited (505).

#### 7.3.1. Multicenter Registry Studies

Several voluntary, nonrandomized, multicenter registries encompassing experience in more than 17,000 patients and large, industry-sponsored postmarket surveillance registries have described outcomes among a broad cohort of carotid stent operators and institutions. The results emphasized the importance of adequate training for optimal operator performance (35,362). The CASES-PMS (Carotid Artery Stenting with Embolic Protection Surveillance) study (362) enrolled 1493 patients at 73 sites and compared results with the pooled results of the pivotal SAPPHERE (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy) (370) stent arms. The rate of occurrence of the primary 30-day endpoint of major adverse events (stroke, MI, or death) was 5.0% for the CASES-PMS group and 6.2% in the pooled SAPPHERE trial arms (362). In the CAPTURE (Carotid ACCULINK/ACCUNET Post-Approval Trial to Uncover Unanticipated or Rare Events) registry, 2,500 high-risk patients underwent CAS performed by more than 300 different specialty operators with a broad range of experience. The 30-day endpoint of MI, stroke, and death occurred in 6.3%, and the 30-day rate of major stroke or death was 2.9% (372).

#### 7.3.2. Risks Associated With Carotid Artery Stenting

The risks and potential complications of CAS involve neurological deficits; injury of the vessels accessed to approach the lesion, the artery in the region of stenosis, and the distal vessels; device malfunction; general medical and access-site complications; restenosis; and mortality.

##### 7.3.2.1. CARDIOVASCULAR COMPLICATIONS

Baroreflex responses such as bradycardia, hypotension, and vasovagal reactions occur in 5% to 10% of cases but have

**Table 10. Trials Comparing Endarterectomy With Stenting in Asymptomatic Patients With Carotid Stenosis**

Trial, Year (Reference)	No. of Patients	Key Features	Death or Any Stroke	p	Comments
SAPPHIRE, 2004 (370)	334	Multicenter randomized trial of patients with >50% symptomatic carotid stenosis (58%) or >80% asymptomatic carotid stenosis (42%) with 1 or more comorbidity criteria* (high-surgical-risk group).	Asymptomatic: CEA: 10.2%† CAS: 5.4%† Combined: CEA: 9.8%† CAS: 4.8%†	0.20  0.09	Terminated prematurely because of a drop in randomization.
SAPPHIRE, 2008 (369)	334	Multicenter randomized trial of patients with >80% asymptomatic carotid stenosis (70%) and ≥50% symptomatic carotid stenosis (30%).	SAPPHIRE 3-y data, Stroke: CEA: 15/167 CAS: 15/197 Death: CEA: 35/167 CAS: 31/167	Stroke: 0.99  Death: 0.68 (OR not reported)	No significant difference could be shown in long-term outcomes between patients who underwent CAS with an EPD and those who underwent CEA.
CREST, 2010 (360)	2,502	The study included 1,321 symptomatic patients and 1,181 asymptomatic patients. Symptomatic patients in the study had ≥50% carotid stenosis by angiography, ≥70% by ultrasound, or ≥70% by CTA or MRA. Asymptomatic patients in the study had carotid stenosis (patients with symptoms beyond 180 d were considered asymptomatic) ≥60% by angiography, ≥70% by ultrasound, or ≥80% by CTA or MRA.	Any periprocedural stroke or postprocedural ipsilateral stroke: Asymptomatic: CAS: 15 (2.5 0.6 SE) CEA: 8 (1.4 0.5 SE) Any periprocedural stroke or death or postprocedural ipsilateral stroke: Asymptomatic: CAS: 15 (2.5 0.6 SE) CEA: 8 (1.4 0.5 SE)	Any periprocedural stroke or postprocedural ipsilateral stroke: Asymptomatic: 0.15  Any periprocedural stroke or death or postprocedural ipsilateral stroke: Asymptomatic: 0.15	The risk of the composite primary outcome of stroke, MI, or death did not differ significantly among symptomatic and asymptomatic patients between CAS and CEA.

\*Criteria for high risk (at least 1 factor required): clinically significant cardiac disease (congestive heart failure, abnormal stress test, or need for open heart surgery); severe pulmonary disease; contralateral carotid occlusion; contralateral laryngeal nerve palsy; previous radical neck surgery or radiation therapy to the neck; recurrent stenosis after endarterectomy; and age >80 years. High risk is defined by age ≥80 years, New York Heart Association class III/IV heart failure, chronic obstructive pulmonary disease, contralateral carotid stenosis 50% or more, prior CEA or CAS, or prior coronary artery bypass graft surgery. †Death, stroke, and MI.

CAS indicates carotid artery stent; CEA, carotid endarterectomy; CREST, Carotid Revascularization Endarterectomy versus Stent Trial; CTA, computed tomography angiography; EPD, embolic protection device; MI, myocardial infarction; MRA, magnetic resonance angiography; OR, odds ratio; SAPPHIRE, Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy; and SE, standard error.

been reported in as many as 33% of patients undergoing CAS (506–508); most are transient and do not require ongoing treatment after the procedure. With appropriate preprocedural management, rates can be kept in the lower range (375,507,509–513). The risk of MI is generally reported as approximately 1% but reached 2.4% in the ARCHeR (ACCULINK for Revascularization of Carotids in High-Risk Patients) trial and was as low as 0.9% in the CAPTURE registry of 3500 patients (361,446,458,508, 514–521).

The risk of arterial dissection or thrombosis in all published series, including the ARCHeR and CAPTURE cohorts, was <1%. Target-vessel perforation occurred in <1% of cases, and external carotid artery stenosis or occlusion occurred in 5% to 10% of cases (361,372,446,458,508,514–539), but this event is typically benign and requires no further intervention. Transient vasospasm occurs in 10% to 15% of procedures related to manipulation of the vessel with guidewires, catheters, or protection devices and is more common in smokers and in those with hypertension (540–543).

The incidence of restenosis after CAS has been reported to be in the range of 3% to 5%. This problem can be minimized by avoiding multiple or high-pressure balloon inflations, particularly in heavily calcified arteries (425,491,544–560).

### 7.3.2.2. NEUROLOGICAL COMPLICATIONS

The incidence of TIA has been reported as 1% to 2% in patients undergoing CAS. In the ARCHeR trial, the overall incidence of stroke was 5.5%, with disabling stroke occurring in 1.5% and relatively minor events occurring in 4.0% of cases (361,458,514,515,517,518,520,521). In the CAPTURE registry, the rate of disabling stroke was 2% and that of nondisabling stroke was 2.9% (372,524–529,531,533, 534). Intracranial hemorrhage and the hyperperfusion syndrome related to hypertension and anticoagulation have been reported as complications in <1% of CAS procedures. Seizures are related predominantly to hypoperfusion and also occur in <1% of cases (561–569). Subclinical ischemic injury has also been detected by MRI (380,570,571). In a recent randomized trial (ICSS), comparisons were possible between patients with CAS and CEA; these injuries, which presumably resulted from microembolism, were more frequent after CAS (368).

Device malfunction that results in deployment failure, stent malformation, and migration after deployment is rare, occurring in <1% of procedures (540,541,572–576). If properly deployed, EPDs can reduce the neurological risks associated with CAS, but these devices may also be associated with failures (372,521,523,572,577–583), including

inability to deliver the device to the target zone because of a large profile and reduced steerability and ischemia if the device becomes overloaded with embolic material during deployment. Sizing of the EPD is important, because undersizing allows passage of debris into the distal circulation and oversizing can cause endothelial damage or provoke vasospasm.

Among the general risks is access-site injury, which complicates 5% of cases, but most such injuries involve pain and hematoma formation and are self-limited (584–587). The risk of groin infection is <1% and that of pseudoaneurysm is 1% to 2%. Blood transfusion is required in 2% to 3% of cases because of bleeding from the catheter insertion site or retroperitoneal hematoma (588–591). Contrast-induced nephropathy has been reported in <1% of cases, because CAS is generally avoided in patients with severe renal dysfunction (592).

### 7.3.3. Prevention of Cerebral Embolism in Patients Undergoing Catheter-Based Carotid Intervention

Designed to prevent cerebral atheroembolism during catheter-based interventions, EPDs are effective in aorto-coronary saphenous vein graft angioplasty, in which there is typically a relatively large burden of thrombus (593,594), but no randomized studies have compared rates of ischemic stroke in patients undergoing CAS with and without these devices. The results of several observational studies suggest that EPDs reduce rates of adverse events during CAS (595–597) when operators are experienced with the apparatus (35); in unfamiliar hands, the devices are associated with worse clinical outcomes (454,456,457) and a higher rate of ischemic abnormalities on postprocedural brain imaging (598). Two postmarketing studies (362,372,375) found similar outcomes when physicians trained in different specialties with various levels of initial experience received training in CAS with EPD techniques. In an international survey of 12,392 CAS procedures performed by experienced operators in 11,243 patients at 53 sites, technical success was achieved in 98.9%, with rates of stroke and death of 2.8% when the devices were used and 6.2% when they were not (595). Although there was no difference in outcomes when experienced operators used the devices with a single CAS system in the ARCHeR trial (361), other studies have found that EPDs improved outcomes (366,369,370,376,580).

### 7.3.4. Intravascular Ultrasound Imaging in Conjunction With Catheter-Based Carotid Intervention

Intravascular ultrasound (IVUS) is an adjunctive imaging technique that can provide detailed information about the diameter of the vascular lumen, extent of atherosclerosis, and degree of calcification. IVUS has been used in coronary and peripheral arteries to verify complete deployment of intravascular stents, to measure plaque protrusion, and to detect arterial dissection after angioplasty. Identification of these complications during the procedure may permit mod-

ification of technique or suggest supplementary interventions to improve outcomes (599,600). Additionally, limited studies suggest that IVUS may be useful to assess plaque burden and composition.

Studies of IVUS in patients with ECVD have focused mainly on the safety of the technique and its potential contribution to the success of carotid revascularization (601,602). Experience to date suggests that IVUS can safely yield imaging information complementary to contrast angiography (603,604), and although incomplete stent expansion or small postprocedural stent diameter may be associated with a greater risk of restenosis (605), the use of IVUS has not been proven to improve outcomes, reduce periprocedural stroke rates, or prevent restenosis. Although the technique has been used safely in a small series of patients undergoing carotid intervention, the additional catheter manipulation required to traverse stenotic lesions carries risk, and more evidence demonstrating benefit is needed before the incremental risk associated with IVUS can be justified as the basis for recommendations regarding routine use of this technology in patients undergoing endovascular evaluation and treatment of ECVD.

### 7.3.5. Management of Patients Undergoing Endovascular Carotid Artery Stenting

#### 7.3.5.1. RECOMMENDATIONS FOR MANAGEMENT OF PATIENTS UNDERGOING CAROTID ARTERY STENTING

##### CLASS I

1. Before and for a minimum of 30 days after CAS, dual-antiplatelet therapy with aspirin (81 to 325 mg daily) plus clopidogrel (75 mg daily) is recommended. For patients intolerant of clopidogrel, ticlopidine (250 mg twice daily) may be substituted. (Level of Evidence: C)
2. Administration of antihypertensive medication is recommended to control blood pressure before and after CAS. (Level of Evidence: C)
3. The findings on clinical neurological examination should be documented within 24 hours before and after CAS. (Level of Evidence: C)

##### CLASS IIa

1. EPD deployment during CAS can be beneficial to reduce the risk of stroke when the risk of vascular injury is low (456,606). (Level of Evidence: C)
2. Noninvasive imaging of the extracranial carotid arteries is reasonable 1 month, 6 months, and annually after revascularization to assess patency and exclude the development of new or contralateral lesions (364). Once stability has been established over an extended period, surveillance at extended intervals may be appropriate. Termination of surveillance is reasonable when the patient is no longer a candidate for intervention. (Level of Evidence: C)

The periprocedural management of patients undergoing CAS can be organized according to distinct time frames. First is the preprocedural evaluation, which includes careful documentation of neurological status and identification of comorbidities that impact the patient's candidacy for endovascular intervention, such as peripheral arterial obstructive disease that limits catheter access, renal insufficiency, and contraindications to intensive platelet-inhibitor therapy. Second is the intraprocedural component, which involves

conscious sedation and analgesia along with monitoring and supportive care. Third is the immediate postprocedure period, when continued in-hospital support and monitoring are required with control of blood pressure, prevention of bleeding and access-site complications, and neurological reassessment. The fourth and final stage involves long-term postprocedural care, which is generally accomplished in the outpatient setting, aimed at preservation of neurological health and secondary prevention of complications of systemic atherosclerosis.

Intraprocedural management includes adequate anticoagulation, continuous assessment of neurological and hemodynamic parameters, and successful technical handling of the CAS procedure. Adequate anticoagulation can be achieved with unfractionated heparin given in sufficient dosage to maintain the activated clotting time between 250 and 300 seconds. Bivalirudin may have advantages over heparin, including obviating the need for monitoring of activated clotting time (607,608).

CAS is associated with a number of periprocedural events, including hypotension and vasovagal and vasodepressor reactions. For this reason, continuous electrocardiogram and blood pressure monitoring has become routine. Several pharmacological agents have been used to correct hemodynamic derangements during CAS. Atropine, 0.5 to 1 mg given intravenously, may be administered prophylactically before the angioplasty or stent portion of the procedure to avoid or attenuate bradycardia. Infrequently, persistent bradycardia may require insertion of a temporary transvenous pacemaker. Sustained hypotension is not rare, and it may be helpful to ensure adequate hydration and careful adjustment of antihypertensive medication immediately before the procedure. In the event of persistent hypotension, intravenous phenylephrine (1 to 10 mcg/kg/min) or dopamine (5 to 15 mcg/kg/min) should be available. Hypertension occasionally develops immediately before, during, or after the procedure, and maintenance of systolic blood pressure below 180 mm Hg is advised to minimize the risk of intracranial hemorrhage or the hyperperfusion syndrome.

The patient's neurological status, particularly level of consciousness, speech, and motor function, should be monitored throughout the stent procedure by the physician or circulating nurse. It is important to avoid excessive sedation to facilitate this ongoing assessment. When neurological dysfunction develops, management is complex and governed by the likely cause and the stage of the procedure at which it becomes manifest. If a neurological event occurs early in the procedure, such as during placement of the guidewire, it may be prudent to abort the procedure and reassess the patient for later intervention, if appropriate. If the event occurs near the completion of the procedure, it may be best to finish as quickly as possible and immediately assess the patient clinically and angiographically for correctable causes. A determination must then be made regarding neurological rescue or alternative management techniques (609).

Immediate postprocedural management includes care of the access site and monitoring of neurological and hemodynamic function. Formal neurological assessment should be documented within 24 hours after intervention. Patients who are stable and neurologically intact may be discharged on the first postprocedural day. In addition to aspirin (81 to 325 mg daily), it is conventional to administer clopidogrel (75 mg daily) for at least 4 weeks, mainly on the basis of experience gained in patients undergoing CAS. Smoking cessation and medications for control of hypertension, hyperlipidemia, and diabetes should be resumed or initiated. For neurologically intact patients with persistent hypotension, an additional period of in-hospital observation may be required. The use of the oral adrenergic agent ephedrine (25 to 50 mg orally, 3 or 4 times daily) may be useful in managing persistent hypotension.

Longer-term postprocedural management includes pharmacotherapy with antiplatelet medication and serial noninvasive imaging to assess stent patency and exclude the development of new areas of stenosis. Atherosclerotic risk factor modification is an ongoing task. The role of risk factor-modifying therapies, including smoking cessation and lipid-lowering and antihypertensive agents, was discussed in Sections 6.1 and 6.3.

Serial follow-up assessment most commonly involves duplex ultrasound imaging. By recent trial convention, surveillance should be performed at 1 month, 6 months, and annually to assess for restenosis. Imaging by CTA or MRA may also be helpful for surveillance after CAS, particularly when Doppler interrogation is difficult because of a superior anatomic location of the region of interest.

## **7.4. Comparative Assessment of Carotid Endarterectomy and Stenting**

### **7.4.1. Nonrandomized Comparison of Carotid Endarterectomy With Carotid Artery Stenting**

The CaRESS (Carotid Revascularization Using Endarterectomy or Stenting Systems) feasibility trial compared CAS and CEA in a broad population of patients with symptomatic carotid stenosis (>50%) or asymptomatic carotid stenosis (>75%) (610,611). To reflect the spectrum of patient characteristics encountered in clinical practice, enrollment was not limited to high-risk surgical candidates. The primary endpoint was the combined incidence of death and stroke within 30 days after the procedure. Treatment was not randomized but was determined on the basis of the recommendation of the treating physicians. A total of 397 patients underwent either CEA or CAS in a ratio of 2:1. Despite the lack of randomization, patient characteristics were reasonably balanced across treatment arms; 87% of patients undergoing CEA and 84% of those treated by CAS were considered high-risk surgical cases, as defined by age >80 years, New York Heart Association class III or IV heart failure, chronic obstructive pulmonary disease, >50%

**Table 11. Kaplan-Meier Estimates of Event Rates in the CaRESS Trial**

Event	≤30 Days (%)		≤365 Days (%)	
	CEA	CAS	CEA	CAS
Death	0.40	0.00	6.60	6.30
Stroke	3.60	2.10	9.80	5.50
MI	0.80	0.00	2.40	1.70
Death/stroke	3.60	2.10	13.60	10.00
Death/stroke/MI	4.40	2.10	14.30	10.90
Restenosis	N/A	N/A	3.60	6.30
Carotid revascularization	N/A	N/A	1.00	1.80

CaRESS indicates Carotid Revascularization Using Endarterectomy or Stenting Systems; CAS, carotid artery stenting; CEA, carotid endarterectomy; MI, myocardial infarction; and N/A, not available.

Modified from CaRESS Steering Committee (611).

contralateral carotid stenosis, prior CEA or CAS, or prior CABG surgery (610,611).

Kaplan-Meier estimates of event rates at 30 and 365 days after the procedure are provided in Table 11, along with observed rates of restenosis and carotid revascularization. There were no significant differences between the CEA and CAS groups for any outcome. Although these results may suggest similar outcomes with CEA and CAS in the first year, the nonrandomized design is an important limitation.

#### 7.4.2. Meta-Analyses Comparing Carotid Endarterectomy and Stenting

A meta-analysis of 5 randomized trials comparing CAS with CEA disclosed no difference in stroke or death rates at 30 days (8.1% versus 6.3%); in MI, stroke, or death rates at 30 days (8.1% versus 7.8%); or in stroke or death rates at 1 year (13.5% versus 13.3%) (458). Another analysis of 6 trials involving 1,177 patients found no difference between CAS and CEA in 30-day or 1-year rates of stroke and death (612). The studies included both symptomatic and asymptomatic patients across a range of surgical risk, as well as stenting with and without EPDs. The authors noted that CAS was associated with a lower rate of MI (RR 0.3, 95% CI 0.1 to 0.8;  $p=0.02$ ) and procedural morbidity such as cranial nerve injury (RR 0.05, 95% CI 0.01 to 0.3;  $p<0.001$ ) (458). Other meta-analyses found CAS to be inferior to CEA or associated with higher rates of periprocedural stroke (613–615). In another meta-analysis of 11 trials that included 4,796 patients (10 of which reported on short-term outcomes [ $n=4,709$ ] and 9 of which reported on intermediate-term outcomes, or 1 to 4 years), the risk of periprocedural mortality or stroke was lower with CEA than with CAS (OR 0.67, 95% CI 0.47 to 0.95;  $p=0.025$ ). This was based mainly on a lower risk of stroke (OR 0.65, 95% CI 0.43 to 1.00;  $p=0.049$ ), because the risk of death (OR 1.14, 95% CI 0.56 to 2.31;  $p=0.727$ ) and the composite endpoint of mortality or disabling stroke (OR 0.74, 95% CI 0.53 to 1.05;  $p=0.088$ ) did not differ significantly. The odds of periprocedural MI (2.69, 95% CI 1.06 to 6.79;  $p=0.036$ ) or cranial nerve injury (10.2, 95% CI 4.0 to 26.1;  $p<0.001$ )

were higher with CEA than with CAS. In the intermediate term, the treatments did not differ significantly for stroke or death (HR 0.90, 95% CI 0.74 to 1.1;  $p=0.314$ ) (616).

#### 7.4.3. Randomized Trials Comparing Carotid Endarterectomy and Carotid Artery Stenting

##### 7.4.3.1. HIGH-RISK PATIENTS

The SAPPHERE study (370,371) is the only randomized trial that specifically enrolled high-risk patients to compare CEA to CAS with an EPD. The inclusion criteria included symptomatic stenosis >50% or asymptomatic stenosis >80%, plus at least 1 high-risk criterion. The trial was stopped prematurely because of slow enrollment after 334 patients were randomized, and many potential participants were excluded because they were considered to be at exceedingly high risk for complications if randomized to undergo CEA. Enrollment in the randomized portion of the trial diminished sharply 12 months after the study was initiated in 2000 (369). Technical success was achieved in 95.6% of patients who underwent CAS. The 30-day incidence of MI, stroke, or death was 4.8% after CAS and 9.8% after CEA ( $p=0.09$ ). The primary endpoint (the composite of MI, stroke, or death within 30 days plus death because of neurological causes or ipsilateral stroke between 31 days and 1 year) occurred in 12.2% of patients assigned to CAS and 20.1% of those assigned to CEA ( $p=0.004$  for noninferiority and  $p=0.053$  for superiority). The protocol required the collection of cardiac serum biomarker data as the basis for diagnosis of periprocedural MI, the majority of which were asymptomatic events. This was not the approach taken in earlier studies of revascularization, and the higher reported incidence of MI should be interpreted accordingly.

In patients with symptomatic stenosis, the occurrence of the primary endpoint was similar after CAS and CEA (16.8% versus 16.5%, respectively). In asymptomatic patients, fewer primary endpoints occurred after CAS (9.9% versus 21.5%). At 1 year, CEA was associated with more cranial nerve palsy (4.9% versus none;  $p=0.004$ ) and target-vessel revascularization (4.3% versus 0.6%;  $p=0.04$ ). The 3-year incidence of stroke (7.1% versus 6.7%;  $p=0.945$ ) and target-vessel revascularization (3% versus 7.1%;  $p=0.084$ ) was similar for CAS and CEA (35,370,371).

##### 7.4.3.2. CONVENTIONAL-RISK PATIENTS

The CAVATAS (Carotid And Vertebral Artery Transluminal Angioplasty Study) international randomized trial of endovascular versus medical therapy involved 504 patients (454). Although the combined stroke or death rate at 30 days was 10% in both groups, the angioplasty and CAS group experienced less cranial neuropathy, major hematoma, MI, and pulmonary embolism and more restenosis at 1 year (14% versus 4%;  $p<0.001$ ), which reflects a relatively low rate of stent use (22%) in the endovascular intervention arm. Stroke or death at 3 years was similar in the 2 groups (14.2%) (454).



**Table 12. SPACE Trial Results at 30 Days After the Procedure**

Study Arm	CEA (N=584), n (%)	CAS (N=599), n (%)	Absolute Difference (CAS-CEA)
Primary response events	37 (6.3)	41 (6.8)	0.51% (-1.89% to 2.91%)*
Death	5 (0.9)	4 (0.7)	
All stroke	36 (6.2)	45 (7.5)	
Ischemic stroke	30 (5.1)	39 (6.5)	
Ipsilateral			
Hemorrhagic stroke	5 (0.9)	1 (0.2)	
Stroke			
Disabling stroke†	17 (2.9)	24 (4.0)	

\*90% confidence interval. †Stroke resulting in a Modified Rankin Scale score of  $\geq 3$ . CAS indicates carotid artery stenting; CEA, carotid endarterectomy; and SPACE, Stent-Protected Angioplasty versus Carotid Endarterectomy.

The SPACE trial was designed to test the hypothesis that CAS would be noninferior to CEA in symptomatic patients with high-grade carotid artery stenosis (Table 12) (457). Patients were required to have >70% carotid stenosis determined by duplex ultrasound, TIA or stroke within the previous 180 days, and a Modified Rankin Scale score <4. Surgical risk status was not a determinant of eligibility. The primary outcome was a composite of ipsilateral stroke or death within 30 days of the procedure. Subjects were randomized between 2001 and 2006 to CEA (n=595) or CAS (n=605). The surgeons were required to have performed at least 25 CEA procedures with acceptable rates of mortality and morbidity in the prior year, and CAS operators were required to have performed at least 25 successful angioplasty or stent procedures, not necessarily involving carotid arteries. The use of shunting during CEA and the use of an EPD during CAS were optional. The 1,200-patient enrollment fell short of the planned sample size of 1,900 when the study was terminated because of inability to enroll the intended number of patients. Patient demographics and lesion characteristics were similar in the 2 groups, and there was no significant difference in outcomes between CAS and CEA at 30 days. Among the limitations of the SPACE trial were the unequal training and experience of surgeons performing CEA (617) and nonuniform use of EPDs during CAS procedures (618).

The EVA-3S (Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis) trial randomized patients within 120 days of TIA or completed stroke who had >60% ipsilateral carotid stenosis determined by duplex ultrasound and angiography (456). Patients were excluded if they had experienced a disabling stroke (Modified Rankin Scale score >3), but surgical risk status was not a specified exclusion criterion. The primary outcome was the composite of stroke or death within 30 days of the procedure. Surgeons were required to have performed at least 25 CEA procedures during the previous year, and operators performing CAS were required to have performed at least 12 CAS procedures or 35 stenting procedures in other vessels. Trainees with little stenting experience were eligible to perform CAS if proctored by qualified operators. The use of EPDs was limited. After 520 patients were randomized, enrollment was stopped in 2005 because of higher 30-day rates of stroke and other adverse events in the CAS arm (Table 13). More patients assigned to CAS had occlusions of the contralateral carotid artery (5% versus 1.2%), a high-risk anatomic feature.

As with the SPACE trial (457), an important criticism of the EVA-3S trial (619) centers on inadequate training requirements for operators performing CAS and the non-uniform requirement to use an EPD, which may have compromised the results of CAS. The single-antiplatelet medication regimen used in some subjects has also been questioned. Although dual-antiplatelet therapy has been the standard in North American carotid stent trials, comparative outcome data from randomized clinical trials are available only for stents deployed in other (mainly coronary) vascular beds. Hence, the optimum dosing, timing, and duration of dual-antiplatelet therapy for patients undergoing CAS have not been established.

At least 4 additional randomized clinical trials have been reported, are in progress, or are under consideration to compare CEA to CAS with EPD in conventional-risk patients. The ICSS is an ongoing randomized trial designed to compare the safety and effectiveness of CEA versus CAS in symptomatic patients with >50% carotid stenosis (368). Participating centers were classified as either experienced or supervised. Experience required that at least 1 surgeon at the center had performed at least 50 CEA procedures (mini-

**Table 13. Result of the EVA-3S Trial at 30 Days After the Procedure**

	CEA (N=259), n (%)	CAS (N=261), n (%)	OR (95% CI)	p
Primary response events	10 (3.9)	25 (9.6)	0.38 (0.16 to 0.84)	0.0133
Death	3 (1.2)	2 (0.8)	0.66 (0.17 to 18.30)	0.6851
All stroke	9 (3.5)	24 (9.2)	0.36 (0.14 to 0.81)	0.0108
Fatal stroke	2 (0.8)	1 (0.4)	2.02 (0.10 to 119.82)	0.6228
Nonfatal stroke	7 (2.7)	23 (8.8)	0.29 (0.10 to 0.71)	0.0041
Disabling stroke*	1 (0.4)	7 (2.7)	0.14 (0.0031 to 1.11)	0.0682

\*Stroke resulting in a Modified Rankin Scale score of >3 with an increase of  $\geq 2$  over the score before the stroke. CAS indicates carotid artery stenting; CEA, carotid endarterectomy; CI, confidence interval; EVA-3S, Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis. Adapted from Ringleb et al. (457) and Mas et al. (456).

mum of 10 per year) and at least 1 interventionist had performed at least 50 stenting procedures and a minimum of 10 carotid stents. Supervised centers were designated as experienced after randomization and treatment of 20 cases by CEA or CAS if the results were acceptable to a proctor and credentialing committee. Under this classification, 88% of patients were treated at experienced centers. The primary endpoint is the 3-year rate of fatal or disabling stroke, but only an interim safety analysis has been reported. Among 1713 randomized patients, the 120-day composite rate of stroke, death, or procedural MI was 8.5% in the CAS group versus 5.2% in the CEA group (HR 1.69, 95% CI 1.16 to 2.45). Although the investigators suggested at that point that CEA should be preferred over CAS in similar patients, firm conclusions await completion of longer-term follow-up of the cohort.

CREST is a randomized multicenter trial comparing CAS to CEA in both symptomatic and asymptomatic patients (620–622). The primary endpoint is the occurrence of stroke, death, or MI during the periprocedural period and ipsilateral stroke thereafter up to 4 years. CREST is unique among the reported randomized trials comparing CAS and CEA in conventional-risk patients because it included both symptomatic patients with >50% carotid stenosis and asymptomatic patients with >60% stenosis. Among 2502 patients followed up for a mean of 2.5 years, there was no significant difference in primary events between the 2 methods of revascularization (7.2% with CAS versus 6.8% with CEA; HR 1.11, 95% CI 0.81 to 1.51). Despite the similarity in primary outcome, there were differences in rates of the component periprocedural events. Stroke was significantly more frequent with CAS (4.1% versus 2.3%;  $p=0.01$ ), and MI was more likely after CEA (2.3% versus 1.1%;  $p=0.03$ ), although the absolute rates of either were low. Questions have arisen regarding the comparative impact of periprocedural stroke and MI on the patient. In CREST at 1 year, quality of life was impacted significantly by major and minor stroke but not by MI. The lack of a detectable impact of MI on quality of life may relate to sensitive ascertainment techniques, including biomarker assessments, such that the rate of MI in CREST was higher than that reported in other randomized trials. The comparative primary results between treatment groups did not vary by sex or symptom status, although event rates were higher among symptomatic patients in both groups than among asymptomatic patients. For both symptomatic and asymptomatic patients, the periprocedural stroke and death rates at the 117 centers in CREST were at or below the recommended safety requirements in current guideline statements (111). Consistent with reports from the SPACE trial, there was a differential outcome based on patient age: For patients younger than 70 years of age, the primary results favored CAS, whereas in those older than 70 years of age, results favored CEA (360). Also, as in previous randomized trials, cranial nerve palsy was more common after CEA (360).

**Table 14. Summary of Recommendations Regarding the Selection of Revascularization Techniques for Patients With Carotid Artery Stenosis**

	Symptomatic Patients		Asymptomatic Patients:
	50% to 69% Stenosis	70% to 99% Stenosis*	70% to 99% Stenosis*
Enderterectomy	Class I LOE: B	Class I LOE: A	Class IIa LOE: A
Stenting	Class I LOE: B	Class I LOE: B	Class IIb LOE: B

The severity of stenosis is defined according to angiographic criteria by the method used in NASCET (70) but generally corresponds as well to assessment by sonography (136) and other accepted methods of measurement. See Sections 7.2 to 7.4.4 for details.

LOE indicates level of evidence.

ACST-2 and ACT-1 (Asymptomatic Carotid Trial) compare CEA with CAS in patients with asymptomatic carotid stenosis (<http://www.ClinicalTrials.gov> and <http://www.controlled-trials.com>), but no outcome data have yet been reported.

#### 7.4.4. Selection of Carotid Endarterectomy or Carotid Artery Stenting for Individual Patients With Carotid Stenosis

Table 14 summarizes recommendations for the selection of revascularization techniques for patients with carotid artery stenosis. Although no adequate studies have validated the specific high-risk criteria that might warrant preferential selection of CAS rather than CEA for individual patients, generally accepted anatomic features are listed in Table 10. In addition to these are comorbid medical conditions associated with increased surgical risk, such as advanced cardiopulmonary disease that might complicate surgical anesthesia.

Recent large trials like CREST make it clear that with adequate training, physicians can perform CAS and CEA with low complication rates. Taken together with the results of previous trials, it appears that CAS is associated with a higher periprocedural risk of stroke or death. Although this difference remained significant in CREST for up to 4 years, a meta-analysis of studies that preceded CREST found CEA to be superior to CAS with regard to short-term but not longer-term outcomes (616). Hence, additional long-term data are needed before clear conclusions can be drawn regarding the relative risks and benefits of the 2 procedures (623). Although the increased risk of nonfatal stroke with CAS is statistically offset by an increased risk of nonfatal MI with CEA, stroke appears to have more detrimental health consequences. Similarly, local complications, particularly cranial nerve palsies, are more frequently associated with CEA, whereas microembolic cerebral injury after CAS may have implications for cognitive function. Although the reasons remain speculative, the interaction of patient age with the outcomes of CAS and CEA must also be considered carefully by clinicians, with CEA favored for elderly patients. Finally, the benefit of revascularization by either method versus modern aggressive medical therapy has not

been established for patients with asymptomatic carotid stenosis.

## 7.5. Durability of Carotid Revascularization

### 7.5.1. Recommendations for Management of Patients Experiencing Restenosis After Carotid Endarterectomy or Stenting

#### **CLASS IIa**

1. In patients with symptomatic cerebral ischemia and recurrent carotid stenosis due to intimal hyperplasia or atherosclerosis, it is reasonable to repeat CEA or perform CAS using the same criteria as recommended for initial revascularization (see Sections 7.5.2 and 7.5.3). (Level of Evidence: C)
2. Reoperative CEA or CAS after initial revascularization is reasonable when duplex ultrasound and another confirmatory imaging method identify rapidly progressive restenosis that indicates a threat of complete occlusion. (Level of Evidence: C)

#### **CLASS IIb**

1. In asymptomatic patients who develop recurrent carotid stenosis due to intimal hyperplasia or atherosclerosis, reoperative CEA or CAS may be considered using the same criteria as recommended for initial revascularization. (Level of Evidence: C)

#### **CLASS III: HARM**

1. Reoperative CEA or CAS should not be performed in asymptomatic patients with less than 70% carotid stenosis that has remained stable over time. (Level of Evidence: C)

### 7.5.2. Clinical Durability of Carotid Surgery and Carotid Stenting

Clinical durability refers to the sustained efficacy of CEA and CAS in preventing stroke, as discussed for CEA in Section 7.2. In the large randomized clinical trials, the ipsilateral stroke rates after the first 30 days were approximately 1% to 2% per year for symptomatic patients (ECST, NASCET) and approximately 0.5% to 0.8% per year for asymptomatic patients (ACAS, ACST). For clinical durability of CEA compared with CAS, longer-term results from EVA-3S and SPACE are now available and show promising results for both procedures. EVA-3S outcomes projected to 4 years showed ipsilateral stroke rates beyond 30 days of <1% per year for both CEA and CAS. In SPACE, at 2 years, the ipsilateral stroke rate was approximately 1% per year for CEA and CAS when periprocedural events were excluded. The clinical durability of CEA and CAS beyond 5 years cannot be clearly determined from available studies (364,379).

The mechanism responsible for arterial restenosis after CEA is related to the postoperative interval. Early restenosis (within 2 years) typically involves intimal hyperplasia, whereas later restenosis usually reflects progression of atherosclerotic disease. Outcomes are similar regardless of whether the patch material is vein, polyethylene terephthalate, polytetrafluoroethylene, or bovine pericardium (624–627). The role of CAS as an alternative to reoperative CEA in patients who experience restenosis after initial CEA is discussed in Section 7.3.

### 7.5.3. Anatomic Durability of Carotid Surgery and Carotid Stenting

The incidence of recurrent carotid stenosis depends on the method used for detection. Restenosis after CEA has been reported in 5% to 10% of cases when assessed by postoperative ultrasonography, but the rate has been consistently below 5% when patching was used in more recent series (407,440,468,624,625,628–630). When periodic duplex scanning is used, hemodynamically significant recurrent stenosis rates of 5% to 7% have been reported in multicenter trials in which the quality of surgery is monitored carefully (396,403,404,406,440,628,631–645).

Recurrent carotid stenosis after CEA is a trimodal phenomenon. The first event is not really recurrence but instead represents an unsatisfactory or incomplete CEA. This is usually detected when the first postoperative duplex ultrasound scan identifies residual stenosis, and its occurrence can be minimized by intraoperative completion angiography or duplex ultrasound imaging. Because the quality of CEA has improved, this phenomenon occurs in <1% of cases. The second peak of recurrent carotid stenosis, occurring within 18 months and usually within 6 months after operation, is due to intimal hyperplasia. This is usually benign, seldom requires reoperation, and has been reduced through the routine incorporation of patch angioplasty closure into the operative procedure. The third form of recurrent stenosis usually develops 5 years or longer after operation and reflects progressive atherosclerotic disease either at the site of CEA or in proximal or distal arterial segments.

For both CEA and CAS, comparative data on restenosis are becoming available but should be interpreted with caution. A minority of patients in contemporary studies have undergone follow-up ultrasound scanning, which introduces potential important selection bias. For CAS, the role of stent-generated artifacts in ultrasound velocity measurements has yet to be resolved with angiographic comparisons. In the CAVATAS study, a stent was used in only 22% of the angioplasty patients, and carotid ultrasound at 1 year detected 70% to 99% stenosis in 4% of the CEA patients and in 14% of the patients managed by CAS ( $p < 0.001$ ). In SAPPHERE, all CAS patients received a stent; 96 of the CEA patients and 122 of the CAS patients underwent carotid ultrasound at 1 year. Four CEA patients (4.2%) and 1 CAS patient (0.8%) had >70% recurrent stenosis ( $p = 0.17$ ). After 1 year of follow-up in the SPACE trial, 4.6% of patients who underwent CEA and 10.7% of those who underwent CAS had developed  $\geq 70\%$  recurrent stenosis as assessed by ultrasound ( $p = 0.0009$ ). Comparative restenosis rates for CEA and CAS are also available from case series (646–649), but inference is limited by potential selection bias.

In patients who develop restenosis after CEA, CAS is an alternative to reoperative CEA (see Section 7.2.4) and may be appropriate in asymptomatic patients with restenosis that

produces >80% luminal narrowing or in symptomatic patients with >50% recurrent stenosis. Contralateral occlusion arguably increases the risk associated with CAS, because the procedure does not provide an option to use a shunt, and little collateral circulation is available in the event of thrombosis or occlusion of an EPD. On the other hand, 3 studies (ARCHEr, a nonrandomized prospective study [361]; SAPHIRE, a randomized comparison [370]; and CAPTURE, a multicenter registry [372]) specifically addressed the use of CAS in patients with carotid stenosis and contralateral carotid occlusion. The prevalence of contralateral carotid occlusion was 16.5% in ARCHEr, 24.5% in SAPHIRE, and 8.2% in CAPTURE. Although the overall results of these limited studies suggested that CAS was noninferior to CEA in patients with various comorbidities (including but not limited to contralateral occlusion), the available data are insufficient to justify a recommendation favoring one procedure over the other in patients with carotid stenosis and occlusion of the contralateral carotid artery. Restenosis is generally a benign condition that does not require revascularization except in selected circumstances, such as when restenosis leads to recurrent ischemic symptoms or progresses to preocclusive severity. Under these circumstances, it may be justifiable to repeat revascularization, either by CEA in the hands of an experienced surgeon or by CAS as in the general approach to patients with unsuitable neck anatomy.

## 8. Vertebral Artery Disease

Symptomatic obstructive disease of the vertebral arteries is encountered less commonly in clinical practice than carotid stenosis, and the volume of evidence available to guide its evaluation and management is less substantial. The prevalence, pathophysiology, and natural history of vertebral artery disease are not as well understood as disease of the extracranial carotid circulation. Like patients with carotid atherosclerosis, however, those with vertebral artery disease face an increased risk of other cardiovascular ischemic events, including MI, PAD, and vascular death.

### 8.1. Anatomy of the Vertebrobasilar Arterial Circulation

The left and right vertebral arteries are typically described as having 4 segments each (V1 through V4), the first 3 of which are extracranial. The first segments (V1) extend cephalad and posteriorly from the origin of the vertebral arteries between the longus colli and scalenus anterior muscles to the level of the transverse foramina, typically adjacent to the sixth cervical vertebra. The second segments (V2) extend cephalad from the point at which the arteries enter the most inferior transverse portion of the foramina to their exits from the transverse foramina at the level of the second cervical vertebra. These segments of the left and right vertebral arteries therefore have an alternating in-

traosseous and interosseous course, a unique anatomic environment that exposes the V2 segments to the possibility of extrinsic compression from spondylotic exostosis of the spine. Small branches from the V2 segments supply the vertebrae and adjacent musculature and, most importantly, may anastomose with the spinal arteries. The third segments (V3) extend laterally from the points at which the arteries exit the C2 transverse foramina, cephalad and posterior to the superior articular process of C2, cephalad and medially across the posterior arch of C1, and then continue into the foramen magnum. Branches of the V3 segments typically anastomose with branches of the occipital artery at the levels of the first and second cervical vertebrae. The fourth segments (V4) of each vertebral artery extend from the point at which the arteries enter the dura to the termination of these arteries at the vertebrobasilar junction. Important branches of the V4 segments include the anterior and posterior spinal arteries, the posterior meningeal artery, small medullary branches, and the posterior inferior cerebellar artery.

Anatomic variants of vertebral artery anatomy are much more common than variants of the carotid circulation. The vertebral arteries typically arise from the subclavian arteries; in approximately 5% of individuals, however, the left vertebral artery arises directly from the aortic arch. The diameter of the left vertebral artery is larger than (in 50% of individuals) or equal to (in 25% of individuals) that of the right vertebral artery. In approximately 10% of people, 1 vertebral artery is markedly smaller than the other. When this is the case, the smaller vertebral artery may terminate in the posterior inferior cerebellar artery or have a hypoplastic segment that extends beyond the posterior inferior cerebellar artery to the basilar artery, contributing little to basilar artery blood flow. These important anatomic variations must be considered in clinical assessment and treatment.

### 8.2. Epidemiology of Vertebral Artery Disease

Because it may be difficult to visualize the origins of the vertebral arteries by ultrasound imaging, the incidence of posterior circulation strokes may be underestimated (650), but vertebral artery atherosclerosis may be the causative basis for approximately 20% of posterior circulation strokes (650–653). In the New England Medical Center Posterior Circulation Registry, 82 of 407 patients with ischemia affecting the posterior circulation had >50% stenosis of the extracranial vertebral artery (654). Annual stroke rates for patients with symptomatic intracranial vertebral and basilar artery stenosis are 8% and 11%, respectively (655–657). A study using contrast-enhanced MRA in consecutive patients with posterior circulation TIA or minor stroke found a greater prevalence of >50% vertebral and basilar arterial stenosis than of >50% carotid stenosis in patients with carotid territory events, and vertebrobasilar arterial stenosis was more often associated with multiple ischemic episodes and a higher risk of early recurrent stroke (658).

### 8.3. Clinical Presentation of Patients With Vertebrobasilar Arterial Insufficiency

Atherosclerotic stenosis most commonly affects the first portion of the vertebral arteries or extends from plaques that compromise the origin of the vertebral arteries as they arise from the brachiocephalic and subclavian arteries. Lesions at the midportion of the vertebral arteries can occur when overgrowth of the transverse process of a vertebra impinges on the artery as it passes through the bony canal. In such cases, symptoms are commonly provoked by head turning, during which an osteophyte obstructs the vertebral artery.

Symptoms associated with vertebral artery occlusive disease include dizziness, vertigo, diplopia, perioral numbness, blurred vision, tinnitus, ataxia, bilateral sensory deficits, and syncope, all of which can be caused by other disease entities, including cardiac arrhythmias, orthostatic hypotension, and vestibular disorders.

### 8.4. Evaluation of Patients With Vertebral Artery Disease

Evaluation of a patient with presumed vertebrobasilar insufficiency should begin with a thorough clinical history and examination followed by noninvasive imaging as for patients with carotid artery disease (659).

### 8.5. Vertebral Artery Imaging

#### 8.5.1. Recommendations for Vascular Imaging in Patients With Vertebral Artery Disease

##### CLASS I

1. Noninvasive imaging by CTA or MRA for detection of vertebral artery disease should be part of the initial evaluation of patients with neurological symptoms referable to the posterior circulation and those with subclavian steal syndrome. (*Level of Evidence: C*)
2. Patients with asymptomatic bilateral carotid occlusions or unilateral carotid artery occlusion and incomplete circle of Willis should undergo noninvasive imaging for detection of vertebral artery obstructive disease. (*Level of Evidence: C*)
3. In patients whose symptoms suggest posterior cerebral or cerebellar ischemia, MRA or CTA is recommended rather than ultrasound imaging for evaluation of the vertebral arteries. (*Level of Evidence: C*)

##### CLASS IIa

1. In patients with symptoms of posterior cerebral or cerebellar ischemia, serial noninvasive imaging of the extracranial vertebral arteries is reasonable to assess the progression of atherosclerotic disease and exclude the development of new lesions. (*Level of Evidence: C*)
2. In patients with posterior cerebral or cerebellar ischemic symptoms who may be candidates for revascularization, catheter-based contrast angiography can be useful to define vertebral artery pathoanatomy when noninvasive imaging fails to define the location or severity of stenosis. (*Level of Evidence: C*)
3. In patients who have undergone vertebral artery revascularization, serial noninvasive imaging of the extracranial vertebral arteries is reasonable at intervals similar to those for carotid revascularization. (*Level of Evidence: C*)

In contrast to the wealth of literature on carotid arterial imaging, published data on noninvasive imaging of the vertebrobasilar arterial system are relatively sparse. A systematic review found 11 studies that evaluated noninvasive imaging methods compared with catheter-based angiography for detection of vertebral artery stenosis. CTA and contrast-enhanced MRA were associated with higher sensitivity (94%) and specificity (95%) than duplex ultrasonography (sensitivity 70%), and CTA had slightly superior accuracy (167). The relative insensitivity of ultrasound reflects the technical difficulty involved in sonographic interrogation and makes this method less suitable for detection of disease in this anatomic region. Local expertise and availability of imaging techniques must also be considered in the selection of noninvasive modalities in a given clinical situation. Because neither MRA nor CTA reliably delineates the origins of the vertebral arteries, catheter-based contrast angiography is typically required before revascularization for patients with symptomatic posterior cerebral ischemia. Digital subtraction arteriography with intravenous contrast administration is sometimes used when selective catheterization of the vertebral arteries cannot be achieved, but the accuracy of this method compared with CTA has not been established.

### 8.6. Medical Therapy of Patients With Vertebral Artery Disease

#### 8.6.1. Recommendations for Management of Atherosclerotic Risk Factors in Patients With Vertebral Artery Disease

##### CLASS I

1. Medical therapy and lifestyle modification to reduce atherosclerotic risk are recommended in patients with vertebral atherosclerosis according to the standards recommended for those with extracranial carotid atherosclerosis (261,660). (*Level of Evidence: B*)
2. In the absence of contraindications, patients with atherosclerosis involving the vertebral arteries should receive antiplatelet therapy with aspirin (75 to 325 mg daily) to prevent MI and other ischemic events (305,661). (*Level of Evidence: B*)
3. Antiplatelet drug therapy is recommended as part of the initial management for patients who sustain ischemic stroke or TIA associated with extracranial vertebral atherosclerosis. Aspirin (81 to 325 mg daily), the combination of aspirin plus extended-release dipyridamole (25 and 200 mg twice daily, respectively), and clopidogrel (75 mg daily) are acceptable options. Selection of an antiplatelet regimen should be individualized on the basis of patient risk factor profiles, cost, tolerance, and other clinical characteristics, as well as guidance from regulatory agencies (260,305,339-342). (*Level of Evidence: B*)

##### CLASS IIa

1. For patients with atherosclerosis of the extracranial vertebral arteries in whom aspirin is contraindicated by factors other than active bleeding, including those with allergy to aspirin, either clopidogrel (75 mg daily) or ticlopidine (250 mg twice daily) is a reasonable alternative. (*Level of Evidence: C*)

Optimum management of patients with symptomatic vertebral artery stenosis is not as well established as that for patients with carotid stenosis. Although various medical, interventional, and surgical approaches have been developed for treatment of patients with vertebral artery disease, none have been evaluated in randomized trials. In fact, few trials involving ischemic stroke have distinguished between anterior or posterior circulatory disease. In general, despite the relative paucity of evidence specifically applicable to patients with vertebral artery disease, we recommend that medical management follow the guidelines set forth for those with disease of the carotid arteries. This is particularly true of measures directed at reduction of systemic atherosclerotic risk and the prevention of ischemic complications in other vascular beds.

For patients with acute ischemic syndromes that involve the vertebral artery territory, studies of intravenous thrombolytic therapy have reported variable outcomes (650,662,663). When there is angiographic evidence of thrombus at the origin or extracranial portion of the vertebral artery, anticoagulation is generally recommended for at least 3 months, whether or not thrombolytic therapy is used initially (662,664–666). The WASID (Warfarin versus Aspirin for Symptomatic Intracranial Disease) trial found aspirin and warfarin to be equally efficacious after initial noncardioembolic ischemic stroke (656,667). Ticlopidine was superior to aspirin for secondary prevention of ischemic events in patients with symptomatic posterior circulation disease (668). In ESPS-2, vertebrobasilar territory stroke or TIA occurred in 5.7% of 255 patients treated with a combination of low-dose aspirin and sustained-release dipyridamole twice daily compared with 10.8% of those given a placebo (669).

## 8.7. Vertebral Artery Revascularization

### 8.7.1. Surgical Management of Vertebral Artery Disease

Compared with CEA, operations are rarely performed to treat vertebral artery occlusive disease. Although no randomized trials have addressed operative procedures for posterior cerebral circulation disease, reports of surgical treatment of patients with extracranial vertebral artery stenosis have demonstrated the feasibility of endarterectomy and vessel reconstruction with favorable outcomes (670–677). For proximal vertebral artery reconstruction, early complication rates of 2.5% to 25% and perioperative mortality rates of 0% to 4% have been reported (671,672). For distal vertebral artery reconstruction, mortality rates have ranged from 2% to 8% (670,673,674, 676,677). Intracranial bypass surgery is associated with mortality rates of 3% to 12% and neurological and systemic complication rates of 22% to 55% (673–677).

When symptoms can be clearly attributed to occlusive disease of the vertebral arteries, corrective surgery may be effective. Indications for surgery on the first portion of the vertebral artery are relatively rare. When both vertebral

arteries are patent and 1 has a significant stenotic lesion, the contralateral vertebral artery usually supplies sufficient blood flow to the basilar artery, provided there is anatomic continuity. This is particularly true if the uninvolved vertebral artery is the larger (dominant) vessel. Compromised vertebrobasilar perfusion is not the only mechanism of symptoms, however, because atheroembolism from lesions at the origin of the vertebral artery may be the source of brainstem or cerebellar infarction.

The surgical approach to atherosclerotic lesions at the origin of the vertebral artery includes trans-subclavian vertebral endarterectomy, transposition of the vertebral artery to the ipsilateral common carotid artery, and reimplantation of the vertebral artery with vein graft extension to the subclavian artery. Distal reconstruction of the vertebral artery, necessitated by total occlusion of the midportion, may be accomplished by anastomosis of the principal trunk of the external carotid artery to the vertebral artery at the level of the second cervical vertebra (678). Such operations, although rare, can relieve symptoms, with low rates of morbidity and mortality in appropriately selected patients (670,679–686).

### 8.7.2. Catheter-Based Endovascular Interventions for Vertebral Artery Disease

Although angioplasty and stenting of the vertebral vessels are technically feasible, as for high-risk patients with carotid disease, there is insufficient evidence from randomized trials to demonstrate that endovascular management is superior to best medical management. In a review of 300 interventions for proximal vertebral artery stenosis, the risk of death was 0.3%, the risk of periprocedural neurological complications was 5.5%, and risk of posterior stroke was 0.7% at a mean follow-up of 14.2 months. Restenosis occurred in 26% of cases (range 0% to 43%) after a mean of 12 months (range 3 to 25 months), although restenosis was not consistently correlated with recurrent symptoms (687). Among 170 angioplasty procedures in patients with distal vertebrobasilar disease, neurological complications developed in 24%, but the rate approached 80% in cases of urgent vertebrobasilar revascularization. Restenosis developed in 10% after a mean follow-up interval of 12.6 months (687). When data from 14 case series were combined, the annual stroke risk after angioplasty for distal vertebrobasilar disease was approximately 3% (687), and rates of stroke and restenosis appeared to be related to ascending (more distal) location and the anatomic complexity of the offending lesion.

CAVATAS (688), the only randomized study to date to compare outcomes after endovascular and medical treatment for patients with vertebral artery stenosis, included only 16 such patients (454,688,689), in contrast to 504 patients with carotid stenosis, and because no patient in either arm had recurrent vertebral basilar territory stroke by 8 years after randomization, there was no difference in outcomes among those treated by stenting or medical therapy. The lower rate of diagnosis of symptomatic verte-

bral artery stenosis versus carotid artery disease illustrates the inherent difficulty in demonstrating a benefit of vertebral artery revascularization.

## 9. Diseases of the Subclavian and Brachiocephalic Arteries

### 9.1. Recommendations for the Management of Patients With Occlusive Disease of the Subclavian and Brachiocephalic Arteries

#### CLASS IIa

1. Extra-anatomic carotid-subclavian bypass is reasonable for patients with symptomatic posterior cerebral or cerebellar ischemia caused by subclavian artery stenosis or occlusion (subclavian steal syndrome) in the absence of clinical factors predisposing to surgical morbidity or mortality (690–692). (*Level of Evidence: B*)
2. Percutaneous endovascular angioplasty and stenting is reasonable for patients with symptomatic posterior cerebral or cerebellar ischemia caused by subclavian artery stenosis (subclavian steal syndrome) who are at high risk of surgical complications. (*Level of Evidence: C*)
3. Revascularization by percutaneous angioplasty and stenting, direct arterial reconstruction, or extra-anatomic bypass surgery is reasonable for patients with symptomatic ischemia involving the anterior cerebral circulation caused by common carotid or brachiocephalic artery occlusive disease. (*Level of Evidence: C*)
4. Revascularization by percutaneous angioplasty and stenting, direct arterial reconstruction, or extra-anatomic bypass surgery is reasonable for patients with symptomatic ischemia involving upper-extremity claudication caused by subclavian or brachiocephalic arterial occlusive disease. (*Level of Evidence: C*)
5. Revascularization by either extra-anatomic bypass surgery or subclavian angioplasty and stenting is reasonable for asymptomatic patients with subclavian artery stenosis when the ipsilateral internal mammary artery is required as a conduit for myocardial revascularization. (*Level of Evidence: C*)

#### CLASS III: NO BENEFIT

1. Asymptomatic patients with asymmetrical upper-limb blood pressure, periclavicular bruit, or flow reversal in a vertebral artery caused by subclavian artery stenosis should not undergo revascularization unless the internal mammary artery is required for myocardial revascularization. (*Level of Evidence: C*)

### 9.2. Occlusive Disease of the Subclavian and Brachiocephalic Arteries

Occlusive disease that involves the subclavian and brachiocephalic arteries is relatively uncommon. Causes include atherosclerosis, Takayasu arteritis, giant cell arteritis, FMD, and radiation-induced arteriopathy; of these, atherosclerosis is the most frequent cause. The clinical presentation depends on the vessel involved and severity of disease. Symptoms may reflect upper-extremity ischemia, such as arm or hand claudication, paresthesia, or rest pain.

Subclavian artery stenosis is generally associated with a favorable prognosis. Some patients with high-grade stenosis and mild upper-extremity claudication become asymptom-

atic as collateral blood supply develops. In asymptomatic patients, subclavian intervention may be performed in preparation for coronary revascularization surgery that requires use of the ipsilateral internal mammary artery as a bypass conduit or to preserve blood flow to the internal mammary artery in patients who require myocardial revascularization. To our knowledge, no randomized trials of subclavian artery or brachiocephalic revascularization have been published.

### 9.3. Subclavian Steal Syndrome

When the proximal subclavian artery becomes stenotic or occluded, branches distal to the obstruction become sources of collateral circulation to the arm by flow reversal in the vertebral artery and internal mammary arteries. Usually, this does not cause symptoms except for muscular fatigue in the affected arm, akin to claudication. Because 2 vertebral arteries normally supply blood to the basilar artery, antegrade flow through 1 is usually sufficient to maintain posterior cerebral circulation. When the dominant vertebral artery is subtended by subclavian obstruction, reversal of flow in the vertebral artery may reduce basilar artery perfusion and cause posterior cerebrovascular insufficiency. Symptoms are typically aggravated by exercising the ipsilateral arm, which amplifies the flow reversal as a source of collateral circulation to the subclavian artery and its branches. The same phenomenon affects the internal mammary artery, compromising its utility as a conduit for CABG surgery.

Detection of a periclavicular or infraclavicular bruit suggests the possibility of subclavian stenosis, but subclavian arterial occlusive disease is most readily recognized on the basis of asymmetry between left and right arm blood pressure measurements. The side with the lower pressure is suspect for subclavian artery stenosis or occlusion, and blood pressure tends to fall further in the affected limb after arm exercise. Blood pressure measurements may not be asymmetrical when bilateral subclavian disease or aortic arch syndrome compromises perfusion of both upper limbs equally.

The diagnosis of subclavian steal syndrome should be considered in patients with symptoms of posterior cerebral circulatory insufficiency aggravated by upper-limb exercise. In the vertebral ischemic form of subclavian steal syndrome, upper-extremity exertion leads to retrograde flow in the ipsilateral vertebral artery, and symptoms of posterior cerebral or cerebellar hypoperfusion, including lightheadedness, syncope, vertigo, ataxia, diplopia, and motor deficits may occur; the patient may also develop upper-limb claudication. In the less common coronary ischemic form of subclavian steal syndrome, blood is diverted from the coronary arteries to the upper limb through an internal mammary artery graft during arm exercise, producing angina pectoris. Involvement of the brachiocephalic or common carotid artery can lead to symptomatic cerebral hypoperfusion. Duplex ultrasonography may identify reversal of flow in a vertebral

artery, and CTA or MRA of the aortic arch may identify stenosis of the subclavian artery.

Asymptomatic patients with asymmetrical upper-limb blood pressure, reversal of flow in a vertebral artery, or other manifestations of subclavian steal syndrome need no specific intervention other than strategies directed at the secondary prevention of ischemic events related to systemic atherosclerosis, unless the ipsilateral internal mammary artery is required for myocardial revascularization. Symptomatic patients should be considered for subclavian revascularization with endovascular or surgical techniques.

#### 9.4. Revascularization of the Brachiocephalic and Subclavian Arteries

The main surgical approach to revascularization involves prosthetic extra-anatomic bypass grafting from the ipsilateral carotid artery to the subclavian artery, which is highly effective in delivering blood to the subclavian artery and restoring antegrade vertebral artery flow to the basilar artery. In addition to carotid-subclavian bypass, commonly used extra-anatomic methods of subclavian artery revascularization include carotid-axillary or axilloaxillary bypass with polytetrafluoroethylene or Dacron grafts and subclavian-carotid arterial transposition. Surgical repair is associated with low morbidity and mortality and excellent long-term patency (690,693).

Subclavian artery stenosis is also amenable to balloon angioplasty, atherectomy, and stenting. No randomized trials have compared these methods with surgical revascularization, but numerous reports from single institutions have provided data about early and long-term results, and 2 reports compared results of catheter-based and surgical revascularization in patients with symptomatic obstructive subclavian artery disease (692,694,695). In a series of 110 patients reported in 2005, the procedure was considered initially successful in 93% of cases (694). In 6% of cases, total occlusion of the subclavian artery precluded cannulation. Of the cases in which the artery was initially opened, the median obstruction-free interval was 23 months, and 89% maintained patency at 5 years. Four recurrent stenoses were treated successfully by percutaneous angioplasty, and 4 required surgical revascularization. In a nonrandomized comparison of endovascular revascularization with extra-anatomic bypass surgery for subclavian stenosis, all bypass grafts remained patent except 1 that occluded 19 years after operation (692). In contrast, 6 of 46 attempted subclavian artery angioplasties could not be completed because of occlusive lesions. Among the arteries successfully opened, the 4-year patency rate was 82%.

In a report that compared 121 patients undergoing stenting and 51 undergoing carotid-subclavian bypass, initial success rates were 98% and 100% for the endovascular and surgical approaches, respectively, whereas periprocedural complication rates were 15.1% and 5.9%, being lower in the surgical group (695). There were no cases of periop-

erative stroke or mortality in those selected for bypass surgery, whereas complications in the stent group included thromboembolism, heart failure, arm edema after reperfusion, arterial pseudoaneurysm, and 1 death. Primary patency after surgical bypass was 100% at 1 year and 96% at 5 years. Among patients managed by endovascular therapy, patency was 93% at 1 year and 70% at 5 years. Freedom from recurrent symptoms was greater in the surgical bypass group ( $p < 0.0001$ ) (695). Whether the use of drug-eluting stents for this application will reduce the need for subsequent revascularization has not been determined.

Balloon angioplasty and stenting are associated with high rates of success and better outcomes than balloon angioplasty alone (694,696–700), which makes endovascular stenting an alternative to open surgery in patients with obstructive disease of the subclavian or brachiocephalic arteries. Few studies have compared these approaches, but 1 demonstrated equal effectiveness and fewer complications with stenting (697). Numerous reports have suggested that angioplasty and stenting of the subclavian and brachiocephalic arteries can be performed with a high degree of technical success and safety, but long-term follow-up data are scant (695,701–704). A retrospective comparison of percutaneous revascularization with carotid-subclavian bypass surgery in patients with isolated subclavian artery disease described excellent technical success with both methods, but the primary patency rates at 1, 3, and 5 years were higher with bypass surgery. Although the currently prevailing view favors bypass surgery for good surgical candidates and percutaneous stenting of the subclavian artery for patients at high risk of surgical complications, physicians experienced with both techniques may prefer to take a percutaneous catheter-based approach initially when the anatomy is suitable and reserve surgery for patients with total arterial occlusion or stenotic lesions that are anatomically unsuited to catheter intervention.

Brachiocephalic artery occlusive disease is often accompanied by carotid or subclavian artery stenosis (705), but the natural history is less well understood. Patients may present with an asymptomatic blood pressure disparity between arms or with upper-extremity claudication, subclavian steal, TIA, or stroke. Transthoracic surgical revascularization involves aorta-innominate or aorta-carotid bypass with subclavian artery reimplantation; brachiocephalic endarterectomy is less commonly used. Transthoracic revascularization is preferred in patients with embolism when the source can be excluded concurrent with distal brachiocephalic artery revascularization. Graft patency is excellent, but the combined rate of perioperative stroke and death is as high as 16% (705,706). Survival after transthoracic arterial reconstruction has been reported as 73% and 52% at 5 and 10 years, respectively (705).



## 10. Special Populations

### 10.1. Neurological Risk Reduction in Patients With Carotid Artery Disease Undergoing Cardiac or Noncardiac Surgery

#### 10.1.1. Recommendations for Carotid Artery Evaluation and Revascularization Before Cardiac Surgery

**CLASS IIa**

1. Carotid duplex ultrasound screening is reasonable before elective CABG surgery in patients older than 65 years of age and in those with left main coronary stenosis, PAD, a history of cigarette smoking, a history of stroke or TIA, or carotid bruit. (Level of Evidence: C)
2. Carotid revascularization by CEA or CAS with embolic protection before or concurrent with myocardial revascularization surgery is reasonable in patients with greater than 80% carotid stenosis who have experienced ipsilateral retinal or hemispheric cerebral ischemic symptoms within 6 months. (Level of Evidence: C)

**CLASS IIb**

1. In patients with asymptomatic carotid stenosis, even if severe, the safety and efficacy of carotid revascularization before or concurrent with myocardial revascularization are not well established. (Level of Evidence: C)

#### 10.1.2. Neurological Risk Reduction in Patients With Carotid Artery Disease Undergoing Coronary Bypass Surgery

Whether or not symptomatic of carotid atherosclerosis, patients with high-grade carotid artery stenosis undergoing CABG surgery face a higher risk of stroke than patients without carotid disease, but most strokes are mechanistically unrelated to carotid disease. Considerable evidence suggests that patients undergoing combined CABG surgery plus CEA are at high risk of stroke, but there is no convincing evidence that such intervention in a patient with asymptomatic stenosis undergoing CABG surgery produces benefit in the majority of cases (707). In patients with symptomatic carotid stenosis, published reports indicate that the performance of CEA before CABG surgery is associated with a lower stroke rate but a higher rate of fatal and nonfatal MI. Combined CEA and CABG surgery has been associated with a lower rate of MI, stroke, and death than staged surgery in some reports, but this strategy has not been tested in prospective trials. Other studies suggest that the combination of CEA with CABG surgery is associated with a higher risk of stroke and death than CABG surgery alone (495,708). Proof is lacking that carotid revascularization reduces adverse events in patients with asymptomatic carotid stenosis who are undergoing myocardial revascularization surgery (709), so clinical practice must follow a patient-specific approach.

Although carotid angioplasty and stenting would appear to be a logical alternative to CEA in this situation, catheter-based carotid interventions require periprocedural treatment with potent platelet-inhibitor drugs such as clopidogrel,

which greatly increases the risk of major bleeding associated with CABG surgery, and delaying antiplatelet therapy raises the risk of stent thrombosis and stroke. Another strategy is to perform carotid intervention immediately before coronary surgery and administer intravenous heparin between the procedures, but this approach and the optimum revascularization strategy in general for patients with combined carotid artery disease and CAD that requires intervention have not been evaluated properly (707,708,710–714). The Nationwide Inpatient Sample included 27,084 patients discharged after undergoing CAS before CABG surgery or combined CEA and CABG surgery during the 5 years from 2000 to 2004 (715). Of these, 96.7% underwent CEA plus CABG surgery versus 3.3% (887 patients) who had CAS plus CABG surgery. Fewer major adverse events were reported among patients undergoing CAS plus CABG surgery than among those undergoing CEA plus CABG surgery. Patients who had CAS plus CABG surgery also had a lower incidence of postoperative stroke (2.4% versus 3.9%) and of combined stroke and death (6.9% versus 8.6%) than those managed by the combination of CEA with CABG surgery ( $p < 0.001$ ), although rates of in-hospital mortality were similar with the 2 approaches (5.2% versus 5.4%). In this nonrandomized cohort, patients undergoing CEA plus CABG surgery faced a 62% greater risk of postoperative stroke than patients undergoing CAS before CABG surgery (OR 1.62, 95% CI 1.1 to 2.5;  $p = 0.02$ ). There was no difference in the combined risk of stroke and death according to treatment strategy (OR 1.26, 95% CI 0.9 to 1.6;  $p = \text{NS}$ ) (715). Whether the lower rate of complications with CAS than with CEA in this population undergoing CABG surgery reflects case-selection bias or an intrinsic safety advantage remains uncertain, and the findings justify the conduct of properly designed prospective studies to compare these approaches.

#### 10.1.3. Neurological Risk Reduction in Patients Undergoing Noncoronary Cardiac or Noncardiac Surgery

For guidance about the management of patients undergoing other types of cardiac and noncardiac surgery, the reader is referred to the 2009 ACCF/AHA Focused Update on Perioperative Beta Blockade Incorporated Into the ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery (716).

## 11. Nonatherosclerotic Carotid and Vertebral Artery Diseases

Compared with atherosclerosis, nonatherosclerotic diseases of the extracranial carotid arteries are relatively uncommon. Among these, FMD and cervical artery dissection are the most common.

## 11.1. Fibromuscular Dysplasia

### 11.1.1. Recommendations for Management of Patients With Fibromuscular Dysplasia of the Extracranial Carotid Arteries

#### CLASS IIa

1. Annual noninvasive imaging of the carotid arteries is reasonable initially for patients with FMD to detect changes in the extent or severity of disease, although the effect on outcomes is unclear. Studies may be repeated less frequently once stability has been confirmed. (Level of Evidence: C)
2. Administration of platelet-inhibitor medication can be beneficial in patients with FMD of the carotid arteries to prevent thromboembolism, but the optimum drug and dosing regimen have not been established. (Level of Evidence: C)
3. Carotid angioplasty with or without stenting is reasonable for patients with retinal or hemispheric cerebral ischemic symptoms related to FMD of the ipsilateral carotid artery, but comparative data addressing these methods of revascularization are not available. (Level of Evidence: C)

#### CLASS III: NO BENEFIT

1. Revascularization is not recommended for patients with asymptomatic FMD of a carotid artery, regardless of the severity of stenosis. (Level of Evidence: C)

FMD is a nonatherosclerotic, noninflammatory vascular disease characterized by either focal stenosis or multiple constrictions due to thickening of a layer of the arterial wall. Multiple histological subtypes have been defined (717), most commonly medial fibroplasia, which imparts a beaded appearance to the carotid artery. Intimal fibroplasia, which causes a focal, concentric, or tubular stenosis similar to atherosclerotic narrowing, is much less common. The disease can affect any portion of the cervical or intracranial arteries but most frequently involves the internal carotid arteries bilaterally. The incidence of carotid FMD is low; it is most commonly encountered in middle-aged women, who may be symptomatic or asymptomatic. When symptomatic, clinical manifestations of FMD depend on the location and the extent of arterial obstruction. Stroke, TIA, carotid dissection, Horner syndrome, cranial nerve palsies, and subarachnoid hemorrhage have been described (717–720).

The pathophysiology and natural history of FMD are unknown. Gross pathological manifestations include elongation, kinking, and coiling of the carotid artery. Web-like lesions may obstruct flow, and aneurysmal dilation of the carotid artery has been described (721). Symptoms are thought to result from reduced blood flow or thromboembolism. The relationship of FMD to carotid arterial dissection is poorly understood, but spontaneous dissection and aneurysmal degeneration are additional causes of symptomatic events in patients with carotid FMD.

Treatment of carotid FMD depends on whether the patient is symptomatic. Antiplatelet therapy and sequential

imaging to monitor changes in the extent of disease over time are generally recommended even for asymptomatic patients. Both surgical revascularization (722) and endovascular approaches have been successful in alleviating ischemic symptoms in patients with FMD of the carotid arteries, and percutaneous angioplasty with or without stenting increasingly has been advocated on the basis of case reports and series of limited scope (723,724).

## 11.2. Cervical Artery Dissection

### 11.2.1. Recommendations for Management of Patients With Cervical Artery Dissection

#### CLASS I

1. Contrast-enhanced CTA, MRA, and catheter-based contrast angiography are useful for diagnosis of cervical artery dissection. (Level of Evidence: C)

#### CLASS IIa

1. Antithrombotic treatment with either an anticoagulant (heparin, low molecular weight heparin, or warfarin\*) or a platelet inhibitor (aspirin, clopidogrel, or the combination of extended-release dipyridamole plus aspirin\*) for at least 3 to 6 months is reasonable for patients with extracranial carotid or vertebral arterial dissection associated with ischemic stroke or TIA (724a–724d). (Level of Evidence: B)

#### CLASS IIb

1. Carotid angioplasty and stenting might be considered when ischemic neurological symptoms have not responded to antithrombotic therapy after acute carotid dissection. (Level of Evidence: C)
2. The safety and effectiveness of pharmacological therapy with a beta-adrenergic antagonist, angiotensin inhibitor, or nondihydropyridine calcium channel antagonist (verapamil or diltiazem) to lower blood pressure to the normal range and reduce arterial wall stress are not well established. (Level of Evidence: C)

Carotid or vertebral artery dissection is an uncommon but sometimes dramatic cause of acute or progressive neurological ischemic symptoms. Carotid artery dissection may occur spontaneously, unheralded by symptoms. Minor trauma such as hyperflexion or hyperextension of the neck (the so-called beauty parlor stroke), chiropractic manipulation, coughing, and nose blowing have been associated with carotid dissection (725).

Dissection results from an intimal tear that initiates an intramural hematoma. Subintimal dissection tends to cause stenosis, whereas subadventitial dissection can result in aneurysmal degeneration. The underlying structural defect of the arterial wall remains unknown, but a number of pathological associations have been described. Specific connective tissue disorders thought to form an etiologic basis for carotid dissection include the Ehlers-Danlos syndrome type IV, Marfan syndrome, autosomal dominant polycystic kidney disease, hyperhomocysteinemia, and osteogenesis imperfecta. There may also be an association with bicuspid aortic valve, but carotid dissection is observed in only 1% to

\*Drugs are not listed in order of preference.

5% of patients with this disorder. The association of carotid dissection with FMD is greater, at approximately 15%, but the mechanistic relation between these disorders is not well understood.

Community-based studies suggest that the annual incidence of spontaneous carotid artery dissection is approximately 2.5 to 3 per 100,000 population and that carotid artery dissection accounts for approximately 2% of ischemic strokes. The proportion is greater among younger patients, in whom carotid dissection may account for 10% to 15% of ischemic strokes (726). The incidence of vertebral artery dissection has not been well defined. One of the 4 segments of the vertebral artery (V3) is connected to highly mobile cervical vertebrae, and this mechanical vulnerability underlies the presumption that sudden or excessive neck movement might increase the risk of vertebral artery dissection (727). Other suspected risk factors for cervical arterial dissection include penetrating trauma (728) and amphetamine abuse (729). A structured review found that the incidence of vertebral artery dissection or occlusion attributable to cervical manipulation in patients <45 years of age was approximately 1.3 per 100,000 within 1 week of manipulative therapy (730).

The clinical presentation of cervical artery dissection is variable. Some patients develop sudden catastrophic neurological events, but the typical presentation involves pain on one side of the head or neck, accompanied by the Horner syndrome of asymmetrical ptosis, meiosis, and anhidrosis. After these warning symptoms occur, cerebral or retinal ischemia develops in 50% to 95% of cases of carotid artery dissection. Patients with vertebral artery dissection may present with headache, neck pain, vertigo, nausea, visual disturbances, or syncope.

The diagnostic algorithm begins with clinical examination and brain imaging, followed by vascular imaging when an ischemic cause is suspected. Carotid duplex ultrasonography may identify a dissection flap and differential flow in the true and false lumens, but CTA or MRA is increasingly used to establish the diagnosis of carotid artery dissection, largely supplanting catheter-based and digital subtraction angiography. Selective catheterization of the arteries that supply the posterior cerebral circulation is sometimes the only way to delineate collateral filling via the circle of Willis, which may be important in guiding management. Dissection that begins cephalad of the angle of the mandible may not be detected by ultrasound, and in these cases contrast-enhanced CTA and MRA are superior modalities.

Treatment is usually conservative, involving anticoagulation with heparin followed by warfarin; with this approach, the prognosis is usually favorable (731–733). There have been no placebo-controlled trials of anticoagulant or antiplatelet agents or randomized trials comparing anticoagulant and antiplatelet therapy (734). In a small observational study of patients with cervical artery dissection conducted by the Canadian Stroke Consortium, the annual rate of recur-

rent stroke, TIA, or death was 12.4% among patients treated with aspirin versus 8.3% in those given anticoagulants (735). Anticoagulation may adversely influence the outcome of subarachnoid hemorrhage in the event of intracranial extension of cervical artery dissection. Regardless of initial antithrombotic therapy during the acute phase, antiplatelet therapy may replace anticoagulation once symptoms resolve, but no uniform approach has been developed regarding the timing of this transition, and no antithrombotic regimen has been established as superior to another.

Surgical or endovascular revascularization is reserved for patients with persistent or recurrent symptoms that fail to respond to anticoagulation. Surgical revascularization techniques include direct carotid repair and resection with vein graft replacement (736,737). Endovascular stent angioplasty has been successful in a small number of patients but has been associated with complications in others (738–748).

## 12. Future Research

As evident from the number of recommendations in this document that are based on consensus in a void of definitive evidence, there are vast opportunities for future research. These begin with the need to define more precisely the scope of clinical carotid artery disease as a cause of stroke in major segments of the population through well-designed population studies of ischemic stroke in which ECVD and intracranial vascular disease are separately and objectively classified to provide accurate estimates of disease prevalence.

A major hurdle to overcome is the lack of sound evidence with which to target asymptomatic patients above specific risk thresholds for detection of hemodynamically significant carotid stenosis and, more pertinent, to identify those who may benefit from therapeutic intervention. To date, no screening program for detection of carotid stenosis has demonstrated the capacity to reduce stroke risk for any defined cohort, and as a result, no solid consensus can be developed concerning which patients should undergo diagnostic screening. More work is also needed to gauge the value of measuring the IMT of the carotid artery wall as a way of directing preventive therapies to those at risk of progressive carotid atherosclerosis. Outcome-based validation of the value of IMT measurements to guide treatment interventions for individual patients would help overcome an important impediment to proper application of this imaging technology and improve understanding of the pathogenesis of the most common cause of ECVD.

Despite considerable progress in understanding the pathophysiology of atherosclerosis, the practical utility of these morphological and biochemical assessments in predicting stroke due to ECVD requires validation by prospective studies. Given the imperfect correlation between the severity of carotid stenosis and ischemic brain events, the search for other indexes of plaque vulnerability linked to stroke risk must advance. The most promising currently

available technology involves detection of metabolic activity in the vessel wall in the region of carotid plaques by PET imaging. Whether the tracers should optimally target the intensity of local inflammation, macrophage activity, angiogenesis, or some combination of these variables has not been clarified. Opportunities exist for combined assessment by PET/CT or PET/MRI to identify carotid plaque instability and enhance the value of biomarkers of inflammation, cytokine activation, and matrix metalloproteinase accumulation as predictors of clinical events.

Advancements in noninvasive imaging technology have accelerated the acquisition of data, overcome motion-based artifacts, and greatly improved diagnostic accuracy to rival that of conventional angiography for evaluation of patients with ECVD. Ever-higher field-strength systems, more powerful magnetic gradients, and simplification of sophisticated software promise to expand the availability of CT and MRA to broader segments of the patient population, but there is an urgent need to overcome limitations that lead to overestimation of stenosis severity and reliably distinguish subtotal from complete arterial occlusion. We must develop intravascular contrast materials free of the nephrotoxicity, osmotic effects, allergic reactions, and other toxicity of agents currently used for catheter angiography, CTA, and MRA to allow application of these technologies across a wider range of patient comorbidities. As these challenges are met, however, it will become more essential to clarify which imaging methods can reliably identify patients at significantly increased risk of stroke, because data of this type ultimately represent the only foundation on which to recommend broad application of techniques for evaluation of patients with cervical arterial disease.

The value of specific therapies to prevent stroke, even in symptomatic patients with severe carotid artery stenosis, largely lacks validation. An example involves antihypertensive therapy in those with impaired cerebral perfusion due to arterial obstructive disease. Clinical trials evaluating treatment of hypertension in patients with ECVD could substantiate specific approaches and better inform future clinical practice guidelines. Similarly, the relationship between cholesterol and ischemic stroke should be buttressed by stronger evidence than currently exists, because findings from population-based studies have been inconsistent. There are multiple causes of ischemic stroke, and available studies have not specifically established a benefit of statins (or other lipid-lowering strategies) to reduce the frequency or severity of stroke in patients with ECVD, so our recommendations are based on inference. Statins not only decrease cholesterol but also stabilize the endothelial cell layer, increase the bioavailability of nitric oxide, reduce oxidative stress, and decrease inflammation in the vascular wall and in the atheromatous plaque itself, and studies focused on these specific mechanisms in patients with ECVD would not only shed light on the optimum timing and intensity of drug therapy but would also provide important clues to other methods of stroke prevention. The

same can be said of interventions to manage blood glucose homeostasis in patients with diabetes, even though the risk of ischemic stroke in patients with diabetes mellitus is manifold higher than in those without this prevalent condition. Finally, among the roster of risk factors, it is not even clear whether regular exercise reduces the risk of first or recurrent stroke independent of beneficial effects on other risk factors, and this plays out daily as an unanswered question faced by thousands of patients with ECVD.

Although antiplatelet drugs reduce the risk of stroke compared with placebo in patients with TIA or previous stroke, no adequately powered studies have demonstrated their efficacy for stroke prevention in asymptomatic patients with ECVD. Further studies are needed to evaluate the safety and efficacy of newer antiplatelet agents, particularly those in the thienopyridine class, relative to aspirin in patients with asymptomatic ECVD. It is critical to define optimum antithrombotic therapy for patients who experience recurrent cerebral ischemia during antiplatelet therapy, which requires not only studies of comparative effectiveness but careful genetic profiling with respect to the factors that contribute to drug resistance. Parallel work is needed to establish the optimum method to assess platelet function as a guide to assessment of drug resistance, to establish whether resistance to platelet inhibitors is associated with a greater risk of stroke, and to clarify whether testing for or treatment of drug resistance leads to improved clinical outcomes.

Few studies have investigated the role of anticoagulant drugs in the management of patients with ECVD who develop acute ischemic stroke, especially after administration of thrombolytic therapy. If parallels to the management of patients with acute MI continue to expand in the care of acute stroke victims, then earlier catheter-based revascularization will be tested, but such studies must be advanced carefully because of the high risk of exacerbating irreversible ischemic injury and functional deficit. The judicious use of thrombin inhibitors, factor Xa inhibitors, and other antithrombotic agents in conjunction with antiplatelet agents is fertile ground for future investigation but one equally fraught with risk.

In the days and weeks after the acute phase of ischemic stroke, it remains unclear whether women benefit as much as men from CEA, and further studies must aim to recruit sufficient numbers of women and older patients to address these important demographic subsets of patients with symptomatic ECVD. This begs the question of how to address differences in the results of CEA based on race, ethnicity, and other clinical features. Such studies must consider not only the differential rates at which patients develop ECVD but also address uncertainties about how these differences reflect biological factors as opposed to inequities in access to diagnosis and treatment. The outcomes of trials that evaluate revascularization in these subjects must incorporate comprehensive atherosclerotic risk factor management to ensure accurate assessment of treatment effects and their

generalizability to contemporary practice. In addition, careful attention should be paid to determining the optimum duration and intensity of antithrombotic therapy after revascularization, because women, older patients, and members of other ethnic groups may not respond the same way as middle-aged white males. This applies during the periprocedural period as well as over the longer term, and it is important to define when in the course of longitudinal care it becomes reasonable for such therapy to merge into the regimen recommended for long-term prevention of ischemic events in patients with atherosclerosis. The reasons for differences in outcomes based on these demographic variables have not been investigated, and there may be a need for both extravascular and intravascular imaging to provide more detailed information about the vascular lumen, pathobiology of atherosclerosis, plaque composition, and calcification, any or all of which could provide useful clues to the myriad clinical manifestations of ECVD.

CREST has answered important questions about the value of CAS relative to CEA but raised several others. Rigorous training and credentialing of the operators contributed to the low absolute rates of stroke, MI, and death during the CREST study, but delivering this level of success in clinical practice outside the rubric of a controlled clinical trial will both raise practical challenges and hopefully stimulate objective studies of which physicians to train, how to train them, and for what period of time. The event rates reported by the CREST investigators were generally low with either method of revascularization among symptomatic patients of either sex, but there was an important difference related to patient age, the explanation for which is unknown. More research is needed to validate this observation and uncover the conditions responsible for the differential advantage of CEA over CAS among older patients. The most pressing question, however, is how either technique of revascularization compares with intensive contemporary medical therapy, particularly among asymptomatic patients, and a direct comparative trial of both methods of revascularization versus modern medical management should be initiated as quickly as feasible and include a sufficiently broad range of patients to permit meaningful analysis of subgroups based on age, gender, ethnicity, and risk status.

Beyond these many issues involving carotid atherosclerosis lie still deeper challenges involving less common forms of ECVD. In this uncharted territory of future research are questions about the pathophysiology and clinical outcomes of patients with FMD of the cervical arteries, including its relationship to carotid arterial dissection and ischemic brain events. The management of dissection itself is fodder for fresh investigation, beginning with placebo-controlled trials of anticoagulant or antiplatelet drug regimens, with or without CAS. Huge gaps in knowledge of vertebral arterial disease will be more difficult to address because of its relative infrequency compared with carotid stenosis. This circumstance requires well-designed collaborative registries that capture in a structured format data about prevalence, patho-

physiology, natural history, and prognosis. Before conclusions can be drawn about which findings on noninvasive imaging are relevant to clinical decision making, the accuracy of each method compared with catheter-based angiography must be established more clearly. Given the plethora of medical, interventional, and surgical approaches available for treatment of patients with vertebral artery disease, clarity about comparative effectiveness can come only from well-designed randomized trials that involve a large number of practitioners and that are conducted across a broad range of clinical sites. Our recommendations that medical management follow guidelines set forth for patients with disease of the carotid arteries are largely extrapolative, awaiting confirmation or refutation through soundly designed prospective studies, but the lower rate of diagnosis of vertebral artery stenosis than carotid artery disease is a root cause of the inherent difficulty in demonstrating therapeutic benefit.

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## REFERENCES

1. ACCF/AHA Task Force on Practice Guidelines. Manual for ACCF/AHA Guideline Writing Committees: Methodologies and Policies from the ACCF/AHA Task Force on Practice Guidelines. Available at: [http://assets.cardiosource.com/Methodology\\_Manual\\_for\\_ACC\\_AHA\\_Writing\\_Committees.pdf](http://assets.cardiosource.com/Methodology_Manual_for_ACC_AHA_Writing_Committees.pdf) and <http://circ.ahajournals.org/manual/>. Accessed October 1, 2010.
2. Adams HP Jr., del Zoppo GJ, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups. *Stroke*. 2007;38:1655–711.
3. Cho L, Mukherjee D. Basic cerebral anatomy for the carotid interventionalist: the intracranial and extracranial vessels. *Catheter Cardiovasc Interv*. 2006;68:104–11.
4. Schneider P. Advanced cerebrovascular arteriography: applications in carotid stenting. In: Schneider, P, Bohannon, W, Silva M, editors. *Carotid Interventions*. New York, NY: Marcel Dekker; 2004:69–91.

5. Bizzarri F, Mattia C, Di Nardo M, et al. Antegrade selective cerebral perfusion in patients with "bovine aortic arch": is it easier? *J Cardiothorac Surg.* 2008;3:60.
6. Layton KF, Kallmes DF, Cloft HJ, et al. Bovine aortic arch variant in humans: clarification of a common misnomer. *AJNR Am J Neuroradiol.* 2006;27:1541–2.
7. Prevalence of disabilities and associated health conditions among adults—United States, 1999. *MMWR Morb Mortal Wkly Rep.* 2001;50:120–5.
8. Broderick J, Brott T, Kothari R, et al. The Greater Cincinnati/Northern Kentucky Stroke Study: preliminary first-ever and total incidence rates of stroke among blacks. *Stroke.* 1998;29:415–21.
9. Casper M, Barnett E, Williams G, et al. Atlas of Stroke Mortality: Racial, Ethnic, and Geographical Disparities in the United States. Available at: <http://www.cdc.gov/dhdsp/library/maps/strokeatlas/03-section1.htm>. Accessed: April 14, 2010.
10. Centers for Disease Control and Prevention. Age-specific excess deaths associated with stroke among racial/ethnic minority populations—United States, 1997. *MMWR Morb Mortal Wkly Rep.* 2000;49:94–7.
11. White H, Boden-Albala B, Wang C, et al. Ischemic stroke subtype incidence among whites, blacks, and Hispanics: the Northern Manhattan Study. *Circulation.* 2005;111:1327–31.
12. Sacco RL, Boden-Albala B, Gan R, et al. Stroke incidence among white, black, and Hispanic residents of an urban community: the Northern Manhattan Stroke Study. *Am J Epidemiol.* 1998;147:259–68.
13. Rosamond W, Flegal K, Friday G, et al. Heart disease and stroke statistics—2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation.* 2007;115:e69–171.
14. Mohr JP, Choi DW, Grotta JC, et al. *Stroke. Pathophysiology, Diagnosis and Management.* 4th ed. Philadelphia, Pa: Churchill Livingstone, 2004.
15. Wolf PA, Kannel WB, Sorlie P, et al. Asymptomatic carotid bruit and risk of stroke. The Framingham Study. *JAMA.* 1981;245:1442–5.
16. Chambless LE, Folsom AR, Clegg LX, et al. Carotid wall thickness is predictive of incident clinical stroke: the Atherosclerosis Risk in Communities (ARIC) study. *Am J Epidemiol.* 2000;151:478–87.
17. Heiss G, Sharrett AR, Barnes R, et al. Carotid atherosclerosis measured by B-mode ultrasound in populations: associations with cardiovascular risk factors in the ARIC study. *Am J Epidemiol.* 1991;134:250–6.
18. Rosamond W, Flegal K, Furie K, et al. Heart disease and stroke statistics—2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation.* 2008;117:e25–146.
19. Muntner P, Garrett E, Klag MJ, et al. Trends in stroke prevalence between 1973 and 1991 in the US population 25 to 74 years of age. *Stroke.* 2002;33:1209–13.
20. Barnett HJ, Taylor DW, Eliasziw M, et al. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. *N Engl J Med.* 1998;339:1415–25.
21. Wolf PA, Clagett GP, Easton JD, et al. Preventing ischemic stroke in patients with prior stroke and transient ischemic attack: a statement for healthcare professionals from the Stroke Council of the American Heart Association. *Stroke.* 1999;30:1991–4.
22. Taylor TN, Davis PH, Torner JC, et al. Lifetime cost of stroke in the United States. *Stroke.* 1996;27:1459–66.
23. Fine-Edelstein JS, Wolf PA, O'Leary DH, et al. Precursors of extracranial carotid atherosclerosis in the Framingham Study. *Neurology.* 1994;44:1046–50.
24. O'Leary DH, Polak JF, Kronmal RA, et al. Distribution and correlates of sonographically detected carotid artery disease in the Cardiovascular Health Study: the CHS Collaborative Research Group. *Stroke.* 1992;23:1752–60.
25. Sacco RL, Roberts JK, Boden-Albala B, et al. Race-ethnicity and determinants of carotid atherosclerosis in a multiethnic population. The Northern Manhattan Stroke Study. *Stroke.* 1997;28:929–35.
26. Lisabeth LD, Ireland JK, Rissler JM, et al. Stroke risk after transient ischemic attack in a population-based setting. *Stroke.* 2004;35:1842–6.
27. Petty GW, Brown RD Jr., Whisnant JP, et al. Ischemic stroke subtypes: a population-based study of incidence and risk factors. *Stroke.* 1999;30:2513–6.
28. National Stroke Association Web site. Available at: <http://www.stroke.org/site/PageNavigator/HOME>. Accessed April 14, 2010.
29. Libby P, Theroux P. Pathophysiology of coronary artery disease. *Circulation.* 2005;111:3481–8.
30. Pickett CA, Jackson JL, Hemann BA, et al. Carotid bruits as a prognostic indicator of cardiovascular death and myocardial infarction: a meta-analysis. *Lancet.* 2008;371:1587–94.
31. Zhu CZ, Norris JW. Role of carotid stenosis in ischemic stroke. *Stroke.* 1990;21:1131–4.
32. Ratchford EV, Jin Z, Tullio MR, et al. Carotid bruit for detection of hemodynamically significant carotid stenosis: the Northern Manhattan Study. *Neurology.* 2009;31:748–52.
33. Goldstein LB, Adams R, Alberts MJ, et al. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Stroke.* 2006;37:1583–633.
34. Qureshi AI, Alexandrov AV, Tegeler CH, et al. Guidelines for screening of extracranial carotid artery disease: a statement for healthcare professionals from the multidisciplinary practice guidelines committee of the American Society of Neuroimaging. *J Neuroimaging.* 2007;17:19–47.
35. Bates ER, Babb JD, Casey DE Jr., et al. ACCF/SCAI/SVMB/SIR/ASITN 2007 clinical expert consensus document on carotid stenting: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents (ACCF/SCAI/SVMB/SIR/ASITN Clinical Expert Consensus Document Committee on Carotid Stenting). *J Am Coll Cardiol.* 2007;49:126–70.
36. U.S. Preventive Services Task Force. Screening for carotid artery stenosis: U.S. Preventive Services Task Force recommendation statement [published correction appears in *Ann Intern Med.* 2008;148:248]. *Ann Intern Med.* 2007;147:854–9.
37. Craven TE, Ryu JE, Espeland MA, et al. Evaluation of the associations between carotid artery atherosclerosis and coronary artery stenosis: a case-control study. *Circulation.* 1990;82:1230–42.
38. Chimowitz MI, Poole RM, Starling MR, et al. Frequency and severity of asymptomatic coronary disease in patients with different causes of stroke. *Stroke.* 1997;28:941–5.
39. Kallikazaros I, Tsioufis C, Sideris S, et al. Carotid artery disease as a marker for the presence of severe coronary artery disease in patients evaluated for chest pain. *Stroke.* 1999;30:1002–7.
40. Alexandrova NA, Gibson WC, Norris JW, et al. Carotid artery stenosis in peripheral vascular disease. *J Vasc Surg.* 1996;23:645–9.
41. Fisher M. Occlusion of the internal carotid artery. *Arch Neurol Psychiatry.* 1951;65:346–77.
42. Bots ML, Hoes AW, Koudstaal PJ, et al. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. *Circulation.* 1997;96:1432–7.
43. Hodis HN, Mack WJ, LaBree L, et al. The role of carotid arterial intima-media thickness in predicting clinical coronary events. *Ann Intern Med.* 1998;128:262–9.
44. O'Leary DH, Polak JF, Kronmal RA, et al. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. *N Engl J Med.* 1999;340:14–22.
45. Sabeti S, Schlager O, Exner M, et al. Progression of carotid stenosis detected by duplex ultrasonography predicts adverse outcomes in cardiovascular high-risk patients. *Stroke.* 2007;38:2887–94.
46. Rundek T, Arif H, Boden-Albala B, et al. Carotid plaque, a subclinical precursor of vascular events: the Northern Manhattan Study. *Neurology.* 2008;70:1200–7.
47. Wiebers DO, Whisnant JP, Sandok BA, et al. Prospective comparison of a cohort with asymptomatic carotid bruit and a population-based cohort without carotid bruit. *Stroke.* 1990;21:984–8.
48. Norris JW, Zhu CZ, Bornstein NM, et al. Vascular risks of asymptomatic carotid stenosis. *Stroke.* 1991;22:1485–90.

49. Gongora-Rivera F, Labreuche J, Jaramillo A, et al. Autopsy prevalence of coronary atherosclerosis in patients with fatal stroke. *Stroke*. 2007;38:1203-10.
50. Kuller LH, Arnold AM, Psaty BM, et al. 10-year follow-up of subclinical cardiovascular disease and risk of coronary heart disease in the Cardiovascular Health Study. *Arch Intern Med*. 2006;166:71-8.
51. Arnold AM, Psaty BM, Kuller LH, et al. Incidence of cardiovascular disease in older Americans: the cardiovascular health study. *J Am Geriatr Soc*. 2005;53:211-8.
52. Kathiresan S, Larson MG, Keyes MJ, et al. Assessment by cardiovascular magnetic resonance, electron beam computed tomography, and carotid ultrasonography of the distribution of subclinical atherosclerosis across Framingham risk strata. *Am J Cardiol*. 2007;99:310-4.
53. Lorenz MW, Markus HS, Bots ML, et al. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation*. 2007;115:459-67.
54. Barrett-Connor E, Laughlin GA, Connor C. Coronary artery calcium versus intima-media thickness as a measure of cardiovascular disease among asymptomatic adults (from the Rancho Bernardo Study). *Am J Cardiol*. 2007;99:227-31.
55. Terry JG, Carr JJ, Tang R, et al. Coronary artery calcium outperforms carotid artery intima-media thickness as a noninvasive index of prevalent coronary artery stenosis. *Arterioscler Thromb Vasc Biol*. 2005;25:1723-8.
56. Nambi V, Chambless L, Folsom AR, et al. Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: the ARIC (Atherosclerosis Risk In Communities) study. *J Am Coll Cardiol*. 2010;55:1600-7.
57. Stein JH, Johnson HM. Carotid intima-media thickness, plaques, and cardiovascular disease risk: implications for preventive cardiology guidelines. *J Am Coll Cardiol*. 2010;55:1608-10.
58. Blankenhorn DH, Selzer RH, Crawford DW, et al. Beneficial effects of colestipol-niacin therapy on the common carotid artery: two- and four-year reduction of intima-media thickness measured by ultrasound. *Circulation*. 1993;88:20-8.
59. Furberg CD, Adams HP Jr, Applegate WB, et al. Effect of lovastatin on early carotid atherosclerosis and cardiovascular events. *Circulation*. 1994;90:1679-87.
60. Hodis HN, Mack WJ, LaBree L, et al. Reduction in carotid arterial wall thickness using lovastatin and dietary therapy: a randomized controlled clinical trial. *Ann Intern Med*. 1996;124:548-56.
61. Mukherjee D, Yadav JS. Carotid artery intimal-medial thickness: indicator of atherosclerotic burden and response to risk factor modification. *Am Heart J*. 2002;144:753-9.
62. Byington RP, Evans GW, Espeland MA, et al. Effects of lovastatin and warfarin on early carotid atherosclerosis: sex-specific analyses: Asymptomatic Carotid Artery Regression Study (ACAPS) Research Group. *Circulation*. 1999;100:e14-7.
63. ICAVL standards for accreditation in noninvasive vascular testing. Part II Vascular Laboratory Operations. Extracranial Cerebrovascular Testing. Available at: <http://www.icavl.org/icavl/pdfs/extracranial2007.pdf>. Accessed August 29, 2008.
64. ICAVL standards for accreditation in noninvasive vascular testing. <http://www.icavl.org/icavl/apply/standards.htm>. Accessed May 5, 2010.
65. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults. *J Am Coll Cardiol*. 2010;56:e50-103.
66. Hirsch AT, Haskal ZJ, Hertzner NR, et al. ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary: a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease). *J Am Coll Cardiol*. 2006;47:1239-312.
67. Adams RJ, Chimowitz MI, Alpert JS, et al. Coronary risk evaluation in patients with transient ischemic attack and ischemic stroke: a scientific statement for healthcare professionals from the Stroke Council and the Council on Clinical Cardiology of the American Heart Association/American Stroke Association. *Stroke*. 2003;34:2310-22.
68. Sacco RL, Kargman DE, Gu Q, et al. Race-ethnicity and determinants of intracranial atherosclerotic cerebral infarction. The Northern Manhattan Stroke Study. *Stroke*. 1995;26:14-20.
69. Wityk RJ, Lehman D, Klag M, et al. Race and sex differences in the distribution of cerebral atherosclerosis. *Stroke*. 1996;27:1974-80.
70. North American Symptomatic Carotid Endarterectomy Trial (NASCET) Investigators. Clinical alert: benefit of carotid endarterectomy for patients with high-grade stenosis of the internal carotid artery. National Institute of Neurological Disorders and Stroke Stroke and Trauma Division. *Stroke*. 1991;22:816-7.
71. Young B, Moore WS, Robertson JT, et al. An analysis of perioperative surgical mortality and morbidity in the asymptomatic carotid atherosclerosis study ACAS Investigators. Asymptomatic Carotid Arteriosclerosis Study. *Stroke*. 1996;27:2216-24.
72. Halliday AW, Thomas D, Mansfield A. The Asymptomatic Carotid Surgery Trial (ACST). Rationale and design. Steering Committee. *Eur J Vasc Surg*. 1994;8:703-10.
73. Riles TS, Fisher FS, Lamparello PJ, et al. Immediate and long-term results of carotid endarterectomy for asymptomatic high-grade stenosis. *Ann Vasc Surg*. 1994;8:144-9.
74. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. *JAMA*. 1995;273:1421-8.
75. Halliday A, Mansfield A, Marro J, et al. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet*. 2004;363:1491-502.
76. Hobson RW, Weiss DG, Fields WS, et al. Efficacy of carotid endarterectomy for asymptomatic carotid stenosis: the Veterans Affairs Cooperative Study Group. *N Engl J Med*. 1993;328:221-7.
77. The CASANOVA Study Group. Carotid surgery versus medical therapy in asymptomatic carotid stenosis. *Stroke*. 1991;22:1229-35.
78. Hertzner NR, Flanagan RA Jr, Beven EG, et al. Surgical versus nonoperative treatment of asymptomatic carotid stenosis: 290 patients documented by intravenous angiography. *Ann Surg*. 1986;204:163-71.
79. Spence JD, Coates V, Li H, et al. Effects of intensive medical therapy on microemboli and cardiovascular risk in asymptomatic carotid stenosis. *Arch Neurol*. 2010;67:180-6.
80. Marquardt L, Geraghty OC, Mehta Z, et al. Low risk of ipsilateral stroke in patients with asymptomatic carotid stenosis on best medical treatment: a prospective, population-based study. *Stroke*. 2010;41:e11-7.
81. Abbott AL, Chambers BR, Stork JL, et al. Embolic signals and prediction of ipsilateral stroke or transient ischemic attack in asymptomatic carotid stenosis: a multicenter prospective cohort study. *Stroke*. 2005;36:1128-33.
82. Goessens BM, Visseren FL, Kappelle LJ, et al. Asymptomatic carotid artery stenosis and the risk of new vascular events in patients with manifest arterial disease: the SMART study. *Stroke*. 2007;38:1470-5.
83. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet*. 1998;351:1379-87.
84. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med*. 1991;325:445-53.
85. Mayberg MR, Wilson SE, Yatsu F, et al. Carotid endarterectomy and prevention of cerebral ischemia in symptomatic carotid stenosis. *JAMA*. 1991;266:3289-94.
86. Fisher M, Paganini-Hill A, Martin A, et al. Carotid plaque pathology: thrombosis, ulceration, and stroke pathogenesis. *Stroke*. 2005;36:253-7.
87. Lal BK, Hobson RW, Pappas PJ, et al. Pixel distribution analysis of B-mode ultrasound scan images predicts histologic features of atherosclerotic carotid plaques. *J Vasc Surg*. 2002;35:1210-7.
88. Redgrave JN, Courts SB, Schulz UG, et al. Systematic review of associations between the presence of acute ischemic lesions on diffusion-weighted imaging and clinical predictors of early stroke risk after transient ischemic attack. *Stroke*. 2007;38:1482-8.

89. Sabetai MM, Tegos TJ, Clifford C, et al. Carotid plaque echogenicity and types of silent CT-brain infarcts: is there an association in patients with asymptomatic carotid stenosis? *Int Angiol.* 2001;20:51–7.
90. El-Barghouty N, Nicolaidis A, Bahal V, et al. The identification of the high risk carotid plaque. *Eur J Vasc Endovasc Surg.* 1996;11:470–8.
91. Kessler C, von Maravic M, Bruckmann H, et al. Ultrasound for the assessment of the embolic risk of carotid plaques. *Acta Neurol Scand.* 1995;92:231–4.
92. Iannuzzi A, Wilcosky T, Mercuri M, et al. Ultrasonographic correlates of carotid atherosclerosis in transient ischemic attack and stroke. *Stroke.* 1995;26:614–9.
93. Tegos TJ, Sabetai MM, Nicolaidis AN, et al. Patterns of brain computed tomography infarction and carotid plaque echogenicity. *J Vasc Surg.* 2001;33:334–9.
94. Takaya N, Yuan C, Chu B, et al. Association between carotid plaque characteristics and subsequent ischemic cerebrovascular events: a prospective assessment with MRI—initial results. *Stroke.* 2006;37:818–23.
95. Tawakol A, Migrino RQ, Hoffmann U, et al. Noninvasive in vivo measurement of vascular inflammation with F-18 fluorodeoxyglucose positron emission tomography. *J Nucl Cardiol.* 2005;12:294–301.
96. Spagnoli LG, Mauriello A, Sangiorgi G, et al. Extracranial thrombotically active carotid plaque as a risk factor for ischemic stroke. *JAMA.* 2004;292:1845–52.
97. Redgrave JN, Lovett JK, Gallagher PJ, et al. Histological assessment of 526 symptomatic carotid plaques in relation to the nature and timing of ischemic symptoms: the Oxford plaque study. *Circulation.* 2006;113:2320–8.
98. Rudd JH, Warburton EA, Fryer TD, et al. Imaging atherosclerotic plaque inflammation with [18F]-fluorodeoxyglucose positron emission tomography. *Circulation.* 2002;105:2708–11.
99. Tawakol A, Migrino RQ, Bashian GG, et al. In vivo 18F-fluorodeoxyglucose positron emission tomography imaging provides a noninvasive measure of carotid plaque inflammation in patients. *J Am Coll Cardiol.* 2006;48:1818–24.
100. Howard G, Chambless LE, Baker WH. A multicenter validation study of Doppler ultrasound versus angiography. *J Stroke Cerebrovasc Dis.* 1991;1:166–73.
101. Winter PM, Morawski AM, Caruthers SD, et al. Molecular imaging of angiogenesis in early-stage atherosclerosis with alpha(v)beta3-integrin-targeted nanoparticles. *Circulation.* 2003;108:2270–74.
102. Alvarez B, Ruiz C, Chacon P, et al. Serum values of metalloproteinase-2 and metalloproteinase-9 as related to unstable plaque and inflammatory cells in patients with greater than 70% carotid artery stenosis. *J Vasc Surg.* 2004;40:469–75.
103. Arthurs ZM, Andersen C, Starnes BW, et al. A prospective evaluation of C-reactive protein in the progression of carotid artery stenosis. *J Vasc Surg.* 2008;47:744–50.
104. Alvarez Garcia B, Ruiz C, Chacon P, et al. High-sensitivity C-reactive protein in high-grade carotid stenosis: risk marker for unstable carotid plaque. *J Vasc Surg.* 2003;38:1018–24.
105. Yonemura A, Momiyama Y, Fayad ZA, et al. Effect of lipid-lowering therapy with atorvastatin on atherosclerotic aortic plaques detected by noninvasive magnetic resonance imaging. *J Am Coll Cardiol.* 2005;45:733–42.
106. Corti R, Fayad ZA, Fuster V, et al. Effects of lipid-lowering by simvastatin on human atherosclerotic lesions: a longitudinal study by high-resolution, noninvasive magnetic resonance imaging. *Circulation.* 2001;104:249–52.
107. Lima JA, Desai MY, Steen H, et al. Statin-induced cholesterol lowering and plaque regression after 6 months of magnetic resonance imaging-monitored therapy. *Circulation.* 2004;110:2336–41.
108. Corti R, Fuster V, Fayad ZA, et al. Lipid lowering by simvastatin induces regression of human atherosclerotic lesions: two years' follow-up by high-resolution noninvasive magnetic resonance imaging. *Circulation.* 2002;106:2884–7.
109. Corti R, Fuster V, Fayad ZA, et al. Effects of aggressive versus conventional lipid-lowering therapy by simvastatin on human atherosclerotic lesions: a prospective, randomized, double-blind trial with high-resolution magnetic resonance imaging. *J Am Coll Cardiol.* 2005;46:106–12.
110. Albers GW, Caplan LR, Easton JD, et al. Transient ischemic attack—proposal for a new definition. *N Engl J Med.* 2002;347:1713–6.
111. Sacco RL, Adams R, Albers G, et al. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention. *Stroke.* 2006;37:577–617.
112. Schneider AT, Pancioli AM, Khoury JC, et al. Trends in community knowledge of the warning signs and risk factors for stroke. *JAMA.* 2003;289:343–6.
113. Pancioli AM, Broderick J, Kothari R, et al. Public perception of stroke warning signs and knowledge of potential risk factors. *JAMA.* 1998;279:1288–92.
114. Moser DK, Kimble LP, Alberts MJ, et al. Reducing delay in seeking treatment by patients with acute coronary syndrome and stroke: a scientific statement from the American Heart Association Council on cardiovascular nursing and stroke council. *Circulation.* 2006;114:168–82.
115. Mandelzweig L, Goldbourt U, Boyko V, et al. Perceptual, social, and behavioral factors associated with delays in seeking medical care in patients with symptoms of acute stroke. *Stroke.* 2006;37:1248–53.
116. Adams HP Jr., Adams RJ, Brott T, et al. Guidelines for the early management of patients with ischemic stroke: A scientific statement from the Stroke Council of the American Stroke Association. *Stroke.* 2003;34:1056–83.
117. Williams JE, Rosamond WD, Morris DL. Stroke symptom attribution and time to emergency department arrival: the delay in accessing stroke healthcare study. *Acad Emerg Med.* 2000;7:93–6.
118. Kleindorfer D, Panagos P, Pancioli A, et al. Incidence and short-term prognosis of transient ischemic attack in a population-based study. *Stroke.* 2005;36:720–3.
119. Lovett JK, Dennis MS, Sandercock PA, et al. Very early risk of stroke after a first transient ischemic attack. *Stroke.* 2003;34:e138–40.
120. Johnston SC, Easton JD. Are patients with acutely recovered cerebral ischemia more unstable? *Stroke.* 2003;34:2446–50.
121. Fisher M. Stroke and TIA: epidemiology, risk factors, and the need for early intervention. *Am J Manag Care.* 2008;14:S204–11.
122. Heyman A, Wilkinson WE, Hurwitz BJ, et al. Risk of ischemic heart disease in patients with TIA. *Neurology.* 1984;34:626–30.
123. Dennis M, Bamford J, Sandercock P, et al. Prognosis of transient ischemic attacks in the Oxfordshire Community Stroke Project. *Stroke.* 1990;21:848–53.
124. Whisnant JP. Clinical epidemiology in transient cerebral ischemic attacks (TIA) in the anterior and posterior circulation. In: Sundt TM, editor. *Occlusive Cerebrovascular Disease: Diagnosis and Surgical Management.* Philadelphia, Pa: WB Saunders;1987:60–5.
125. Johnston SC, Rothwell PM, Nguyen-Huynh MN, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *Lancet.* 2007;369:283–92.
126. Naylor AR. Occam's razor: intervene early to prevent more strokes! *J Vasc Surg.* 2008;48:1053–9.
127. Gautier JC. Amaurosis fugax. *N Engl J Med.* 1993;329:426–8.
128. Benavente O, Eliasziw M, Streifler JY, et al. Prognosis after transient monocular blindness associated with carotid-artery stenosis. *N Engl J Med.* 2001;345:1084–90.
129. Gaul JJ, Marks SJ, Weinberger J. Visual disturbance and carotid artery disease: 500 symptomatic patients studied by non-invasive carotid artery testing including B-mode ultrasonography. *Stroke.* 1986;17:393–8.
130. Gallego CJ, Herrera M, Navarro M. [Ophthalmological manifestations of cerebrovascular disease]. *An Sist Sanit Navar.* 2008;31 Suppl 3:111–26.
131. Amareno P, Cohen A, Tzourio C, et al. Atherosclerotic disease of the aortic arch and the risk of ischemic stroke. *N Engl J Med.* 1994;331:1474–9.
132. Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology,



- American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. *J Am Coll Cardiol*. 2010;55:e27-129.
133. Bos MJ, van Rijn MJ, Witteman JC, et al. Incidence and prognosis of transient neurological attacks. *JAMA*. 2007;298:2877-85.
134. Toledo M, Pujadas F, Grive E, et al. Lack of evidence for arterial ischemia in transient global amnesia. *Stroke*. 2008;39:476-9.
135. Evans JG. Transient neurological dysfunction and risk of stroke in an elderly English population: the different significance of vertigo and non-rotatory dizziness. *Age Ageing*. 1990;19:43-9.
136. Grant EG, Benson CB, Moneta GL, et al. Carotid artery stenosis: gray-scale and Doppler US diagnosis—Society of Radiologists in Ultrasound Consensus Conference. *Radiology*. 2003;229:340-6.
137. Wyman RA, Mays ME, McBride PE, et al. Ultrasound-detected carotid plaque as a predictor of cardiovascular events. *Vasc Med*. 2006;11:123-30.
138. Culebras A, Kase CS, Masdeu JC, et al. Practice guidelines for the use of imaging in transient ischemic attacks and acute stroke: a report of the Stroke Council, American Heart Association. *Stroke*. 1997;28:1480-97.
139. Khan S, Cloud GC, Kerry S, et al. Imaging of vertebral artery stenosis: a systematic review. *J Neurol Neurosurg Psychiatry*. 2007;78:1218-25.
140. Malhotra AK, Camacho M, Ivatury RR, et al. Computed tomographic angiography for the diagnosis of blunt carotid/vertebral artery injury: a note of caution. *Ann Surg*. 2007;246:632-42.
141. Utter GH, Hollingworth W, Hallam DK, et al. Sixteen-slice CT angiography in patients with suspected blunt carotid and vertebral artery injuries. *J Am Coll Surg*. 2006;203:838-48.
142. Grant EG, Duerinckx AJ, El Saden SM, et al. Ability to use duplex US to quantify internal carotid arterial stenoses: fact or fiction? *Radiology*. 2000;214:247-52.
143. Blakeley DD, Oddone EZ, Hasselblad V, et al. Noninvasive carotid artery testing: a meta-analytic review. *Ann Intern Med*. 1995;122:360-7.
144. AbuRahma AF, Robinson PA, Strickler DL, et al. Proposed new duplex classification for threshold stenoses used in various symptomatic and asymptomatic carotid endarterectomy trials. *Ann Vasc Surg*. 1998;12:349-58.
145. Comerota AJ, Salles-Cunha SX, Daoud Y, et al. Gender differences in blood velocities across carotid stenoses. *J Vasc Surg*. 2004;40:939-44.
146. Busuttill SJ, Franklin DP, Youkey JR, et al. Carotid duplex overestimation of stenosis due to severe contralateral disease. *Am J Surg*. 1996;172:144-7.
147. Chi YW, White CJ, Woods TC, et al. Ultrasound velocity criteria for carotid in-stent restenosis. *Catheter Cardiovasc Interv*. 2007;69:349-54.
148. Sitzer M, Rose G, Furst G, et al. Characteristics and clinical value of an intravenous echo-enhancement agent in evaluation of high-grade internal carotid stenosis. *J Neuroimaging*. 1997;7 Suppl 1:S22-5.
149. Ferrer JM, Samso JJ, Serrando JR, et al. Use of ultrasound contrast in the diagnosis of carotid artery occlusion. *J Vasc Surg*. 2000;31:736-41.
150. Hensley S. Ultrasound drugs face black-box warning: *Wall Street Journal*. October 8, 2007.
151. Howard G, Baker WH, Chambless LE, et al. Asymptomatic Carotid Atherosclerosis Study Investigators. An approach for the use of Doppler ultrasound as a screening tool for hemodynamically significant stenosis (despite heterogeneity of Doppler performance): a multicenter experience. *Stroke*. 1996;27:1951-7.
152. Kuntz KM, Polak JF, Whittemore AD, et al. Duplex ultrasound criteria for the identification of carotid stenosis should be laboratory specific. *Stroke*. 1997;28:597-602.
153. Alexandrov AV. Ultrasound and angiography in the selection of patients for carotid endarterectomy. *Curr Cardiol Rep*. 2003;5:141-7.
154. Perkins JM, Galland RB, Simmons MJ, et al. Carotid duplex imaging: variation and validation. *Br J Surg*. 2000;87:320-22.
155. Robless P, Emson M, Thomas D, et al. Are we detecting and operating on high risk patients in the asymptomatic carotid surgery trial? *Eur J Vasc Endovasc Surg*. 1998;16:59-64.
156. Alexandrov AV, Vital D, Brodie DS, et al. Grading carotid stenosis with ultrasound: an interlaboratory comparison. *Stroke*. 1997;28:1208-10.
157. Schwartz SW, Chambless LE, Baker WH, et al. Asymptomatic Carotid Atherosclerosis Study Investigators. Consistency of Doppler parameters in predicting arteriographically confirmed carotid stenosis. *Stroke*. 1997;28:343-7.
158. Fillinger MF, Baker RJ Jr., Zwolak RM, et al. Carotid duplex criteria for a 60% or greater angiographic stenosis: variation according to equipment. *J Vasc Surg*. 1996;24:856-64.
159. Ranke C, Creutzig A, Becker H, et al. Standardization of carotid ultrasound: a hemodynamic method to normalize for interindividual and interequipment variability. *Stroke*. 1999;30:402-6.
160. Wolstenhulme S, Evans JA, Weston MJ. The agreement between colour Doppler systems in measuring internal carotid artery peak systolic velocities. *Br J Radiol*. 1997;70:1043-52.
161. Daigle RJ, Stavros AT, Lee RM. Overestimation of velocity and frequency values by multielement linear array dopplers. *J Vasc Technol*. 1990;14:206-13.
162. Paciaroni M, Caso V, Cardaioli G, et al. Is ultrasound examination sufficient in the evaluation of patients with internal carotid artery severe stenosis or occlusion? *Cerebrovasc Dis*. 2003;15:173-6.
163. Filis KA, Arko FR, Johnson BL, et al. Duplex ultrasound criteria for defining the severity of carotid stenosis. *Ann Vasc Surg*. 2002;16:413-21.
164. Mattos MA, Hodgson KJ, Faught WE, et al. Carotid endarterectomy without angiography: is color-flow duplex scanning sufficient? *Surgery*. 1994;116:776-82.
165. Jahromi AS, Cina CS, Liu Y, et al. Sensitivity and specificity of color duplex ultrasound measurement in the estimation of internal carotid artery stenosis: a systematic review and meta-analysis. *J Vasc Surg*. 2005;41:962-72.
166. Nederkoorn PJ, van der Graaf Y, Hunink MG. Duplex ultrasound and magnetic resonance angiography compared with digital subtraction angiography in carotid artery stenosis: a systematic review. *Stroke*. 2003;34:1324-32.
167. Long A, Lepoutre A, Corbillon E, et al. Critical review of non- or minimally invasive methods (duplex ultrasonography, MR- and CT-angiography) for evaluating stenosis of the proximal internal carotid artery. *Eur J Vasc Endovasc Surg*. 2002;24:43-52.
168. Serfaty JM, Chirossel P, Chevallier JM, et al. Accuracy of three-dimensional gadolinium-enhanced MR angiography in the assessment of extracranial carotid artery disease. *AJR Am J Roentgenol*. 2000;175:455-63.
169. Hood DB, Mattos MA, Mansour A, et al. Prospective evaluation of new duplex criteria to identify 70% internal carotid artery stenosis. *J Vasc Surg*. 1996;23:254-61.
170. White JE, Russell WL, Greer MS, et al. Efficacy of screening MR angiography and Doppler ultrasonography in the evaluation of carotid artery stenosis. *Am Surg*. 1994;60:340-8.
171. Turnipseed WD, Kennell TW, Turski PA, et al. Combined use of duplex imaging and magnetic resonance angiography for evaluation of patients with symptomatic ipsilateral high-grade carotid stenosis. *J Vasc Surg*. 1993;17:832-9.
172. Riles TS, Eidelman EM, Litt AW, et al. Comparison of magnetic resonance angiography, conventional angiography, and duplex scanning. *Stroke*. 1992;23:341-6.
173. Johnson MB, Wilkinson ID, Wattam J, et al. Comparison of Doppler ultrasound, magnetic resonance angiographic techniques and catheter angiography in evaluation of carotid stenosis. *Clin Radiol*. 2000;55:912-20.
174. Huston J, Nichols DA, Luetmer PH, et al. MR angiographic and sonographic indications for endarterectomy. *AJNR Am J Neuroradiol*. 1998;19:309-15.
175. Link J, Brossmann J, Penselin V, et al. Common carotid artery bifurcation: preliminary results of CT angiography and color-coded duplex sonography compared with digital subtraction angiography. *AJR Am J Roentgenol*. 1997;168:361-5.
176. Bray JM, Galland F, Lhoste P, et al. Colour Doppler and duplex sonography and angiography of the carotid artery bifurcations: prospective, double-blind study. *Neuroradiology*. 1995;37:219-24.
177. Patel MR, Kuntz KM, Klufas RA, et al. Preoperative assessment of the carotid bifurcation. Can magnetic resonance angiography and

- duplex ultrasonography replace contrast arteriography? *Stroke*. 1995; 26:1753–8.
178. Bluth EI, Sunshine JH, Lyons JB, et al. Power Doppler imaging: initial evaluation as a screening examination for carotid artery stenosis. *Radiology*. 2000;215:791–800.
179. Jackson MR, Chang AS, Robles HA, et al. Determination of 60% or greater carotid stenosis: a prospective comparison of magnetic resonance angiography and duplex ultrasound with conventional angiography. *Ann Vasc Surg*. 1998;12:236–43.
180. Walters GK, Jones CE, Meyd CJ, et al. The role of carotid duplex ultrasonography in the therapeutic algorithm of extracranial carotid disease. *J Vasc Technol*. 1993;17:177–82.
181. Biasi GM, Froio A, Diethrich EB, et al. Carotid plaque echolucency increases the risk of stroke in carotid stenting: the Imaging in Carotid Angioplasty and Risk of Stroke (ICAROS) study. *Circulation*. 2004;110:756–62.
182. DeMarco JK, Huston J, III, Bernstein MA. Evaluation of classic 2D time-of-flight MR angiography in the depiction of severe carotid stenosis. *AJR Am J Roentgenol*. 2004;183:787–93.
183. Wutke R, Lang W, Fellner C, et al. High-resolution, contrast-enhanced magnetic resonance angiography with elliptical centric k-space ordering of supra-aortic arteries compared with selective X-ray angiography. *Stroke*. 2002;33:1522–9.
184. Alvarez-Linera J, Benito-Leon J, Escribano J, et al. Prospective evaluation of carotid artery stenosis: elliptic centric contrast-enhanced MR angiography and spiral CT angiography compared with digital subtraction angiography. *AJNR Am J Neuroradiol*. 2003;24:1012–9.
185. Remonda L, Senn P, Barth A, et al. Contrast-enhanced 3D MR angiography of the carotid artery: comparison with conventional digital subtraction angiography. *AJNR Am J Neuroradiol*. 2002;23: 213–9.
186. Cosottini M, Pingitore A, Puglioli M, et al. Contrast-enhanced three-dimensional magnetic resonance angiography of atherosclerotic internal carotid stenosis as the noninvasive imaging modality in revascularization decision making. *Stroke*. 2003;34:660–4.
187. Glor FP, Ariff B, Crowe LA, et al. Carotid geometry reconstruction: a comparison between MRI and ultrasound. *Med Phys*. 2003;30: 3251–61.
188. Teng MM, Tsai F, Liou AJ, et al. Three-dimensional contrast-enhanced magnetic resonance angiography of carotid artery after stenting. *J Neuroimaging*. 2004;14:336–41.
189. Yucel EK, Anderson CM, Edelman RR, et al. AHA scientific statement: magnetic resonance angiography: update on applications for extracranial arteries. *Circulation*. 1999;100:2284–301.
190. Yuan C, Mitsumori LM, Ferguson MS, et al. In vivo accuracy of multispectral magnetic resonance imaging for identifying lipid-rich necrotic cores and intraplaque hemorrhage in advanced human carotid plaques. *Circulation*. 2001;104:2051–6.
191. Rutt BK, Clarke SE, Fayad ZA. Atherosclerotic plaque characterization by MR imaging. *Curr Drug Targets Cardiovasc Haematol Disord*. 2004;4:147–59.
192. Cowper SE, Kuo PH, Bucala R. Nephrogenic systemic fibrosis and gadolinium exposure: association and lessons for idiopathic fibrosing disorders. *Arthritis Rheum*. 2007;56:3173–5.
193. Belsky M, Gaitini D, Goldsher D, et al. Color-coded duplex ultrasound compared to CT angiography for detection and quantification of carotid artery stenosis. *Eur J Ultrasound*. 2000;12:49–60.
194. Gronholdt ML. B-mode ultrasound and spiral CT for the assessment of carotid atherosclerosis. *Neuroimaging Clin N Am*. 2002;12: 421–35.
195. Hollingworth W, Nathens AB, Kanne JP, et al. The diagnostic accuracy of computed tomography angiography for traumatic or atherosclerotic lesions of the carotid and vertebral arteries: a systematic review. *Eur J Radiol*. 2003;48:88–102.
196. Koelemay MJ, Nederkoorn PJ, Reitsma JB, et al. Systematic review of computed tomographic angiography for assessment of carotid artery disease. *Stroke*. 2004;35:2306–12.
197. Enterline DS, Kapoor G. A practical approach to CT angiography of the neck and brain. *Tech Vasc Interv Radiol*. 2006;9:192–204.
198. Titi M, George C, Bhattacharya D, et al. Comparison of carotid Doppler ultrasound and computerised tomographic angiography in the evaluation of carotid artery stenosis. *Surgeon*. 2007;5:132–6.
199. Clevert DA, Johnson T, Jung EM, et al. Color Doppler, power Doppler and B-flow ultrasound in the assessment of ICA stenosis: comparison with 64-MD-CT angiography. *Eur Radiol*. 2007;17: 2149–59.
200. Mori S, Endo M, Obata T, et al. Clinical potentials of the prototype 256-detector row CT-scanner. *Acad Radiol*. 2005;12:148–54.
201. Kido T, Kurata A, Higashino H, et al. Cardiac imaging using 256-detector row four-dimensional CT: preliminary clinical report. *Radiat Med*. 2007;25:38–44.
202. Addis KA, Hopper KD, Iyriboz TA, et al. CT angiography: in vitro comparison of five reconstruction methods. *AJR Am J Roentgenol*. 2001;177:1171–6.
203. Lell MM, Ditt H, Panknin C, et al. Bone-subtraction CT angiography: evaluation of two different fully automated image-registration procedures for interscan motion compensation. *AJNR Am J Neuroradiol*. 2007;28:1362–8.
204. Bucek RA, Puchner S, Kanitsar A, et al. Automated CTA quantification of internal carotid artery stenosis: a pilot trial. *J Endovasc Ther*. 2007;14:70–6.
205. Lell M, Fellner C, Baum U, et al. Evaluation of carotid artery stenosis with multisection CT and MR imaging: influence of imaging modality and postprocessing. *AJNR Am J Neuroradiol*. 2007;28: 104–10.
206. Josephson SA, Bryant SO, Mak HK, et al. Evaluation of carotid stenosis using CT angiography in the initial evaluation of stroke and TIA. *Neurology*. 2004;63:457–60.
207. Anderson GB, Ashforth R, Steinke DE, et al. CT angiography for the detection and characterization of carotid artery bifurcation disease. *Stroke*. 2000;31:2168–74.
208. Leclerc X, Godefroy O, Lucas C, et al. Internal carotid arterial stenosis: CT angiography with volume rendering. *Radiology*. 1999; 210:673–82.
209. Marcus CD, Ladam-Marcus VJ, Bigot JL, et al. Carotid arterial stenosis: evaluation at CT angiography with the volume-rendering technique. *Radiology*. 1999;211:775–80.
210. Verhoek G, Costello P, Khoo EW, et al. Carotid bifurcation CT angiography: assessment of interactive volume rendering. *J Comput Assist Tomogr*. 1999;23:590–6.
211. Magarelli N, Scarabino T, Simeone AL, et al. Carotid stenosis: a comparison between MR and spiral CT angiography. *Neuroradiology*. 1998;40:367–73.
212. Leclerc X, Godefroy O, Pruvo JP, et al. Computed tomographic angiography for the evaluation of carotid artery stenosis. *Stroke*. 1995;26:1577–81.
213. Dillon EH, van Leeuwen MS, Fernandez MA, et al. CT angiography: application to the evaluation of carotid artery stenosis. *Radiology*. 1993;189:211–9.
214. Schwartz RB, Jones KM, LeClerc GT, et al. The value of cerebral angiography in predicting cerebral ischemia during carotid endarterectomy. *AJR Am J Roentgenol*. 1992;159:1057–61.
215. Chappell FM, Wardlaw JM, Young GR, et al. Carotid artery stenosis: accuracy of noninvasive tests—individual patient data meta-analysis. *Radiology*. 2009;251:493–502.
216. Chen CJ, Lee TH, Hsu HL, et al. Multi-slice CT angiography in diagnosing total versus near occlusions of the internal carotid artery: comparison with catheter angiography. *Stroke*. 2004;35:83–5.
217. Osborn AG. *Diagnostic Cerebral Angiography*. 2nd edition. Philadelphia, Pa: Lippincott Williams & Wilkins, 1999.
218. Eisenberg RL, Bank WO, Hedgcock MW. Neurologic complications of angiography in patients with critical stenosis of the carotid artery. *Neurology*. 1980;30:892–5.
219. Earnest F, Forbes G, Sandok BA, et al. Complications of cerebral angiography: prospective assessment of risk. *AJR Am J Roentgenol*. 1984;142:247–53.
220. Dion JE, Gates PC, Fox AJ, et al. Clinical events following neuroangiography: a prospective study. *Stroke*. 1987;18:997–1004.
221. Grzyska U, Freitag J, Zeumer H. Selective cerebral intraarterial DSA: complication rate and control of risk factors. *Neuroradiology*. 1990; 32:296–9.
222. Hankey GJ, Warlow CP, Sellar RJ. Cerebral angiographic risk in mild cerebrovascular disease. *Stroke*. 1990;21:209–22.
223. Hankey GJ, Warlow CP, Molyneux AJ. Complications of cerebral angiography for patients with mild carotid territory ischaemia being considered for carotid endarterectomy. *J Neurol Neurosurg Psychiatry*. 1990;53:542–8.

224. Davies KN, Humphrey PR. Complications of cerebral angiography in patients with symptomatic carotid territory ischaemia screened by carotid ultrasound. *J Neurol Neurosurg Psychiatry*. 1993;56:967-72.
225. Leonardi M, Cenni P, Simonetti L, et al. Retrospective study of complications arising during cerebral and spinal diagnostic angiography from 1998 to 2003. *Interv Neuroradiol*. 2005;11:213-21.
226. Fayed AM, White CJ, Ramee SR, et al. Carotid and cerebral angiography performed by cardiologists: cerebrovascular complications. *Catheter Cardiovasc Interv*. 2002;55:277-80.
227. American College of Radiology. Standard for the performance of diagnostic cervicocerebral angiography in adults. American College of Radiology Standards 2000-2001. Reston, Va: American College of Radiology; 2000:415-26.
228. Rashid P, Leonardi-Bee J, Bath P. Blood pressure reduction and secondary prevention of stroke and other vascular events: a systematic review. *Stroke*. 2003;34:2741-8.
229. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet*. 2001;358:1033-41.
230. Lawes CM, Bennett DA, Feigin VL, et al. Blood pressure and stroke: an overview of published reviews. *Stroke*. 2004;35:776-85.
231. Neal B, MacMahon S, Chapman N. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. *Lancet*. 2000;356:1955-64.
232. MacMahon S, Peto R, Cutler J, et al. Blood pressure, stroke, and coronary heart disease: part 1, prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet*. 1990;335:765-74.
233. Rodgers A, MacMahon S, Gamble G, et al. Blood pressure and risk of stroke in patients with cerebrovascular disease: the United Kingdom Transient Ischaemic Attack Collaborative Group. *BMJ*. 1996;313:147.
234. Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360:1903-3.
235. Meta-analysis of hypertension treatment trials. *Lancet*. 1990;335:1092-4.
236. Howard G, Manolio TA, Burke GL, et al., The Atherosclerosis Risk in Communities (ARIC) and Cardiovascular Health Study (CHS) Investigators. Does the association of risk factors and atherosclerosis change with age? An analysis of the combined ARIC and CHS cohorts. *Stroke*. 1997;28:1693-701.
237. Wilson PW, Hoeg JM, D'Agostino RB, et al. Cumulative effects of high cholesterol levels, high blood pressure, and cigarette smoking on carotid stenosis. *N Engl J Med*. 1997;337:516-22.
238. Psaty BM, Arnold AM, Olson J, et al. Association between levels of blood pressure and measures of subclinical disease multi-ethnic study of atherosclerosis. *Am J Hypertens*. 2006;19:1110-7.
239. Tell GS, Rutan GH, Kronmal RA, et al. Correlates of blood pressure in community-dwelling older adults: the Cardiovascular Health Study: Cardiovascular Health Study (CHS) Collaborative Research Group. *Hypertension*. 1994;23:59-67.
240. Crouse JR, Toole JF, McKinney WM, et al. Risk factors for extracranial carotid artery atherosclerosis. *Stroke*. 1987;18:990-6.
241. Sutton-Tyrrell K, Alcorn HG, Wolfson SK Jr., et al. Predictors of carotid stenosis in older adults with and without isolated systolic hypertension. *Stroke*. 1993;24:355-61.
242. MacMahon S, Rodgers A. Blood pressure, antihypertensive treatment and stroke risk. *J Hypertens Suppl*. 1994;12:S5-14.
243. Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med*. 2000;342:145-53.
244. Silvestrini M, Vernieri F, Pasqualetti P, et al. Impaired cerebral vasoreactivity and risk of stroke in patients with asymptomatic carotid artery stenosis. *JAMA*. 2000;283:2122-7.
245. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289:2560-72.
246. Wolf PA, D'Agostino RB, Kannel WB, et al. Cigarette smoking as a risk factor for stroke, The Framingham Study. *JAMA*. 1988;259:1025-9.
247. Shinton R, Beevers G. Meta-analysis of relation between cigarette smoking and stroke. *BMJ*. 1989;298:789-94.
248. Kawachi I, Colditz GA, Stampfer MJ, et al. Smoking cessation and decreased risk of stroke in women. *JAMA*. 1993;269:232-6.
249. Robbins AS, Manson JE, Lee IM, et al. Cigarette smoking and stroke in a cohort of U.S. male physicians. *Ann Intern Med*. 1994;120:458-62.
250. Wannamethee SG, Shaper AG, Whincup PH, et al. Smoking cessation and the risk of stroke in middle-aged men. *JAMA*. 1995;274:155-60.
251. Rohr J, Kittner S, Feeser B, et al. Traditional risk factors and ischemic stroke in young adults: the Baltimore-Washington Cooperative Young Stroke Study. *Arch Neurol*. 1996;53:603-7.
252. Howard G, Wagenknecht LE, Cai J, et al. Cigarette smoking and other risk factors for silent cerebral infarction in the general population. *Stroke*. 1998;29:913-7.
253. Lu M, Ye W, Adami HO, et al. Stroke incidence in women under 60 years of age related to alcohol intake and smoking habit. *Cerebrovasc Dis*. 2008;25:517-25.
254. Dobs AS, Nieto FJ, Szklo M, et al. Risk factors for popliteal and carotid wall thicknesses in the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Epidemiol*. 1999;150:1055-67.
255. O'Leary DH, Polak JF, Kronmal RA, et al. Thickening of the carotid wall: a marker for atherosclerosis in the elderly? *Stroke*. 1996;27:224-31.
256. Sharrett AR, Ding J, Criqui MH, et al. Smoking, diabetes, and blood cholesterol differ in their associations with subclinical atherosclerosis: the Multiethnic Study of Atherosclerosis (MESA). *Atherosclerosis*. 2006;186:441-7.
257. Djousse L, Myers RH, Province MA, et al. Influence of apolipoprotein E, smoking, and alcohol intake on carotid atherosclerosis: National Heart, Lung, and Blood Institute Family Heart Study. *Stroke*. 2002;33:1357-61.
258. Mast H, Thompson JL, Lin IF, et al. Cigarette smoking as a determinant of high-grade carotid artery stenosis in Hispanic, black, and white patients with stroke or transient ischemic attack. *Stroke*. 1998;29:908-12.
259. Amarenco P, Bogousslavsky J, Callahan A III, et al. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med*. 2006;355:549-59.
260. Adams RJ, Albers G, Alberts MJ, et al. Update to the AHA/ASA recommendations for the prevention of stroke in patients with stroke and transient ischemic attack. *Stroke*. 2008;39:1647-52.
261. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106:3143-421.
262. Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia: Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med*. 1987;317:1237-45.
263. Kris-Etherton PM, Harris WS, Appel LJ. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation*. 2002;106:2747-57.
264. Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. *N Engl J Med*. 1999;341:410-8.
265. Brown BG, Zhao XQ, Chait A, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med*. 2001;345:1583-92.
266. Iso H, Jacobs DR, Wentworth D Jr., et al. Serum cholesterol levels and six-year mortality from stroke in 350,977 men screened for the multiple risk factor intervention trial. *N Engl J Med*. 1989;320:904-10.
267. Cholesterol, diastolic blood pressure, and stroke: 13,000 strokes in 450,000 people in 45 prospective cohorts. Prospective studies collaboration. *Lancet*. 1995;346:1647-53.
268. Shahar E, Chambless LE, Rosamond WD, et al. Plasma lipid profile and incident ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) study. *Stroke*. 2003;34:623-31.

269. Kurth T, Everett BM, Buring JE, et al. Lipid levels and the risk of ischemic stroke in women. *Neurology*. 2007;68:556–62.
270. Lewington S, Whitlock G, Clarke R, et al. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. *Lancet*. 2007;370:1829–39.
271. Sharrett AR, Patsch W, Sorlie PD, et al. Associations of lipoprotein cholesterols, apolipoproteins A-I and B, and triglycerides with carotid atherosclerosis and coronary heart disease. The Atherosclerosis Risk in Communities (ARIC) Study. *Arterioscler Thromb*. 1994;14:1098–104.
272. Wasserman BA, Sharrett AR, Lai S, et al. Risk factor associations with the presence of a lipid core in carotid plaque of asymptomatic individuals using high-resolution MRI: the Multi-Ethnic Study of Atherosclerosis (MESA). *Stroke*. 2008;39:329–35.
273. Briel M, Studer M, Glass TR, et al. Effects of statins on stroke prevention in patients with and without coronary heart disease: a meta-analysis of randomized controlled trials. *Am J Med*. 2004;117:596–606.
274. Amarenco P, Labreuche J, Lavalley P, et al. Statins in stroke prevention and carotid atherosclerosis: systematic review and up-to-date meta-analysis. *Stroke*. 2004;35:2902–9.
275. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet*. 2005;366:1267–78.
276. Sillesen H, Amarenco P, Hennerici MG, et al. Atorvastatin reduces the risk of cardiovascular events in patients with carotid atherosclerosis: a secondary analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. *Stroke*. 2008;39:3297–302.
277. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:7–22.
278. Crouse JR III, Raichlen JS, Riley WA, et al. Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the METEOR Trial. *JAMA*. 2007;297:1344–53.
279. Taylor AJ, Kent SM, Flaherty PJ, et al. ARBITER: Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol: a randomized trial comparing the effects of atorvastatin and pravastatin on carotid intima medial thickness. *Circulation*. 2002;106:2055–60.
280. Smilde TJ, van Wissen S, Wollersheim H, et al. Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): a prospective, randomised, double-blind trial. *Lancet*. 2001;357:577–81.
281. Canner PL, Berge KG, Wenger NK, et al. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. *J Am Coll Cardiol*. 1986;8:1245–55.
282. Bloomfield RH, Davenport J, Babikian V, et al. Reduction in stroke with gemfibrozil in men with coronary heart disease and low HDL cholesterol: The Veterans Affairs HDL Intervention Trial (VA-HIT). *Circulation*. 2001;103:2828–33.
283. Keech A, Simes RJ, Barter P, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet*. 2005;366:1849–61.
284. Taylor AJ, Sullenberger LE, Lee HJ, et al. Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2: a double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. *Circulation*. 2004;110:3512–7.
285. Kastelein JJ, Akdim F, Stroes ES, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med*. 2008;358:1431–43.
286. Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358:2545–59.
287. Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008;358:2560–72.
288. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet*. 2004;364:685–96.
289. Manson JE, Colditz GA, Stampfer MJ, et al. A prospective study of maturity-onset diabetes mellitus and risk of coronary heart disease and stroke in women. *Arch Intern Med*. 1991;151:1141–7.
290. Karapanayiotides T, Piechowski-Jozwiak B, van Melle G, et al. Stroke patterns, etiology, and prognosis in patients with diabetes mellitus. *Neurology*. 2004;62:1558–62.
291. Folsom AR, Rasmussen ML, Chambless LE, et al. The Atherosclerosis Risk in Communities (ARIC) Study Investigators. Prospective associations of fasting insulin, body fat distribution, and diabetes with risk of ischemic stroke. *Diabetes Care*. 1999;22:1077–83.
292. Smith NL, Barzilay JI, Shaffer D, et al. Fasting and 2-hour postchallenge serum glucose measures and risk of incident cardiovascular events in the elderly: the Cardiovascular Health Study. *Arch Intern Med*. 2002;162:209–16.
293. Wagenknecht LE, D'Agostino R Jr., Savage PJ, et al. Duration of diabetes and carotid wall thickness: the Insulin Resistance Atherosclerosis Study (IRAS). *Stroke*. 1997;28:999–1005.
294. Haffner SM, Agostino RD Jr., Saad MF, et al. Carotid artery atherosclerosis in type-2 diabetic and nondiabetic subjects with and without symptomatic coronary artery disease (The Insulin Resistance Atherosclerosis Study). *Am J Cardiol*. 2000;85:1395–400.
295. Wagenknecht LE, Zaccaro D, Espeland MA, et al. Diabetes and progression of carotid atherosclerosis: the insulin resistance atherosclerosis study. *Arterioscler Thromb Vasc Biol*. 2003;23:1035–41.
296. Chambless LE, Folsom AR, Davis V, et al. Risk factors for progression of common carotid atherosclerosis: the Atherosclerosis Risk in Communities Study, 1987–1998. *Am J Epidemiol*. 2002;155:38–47.
297. van der Meer I, Iglesias del Sol A, Hak AE, et al. Risk factors for progression of atherosclerosis measured at multiple sites in the arterial tree: the Rotterdam Study. *Stroke*. 2003;34:2374–9.
298. Nathan DM, Lachin J, Cleary P, et al. Intensive diabetes therapy and carotid intima-media thickness in type 1 diabetes mellitus. *N Engl J Med*. 2003;348:2294–303.
299. Langenfeld MR, Forst T, Hohberg C, et al. Pioglitazone decreases carotid intima-media thickness independently of glycemic control in patients with type 2 diabetes mellitus: results from a controlled randomized study. *Circulation*. 2005;111:2525–31.
300. Mazzone T, Meyer PM, Feinstein SB, et al. Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: a randomized trial. *JAMA*. 2006;296:2572–81.
301. Laakso M. Benefits of strict glucose and blood pressure control in type 2 diabetes: lessons from the UK Prospective Diabetes Study. *Circulation*. 1999;99:461–2.
302. Nathan DM, Cleary P, Backlund JY, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med*. 2005;353:2643–53.
303. UK-TIA Study Group. United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: interim results. *Br Med J (Clin Res Ed)*. 1988;296:316–320.
304. Keech A, Simes J, Barter P, et al. Correction to the FIELD study report. *Lancet*. 2006;368:1415.
305. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ*. 2002;324:71–86.
306. Selhub J, Jacques PF, Bostom AG, et al. Association between plasma homocysteine concentrations and extracranial carotid-artery stenosis. *N Engl J Med*. 1995;332:286–91.
307. Malinow MR, Nieto FJ, Szklo M, et al. Carotid artery intimal-medial wall thickening and plasma homocyst(e)ine in asymptomatic adults. The Atherosclerosis Risk in Communities Study. *Circulation*. 1993;87:1107–13.
308. McQuillan BM, Beilby JP, Nidorf M, et al. Hyperhomocysteinemia but not the C677T mutation of methylenetetrahydrofolate reductase is an independent risk determinant of carotid wall thickening. The Perth Carotid Ultrasound Disease Assessment Study (CUDAS). *Circulation*. 1999;99:2383–8.

309. Potter K, Hankey GJ, Green DJ, et al. Homocysteine or renal impairment: which is the real cardiovascular risk factor? *Arterioscler Thromb Vasc Biol.* 2008;28:1158-64.
310. Yang Q, Botto LD, Erickson JD, et al. Improvement in stroke mortality in Canada and the United States, 1990 to 2002. *Circulation.* 2006;113:1335-43.
311. Wang X, Qin X, Demirtas H, et al. Efficacy of folic acid supplementation in stroke prevention: a meta-analysis. *Lancet.* 2007;369:1876-82.
312. Toole JF, Malinow MR, Chambless LE, et al. Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death: the Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial. *JAMA.* 2004;291:565-75.
313. Lonn E, Yusuf S, Arnold MJ, et al. Homocysteine lowering with folic acid and B vitamins in vascular disease. *N Engl J Med.* 2006;354:1567-77.
314. Albert CM, Cook NR, Gaziano JM, et al. Effect of folic acid and B vitamins on risk of cardiovascular events and total mortality among women at high risk for cardiovascular disease: a randomized trial. *JAMA.* 2008;299:2027-36.
315. McNeill AM, Rosamond WD, Girman CJ, et al. Prevalence of coronary heart disease and carotid arterial thickening in patients with the metabolic syndrome (The ARIC Study). *Am J Cardiol.* 2004;94:1249-54.
316. Montalcini T, Gorgone G, Federico D, et al. Association of LDL cholesterol with carotid atherosclerosis in menopausal women affected by the metabolic syndrome. *Nutr Metab Cardiovasc Dis.* 2005;15:368-72.
317. Kawamoto R, Ohtsuka N, Ninomiya D, et al. Carotid atherosclerosis in normal-weight metabolic syndrome. *Intern Med.* 2007;46:1771-7.
318. Rundek T, White H, Boden-Albala B, et al. The metabolic syndrome and subclinical carotid atherosclerosis: the Northern Manhattan Study. *J Cardiometab Syndr.* 2007;2:24-9.
319. Montalcini T, Gorgone G, Gazzaruso C, et al. Carotid atherosclerosis associated to metabolic syndrome but not BMI in healthy menopausal women. *Diabetes Res Clin Pract.* 2007;76:378-82.
320. Kawamoto R, Tomita H, Inoue A, et al. Metabolic syndrome may be a risk factor for early carotid atherosclerosis in women but not in men. *J Atheroscler Thromb.* 2007;14:36-43.
321. Ishizaka N, Ishizaka Y, Toda E, et al. Association between cigarette smoking, metabolic syndrome, and carotid arteriosclerosis in Japanese individuals. *Atherosclerosis.* 2005;181:381-8.
322. Wallenfeldt K, Hulthe J, Fagerberg B. The metabolic syndrome in middle-aged men according to different definitions and related changes in carotid artery intima-media thickness (IMT) during 3 years of follow-up. *J Intern Med.* 2005;258:28-37.
323. Iglseider B, Cip P, Malaimare L, et al. The metabolic syndrome is a stronger risk factor for early carotid atherosclerosis in women than in men. *Stroke.* 2005;36:1212-7.
324. Scuteri A, Najjar SS, Muller DC, et al. Metabolic syndrome amplifies the age-associated increases in vascular thickness and stiffness. *J Am Coll Cardiol.* 2004;43:1388-95.
325. Kawamoto R, Tomita H, Oka Y, et al. Metabolic syndrome amplifies the LDL-cholesterol associated increases in carotid atherosclerosis. *Intern Med.* 2005;44:1232-8.
326. Kawamoto R, Tomita H, Oka Y, et al. Metabolic syndrome and carotid atherosclerosis: role of elevated blood pressure. *J Atheroscler Thromb.* 2005;12:268-75.
327. Irace C, Cortese C, Fiaschi E, et al. Components of the metabolic syndrome and carotid atherosclerosis: role of elevated blood pressure. *Hypertension.* 2005;45:597-601.
328. Teramura M, Emoto M, Araki T, et al. Clinical impact of metabolic syndrome by modified NCEP-ATP III criteria on carotid atherosclerosis in Japanese adults. *J Atheroscler Thromb.* 2007;14:172-8.
329. Empana JP, Zureik M, Garipey J, et al. The metabolic syndrome and the carotid artery structure in noninstitutionalized elderly subjects: the three-city study. *Stroke.* 2007;38:893-9.
330. Skilton MR, Moulin P, Serusclat A, et al. A comparison of the NCEP-ATP III, IDF and AHA/NHLBI metabolic syndrome definitions with relation to early carotid atherosclerosis in subjects with hypercholesterolemia or at risk of CVD: evidence for sex-specific differences. *Atherosclerosis.* 2007;190:416-22.
331. Winter Y, Rohrmann S, Linseisen J, et al. Contribution of obesity and abdominal fat mass to risk of stroke and transient ischemic attacks. *Stroke.* 2008;39:3145-51.
332. Sacco RL, Gan R, Boden-Albala B, et al. Leisure-time physical activity and ischemic stroke risk: the Northern Manhattan Stroke Study. *Stroke.* 1998;29:380-7.
333. Hankey GJ. Potential new risk factors for ischemic stroke: what is their potential? *Stroke.* 2006;37:2181-8.
334. Kronenberg F, Pereira MA, Schmitz MK, et al. Influence of leisure time physical activity and television watching on atherosclerosis risk factors in the NHLBI Family Heart Study. *Atherosclerosis.* 2000;153:433-43.
335. Lakka TA, Laukkanen JA, Rauramaa R, et al. Cardiorespiratory fitness and the progression of carotid atherosclerosis in middle-aged men. *Ann Intern Med.* 2001;134:12-20.
336. Tanaka H, Seals DR, Monahan KD, et al. Regular aerobic exercise and the age-related increase in carotid artery intima-media thickness in healthy men. *J Appl Physiol.* 2002;92:1458-64.
337. Wildman RP, Schott LL, Brockwell S, et al. A dietary and exercise intervention slows menopause-associated progression of subclinical atherosclerosis as measured by intima-media thickness of the carotid arteries. *J Am Coll Cardiol.* 2004;44:579-85.
338. The Canadian Cooperative Study Group. A randomized trial of aspirin and sulfinpyrazone in threatened stroke. *N Engl J Med.* 1978;299:53-9.
339. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet.* 1996;348:1329-39.
340. Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet.* 2004;364:331-7.
341. Diener HC, Cunha L, Forbes C, et al. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci.* 1996;143:1-13.
342. Sacco RL, Diener HC, Yusuf S, et al. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *N Engl J Med.* 2008;359:1238-51.
343. Mohr JP, Thompson JL, Lazar RM, et al. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. *N Engl J Med.* 2001;345:1444-51.
344. Halkes PH, van Gijn J, Kappelle LJ, et al. Medium intensity oral anticoagulants versus aspirin after cerebral ischaemia of arterial origin (ESPRIT): a randomised controlled trial. *Lancet Neurol.* 2007;6:115-24.
345. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med.* 1994;154:1449-57.
346. Woessner R, Grauer M, Bianchi O, et al. Treatment with anticoagulants in cerebral events (TRACE). *Thromb Haemost.* 2004;91:690-3.
347. The Publications Committee for the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Investigators. Low molecular weight heparinoid, ORG 10172 (danaparoid), and outcome after acute ischemic stroke: a randomized controlled trial. *JAMA.* 1998;279:1265-72.
348. Cote R, Battista RN, Abrahamowicz M, et al., The Asymptomatic Cervical Bruit Study Group. Lack of effect of aspirin in asymptomatic patients with carotid bruits and substantial carotid narrowing. *Ann Intern Med.* 1995;123:649-55.
349. Goldstein LB, Adams R, Becker K, et al. Primary prevention of ischemic stroke: a statement for healthcare professionals from the Stroke Council of the American Heart Association. *Circulation.* 2001;103:163-82.
350. Bhatt DL, Fox KA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med.* 2006;354:1706-17.
351. Alberts MJ, Bergman DL, Molner E, et al. Antiplatelet effect of aspirin in patients with cerebrovascular disease. *Stroke.* 2004;35:175-8.
352. Mega JL, Close SL, Wiviott SD, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. *N Engl J Med.* 2009;360:354-62.

353. US Food and Drug Administration. FDA Drug Safety Communication: Reduced effectiveness of Plavix (clopidogrel) in patients who are poor metabolizers of the drug. Available at: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm203888.htm>. Accessed April 28, 2010.
354. Holmes DR Jr., Dehmer GJ, Kaul S, et al. ACCF/AHA clopidogrel clinical alert: approaches to the FDA "boxed warning": a report of the American College of Cardiology Foundation Task Force on clinical expert consensus documents and the American Heart Association. *J Am Coll Cardiol*. 2010;56:321–41.
355. Bath PM, Iddenden R, Bath FJ. Low-molecular-weight heparins and heparinoids in acute ischemic stroke: a meta-analysis of randomized controlled trials. *Stroke*. 2000;31:1770–8.
356. Deleted in proof.
357. Bak S, Andersen M, Tsiropoulos I, et al. Risk of stroke associated with nonsteroidal anti-inflammatory drugs: a nested case-control study. *Stroke*. 2003;34:379–86.
358. Chen LC, Ashcroft DM. Do selective COX-2 inhibitors increase the risk of cerebrovascular events? A meta-analysis of randomized controlled trials. *J Clin Pharm Ther*. 2006;31:565–76.
359. Rothwell PM, Slattery J, Warlow CP. A systematic review of the risks of stroke and death due to endarterectomy for symptomatic carotid stenosis. *Stroke*. 1996;27:260–5.
360. Brott TG, Hobson RW, Howard G, et al. Stenting versus Endarterectomy for Treatment of Carotid-Artery Stenosis. *N Engl J Med*. 2010;363:11–23.
361. Gray WA, Hopkins LN, Yadav S, et al. Protected carotid stenting in high-surgical-risk patients: the ARCHEr results. *J Vasc Surg*. 2006;44:258–68.
362. Katzen BT, Criado FJ, Ramee SR, et al. Carotid artery stenting with emboli protection surveillance study: thirty-day results of the CAGES-PMS study. *Catheter Cardiovasc Interv*. 2007;70:316–23.
363. Rothwell PM, Goldstein LB. Carotid endarterectomy for asymptomatic carotid stenosis: asymptomatic carotid surgery trial. *Stroke*. 2004;35:2425–7.
364. Eckstein HH, Ringleb P, Allenberg JR, et al. Results of the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) study to treat symptomatic stenoses at 2 years: a multinational, prospective, randomised trial. *Lancet Neurol*. 2008;7:893–902.
365. Chiam PT, Roubin GS, Panagopoulos G, et al. One-year clinical outcomes, midterm survival, and predictors of mortality after carotid stenting in elderly patients. *Circulation*. 2009;119:2343–8.
366. Roubin GS, New G, Iyer SS, et al. Immediate and late clinical outcomes of carotid artery stenting in patients with symptomatic and asymptomatic carotid artery stenosis: a 5-year prospective analysis. *Circulation*. 2001;103:532–7.
367. Zahn R, Ischinger T, Hochadel M, et al. Carotid artery stenting in octogenarians: results from the ALKK Carotid Artery Stent (CAS) Registry. *Eur Heart J*. 2007;28:370–5.
368. Ederle J, Dobson J, Featherstone RL, et al. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. *Lancet*. 2010;375:985–97.
369. Gurm HS, Yadav JS, Fayad P, et al. Long-term results of carotid stenting versus endarterectomy in high-risk patients. *N Engl J Med*. 2008;358:1572–9.
370. Yadav JS, Wholey MH, Kuntz RE, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med*. 2004;351:1493–501.
371. Yadav JS, Sneed D, Ouriel K, et al. Durability of carotid stenting for the prevention of stroke: 3-year follow-up of the SAPHIRE trial and the US Carotid Feasibility. *Circulation*. 2005;112:416. Abstract.
372. Gray WA, Yadav JS, Verta P, et al. The CAPTURE registry: results of carotid stenting with embolic protection in the post approval setting. *Catheter Cardiovasc Interv*. 2007;69:341–8.
373. Harrod-Kim P, Kadhodayan Y, Derdeyn CP, et al. Outcomes of carotid angioplasty and stenting for radiation-associated stenosis. *AJNR Am J Neuroradiol*. 2005;26:1781–8.
374. Rothwell PM, Eliasziw M, Gutnikov SA, et al. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. *Lancet*. 2004;363:915–24.
375. Safian RD, Bacharach JM, Ansel GM, et al. Carotid stenting with a new system for distal embolic protection and stenting in high-risk patients: the Carotid Revascularization with Ev3 Arterial Technology Evolution (CREATE) feasibility trial. *Catheter Cardiovasc Interv*. 2004;63:1–6.
376. White CJ, Iyer SS, Hopkins LN, et al. Carotid stenting with distal protection in high surgical risk patients: the BEACH trial 30 day results. *Catheter Cardiovasc Interv*. 2006;67:503–12.
377. Barnett HJ. Carotid endarterectomy. *Lancet*. 2004;363:1486–7.
378. Rothwell PM, Gutnikov SA, Warlow CP. Reanalysis of the final results of the European Carotid Surgery Trial. *Stroke*. 2003;34:514–23.
379. Mas JL, Trinquart L, Leys D, et al. Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial: results up to 4 years from a randomised, multicentre trial. *Lancet Neurol*. 2008;7:885–92.
380. Bonati LH, Jongen LM, Haller S, et al. New ischaemic brain lesions on MRI after stenting or endarterectomy for symptomatic carotid stenosis: a substudy of the International Carotid Stenting Study (ICSS). *Lancet Neurol*. 2010;9:353–62.
381. North American Symptomatic Carotid Endarterectomy Trial: methods, patient characteristics, and progress. *Stroke*. 1991;22:711–20.
- 381a. Suissa S. Calculation of number needed to treat. *N Engl J Med*. 2009;361:424–5.
382. Rothwell PM, Eliasziw M, Gutnikov SA, et al. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet*. 2003;361:107–16.
383. Goldstein LB, Hasselblad V, Matchar DB, et al. Comparison and meta-analysis of randomized trials of endarterectomy for symptomatic carotid artery stenosis. *Neurology*. 1995;45:1965–70.
384. Rothwell PM, Warlow CP, on behalf of the European Carotid Surgery Trialists' Collaborative Group. Low risk of ischemic stroke in patients with reduced internal carotid artery lumen diameter distal to severe symptomatic carotid stenosis: cerebral protection due to low poststenotic flow? *Stroke*. 2000;31:622–30.
385. Henderson RD, Eliasziw M, Fox AJ, et al. Angiographically defined collateral circulation and risk of stroke in patients with severe carotid artery stenosis. *Stroke*. 2000;31:128–32.
386. Role of carotid endarterectomy in asymptomatic carotid stenosis. A Veterans Administration Cooperative Study. *Stroke*. 1986;17:534–9.
387. Towne JB, Weiss DG, Hobson RW. First phase report of cooperative Veterans Administration asymptomatic carotid stenosis study—operative morbidity and mortality. *J Vasc Surg*. 1990;11:252–8.
388. The Asymptomatic Carotid Atherosclerosis Study Group. Study design for randomized prospective trial of carotid endarterectomy for asymptomatic atherosclerosis. *Stroke*. 1989;20:844–9.
389. Moore WS, Vescera CL, Robertson JT, et al. Selection process for surgeons in the Asymptomatic Carotid Atherosclerosis Study. *Stroke*. 1991;22:1353–7.
390. Clinical advisory: carotid endarterectomy for patients with asymptomatic internal carotid artery stenosis. *Stroke*. 1994;25:2523–4.
391. Moore WS, Young B, Baker WH, et al. Surgical results: a justification of the surgeon selection process for the ACAS trial. *J Vasc Surg*. 1996;23:323–8.
392. Baker JD, Gluecklich B, Watson CW, et al. An evaluation of electroencephalographic monitoring for carotid study. *Surgery*. 1975;78:787–94.
393. Elmore JR, Eldrup-Jorgensen J, Leschey WH, et al. Computerized topographic brain mapping during carotid endarterectomy. *Arch Surg*. 1990;125:734–7.
394. Moore WS, Yee JM, Hall AD. Collateral cerebral blood pressure: an index of tolerance to temporary carotid occlusion. *Arch Surg*. 1973;106:521–3.
395. Golledge J, Cuming R, Davies AH, et al. Outcome of selective patching following carotid endarterectomy. *Eur J Vasc Endovasc Surg*. 1996;11:458–63.
396. Gelabert HA, El-Massry S, Moore WS. Carotid endarterectomy with primary closure does not adversely affect the rate of recurrent stenosis. *Arch Surg*. 1994;129:648–54.
397. Myers SI, Valentine RJ, Chervu A, et al. Saphenous vein patch versus primary closure for carotid endarterectomy: long-term assessment of a randomized prospective study. *J Vasc Surg*. 1994;19:15–22.
398. De Letter JA, Moll FL, Welten RJ, et al. Benefits of carotid patching: a prospective randomized study with long-term follow-up. *Ann Vasc Surg*. 1994;8:54–8.

399. Fietsam R, Ranval T, Cohn S, et al. Hemodynamic effects of primary closure versus patch angioplasty of the carotid artery. *Ann Vasc Surg.* 1992;6:443-9.
400. Rosenthal D, Archie JP Jr., Garcia-Rinaldi R, et al. Carotid patch angioplasty: immediate and long-term results. *J Vasc Surg.* 1990;12:326-33.
401. Vanmaele R, Van Schil P, De Maeseener M. Closure of the internal carotid artery after endarterectomy: the advantages of patch angioplasty without its disadvantages. *Ann Vasc Surg.* 1990;4:81-4.
402. Clagett GP, Patterson CB, Fisher DF Jr., et al. Vein patch versus primary closure for carotid endarterectomy. A randomized prospective study in a selected group of patients. *J Vasc Surg.* 1989;9:213-23.
403. Eikelboom BC, Ackerstaff RG, Hoeneveld H, et al. Benefits of carotid patching: a randomized study. *J Vasc Surg.* 1988;7:240-7.
404. Hertzner NR, Beven EG, O'Hara PJ, et al. A prospective study of vein patch angioplasty during carotid endarterectomy. Three-year results for 801 patients and 917 operations. *Ann Surg.* 1987;206:628-35.
405. Katz MM, Jones GT, Degenhardt J, et al. The use of patch angioplasty to alter the incidence of carotid restenosis following thromboendarterectomy. *J Cardiovasc Surg (Torino).* 1987;28:2-8.
406. AbuRahma AF, Robinson PA, Saiedy S, et al. Prospective randomized trial of bilateral carotid endarterectomies: primary closure versus patching. *Stroke.* 1999;30:1185-9.
407. Bond R, Rerkasem K, AbuRahma AF, et al. Patch angioplasty versus primary closure for carotid endarterectomy. *Cochrane Database Syst Rev.* 2004;CD000160.
408. Cao P, De Rango P, Cieri E, et al. Eversion versus conventional endarterectomy. *Semin Vasc Surg.* 2004;17:236-42.
409. Crawford RS, Chung TK, Hodgman T, et al. Restenosis after eversion vs patch closure carotid endarterectomy. *J Vasc Surg.* 2007;46:41-8.
410. Nazarian SM, Yenokyan G, Thompson RE, et al. Statistical modeling of the volume-outcome effect for carotid endarterectomy for 10 years of a statewide database. *J Vasc Surg.* 2008;48:343-50.
411. Chappel AR, Zuckerman RS, Finlayson SR. Small rural hospitals and high-risk operations: how would regionalization affect surgical volume and hospital revenue? *J Am Coll Surg.* 2006;203:599-604.
412. Matsen SL, Chang DC, Perler BA, et al. Trends in the in-hospital stroke rate following carotid endarterectomy in California and Maryland. *J Vasc Surg.* 2006;44:488-95.
413. Goodney PP, Stukel TA, Lucas FL, et al. Hospital volume, length of stay, and readmission rates in high-risk surgery. *Ann Surg.* 2003;238:161-7.
414. Deen HG. Surgeon volume and carotid endarterectomy. *J Am Coll Surg.* 2003;196:826-7.
415. Cowan JA Jr., Dimick JB, Thompson BG, et al. Surgeon volume as an indicator of outcomes after carotid endarterectomy: an effect independent of specialty practice and hospital volume. *J Am Coll Surg.* 2002;195:814-21.
416. Feasby TE, Quan H, Ghali WA. Hospital and surgeon determinants of carotid endarterectomy outcomes. *Arch Neurol.* 2002;59:1877-81.
417. Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. *N Engl J Med.* 2002;346:1128-37.
418. Birkmeyer JD, Finlayson EV, Birkmeyer CM. Volume standards for high-risk surgical procedures: potential benefits of the Leapfrog initiative. *Surgery.* 2001;130:415-22.
419. Peck C, Peck J, Peck A. Comparison of carotid endarterectomy at high- and low-volume hospitals. *Am J Surg.* 2001;181:450-3.
420. Khuri SF, Daley J, Henderson W, et al. Relation of surgical volume to outcome in eight common operations: results from the VA National Surgical Quality Improvement Program. *Ann Surg.* 1999;230:414-29.
421. Hannan EL, Popp AJ, Tranmer B, et al. Relationship between provider volume and mortality for carotid endarterectomies in New York state. *Stroke.* 1998;29:2292-7.
422. Killeen SD, Andrews EJ, Redmond HP, et al. Provider volume and outcomes for abdominal aortic aneurysm repair, carotid endarterectomy, and lower extremity revascularization procedures. *J Vasc Surg.* 2007;45:615-26.
423. Holt PJ, Poloniecki JD, Loftus IM, et al. Meta-analysis and systematic review of the relationship between hospital volume and outcome following carotid endarterectomy. *Eur J Vasc Endovasc Surg.* 2007;33:645-51.
424. Dorafshar AH, Reil TD, Moore WS, et al. Cost analysis of carotid endarterectomy: is age a factor? *Ann Vasc Surg.* 2004;18:729-35.
425. Kadhodayan Y, Moran CJ, Derdeyn CP, et al. Carotid angioplasty and stent placement for restenosis after endarterectomy. *Neuroradiology.* 2007;49:357-64.
426. Kazmers A, Perkins AJ, Huber TS, et al. Carotid surgery in octogenarians in Veterans Affairs medical centers. *J Surg Res.* 1999;81:87-90.
427. Wennberg DE, Lucas FL, Birkmeyer JD, et al. Variation in carotid endarterectomy mortality in the Medicare population: trial hospitals, volume, and patient characteristics. *JAMA.* 1998;279:1278-81.
428. Debing E, Van den Brande P. Carotid endarterectomy in the elderly: are the patient characteristics, the early outcome, and the predictors the same as those in younger patients? *Surg Neurol.* 2007;67:467-71.
429. Hellings WE, Pasterkamp G, Verhoeven BA, et al. Gender-associated differences in plaque phenotype of patients undergoing carotid endarterectomy. *J Vasc Surg.* 2007;45:289-96.
430. Debing E, Von Kemp K, Van den Brande P. Gender differences in cardiovascular risk factors in a carotid endarterectomy population. *Int Angiol.* 2006;25:18-25.
431. Alamowitch S, Eliasziw M, Barnett HJ. The risk and benefit of endarterectomy in women with symptomatic internal carotid artery disease. *Stroke.* 2005;36:27-31.
432. AbuRahma AF, Robinson PA, Saiedy S, et al. Prospective randomized trial of carotid endarterectomy with primary closure and patch angioplasty with saphenous vein, jugular vein, and polytetrafluoroethylene: long-term follow-up. *J Vasc Surg.* 1998;27:222-32.
433. Mattos MA, Sumner DS, Bohannon WT, et al. Carotid endarterectomy in women: challenging the results from ACAS and NASCET. *Ann Surg.* 2001;234:438-45.
434. Chen WH, Ho DS, Ho SL, et al. Prevalence of extracranial carotid and vertebral artery disease in Chinese patients with coronary artery disease. *Stroke.* 1998;29:631-4.
435. Conrad MF, Shepard AD, Pandurangi K, et al. Outcome of carotid endarterectomy in African Americans: is race a factor? *J Vasc Surg.* 2003;38:129-37.
436. Uehara T, Tabuchi M, Kozawa S, et al. MR angiographic evaluation of carotid and intracranial arteries in Japanese patients scheduled for coronary artery bypass grafting. *Cerebrovasc Dis.* 2001;11:341-5.
437. Ferguson GG, Eliasziw M, Barr HW, et al. The North American Symptomatic Carotid Endarterectomy Trial: surgical results in 1415 patients. *Stroke.* 1999;30:1751-8.
438. Bond R, Rerkasem K, Cuffe R, et al. A systematic review of the associations between age and sex and the operative risks of carotid endarterectomy. *Cerebrovasc Dis.* 2005;20:69-77.
439. Bond R, Rerkasem K, Shearman CP, et al. Time trends in the published risks of stroke and death due to endarterectomy for symptomatic carotid stenosis. *Cerebrovasc Dis.* 2004;18:37-46.
440. Bond R, Rerkasem K, Naylor AR, et al. Systematic review of randomized controlled trials of patch angioplasty versus primary closure and different types of patch materials during carotid endarterectomy. *J Vasc Surg.* 2004;40:1126-35.
441. Halm EA, Hannan EL, Rojas M, et al. Clinical and operative predictors of outcomes of carotid endarterectomy. *J Vasc Surg.* 2005;42:420-8.
442. Meyer FB, Piepgras DG, Sundt TM. Recurrent carotid stenosis. In: Meyer FB, editor. *Sundt's Occlusive Cerebrovascular Disease*. 2nd edition. Philadelphia, Pa: WB Saunders;1994:310-21.
443. Mericle RA, Kim SH, Lanzino G, et al. Carotid artery angioplasty and use of stents in high-risk patients with contralateral occlusions. *J Neurosurg.* 1999;90:1031-6.
444. Gasparis AP, Ricotta L, Cuadra SA, et al. High-risk carotid endarterectomy: fact or fiction. *J Vasc Surg.* 2003;37:40-6.
445. Hill BB, Olcott C, Dalman RL, et al. Reoperation for carotid stenosis is as safe as primary carotid endarterectomy. *J Vasc Surg.* 1999;30:26-35.
446. Illig KA, Zhang R, Tanski W, et al. Is the rationale for carotid angioplasty and stenting in patients excluded from NASCET/ACAS or eligible for ARCHEr justified? *J Vasc Surg.* 2003;37:575-81.
447. Jordan WD Jr., Alcocer F, Wirthlin DJ, et al. High-risk carotid endarterectomy: challenges for carotid stent protocols. *J Vasc Surg.* 2002;35:16-21.
448. Leseche G, Castier Y, Chataigner O, et al. Carotid artery revascularization through a radiated field. *J Vasc Surg.* 2003;38:244-50.

449. Mozes G, Sullivan TM, Torres-Russotto DR, et al. Carotid endarterectomy in SAPHIRE-eligible high-risk patients: implications for selecting patients for carotid angioplasty and stenting. *J Vasc Surg.* 2004;39:958–65.
450. Rockman CB, Su W, Lamparello PJ, et al. A reassessment of carotid endarterectomy in the face of contralateral carotid occlusion: surgical results in symptomatic and asymptomatic patients. *J Vasc Surg.* 2002;36:668–73.
451. Stoner MC, Cambria RP, Brewster DC, et al. Safety and efficacy of reoperative carotid endarterectomy: a 14-year experience. *J Vasc Surg.* 2005;41:942–9.
452. Ouriel K, Hertzner NR, Beven EG, et al. Preprocedural risk stratification: identifying an appropriate population for carotid stenting. *J Vasc Surg.* 2001;33:728–32.
453. Naylor AR, Bolia A, Abbott RJ, et al. Randomized study of carotid angioplasty and stenting versus carotid endarterectomy: a stopped trial. *J Vasc Surg.* 1998;28:326–34.
454. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. *Lancet.* 2001;357:1729–37.
455. Brooks WH, McClure RR, Jones MR, et al. Carotid angioplasty and stenting versus carotid endarterectomy: randomized trial in a community hospital. *J Am Coll Cardiol.* 2001;38:1589–95.
456. Mas JL, Chatellier G, Beyssen B, et al. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. *N Engl J Med.* 2006;355:1660–71.
457. Ringleb PA, Allenberg J, Bruckmann H, et al. 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial [published correction appears in *Lancet.* 2006;368:1238]. *Lancet.* 2006;368:1239–47.
458. Coward LJ, Featherstone RL, Brown MM. Safety and efficacy of endovascular treatment of carotid artery stenosis compared with carotid endarterectomy: a Cochrane systematic review of the randomized evidence. *Stroke.* 2005;36:905–11.
459. Gurm HS, Nallamothu BK, Yadav J. Safety of carotid artery stenting for symptomatic carotid artery disease: a meta-analysis. *Eur Heart J.* 2008;29:113–9.
460. Ederle J, Featherstone RL, Brown MM. Percutaneous transluminal angioplasty and stenting for carotid artery stenosis. *Cochrane Database Syst Rev.* 2007;CD000515.
461. Gupta AK, Purkayastha S, Unnikrishnan M, et al. Hyperperfusion syndrome after supraaortic vessel interventions and bypass surgery. *J Neuroradiol.* 2005;32:352–8.
462. van Mook WN, Rennenberg RJ, Schurink GW, et al. Cerebral hyperperfusion syndrome. *Lancet Neurol.* 2005;4:877–88.
463. Nouraei SA, Al-Rawi PG, Sigauco-Roussel D, et al. Carotid endarterectomy impairs blood pressure homeostasis by reducing the physiologic baroreflex reserve. *J Vasc Surg.* 2005;41:631–7.
464. Posner SR, Boxer L, Proctor M, et al. Uncomplicated carotid endarterectomy: factors contributing to blood pressure instability precluding safe early discharge. *Vascular.* 2004;12:278–84.
465. Bond R, Warlow CP, Naylor AR, et al. Variation in surgical and anaesthetic technique and associations with operative risk in the European carotid surgery trial: implications for trials of ancillary techniques. *Eur J Vasc Endovasc Surg.* 2002;23:117–26.
466. Maroulis J, Karkanevatos A, Papakostas K, et al. Cranial nerve dysfunction following carotid endarterectomy. *Int Angiol.* 2000;19:237–41.
467. Sajid MS, Vijaynagar B, Singh P, et al. Literature review of cranial nerve injuries during carotid endarterectomy. *Acta Chir Belg.* 2007;107:25–8.
468. Cunningham EJ, Bond R, Mayberg MR, et al. Risk of persistent cranial nerve injury after carotid endarterectomy. *J Neurosurg.* 2004;101:445–8.
469. Sternbach Y, Illig KA, Zhang R, et al. Hemodynamic benefits of regional anesthesia for carotid endarterectomy. *J Vasc Surg.* 2002;35:333–9.
470. Cywinski JB, Koch CG, Krajewski LP, et al. Increased risk associated with combined carotid endarterectomy and coronary artery bypass graft surgery: a propensity-matched comparison with isolated coronary artery bypass graft surgery. *J Cardiothorac Vasc Anesth.* 2006;20:796–802.
471. Stoner MC, Abbott WM, Wong DR, et al. Defining the high-risk patient for carotid endarterectomy: an analysis of the prospective National Surgical Quality Improvement Program database. *J Vasc Surg.* 2006;43:285–95.
472. Debing E, Van den Brande P. Does the type, number or combinations of traditional cardiovascular risk factors affect early outcome after carotid endarterectomy? *Eur J Vasc Endovasc Surg.* 2006;31:622–6.
473. Gangireddy C, Rectenwald JR, Upchurch GR, et al. Risk factors and clinical impact of postoperative symptomatic venous thromboembolism. *J Vasc Surg.* 2007;45:335–41.
474. Finsterer J, Senbach-Glaninger A, Krugluger W, et al. Risk-factor profile in severe, generalized, obliterating vascular disease. *South Med J.* 2004;97:87–92.
475. Lensing AW. Anticoagulation in acute ischaemic stroke: deep vein thrombosis prevention and long-term stroke outcomes. *Blood Coagul Fibrinolysis.* 1999;10 Suppl 2:S123–7.
476. Paciaroni M, Eliasziw M, Kappelle LJ, et al. Medical complications associated with carotid endarterectomy: North American Symptomatic Carotid Endarterectomy Trial (NASCET). *Stroke.* 1999;30:1759–63.
477. Inzitari D, Eliasziw M, Gates P, et al. The causes and risk of stroke in patients with asymptomatic internal-carotid-artery stenosis. *N Engl J Med.* 2000;342:1693–700.
478. Alamowitch S, Eliasziw M, Algra A, et al. Risk, causes, and prevention of ischaemic stroke in elderly patients with symptomatic internal-carotid-artery stenosis. *Lancet.* 2001;357:1154–60.
479. Ascitutto G, Geier B, Marpe B, et al. Dacron patch infection after carotid angioplasty. A report of 6 cases. *Eur J Vasc Endovasc Surg.* 2007;33:55–7.
480. Borazjani BH, Wilson SE, Fujitani RM, et al. Postoperative complications of carotid patching: pseudoaneurysm and infection. *Ann Vasc Surg.* 2003;17:156–61.
481. Moore M, Power M. Perioperative hemorrhage and combined clopidogrel and aspirin therapy. *Anesthesiology.* 2004;101:792–4.
482. Reed AB, Gaccione P, Belkin M, et al. Preoperative risk factors for carotid endarterectomy: defining the patient at high risk. *J Vasc Surg.* 2003;37:1191–9.
483. Bapojie SR, Whitaker JF, Schulz T, et al. Preoperative evaluation of the patient with pulmonary disease. *Chest.* 2007;132:1637–45.
484. Sidawy AN, Aidinian G, Johnson ON III, et al. Effect of chronic renal insufficiency on outcomes of carotid endarterectomy. *J Vasc Surg.* 2008;48:1423–30.
485. Reil T, Shekherdimian S, Golchet P, et al. The safety of carotid endarterectomy in patients with preoperative renal dysfunction. *Ann Vasc Surg.* 2002;16:176–80.
486. Debing E, Van den Brande P. Chronic renal insufficiency and risk of early mortality in patients undergoing carotid endarterectomy. *Ann Vasc Surg.* 2006;20:609–13.
487. Ascher E, Marks NA, Schutzer RW, et al. Carotid endarterectomy in patients with chronic renal insufficiency: a recent series of 184 cases. *J Vasc Surg.* 2005;41:24–9.
488. Bryant MF. Anatomic considerations in carotid endarterectomy. *Surg Clin North Am.* 1974;54:1291–6.
489. Hans SS, Shah S, Hans B. Carotid endarterectomy for high plaques. *Am J Surg.* 1989;157:431–4.
490. Kashyap VS, Moore WS, Quinones-Baldrich WJ. Carotid artery repair for radiation-associated atherosclerosis is a safe and durable procedure. *J Vasc Surg.* 1999;29:90–6.
491. Protack CD, Bakken AM, Saad WA, et al. Radiation arteritis: a contraindication to carotid stenting? *J Vasc Surg.* 2007;45:110–7.
492. Favre JP, Nourissat A, Duprey A, et al. Endovascular treatment for carotid artery stenosis after neck irradiation. *J Vasc Surg.* 2008;48:852–8.
493. Flanigan DP, Flanigan ME, Dorne AL, et al. Long-term results of 442 consecutive, standardized carotid endarterectomy procedures in standard-risk and high-risk patients. *J Vasc Surg.* 2007;46:876–82.
494. Harthun NL, Baglioni AJ Jr, Kongable GL, et al. Carotid endarterectomy: update on the gold standard treatment for carotid stenosis. *Am Surg.* 2005;71:647–51.
495. Kresowik TF, Bratzler DW, Kresowik RA, et al. Multistate improvement in process and outcomes of carotid endarterectomy. *J Vasc Surg.* 2004;39:372–80.



496. Middleton S, Donnelly N. Outcomes of carotid endarterectomy: how does the Australian state of New South Wales compare with international benchmarks? *J Vasc Surg.* 2002;36:62-9.
497. Chiesa R, Melissano G, Castellano R, et al. Carotid endarterectomy: experience in 5425 cases. *Ann Vasc Surg.* 2004;18:527-34.
498. Kragsterman B, Parsson H, Lindback J, et al. Outcomes of carotid endarterectomy for asymptomatic stenosis in Sweden are improving: results from a population-based registry. *J Vasc Surg.* 2006;44:79-5.
499. Kennedy J, Quan H, Buchan AM, et al. Statins are associated with better outcomes after carotid endarterectomy in symptomatic patients. *Stroke.* 2005;36:2072-6.
500. Taylor DW, Barnett HJ, Haynes RB, et al. Low-dose and high-dose acetylsalicylic acid for patients undergoing carotid endarterectomy: a randomised controlled trial. *Lancet.* 1999;353:2179-84.
501. Lamuraglia GM, Stoner MC, Brewster DC, et al. Determinants of carotid endarterectomy anatomic durability: effects of serum lipids and lipid-lowering drugs. *J Vasc Surg.* 2005;41:762-8.
502. Roth SM, Back MR, Bandyk DF, et al. A rational algorithm for duplex scan surveillance after carotid endarterectomy. *J Vasc Surg.* 1999;30:453-60.
503. McGirt MJ, Perler BA, Brooke BS, et al. 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors reduce the risk of perioperative stroke and mortality after carotid endarterectomy. *J Vasc Surg.* 2005;42:829-36.
504. McPhee JT, Hill JS, Ciocca RG, et al. Carotid endarterectomy was performed with lower stroke and death rates than carotid artery stenting in the United States in 2003 and 2004. *J Vasc Surg.* 2007;46:1112-8.
505. White CJ. Liar, liar, pants on fire. *Catheter Cardiovasc Interv.* 2008;72:430-1.
506. Cayne NS, Faries PL, Trocciola SM, et al. Carotid angioplasty and stent-induced bradycardia and hypotension: impact of prophylactic atropine administration and prior carotid endarterectomy. *J Vasc Surg.* 2005;41:956-61.
507. Leisch F, Kerschner K, Hofmann R, et al. Carotid sinus reactions during carotid artery stenting: predictors, incidence, and influence on clinical outcome. *Catheter Cardiovasc Interv.* 2003;58:516-23.
508. Coward LJ, Featherstone RL, Brown MM. Percutaneous transluminal angioplasty and stenting for carotid artery stenosis. *Cochrane Database Syst Rev.* 2004;CD000515.
509. Criado E, Doblas M, Fontcuberta J, et al. Carotid angioplasty with internal carotid artery flow reversal is well tolerated in the awake patient. *J Vasc Surg.* 2004;40:92-7.
510. Sganzerla P, Bocciarelli M, Savasta C, et al. The treatment of carotid artery bifurcation stenoses with systematic stenting: experience of first 100 consecutive cardiologic procedures. *J Invasive Cardiol.* 2004;16:592-5.
511. Tan KT, Cleveland TJ, Berci V, et al. Timing and frequency of complications after carotid artery stenting: what is the optimal period of observation? *J Vasc Surg.* 2003;38:236-43.
512. Srimahachota S, Singhatanadgige S, Boonyaratavej S, et al. Bilateral carotid stenting prior to coronary artery bypass graft: a case report. *J Med Assoc Thai.* 2002;85:1232-5.
513. Leisch F, Kerschner K, Hofman R, et al. Carotid stenting: acute results and complications [in German]. *Z Kardiol.* 1999;88:661-8.
514. Back MR. Commentary. Protected carotid stenting in high-surgical-risk patients: the ARCHeR results. *Perspect Vasc Surg Endovasc Ther.* 2006;18:349-51.
515. Coward LJ, Featherstone RL, Brown MM. Percutaneous transluminal angioplasty and stenting for vertebral artery stenosis. *Cochrane Database Syst Rev.* 2005;CD000516.
516. Crawley F, Brown MM. Percutaneous transluminal angioplasty and stenting for carotid artery stenosis. *Cochrane Database Syst Rev.* 2000;CD000515.
517. Gray WA. Endovascular treatment of extra-cranial carotid artery bifurcation disease. *Minerva Cardioangiol.* 2005;53:69-77.
518. Gray WA. A cardiologist in the carotids. *J Am Coll Cardiol.* 2004;43:1602-5.
519. Kasirajan K. What is the latest in inventory for carotid stenting and cerebral protection? *Perspect Vasc Surg Endovasc Ther.* 2005;17:135-41.
520. Naylor AR. Regarding "protected carotid stenting in high-surgical-risk patients: the ARCHeR results". *J Vasc Surg.* 2007;45:222-3.
521. Schonholz CJ, Uflacker R, Parodi JC, et al. Is there evidence that cerebral protection is beneficial? Clinical data. *J Cardiovasc Surg (Torino).* 2006;47:137-41.
522. Devlin TG, Baxter BW, Feintuch TA, et al. The Merci Retrieval System for acute stroke: the Southeast Regional Stroke Center experience. *Neurocrit Care.* 2007;6:11-21.
523. DeRubertis BG, Chaer RA, Gordon R, et al. Determining the quantity and character of carotid artery embolic debris by electron microscopy and energy dispersive spectroscopy. *J Vasc Surg.* 2007;45:716-24.
524. Maleux G, Demaerel P, Verbeken E, et al. Cerebral ischemia after filter-protected carotid artery stenting is common and cannot be predicted by the presence of substantial amount of debris captured by the filter device. *AJNR Am J Neuroradiol.* 2006;27:1830-3.
525. Reimers B, Tubler T, de Donato G, et al. Endovascular treatment of in-stent restenosis after carotid artery stenting: immediate and midterm results. *J Endovasc Ther.* 2006;13:429-35.
526. Imai K, Mori T, Izumoto H, et al. Successful stenting seven days after atherothrombotic occlusion of the intracranial internal carotid artery. *J Endovasc Ther.* 2006;13:254-9.
527. Macdonald S. Is there any evidence that cerebral protection is beneficial? Experimental data. *J Cardiovasc Surg (Torino).* 2006;47:127-36.
528. Quan VH, Huynh R, Seifert PA, et al. Morphometric analysis of particulate debris extracted by four different embolic protection devices from coronary arteries, aortocoronary saphenous vein conduits, and carotid arteries. *Am J Cardiol.* 2005;95:1415-9.
529. Sprouse LR, Peeters P, Bosiers M. The capture of visible debris by distal cerebral protection filters during carotid artery stenting: Is it predictable? *J Vasc Surg.* 2005;41:950-5.
530. Bush RL, Lin PH, Bianco CC, et al. Reevaluation of temporary transvenous cardiac pacemaker usage during carotid angioplasty and stenting: a safe and valuable adjunct. *Vasc Endovascular Surg.* 2004;38:229-35.
531. Ohki T, Veith FJ. Critical analysis of distal protection devices. *Semin Vasc Surg.* 2003;16:317-25.
532. Bosiers M, Peeters P, Verbist J, et al. Belgian experience with FilterWire EX in the prevention of embolic events during carotid stenting. *J Endovasc Ther.* 2003;10:695-701.
533. Grube E, Colombo A, Hauptmann E, et al. Initial multicenter experience with a novel distal protection filter during carotid artery stent implantation. *Catheter Cardiovasc Interv.* 2003;58:139-46.
534. Sievert H, Rabe K. Role of distal protection during carotid stenting. *J Interv Cardiol.* 2002;15:499-504.
535. Al-Mubarak N, Colombo A, Gaines PA, et al. Multicenter evaluation of carotid artery stenting with a filter protection system. *J Am Coll Cardiol.* 2002;39:841-6.
536. Jaeger H, Mathias K, Drescher R, et al. Clinical results of cerebral protection with a filter device during stent implantation of the carotid artery. *Cardiovasc Intervent Radiol.* 2001;24:249-56.
537. Tubler T, Schluter M, Dirsch O, et al. Balloon-protected carotid artery stenting: relationship of periprocedural neurological complications with the size of particulate debris. *Circulation.* 2001;104:2791-6.
538. Parodi JC, La Mura R, Ferreira LM, et al. Initial evaluation of carotid angioplasty and stenting with three different cerebral protection devices. *J Vasc Surg.* 2000;32:1127-36.
539. Ohki T, Roubin GS, Veith FJ, et al. Efficacy of a filter device in the prevention of embolic events during carotid angioplasty and stenting: an ex vivo analysis. *J Vasc Surg.* 1999;30:1034-44.
540. Kwon BJ, Han MH, Kang HS, et al. Protection filter-related events in extracranial carotid artery stenting: a single-center experience. *J Endovasc Ther.* 2006;13:711-22.
541. Cardaioli P, Giordan M, Panfili M, et al. Complication with an embolic protection device during carotid angioplasty. *Catheter Cardiovasc Interv.* 2004;62:234-6.
542. van den Berg JC. The nature and management of complications in carotid artery stenting. *Acta Chir Belg.* 2004;104:60-4.
543. Griewing B, Brassel F, von Smekal U, et al. Carotid artery stenting in patients at surgical high risk: clinical and ultrasound findings. *Cerebrovasc Dis.* 2000;10:44-8.
544. Kitta Y, Obata JE, Takano H, et al. Echolucent carotid plaques predict in-stent restenosis after bare metal stenting in native coronary arteries. *Atherosclerosis.* 2008;197:177-82.

545. Geary GG. The vascular therapist. *Heart Lung Circ.* 2007;16:193–9.
546. Teng ZZ, Ji GY, Chu HJ, et al. Does PGA external stenting reduce compliance mismatch in venous grafts? *Biomed Eng Online.* 2007;6:12.
547. Bosiers M, de Donato G, Deloose K, et al. Are there predictive risk factors for complications after carotid artery stenting? *J Cardiovasc Surg (Torino).* 2007;48:125–30.
548. Parodi JC, Schonholz C, Parodi FE, et al. Initial 200 cases of carotid artery stenting using a reversal-of-flow cerebral protection device. *J Cardiovasc Surg (Torino).* 2007;48:117–24.
549. Peynircioglu B, Geyik S, Yavuz K, et al. Exclusion of atherosclerotic plaque from the circulation using stent-grafts: alternative to carotid stenting with a protection device? *Cardiovasc Intervent Radiol.* 2007;30:854–60.
550. Younis GA, Gupta K, Mortazavi A, et al. Predictors of carotid stent restenosis. *Catheter Cardiovasc Interv.* 2007;69:673–82.
551. de Souza JM, Espinosa G, Santos MM, et al. Bilateral occlusion associated to steal phenomenon of internal carotid and left subclavian arteries: treatment by angioplasty and stenting. *Surg Neurol.* 2007;67:298–302.
552. Chahwan S, Miller MT, Pigott JP, et al. Carotid artery velocity characteristics after carotid artery angioplasty and stenting. *J Vasc Surg.* 2007;45:523–6.
553. de Borst GJ, Ackerstaff RG, De Vries JP, et al. Carotid angioplasty and stenting for postendarterectomy stenosis: long-term follow-up. *J Vasc Surg.* 2007;45:118–23.
554. Ali ZA, Alp NJ, Lupton H, et al. Increased in-stent stenosis in ApoE knockout mice: insights from a novel mouse model of balloon angioplasty and stenting. *Arterioscler Thromb Vasc Biol.* 2007;27:833–40.
555. Park B, Aiello F, Dahn M, et al. Follow-up results of carotid angioplasty with stenting as assessed by duplex ultrasound surveillance. *Am J Surg.* 2006;192:583–8.
556. Gupta R, Al-Ali F, Thomas AJ, et al. Safety, feasibility, and short-term follow-up of drug-eluting stent placement in the intracranial and extracranial circulation. *Stroke.* 2006;37:2562–6.
557. Hauth EA, Drescher R, Jansen C, et al. Complications and follow-up after unprotected carotid artery stenting. *Cardiovasc Intervent Radiol.* 2006;29:511–8.
558. Cao P, De Rango P, Verzini F, et al. Outcome of carotid stenting versus endarterectomy: a case-control study. *Stroke.* 2006;37:1221–6.
559. Lal BK, Hobson RW. Management of carotid restenosis. *J Cardiovasc Surg (Torino).* 2006;47:153–60.
560. Halabi M, Gruberg L, Pitchersky S, et al. Carotid artery stenting in surgical high-risk patients. *Catheter Cardiovasc Interv.* 2006;67:513–8.
561. Eskandari MK, Longo GM, Matsumura JS, et al. Carotid stenting done exclusively by vascular surgeons: first 175 cases. *Ann Surg.* 2005;242:431–6.
562. Morrish W, Grahovac S, Douen A, et al. Intracranial hemorrhage after stenting and angioplasty of extracranial carotid stenosis. *AJNR Am J Neuroradiol.* 2000;21:1911–6.
563. Ho DS, Wang Y, Chui M, et al. Epileptic seizures attributed to cerebral hyperperfusion after percutaneous transluminal angioplasty and stenting of the internal carotid artery. *Cerebrovasc Dis.* 2000;10:374–9.
564. Buhk JH, Cepek L, Knauth M. Hyperacute intracerebral hemorrhage complicating carotid stenting should be distinguished from hyperperfusion syndrome. *AJNR Am J Neuroradiol.* 2006;27:1508–13.
565. Henry M, Gopalakrishnan L, Rajagopal S, et al. Bilateral carotid angioplasty and stenting. *Catheter Cardiovasc Interv.* 2005;64:275–82.
566. Nicosia A, Leotta E, Moshiri S, et al. Carotid artery stenting in the presence of contralateral carotid occlusion: mind the hyperperfusion syndrome! *Ital Heart J.* 2004;5:152–6.
567. Chen MS, Bhatt DL, Mukherjee D, et al. Feasibility of simultaneous bilateral carotid artery stenting. *Catheter Cardiovasc Interv.* 2004;61:437–42.
568. Hartmann M, Weber R, Zoubaa S, et al. Fatal subarachnoid hemorrhage after carotid stenting. *J Neuroradiol.* 2004;31:63–6.
569. Chuang YM, Wu HM. Early recognition of cerebral hyperperfusion syndrome after carotid stenting—a case report. *Kaohsiung J Med Sci.* 2001;17:489–94.
570. Capoccia L, Speziale F, Gazzetti M, et al. Comparative study on carotid revascularization (endarterectomy vs stenting) using markers of cellular brain injury, neuropsychometric tests, and diffusion-weighted magnetic resonance imaging. *J Vasc Surg.* 2010;51:584–91.
571. Tedesco MM, Lee JT, Dalman RL, et al. Postprocedural microembolic events following carotid surgery and carotid angioplasty and stenting. *J Vasc Surg.* 2007;46:244–50.
572. Eskandari MK, Najjar SF, Matsumura JS, et al. Technical limitations of carotid filter embolic protection devices. *Ann Vasc Surg.* 2007;21:403–7.
573. Valibhoj AR, Mwipatayi BP, Sieunarine K. Fracture of a carotid stent: an unexpected complication. *J Vasc Surg.* 2007;45:603–6.
574. Yallampalli S, Zhou W, Lin PH, et al. Delayed deformation of self-expanding stents after carotid artery stenting for postendarterectomy restenoses. *J Vasc Surg.* 2006;44:412–5.
575. Setacci C, de Donato G, Setacci F, et al. In-stent restenosis after carotid angioplasty and stenting: a challenge for the vascular surgeon. *Eur J Vasc Endovasc Surg.* 2005;29:601–7.
576. Schillinger M, Exner M, Sabeti S, et al. Excessive carotid in-stent neointimal formation predicts late cardiovascular events. *J Endovasc Ther.* 2004;11:229–9.
577. Rapp JH, Wakil L, Sawhney R, et al. Subclinical embolization after carotid artery stenting: new lesions on diffusion-weighted magnetic resonance imaging occur postprocedure. *J Vasc Surg.* 2007;45:867–72.
578. Hart JP, Peeters P, Verbist J, et al. Do device characteristics impact outcome in carotid artery stenting? *J Vasc Surg.* 2006;44:725–30.
579. Powell RJ, Alessi C, Nolan B, et al. Comparison of embolization protection device-specific technical difficulties during carotid artery stenting. *J Vasc Surg.* 2006;44:56–61.
580. Safian RD, Bresnahan JF, Jaff MR, et al. Protected carotid stenting in high-risk patients with severe carotid artery stenosis. *J Am Coll Cardiol.* 2006;47:2384–9.
581. Hamood H, Makhoul N, Hassan A, et al. Embolic protection: limitations of current technology and novel concepts. *Int J Cardiovasc Intervent.* 2005;7:176–82.
582. Gruberg L, Beyar R. Cerebral embolic protection devices and percutaneous carotid artery stenting. *Int J Cardiovasc Intervent.* 2005;7:117–21.
583. Yadav JS. Embolic protection devices: methods, techniques, and data. *Tech Vasc Interv Radiol.* 2004;7:190–3.
584. Cil BE, Turkbey B, Canyigit M, et al. An unusual complication of carotid stenting: spontaneous rectus sheath hematoma and its endovascular management. *Diagn Interv Radiol.* 2007;13:46–8.
585. Pipinos II, Johannig JM, Pham CN, et al. Transcervical approach with protective flow reversal for carotid angioplasty and stenting. *J Endovasc Ther.* 2005;12:446–53.
586. Zorger N, Finkenzeller T, Lenhart M, et al. Safety and efficacy of the Perclose suture-mediated closure device following carotid artery stenting under clopidogrel platelet blockade. *Eur Radiol.* 2004;14:719–22.
587. Gupta A, Bhatia A, Ahuja A, et al. Carotid stenting in patients older than 65 years with inoperable carotid artery disease: a single-center experience. *Catheter Cardiovasc Interv.* 2000;50:1–8.
588. Chamberlin JR, Lardi AB, McKeever LS, et al. Use of vascular sealing devices (VasoSeal and Perclose) versus assisted manual compression (Femostop) in transcatheter coronary interventions requiring abciximab (ReoPro). *Catheter Cardiovasc Interv.* 1999;47:143–7.
589. Eggebrecht H, Haude M, Woertgen U, et al. Systematic use of a collagen-based vascular closure device immediately after cardiac catheterization procedures in 1,317 consecutive patients. *Catheter Cardiovasc Interv.* 2002;57:486–95.
590. Nikolsky E, Mehran R, Halkin A, et al. Vascular complications associated with arteriotomy closure devices in patients undergoing percutaneous coronary procedures: a meta-analysis. *J Am Coll Cardiol.* 2004;44:1200–9.
591. Rogers JH, Caruthers SD, Williams T, et al. Clinical utility of rapid prescreening magnetic resonance angiography of peripheral vascular disease prior to cardiac catheterization. *J Cardiovasc Magn Reson.* 2004;6:25–31.
592. Schneider LM, Roubin GS. Minimal contrast use in carotid stenting: avoiding contrast pitfalls. *J Invasive Cardiol.* 2007;19:37–8.
593. Coolong A, Baim DS, Kuntz RE, et al. Saphenous vein graft stenting and major adverse cardiac events: a predictive model derived from a pooled analysis of 3958 patients. *Circulation.* 2008;117:790–7.

594. Naidu SS, Turco MA, Mauri L, et al. Contemporary incidence and predictors of major adverse cardiac events after saphenous vein graft intervention with embolic protection (an AMETHYST trial substudy). *Am J Cardiol.* 2010;105:1060-4.
595. Wholey MH, Al-Mubarek N, Wholey MH. Updated review of the global carotid artery stent registry. *Catheter Cardiovasc Interv.* 2003;60:259-66.
596. Theiss W, Hermanek P, Mathias K, et al. Pro-CAS: a prospective registry of carotid angioplasty and stenting. *Stroke.* 2004;35:2134-9.
597. Kastrup A, Groschel K, Krapf H, et al. Early outcome of carotid angioplasty and stenting with and without cerebral protection devices: a systematic review of the literature. *Stroke.* 2003;34:813-9.
598. Barbato JE, Dillavou E, Horowitz MB, et al. A randomized trial of carotid artery stenting with and without cerebral protection. *J Vasc Surg.* 2008;47:760-5.
599. Nishanian G, Kopchok GE, Donayre CE, et al. The impact of intravascular ultrasound (IVUS) on endovascular interventions. *Semin Vasc Surg.* 1999;12:285-99.
600. Reid DB, Douglas M, Diethrich EB. The clinical value of three-dimensional intravascular ultrasound imaging. *J Endovasc Surg.* 1995;2:356-64.
601. Wehman JC, Holmes DR Jr., Ecker RD, et al. Intravascular ultrasound identification of intraluminal embolic plaque material during carotid angioplasty with stenting. *Catheter Cardiovasc Interv.* 2006;68:853-7.
602. Irshad K, Millar S, Velu R, et al. Virtual histology intravascular ultrasound in carotid interventions. *J Endovasc Ther.* 2007;14:198-207.
603. Manninen HI, Rasanen HT, Vanninen RL, et al. Stent placement versus percutaneous transluminal angioplasty of human carotid arteries in cadavers in situ: distal embolization and findings at intravascular US, MR imaging and histopathologic analysis. *Radiology.* 1999;212:483-92.
604. Clark DJ, Lessio S, O'Donoghue M, et al. Safety and utility of intravascular ultrasound-guided carotid artery stenting. *Catheter Cardiovasc Interv.* 2004;63:355-62.
605. Clark AL. Impairment of ventilatory efficiency in heart failure. *Circulation.* 2001;103:E97.
606. Garg N, Karagiorgos N, Pisisimis GT, et al. Cerebral protection devices reduce periprocedural strokes during carotid angioplasty and stenting: a systematic review of the current literature. *J Endovasc Ther.* 2009;16:412-27.
607. Katzen BT, Ardid MI, MacLean AA, et al. Bivalirudin as an anticoagulation agent: safety and efficacy in peripheral interventions. *J Vasc Interv Radiol.* 2005;16:1183-7.
608. Schneider LM, Polena S, Roubin G, et al. Carotid stenting and bivalirudin with and without vascular closure: 3-year analysis of procedural outcomes. *Catheter Cardiovasc Interv.* 2010;75:420-6.
609. Heyer KS, Eskandari MK. Carotid stenting: risk factors for periprocedural stroke. *Expert Rev Neurother.* 2008;8:469-77.
610. CARESS Steering Committee. Carotid revascularization using endarterectomy or stenting systems (CARESS): phase I clinical trial. *J Endovasc Ther.* 2003;10:1021-30.
611. CARESS Steering Committee. Carotid Revascularization Using Endarterectomy or Stenting Systems (CaRESS) phase I clinical trial: 1-year results. *J Vasc Surg.* 2005;42:213-9.
612. Qureshi AI, Kirmani JF, Divani AA, et al. Carotid angioplasty with or without stent placement versus carotid endarterectomy for treatment of carotid stenosis: a meta-analysis. *Neurosurgery.* 2005;56:1171-9.
613. Brahmanandam S, Ding EL, Conte MS, et al. Clinical results of carotid artery stenting compared with carotid endarterectomy. *J Vasc Surg.* 2008;47:343-9.
614. Luebke T, Aleksic M, Brunkwall J. Meta-analysis of randomized trials comparing carotid endarterectomy and endovascular treatment. *Eur J Vasc Endovasc Surg.* 2007;34:470-9.
615. Murad MH, Flynn DN, Elamin MB, et al. Endarterectomy vs stenting for carotid artery stenosis: a systematic review and meta-analysis. *J Vasc Surg.* 2008;48:487-93.
616. Meier P, Knapp G, Tamhane U, et al. Short term and intermediate term comparison of endarterectomy versus stenting for carotid artery stenosis: systematic review and meta-analysis of randomised controlled clinical trials. *BMJ.* 2010;340:e467.
617. Roffi M, Sievert H, Gray WA, et al. Carotid artery stenting versus surgery: adequate comparisons? *Lancet Neurol.* 2010;9:339-41.
618. Forsting M. Shortcomings and promises of recent carotid-stenting trials. *Lancet Neurol.* 2007;6:101-2.
619. Qureshi AI. Carotid angioplasty and stent placement after EVA-3S trial. *Stroke.* 2007;38:1993-6.
620. Hobson RW. CREST (Carotid Revascularization Endarterectomy versus Stent Trial): background, design, and current status. *Semin Vasc Surg.* 2000;13:139-43.
621. Hobson RW, Howard VJ, Roubin GS, et al. Carotid artery stenting is associated with increased complications in octogenarians: 30-day stroke and death rates in the CREST lead-in phase. *J Vasc Surg.* 2004;40:1106-11.
622. Roubin GS, Clark WM, Chakhtoura EY, et al. Low complication rates for carotid artery stenting in the credentialing phase of the carotid revascularization endarterectomy versus stenting trial. *Stroke.* 2006;37:620. Abstract.
623. Davis SM, Donnan GA. Carotid-artery stenting in stroke prevention. *N Engl J Med.* 2010;363:80-2.
624. Bond R, Rerkasem K, Naylor R, et al. Patches of different types for carotid patch angioplasty. *Cochrane Database Syst Rev* 2004; CD000071.
625. Matsagas MI, Bali C, Arnaoutoglou E, et al. Carotid endarterectomy with bovine pericardium patch angioplasty: mid-term results. *Ann Vasc Surg.* 2006;20:614-9.
626. Mannheim D, Weller B, Vahadim E, et al. Carotid endarterectomy with a polyurethane patch versus primary closure: a prospective randomized study. *J Vasc Surg.* 2005;41:403-7.
627. Krishnan S, Clowes AW. Dacron patch infection after carotid endarterectomy: case report and review of the literature. *Ann Vasc Surg.* 2006;20:672-7.
628. Moore WS, Kempczinski RF, Nelson JJ, et al. Recurrent carotid stenosis: results of the asymptomatic carotid atherosclerosis study. *Stroke.* 1998;29:2018-25.
629. Cunningham EJ, Bond R, Mehta Z, et al. Long-term durability of carotid endarterectomy for symptomatic stenosis and risk factors for late postoperative stroke. *Stroke.* 2002;33:2658-63.
630. Cikrit DF, Larson DM, Sawchuk AP, et al. Discretionary carotid patch angioplasty leads to good results. *Am J Surg.* 2006;192:e46-50.
631. Rockman CB, Halm EA, Wang JJ, et al. Primary closure of the carotid artery is associated with poorer outcomes during carotid endarterectomy. *J Vasc Surg.* 2005;42:870-7.
632. Hansen F, Lindblad B, Persson NH, et al. Can recurrent stenosis after carotid endarterectomy be prevented by low-dose acetylsalicylic acid? A double-blind, randomised and placebo-controlled study. *Eur J Vasc Surg.* 1993;7:380-5.
633. Petrik PV, Gelabert HA, Moore WS, et al. Cigarette smoking accelerates carotid artery intimal hyperplasia in a dose-dependent manner. *Stroke.* 1995;26:1409-14.
634. Salvian A, Baker JD, Machleder HI, et al. Cause and noninvasive detection of restenosis after carotid endarterectomy. *Am J Surg.* 1983;146:29-34.
635. AbuRahma AF, Robinson PA, Saiedy S, et al. Prospective randomized trial of carotid endarterectomy with primary closure and patch angioplasty with saphenous vein, jugular vein, and polytetrafluoroethylene: long-term follow-up. *J Vasc Surg.* 1998;27:222-32.
636. Lord RS, Raj TB, Sary DL, et al. Comparison of saphenous vein patch, polytetrafluoroethylene patch, and direct arteriotomy closure after carotid endarterectomy: part I: perioperative results. *J Vasc Surg.* 1989;9:521-9.
637. Curley S, Edwards WS, Jacob TP. Recurrent carotid stenosis after autologous tissue patching. *J Vasc Surg.* 1987;6:350-4.
638. Awad IA, Little JR. Patch angioplasty in carotid endarterectomy: advantages, concerns, and controversies. *Stroke.* 1989;20:417-22.
639. Bernstein EF, Torem S, Dilley RB. Does carotid restenosis predict an increased risk of late symptoms, stroke, or death? *Ann Surg.* 1990; 212:629-36.
640. Nicholls SC, Phillips DJ, Bergelin RO, et al. Carotid endarterectomy. Relationship of outcome to early restenosis. *J Vasc Surg.* 1985;2:375-81.
641. O'Donnell TF Jr., Callow AD, Scott G, et al. Ultrasound characteristics of recurrent carotid disease: hypothesis explaining the low incidence of symptomatic recurrence. *J Vasc Surg.* 1985;2:26-41.

642. Zierler RE, Bandyk DF, Thiele BL, et al. Carotid artery stenosis following endarterectomy. *Arch Surg.* 1982;117:1408–15.
643. Stoney RJ, String ST. Recurrent carotid stenosis. *Surgery.* 1976;80:705–10.
644. Hertzner NR, Martinez BD, Benjamin SP, et al. Recurrent stenosis after carotid endarterectomy. *Surg Gynecol Obstet.* 1979;149:360–4.
645. DeGroot RD, Lynch TG, Jamil Z, et al. Carotid restenosis: long-term noninvasive follow-up after carotid endarterectomy. *Stroke.* 1987;18:1031–6.
646. Shawl FA. Carotid artery stenting: acute and long-term results. *Curr Opin Cardiol.* 2002;17:671–6.
647. Christiaans MH, Ernst JM, Suttorp MJ, et al. Restenosis after carotid angioplasty and stenting: a follow-up study with duplex ultrasonography. *Eur J Vasc Endovasc Surg.* 2003;26:141–4.
648. de Borst GJ, Ackerstaff RG, Mauser HW, et al. Operative management of carotid artery in-stent restenosis: first experiences and duplex follow-up. *Eur J Vasc Endovasc Surg.* 2003;26:137–40.
649. Chakhtoura EY, Hobson RW, Goldstein J, et al. In-stent restenosis after carotid angioplasty-stenting: incidence and management. *J Vasc Surg.* 2001;33:220–5.
650. Wehman JC, Hanel RA, Guidot CA, et al. Atherosclerotic occlusive extracranial vertebral artery disease: indications for intervention, endovascular techniques, short-term and long-term results. *J Interv Cardiol.* 2004;17:219–32.
651. Wityk RJ, Chang HM, Rosengart A, et al. Proximal extracranial vertebral artery disease in the New England Medical Center Posterior Circulation Registry. *Arch Neurol.* 1998;55:470–8.
652. Chimowitz MI, Lynn MJ, Howlett-Smith H, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *N Engl J Med.* 2005;352:1305–16.
653. Hornig CR, Lammers C, Buttner T, et al. Long-term prognosis of infratentorial transient ischemic attacks and minor strokes. *Stroke.* 1992;23:199–204.
654. Glass TA, Hennessey PM, Pazdera L, et al. Outcome at 30 days in the New England Medical Center Posterior Circulation Registry. *Arch Neurol.* 2002;59:369–76.
655. Feldmann E, Wilterdink JL, Kosinski A, et al. The Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis (SONIA) trial. *Neurology.* 2007;68:2099–106.
656. Kasner SE, Lynn MJ, Chimowitz MI, et al. Warfarin vs aspirin for symptomatic intracranial stenosis: subgroup analyses from WASID. *Neurology.* 2006;67:1275–8.
657. Kasner SE, Chimowitz MI, Lynn MJ, et al. Predictors of ischemic stroke in the territory of a symptomatic intracranial arterial stenosis. *Circulation.* 2006;113:555–63.
658. Marquardt L, Kuker W, Chandratheva A, et al. Incidence and prognosis of  $\geq 50\%$  symptomatic vertebral or basilar artery stenosis: prospective population-based study. *Brain.* 2009;132:982–8.
659. Blacker DJ, Flemming KD, Wijedicks EF. Risk of ischemic stroke in patients with symptomatic vertebral/basilar stenosis undergoing surgical procedures. *Stroke.* 2003;34:2659–63.
660. Ginsberg HN, Kris-Etherton P, Dennis B, et al. Effects of reducing dietary saturated fatty acids on plasma lipids and lipoproteins in healthy subjects: the DELTA Study, protocol 1. *Arterioscler Thromb Vasc Biol.* 1998;18:441–9.
661. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy—I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ.* 1994;308:81–106.
662. Eckert B. Acute vertebral/basilar occlusion: current treatment strategies. *Neurol Res.* 2005;27 Suppl 1:S36–41.
663. Cloud GC, Markus HS. Vertebral artery stenosis. *Curr Treat Options Cardiovasc Med.* 2004;6:121–7.
664. Savitz SI, Caplan LR. Vertebral/basilar disease. *N Engl J Med.* 2005;352:2618–26.
665. Caplan LR. Atherosclerotic vertebral artery disease in the neck. *Curr Treat Options Cardiovasc Med.* 2003;5:251–6.
666. Canyigit M, Arat A, Cil BE, et al. Management of vertebral stenosis complicated by presence of acute thrombus. *Cardiovasc Intervent Radiol.* 2007;30:317–20.
667. Benesch CG, Chimowitz MI. Best treatment for intracranial arterial stenosis? 50 years of uncertainty. The WASID Investigators. *Neurology.* 2000;55:465–6.
668. Grotta JC, Norris JW, Kamm B. Prevention of stroke with ticlopidine: who benefits most? *Neurology.* 1992;42:111–5.
669. Sivenius J, Riekkinen PJ, Smets P, et al. The European Stroke Prevention Study (ESPS): results by arterial distribution. *Ann Neurol.* 1991;29:596–600.
670. Berguer R, Flynn LM, Kline RA, et al. Surgical reconstruction of the extracranial vertebral artery: management and outcome. *J Vasc Surg.* 2000;31:9–18.
671. Berguer R. Suboccipital approach to the distal vertebral artery. *J Vasc Surg.* 1999;30:344–9.
672. Berguer R, Morasch MD, Kline RA. A review of 100 consecutive reconstructions of the distal vertebral artery for embolic and hemodynamic disease. *J Vasc Surg.* 1998;27:852–9.
673. Spetzler RF, Hadley MN, Martin NA, et al. Vertebral/basilar insufficiency: part 1: microsurgical treatment of extracranial vertebral/basilar disease. *J Neurosurg.* 1987;66:648–61.
674. Hopkins LN, Martin NA, Hadley MN, et al. Vertebral/basilar insufficiency: part 2: Microsurgical treatment of intracranial vertebral/basilar disease. *J Neurosurg.* 1987;66:662–74.
675. Hopkins LN, Budny JL. Complications of intracranial bypass for vertebral/basilar insufficiency. *J Neurosurg.* 1989;70:207–11.
676. Hopkins LN, Budny JL, Castellani D. Extracranial-intracranial arterial bypass and basilar artery ligation in the treatment of giant basilar artery aneurysms. *Neurosurgery.* 1983;13:189–94.
677. Hopkins LN, Budny JL, Spetzler RF. Revascularization of the rostral brain stem. *Neurosurgery.* 1982;10:364–69.
678. Berguer R, Bauer RB. Vertebral artery reconstruction: a successful technique in selected patients. *Ann Surg.* 1981;193:441–7.
679. Berguer R, Bauer RB. *Vertebral Arterial Occlusive Disease: Medical and Surgical Management.* New York, NY: Raven Press, 1984.
680. Roon AJ, Ehrenfeld WK, Cooke PB, et al. Vertebral artery reconstruction. *Am J Surg.* 1979;138:29–36.
681. Malone JM, Moore WS, Hamilton R, et al. Combined carotid-vertebral vascular disease: a new surgical approach. *Arch Surg.* 1980;115:783–5.
682. Caplan L, Tettenborn B. Embolism in the posterior circulation. In: Berguer, R. and Caplan, L, editors. *Vertebral Arterial Disease.* St. Louis, Mo: Quality Medical; 1992.
683. Thevenet A, Ruotolo C. Surgical repair of vertebral artery stenoses. *J Cardiovasc Surg (Torino).* 1984;25:101–10.
684. Edwards WH, Mulherin JL Jr. The surgical reconstruction of the proximal subclavian and vertebral artery. *J Vasc Surg.* 1985;2:634–42.
685. Diaz FG, Ausman JI, de los Reyes RA, et al. Surgical reconstruction of the proximal vertebral artery. *J Neurosurg.* 1984;61:874–81.
686. Imparato AM, Riles TS, Kim GE. Cervical vertebral angioplasty for brain stem ischemia. *Surgery.* 1981;90:842–52.
687. Eberhardt O, Naegele T, Raygrotzki S, et al. Stenting of vertebral/basilar arteries in symptomatic atherosclerotic disease and acute occlusion: case series and review of the literature. *J Vasc Surg.* 2006;43:1145–54.
688. Coward LJ, McCabe DJ, Ederle J, et al. Long-term outcome after angioplasty and stenting for symptomatic vertebral artery stenosis compared with medical treatment in the Carotid And Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomized trial. *Stroke.* 2007;38:1526–30.
689. McCabe DJ, Pereira AC, Clifton A, et al. Restenosis after carotid angioplasty, stenting, or endarterectomy in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS). *Stroke.* 2005;36:281–6.
690. Berguer R, Morasch MD, Kline RA, et al. Cervical reconstruction of the supra-aortic trunks: a 16-year experience. *J Vasc Surg.* 1999;29:239–46.
691. Moore WS, Malone JM, Goldstone J. Extrathoracic repair of branch occlusions of the aortic arch. *Am J Surg.* 1976;132:249–57.
692. Modarai B, Ali T, Dourado R, et al. Comparison of extra-anatomic bypass grafting with angioplasty for atherosclerotic disease of the supra-aortic trunks. *Br J Surg.* 2004;91:1453–7.
693. Law MM, Colburn MD, Moore WS, et al. Carotid-subclavian bypass for brachiocephalic occlusive disease. Choice of conduit and long-term follow-up. *Stroke.* 1995;26:1565–71.
694. De Vries JP, Jager LC, van den Berg JC, et al. Durability of percutaneous transluminal angioplasty for obstructive lesions of

- proximal subclavian artery: long-term results. *J Vasc Surg.* 2005;41:19-23.
695. AbuRahma AF, Bates MC, Stone PA, et al. Angioplasty and stenting versus carotid-subclavian bypass for the treatment of isolated subclavian artery disease. *J Endovasc Ther.* 2007;14:698-704.
696. Sullivan TM, Gray BH, Bacharach JM, et al. Angioplasty and primary stenting of the subclavian, innominate, and common carotid arteries in 83 patients. *J Vasc Surg.* 1998;28:1059-65.
697. Brountzos EN, Petersen B, Binkert C, et al. Primary stenting of subclavian and innominate artery occlusive disease: a single center's experience. *Cardiovasc Intervent Radiol.* 2004;27:616-23.
698. Hadjipetrou P, Cox S, Piemonte T, et al. Percutaneous revascularization of atherosclerotic obstruction of aortic arch vessels. *J Am Coll Cardiol.* 1999;33:1238-45.
699. Whitbread T, Cleveland TJ, Beard JD, et al. A combined approach to the treatment of proximal arterial occlusions of the upper limb with endovascular stents. *Eur J Vasc Endovasc Surg.* 1998;15:29-35.
700. Rodriguez-Lopez JA, Werner A, Martinez R, et al. Stenting for atherosclerotic occlusive disease of the subclavian artery. *Ann Vasc Surg.* 1999;13:254-60.
701. Van Noord BA, Lin AH, Cavendish JJ. Rates of symptom recurrence after endovascular therapy in subclavian artery stenosis and prevalence of subclavian artery stenosis prior to coronary artery bypass grafting. *Vasc Health Risk Manag.* 2007;3:759-62.
702. Peterson BG, Resnick SA, Morasch MD, et al. Aortic arch vessel stenting: a single-center experience using cerebral protection. *Arch Surg.* 2006;141:560-63.
703. Filippo F, Francesco M, Francesco R, et al. Percutaneous angioplasty and stenting of left subclavian artery lesions for the treatment of patients with concomitant vertebral and coronary subclavian steal syndrome. *Cardiovasc Intervent Radiol.* 2006;29:348-53.
704. van Hattum ES, De Vries JP, Lalezari F, et al. Angioplasty with or without stent placement in the brachiocephalic artery: feasible and durable? A retrospective cohort study. *J Vasc Interv Radiol.* 2007;18:1088-93.
705. Berguer R, Morasch MD, Kline RA. Transthoracic repair of innominate and common carotid artery disease: immediate and long-term outcome for 100 consecutive surgical reconstructions. *J Vasc Surg.* 1998;27:34-41.
706. Ligush J Jr., Criado E, Keagy BA. Innominate artery occlusive disease: management with central reconstructive techniques. *Surgery.* 1997;121:556-62.
707. Naylor AR, Cuffe RL, Rothwell PM, et al. A systematic review of outcomes following staged and synchronous carotid endarterectomy and coronary artery bypass. *Eur J Vasc Endovasc Surg.* 2003;25:380-9.
708. Dubinsky RM, Lai SM. Mortality from combined carotid endarterectomy and coronary artery bypass surgery in the US. *Neurology.* 2007;68:195-7.
709. Moussa I, Rundek T, Mohr JP. Asymptomatic carotid artery stenosis: risk stratification and management. London, UK: Informa Healthcare Publishers, 2006.
710. Brener B, Hermans H, Eisenbud D, et al. The management of patients requiring coronary bypass and carotid endarterectomy. In: Moore, W. S., editors. *Surgery for Cerebrovascular Disease.* 2nd ed. Philadelphia, Pa: W.B. Saunders Company; 1996:278-9.
711. Ricotta JJ, Wall LP, Blackstone E. The influence of concurrent carotid endarterectomy on coronary bypass: a case-controlled study. *J Vasc Surg.* 2005;41:397-401.
712. Byrne J, Darling RC, III, Roddy SP, et al. Combined carotid endarterectomy and coronary artery bypass grafting in patients with asymptomatic high-grade stenoses: an analysis of 758 procedures. *J Vasc Surg.* 2006;44:67-72.
713. Kougiass P, Kappa JR, Sewell DH, et al. Simultaneous carotid endarterectomy and coronary artery bypass grafting: results in specific patient groups. *Ann Vasc Surg.* 2007;21:408-14.
714. Van der Heyden J, Suttorp MJ, Bal ET, et al. Staged carotid angioplasty and stenting followed by cardiac surgery in patients with severe asymptomatic carotid artery stenosis: early and long-term results. *Circulation.* 2007;116:2036-42.
715. Timaran CH, Rosero EB, Smith ST, et al. Trends and outcomes of concurrent carotid revascularization and coronary bypass. *J Vasc Surg.* 2008;48:355-60.
716. Fleisher LA, Beckman JA, Brown KA, et al. 2009 ACCF/AHA focused update on perioperative beta blockade incorporated into the ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery. *J Am Coll Cardiol.* 2009;54:e13-118.
717. Slovut DP, Olin JW. Fibromuscular dysplasia. *N Engl J Med.* 2004;350:1862-71.
718. Olin JW. Recognizing and managing fibromuscular dysplasia. *Cleve Clin J Med.* 2007;74:273-82.
719. Zhou W, Bush RL, Lin PL, et al. Fibromuscular dysplasia of the carotid artery. *J Am Coll Surg.* 2005;200:807.
720. Dayes LA, Gardiner N. The neurological implications of fibromuscular dysplasia. *Mt Sinai J Med.* 2005;72:418-20.
721. Stahlfeld KR, Means JR, Didomenico P. Carotid artery fibromuscular dysplasia. *Am J Surg.* 2007;193:71-2.
722. Ballotta E, Thiene G, Baracchini C, et al. Surgical vs medical treatment for isolated internal carotid artery elongation with coiling or kinking in symptomatic patients: a prospective randomized clinical study. *J Vasc Surg.* 2005;42:838-46.
723. Assadian A, Senekowitsch C, Assadian O, et al. Combined open and endovascular stent grafting of internal carotid artery fibromuscular dysplasia: long term results. *Eur J Vasc Endovasc Surg.* 2005;29:345-9.
724. Finsterer J, Strassegger J, Haymerle A, et al. Bilateral stenting of symptomatic and asymptomatic internal carotid artery stenosis due to fibromuscular dysplasia. *J Neurol Neurosurg Psychiatry.* 2000;69:683-6.
- 724a. Metso TM, Metso AJ, Helenius J, et al. Prognosis and safety of anticoagulation in intracranial artery dissections in adults. *Stroke.* 2007;38:1837-42.
- 724b. Engelter ST, Brandt T, Dettmer S, et al., for the Cervical Artery Dissection in Ischemic Stroke Patients (CADISP) Study Group. Antiplatelets versus anticoagulation in cervical artery dissection. *Stroke.* 2007;38:2605-11.
- 724c. Menon R, Kerry S, Norris JW, Markus HS. Treatment of cervical artery dissection: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry.* 2008;79:1122-7.
- 724d. Georgiadis D, Arnold M, von Buedingen HC, et al. Aspirin vs anticoagulation in carotid artery dissection: a study of 298 patients. *Neurology.* 2009;72:1810-5.
725. Dziewas R, Konrad C, Drager B, et al. Cervical artery dissection—clinical features, risk factors, therapy and outcome in 126 patients. *J Neurol.* 2003;250:1179-84.
726. Schievink WI. Spontaneous dissection of the carotid and vertebral arteries. *N Engl J Med.* 2001;344:898-906.
727. Kawchuk GN, Jhangri GS, Hurwitz EL, et al. The relation between the spatial distribution of vertebral artery compromise and exposure to cervical manipulation. *J Neurol.* 2008;255:371-7.
728. DiLuna ML, Bydon M, Gunel M, et al. Neurological picture: complications from cervical intra-arterial heroin injection. *J Neurol Neurosurg Psychiatry.* 2007;78:1198.
729. Zaidat OO, Frank J. Vertebral artery dissection with amphetamine abuse. *J Stroke Cerebrovasc Dis.* 2001;10:27-9.
730. Miley ML, Wellik KE, Wingerchuk DM, et al. Does cervical manipulative therapy cause vertebral artery dissection and stroke? *Neurologist.* 2008;14:66-73.
731. Cohen JE, Gomori JM, Umansky F. Endovascular management of symptomatic vertebral artery dissection achieved using stent angioplasty and emboli protection device. *Neurol Res.* 2003;25:418-22.
732. Shah Q, Messe SR. Cervicocranial arterial dissection. *Curr Treat Options Neurol.* 2007;9:55-62.
733. Turowski B, Hanggi D, Siebler M. Intracranial bilateral vertebral artery dissection during anticoagulation after cerebral venous and sinus thrombosis (CSVT). *Acta Neurochir (Wien.)* 2007;149:793-7.
734. Lyrer P, Engelter S. Antithrombotic drugs for carotid artery dissection. *Stroke.* 2004;35:613-4.
735. Beletsky V, Nadareishvili Z, Lynch J, et al. Cervical arterial dissection: time for a therapeutic trial? *Stroke.* 2003;34:2856-60.
736. Muller BT, Luther B, Hort W, et al. Surgical treatment of 50 carotid dissections: indications and results. *J Vasc Surg.* 2000;31:980-8.
737. Chiche L, Bahnini A, Koskas F, et al. Occlusive fibromuscular disease of arteries supplying the brain: results of surgical treatment. *Ann Vasc Surg.* 1997;11:496-504.

738. Edgell RC, Abou-Chebl A, Yadav JS. Endovascular management of spontaneous carotid artery dissection. *J Vasc Surg.* 2005;42:854–60.

739. Sbarigia E, Battocchio C, Panico MA, et al. Endovascular management of acute carotid artery dissection with a waxing and waning neurological deficit. *J Endovasc Ther.* 2003;10:45–8.

740. Malek AM, Higashida RT, Phatouros CC, et al. Endovascular management of extracranial carotid artery dissection achieved using stent angioplasty. *AJNR Am J Neuroradiol.* 2000;21:1280–92.

741. Yamashita K, Okamoto S, Kim C, et al. Emergent treatment of iatrogenic dissection of the internal carotid artery with the Palmaz-Schatz stent—case report. *Neurol Med Chir (Tokyo).* 1997;37:336–9.

742. Hong MK, Satler LF, Gallino R, et al. Intravascular stenting as a definitive treatment of spontaneous carotid artery dissection. *Am J Cardiol.* 1997;79:538.

743. Liu AY, Paulsen RD, Marcellus ML, et al. Long-term outcomes after carotid stent placement treatment of carotid artery dissection. *Neurosurgery.* 1999;45:1368–73.

744. Anzuini A, Briguori C, Roubin GS, et al. Emergency stenting to treat neurological complications occurring after carotid endarterectomy. *J Am Coll Cardiol.* 2001;37:2074–9.

745. Bejjani GK, Monsein LH, Laird JR, et al. Treatment of symptomatic cervical carotid dissections with endovascular stents. *Neurosurgery.* 1999;44:755–60.

746. DeOcampo J, Brillman J, Levy DI. Stenting: a new approach to carotid dissection. *J Neuroimaging.* 1997;7:187–90.

747. Albuquerque FC, Han PP, Spetzler RF, et al. Carotid dissection: technical factors affecting endovascular therapy. *Can J Neurol Sci.* 2002;29:54–60.

748. Kadkhodayan Y, Jeck DT, Moran CJ, et al. Angioplasty and stenting in carotid dissection with or without associated pseudoaneurysm. *AJNR Am J Neuroradiol.* 2005;26:2328–35.

**Key Words:** ACCF/AHA Practice Guidelines ■ carotid endarterectomy ■ carotid stenosis ■ carotid stenting ■ extracranial carotid artery ■ revascularization ■ stroke ■ vertebral artery disease.

**APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES—2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS GUIDELINE ON THE MANAGEMENT OF PATIENTS WITH EXTRACRANIAL CAROTID AND VERTEBRAL ARTERY DISEASE**

Committee Member	Employment	Consultant	Speaker	Ownership/ Partnership/ Principal	Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Thomas G. Brott, Co-Chair	Mayo Clinic—Director for Research	None	None	None	<ul style="list-style-type: none"> <li>• Abbott</li> <li>• NIH* (CREST-PI)</li> </ul>	None	None
Jonathan L. Halperin, Co-Chair	Mount Sinai Medical Center—Professor of Medicine	<ul style="list-style-type: none"> <li>• Astellas Pharma</li> <li>• Bayer HealthCare</li> <li>• Biotronik*</li> <li>• Boehringer Ingelheim</li> <li>• Daiichi Sankyo</li> <li>• U.S. Food and Drug Administration Cardiovascular and Renal Drugs Advisory Committee</li> <li>• GlaxoSmithKline</li> <li>• Johnson &amp; Johnson</li> <li>• Portola</li> <li>• Sanofi-aventis</li> </ul>	None	None	<ul style="list-style-type: none"> <li>• NIH (National Heart, Lung, and Blood Institute)</li> </ul>	None	None
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Peer Reviewer	Representation	Consultant	Speaker	Ownership/ Partnership/ Principal	Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
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Peer Reviewer	Representation	Consultant	Speaker	Ownership/ Partnership/ Principal	Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
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Peer Reviewer	Representation	Consultant	Speaker	Ownership/ Partnership/ Principal	Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
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\*Significant relationship.

ACCF indicates American College of Cardiology Foundation; AHA, American Heart Association; ASA, American Stroke Association; CREST, Carotid Revascularization Endarterectomy versus Stenting Trial; NIH, National Institutes of Health; and NINDS, National Institute of Neurological Disorders and Stroke.

### APPENDIX 3. ABBREVIATION LIST

CABG = coronary artery bypass graft	IVUS = intravascular ultrasound
CAD = coronary artery disease	LDL = low-density lipoprotein
CAS = carotid artery stenting	MI = myocardial infarction
CEA = carotid endarterectomy	MRA = magnetic resonance angiography
CT = computed tomography	MRI = magnetic resonance imaging
CTA = computed tomography angiography	NSAID = nonsteroidal anti-inflammatory drugs
ECVD = extracranial carotid and vertebral artery disease	PAD = peripheral arterial disease
EPD = embolic protection device	PET = positron emission tomography
FMD = fibromuscular dysplasia	TIA = transient ischemic attack
IMT = intima-media thickness	

**Management of Carotid Atherosclerosis**

**Medicare Evidence Development and Coverage Advisory  
Committee (MEDCAC)**

**Pre-Meeting Submission**

**Abbott Vascular**

**December 19, 2011**

## Table of Contents

<b>Overview</b> .....	2
<b>1 Disease and Treatment Options</b> .....	3
1.1 Carotid Artery Disease.....	3
1.2 Treatment Options .....	3
1.3 Current Medicare National Coverage Policy.....	3
1.4 Existing Facility Accreditation Programs and Registries .....	4
<b>2 Questions Posed to the MEDCAC Panel</b> .....	5
2.1 Q1 - Identification of Asymptomatic Patients at High Risk for Stroke.....	5
2.2 Q2 - Determination of High Risk for Adverse Events from CEA.....	7
2.3 Q3 - Evidence in the Symptomatic, Standard Surgical Risk Population.....	9
2.4 Q4 - Evidence in the Asymptomatic, Standard Surgical Risk Population.....	18
2.5 Q5- Evidence in the Asymptomatic, Non-High Risk for Stroke Population.....	24
2.6 Q6- Determination of Screening in Asymptomatic Population.....	25
2.7 Q7- Additional Research and Diagnostic Tools .....	26
<b>3 Appendices</b> .....	29
3.1 Summary: Carotid Artery Disease Treatments & FDA Approval of Carotid Stent Systems .....	29
3.2 Classification of Recommendations & Level of Evidence .....	31
3.3 Summary: Multi-Society Guidelines for Screening of Asymptomatic Patients	32
3.4 Supplemental Analyses: Age - Symptomatic Elderly Patients .....	33
3.5 Supplemental Analyses: Gender - Symptomatic Elderly Patients.....	35
3.6 Supplemental Analyses: Age - Asymptomatic Elderly Patients.....	36
3.7 Supplemental Analyses: Gender - Asymptomatic Elderly Patients.....	38
<b>4 References</b> .....	40

## Overview

### Carotid Artery Disease

- Carotid artery disease accounts for 15-20% of all ischemic strokes in the U.S.
- There are three primary treatment options: (1) medical management (best medical therapy or BMT), (2) carotid endarterectomy (CEA), and (3) carotid artery stenting (CAS). Medical management generally begins well before, and continues after interventions (CEA or CAS).

### Evidence on Treatment Alternatives

- Best Medical Therapy (BMT):
  - Multiple randomized controlled trials (RCTs) demonstrated that revascularization (CEA) results in better outcomes than BMT alone for both symptomatic and asymptomatic patients with carotid stenosis.
- Revascularization Strategies - Carotid Endarterectomy (CEA) Compared to Carotid Artery Stenting (CAS):
  - Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) was designed to determine whether the CAS event rate\* was as low as, or lower than the CEA event rate (within 2.6%).
  - CREST met its primary endpoints,† thus confirming that CAS and CEA provide clinically equivalent outcomes among both symptomatic and asymptomatic patients at standard surgical risk.
  - CREST involved largely U.S. physicians (92%) and a majority of participants (68%) were of Medicare age.
  - CREST addressed many of the limitations of previous randomized studies comparing CAS to CEA, including consistent use of embolic protection devices (EPDs), equivalent training/experience between the treatment modalities, rigorous methods to assess myocardial infarction (MI), and the inclusion of MI in the composite endpoint.

### Key Points to Consider Regarding the Questions Posed to MEDCAC

- CAS and CEA are comparable alternatives and should be available as treatment options based on individual patient needs, consistent with multi-society guidelines that recommend a personalized approach to treating carotid artery disease.
- Voting questions 3 and 4, as currently framed, do not permit the Panel to make the determination that CAS and CEA are clinically equivalent alternatives that are beneficial for the Medicare population.
- MEDCAC panel should reframe these questions so that the revascularization techniques may be assessed as “alternative treatment strategies,” rather than “favored treatment strategies.” The evidence does not support a finding that one approach is favored (superior) to the other.
- The Panel should have strong confidence that these revascularizations strategies are superior to BMT alone, and reasonable alternatives to one another.

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\* CREST composite endpoint events included: death, stroke or MI to 30 days, ipsilateral stroke to 4 years.

† As is discussed subsequently, CREST was designed to involve two distinct pre-specified analyses, later referred to as the NIH and FDA / PMA analyses. The primary endpoints were met for both analyses at the 0.05 level.



# 1 Disease and Treatment Options

## 1.1 Carotid Artery Disease

- **Carotid artery disease accounts for 15-20% of all ischemic strokes, and there is a need for additional treatment options for Medicare beneficiaries.**

There is an urgent need for effective stroke prevention strategies to address the national stroke burden that is concentrated in the Medicare population.<sup>1</sup> Stroke is the third most common cause of mortality, a leading cause of disability and results in costs in excess of \$62 billion per year.<sup>2, 3</sup>

Extra-cranial carotid artery disease represents the single most common cause of stroke – accounting for up to 15 to 20% of all ischemic strokes.<sup>4, 5, 6</sup> Research into the unique anatomy and physiology of the carotid bifurcation suggests that complex hemodynamics predispose this area, particularly the internal carotid artery, to atherosclerosis.<sup>7, 8, 9</sup>

For a comprehensive review of evidence related to carotid artery disease and appropriate treatment options, please refer to the 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/ SVM/SVS Guideline on the Management of Patients With Extra-Cranial Carotid and Vertebral Artery Disease, hereafter referred to as the multi-society guidelines (See e-file attached to submission).<sup>10</sup>

## 1.2 Treatment Options

- **Medical management (best medical therapy or BMT), carotid endarterectomy (CEA) and carotid artery stenting (CAS) are the three primary treatment options for carotid artery disease.**
- **The primary objective of treatment is the prevention of stroke and death.**
- **Most recent stroke prevention guidelines recommend evaluation of treatment options based on consideration of all vascular-related patient outcomes, including stroke, myocardial infarction (MI) and vascular death.**
- **Selection of an appropriate treatment option should be made individually, based on patient considerations.**

There are three primary treatment options for carotid artery disease: medical management (best medical therapy or BMT), carotid endarterectomy (CEA) and carotid artery stenting (CAS). Selection of appropriate treatment option(s) for carotid artery disease should involve consideration of the overall impact on patient morbidity and mortality.<sup>11, 12</sup> The primary objective of all treatment strategies is the prevention of stroke and death, and the updated 2011 AHA/ASA stroke prevention guidelines recommend evaluation of treatment options based on consideration of all vascular-related patient outcomes including stroke, myocardial infarction (MI) and vascular death.<sup>13</sup> Personalized decision-making for individual patients should also take into account the patient's co-morbidities, risk factors, carotid anatomy, stenosis severity and lesion characteristics. For additional details regarding these three treatment options and regulatory approvals for CAS-associated devices, please refer to **Appendix 3.1**.

## 1.3 Current Medicare National Coverage Policy

Medicare provides national coverage for CAS (NCD 20.7, Percutaneous Transluminal Angioplasty) in the following patient population:<sup>14</sup>

- High Surgical Risk, Symptomatic Patients with  $\geq 70\%$  stenosis

Coverage is available with enrollment in an FDA-Approved Post-Approval Study for the following populations:

- High Surgical Risk, Symptomatic Patients with 50-70% stenosis
- High Surgical Risk, Asymptomatic Patients with  $\geq 80\%$  stenosis

All facilities must meet CMS accreditation standards in order to receive coverage for carotid artery stenting.<sup>15</sup>

#### **1.4 Existing Facility Accreditation Programs and Registries**

Two national accreditation programs have been established that certify hospital facilities to ensure high quality of care and monitor real-world patient outcomes:

- Intersocietal Commission for the Accreditation of Carotid Stenting Facilities (ICACSF),<sup>16</sup> and
- Accreditation for Cardiovascular Excellence (ACE) programs.<sup>17</sup>

Both are rigorous programs sponsored and endorsed by all physician specialty societies involved in treating patients with carotid artery disease.<sup>‡</sup>

Two specialty societies (the American College of Cardiology and the Society of Vascular Surgery) administer registries that include carotid procedures [the Carotid Artery Revascularization and Endarterectomy (CARE) Registry<sup>18, 19</sup> and the Vascular Registry,<sup>20</sup> respectively]. These registries collect patient-level data and were designed to focus on clinical outcomes.

These existing accreditation programs and registries provide ready mechanisms for CMS to monitor facilities providing carotid interventions and associated patient outcomes.

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<sup>‡</sup> ICACSF is supported by the following physician specialty societies: American Academy of Neurology (AAN), American Association of Neurologic Surgeons (AANS) and Congress of Neurologic Surgeons (CNS) Cerebrovascular Section, American Society of Neuroradiology (ASN), American Association of Physicists in Medicine, Neurocritical Care Society, Society of Interventional Radiology (SIR), Society of NeuroInterventional Surgery (SNIS), Society of Vascular and Interventional Neurology (SVIN), Society for Vascular Medicine (SVM), Society for Vascular Surgery (SVS).

ACE is supported by the following physician specialty societies: American College of Cardiology (ACC), Society for Cardiovascular Angiography and Interventions (SCAI).

## 2 Questions Posed to the MEDCAC Panel

### 2.1 Q1 - Identification of Asymptomatic Patients at High Risk for Stroke

*Question 1. How confident are you that there is adequate evidence to determine if persons in the Medicare population who are asymptomatic for carotid atherosclerosis can be identified as being at high risk for stroke in either cerebral hemisphere?*

- **There is adequate evidence to determine if a patient with asymptomatic carotid atherosclerosis is at increased risk of stroke (suggested rating: 3 or 4).**
- **Class II evidence supports efforts to identify high-risk asymptomatic patients with hemodynamically significant stenoses. The 2011 multi-society guidelines recommend such an approach.**
- **Promising new diagnostic tests are being studied to further risk stratify asymptomatic patients with hemodynamically significant stenoses.**

CONSIDERATIONS REGARDING QUESTION 1:

There is evidence from randomized trials that asymptomatic patients with hemodynamically significant carotid stenosis, generally defined as  $\geq 70\%$  occlusion by ultrasound or  $\geq 60\%$  by angiography, are at elevated risk of stroke. Such patients benefit from therapeutic intervention.<sup>21</sup> Therefore, the goal of evaluating asymptomatic patients is, first, to determine if they have carotid atherosclerosis, and then to ascertain whether their stenosis corresponds to a substantially increased risk for stroke.<sup>22 23</sup>

Based on a detailed medical history, physical examination, auscultation of the cervical arteries for bruits and the results of non-invasive duplex ultrasound, physicians can reasonably determine if a patient at risk of carotid artery disease, and if stenosis of the carotid artery(ies) is hemodynamically significant. The multi-society guidelines recommend referral to ultrasound to evaluate asymptomatic patients with known or suspected carotid stenosis. For details regarding multi-society guidelines for referral for ultrasound, see **Appendix 3.3**. These guidelines also discuss situations where screening to identify asymptomatic patients at high risk for stroke would not be warranted. These populations are discussed in response to Question 5.

In addition to the most widely utilized diagnostic methods, research into new and evolving technologies such as 3-dimensional ultrasound (3-D US), transcranial doppler (TCD) and serum biomarkers is being assessed for a potential role in patient risk assessment.

***Discussion Question Related to Q1: If there is at least intermediate confidence (score  $\geq 2.5$  above), are there ethical concerns to conducting randomized controlled trials of CAS/CEA/BMT in the general asymptomatic population? Would such trials only be appropriate for those identified to be at high risk for stroke?***

- **When appropriately designed, we do not believe that there are ethical concerns associated with conducting RCTs of CAS/CEA/BMT in the general asymptomatic population.**

CONSIDERATIONS REGARDING DISCUSSION QUESTION:

While there already is Class IIa evidence from multiple randomized trials to support revascularization in patients with hemodynamically significant asymptomatic stenoses, we do not believe that there are ethical concerns about additional randomized controlled trials being performed. All three treatments have improved over time and additional studies may provide

useful data. While new imaging-based strategies to identify high risk patients appear to be promising, it is unclear what specific techniques are most predictive at this time. Accordingly, we believe it is important to give careful attention to appropriate trial design. We also suggest that it may be possible to “nest” investigation of one or more imaging strategies within an overall randomized trial of interventional treatment strategies.

Since a majority of strokes from carotid disease occur without warning in asymptomatic patients, there continues to be an important public health interest in preventing these potentially devastating strokes.

## 2.2 Q2 - Determination of High Risk for Adverse Events from CEA

**Question 2.** *How confident are you that there is adequate evidence to determine if persons in the Medicare population, who are considering carotid revascularization, can be identified as being at high risk for adverse events from CEA?*

- **There is adequate evidence from multiple studies that confirm some patients are at elevated risk of adverse events from CEA (suggested rating: 4 or 5).**
- **There remains some debate about whether criteria used in the past (e.g., age 80+) are applicable today.**

CONSIDERATIONS REGARDING QUESTION 2:

The basis for categorizing candidates for carotid revascularization into ‘high risk’ and ‘standard risk’ for CEA was introduced in the landmark trials, the VA Study,<sup>24</sup> NASCET<sup>25</sup> and ECST,<sup>26</sup> and has been further defined in multiple single-arm, high-risk studies, including ARCHeR,<sup>27</sup> SECuRITY,<sup>28</sup> BEACH,<sup>29 30</sup> CREATE<sup>31</sup>, CAPTURE,<sup>32</sup> CAPTURE2,<sup>33</sup> PROTECT,<sup>34</sup> and the SAPPHERE randomized trial.<sup>35</sup> These studies demonstrated the safety and effectiveness of CAS in the high-risk population, served as the basis for FDA approval of many CAS devices used today (**Appendix 3.1**) or provide post-approval data on the use of these devices in real-world settings.

While high-risk criteria differed somewhat between the original studies, the definition for high-risk has evolved from *exclusion* criteria in the landmark studies to *inclusion* criteria in high-risk registry studies. Because of the evolutionary nature of this high-risk determination, what was once considered a high-risk criterion may no longer be considered high-risk today. Nonetheless, major criteria have remained consistent.

The risk factors for surgical intervention have been updated in the current multi-society guidelines.<sup>36</sup> The definition of high-risk patients now includes those with advanced congestive heart failure (New York Heart Association class III or IV heart failure), recent cardiac surgery (previous 30 days), recent myocardial infarction (within 30 days), active angina pectoris, left ventricular ejection fraction  $\leq 30\%$ , severe chronic lung disease, severe renal insufficiency, and in some cases, advanced age (80+).<sup>37, 38, 39</sup>

A number of anatomical and related factors also increase the complexity, and, therefore the risk of adverse events from CEA.<sup>40</sup> Patient circumstances requiring a high cervical exposure, such as a high carotid bifurcation, a lesion that extends into the internal carotid or a lesion above the second cervical vertebra, increase the risk of cranial nerve injury. Similarly, lesions below the clavicle can be problematic. Finally, prior treatments or interventions (e.g., previous CEA, prior radiation therapy, radical neck surgery or tracheostomy) increase risk for patients undergoing CEA.

**Discussion Question Related to Q2:** *If there is at least intermediate confidence (score  $\geq 2.5$  above), how does one reliably (across medical and surgical specialties) identify these individuals?*

- **With CEA, like many procedures, risk assessment is rarely straight-forward. No simple test or other indicator is available to guide physicians and their patients regarding the potential risk of adverse events from CEA. The risk assessment must consider multiple factors, such as the nature of the patient’s carotid disease, medical judgment and experience, as well as sensitivity to unique patient considerations.**

#### CONSIDERATIONS REGARDING DISCUSSION QUESTION

The identification of patients at high-risk for CEA relies on a thorough history-taking, physical examination, ultrasound imaging, consideration of patient anatomy, and adequate communication between the many physicians responsible for managing a given patient's care (e.g., primary care physician, medical cardiologist, neurologist, interventional radiologist, interventional cardiologist, vascular surgeon, neurosurgeon). Given the multi-systemic nature of the atherosclerotic process, a multi-disciplinary team of physicians should be responsible for assessing a patient's risk status for CEA, in concert with the patient.

## 2.3 Q3 - Evidence in the Symptomatic, Standard Surgical Risk Population

**Question 3. For persons with symptomatic carotid atherosclerosis and carotid narrowing ( $\geq 50\%$  by angiography or  $\geq 70\%$  by ultrasound) who are not generally considered at high risk for adverse events from CEA:**

**a. How confident are you that there is adequate evidence to determine whether or not either CAS or CEA is the favored treatment strategy, as compared to BMT alone, to decrease stroke or death in the Medicare population?**

- There is adequate evidence from multiple RCTs demonstrating that revascularization with CEA results in better outcomes than BMT alone for symptomatic patients with carotid stenosis (suggested rating: 4 or 5).
- Continuing changes in BMT may impact the underlying stroke risk of symptomatic patients.

CONSIDERATIONS REGARDING QUESTION 3a:

Strong evidence (Class I, Level A) supports revascularization with CEA in symptomatic patients with carotid stenoses. This is based on multiple landmark randomized controlled trials, including the North American Symptomatic Carotid Endarterectomy Trial (NASCET),<sup>41</sup> the European Carotid Surgery Trial (ECST),<sup>42</sup> and the VA study.<sup>43</sup> These studies compared revascularization (CEA) to best medical therapy available at the time.

CEA vs. BMT among Symptomatic Patients - NASCET was designed to determine if symptomatic patients (having TIA or mild stroke) and 30% to 99% ipsilateral carotid stenosis would have fewer strokes after CEA and medical management than those given medical therapy (including aspirin) alone.<sup>44</sup> ECST was conducted at about the same time as NASCET, and similar to NASCET, patients were stratified into 3 categories that corresponded to mild (10% to 29%), moderate (30% to 69%), and severe (70% to 99%) carotid stenosis.<sup>45</sup> However, a different method of measurement was employed in ECST than by NASCET researchers. The VA Study was an earlier, smaller study that was stopped early when the results of these two larger studies were published.<sup>46</sup>

More recently, the Carotid Endarterectomy Trialists' Collaboration has pooled the data from NASCET, ECST and VA studies (6,092 patients, representing 35,000 patient-years of follow-up), applying uniform measurements and definitions. Pooled results yielded highly consistent findings with the individual studies, demonstrating a clear benefit in those patients with 50-69% stenosis, and those with 70% or greater stenosis without near-occlusion.<sup>47</sup> The pooled results reported an absolute risk-reduction for CEA over medical therapy at 5-years of 4.6% in those with 50-69% stenosis (n=1549, p=0.04), and an absolute risk-reduction of 16.0% in those with 70% stenosis or greater without near-occlusion (n=1095, p<0.001).

**b. If there is at least intermediate confidence (score  $\geq 2.5$  above), how confident are you that**

**i. CAS is the favored treatment strategy in this [Symptomatic, Standard Surgical Risk] population?**

- Results of CREST demonstrate that CAS and CEA provide clinically equivalent outcomes among symptomatic patients. As the two

therapies are comparable alternatives, neither should be viewed as the “favored treatment strategy.” Both CAS and CEA should be made available as treatment options for physicians based on their patients’ individual clinical needs.

- **Multiple organizations including the NIH, the FDA and multi-society guideline authors have advocated a personalized approach for treatment of carotid artery disease. Individual patient circumstances should dictate which revascularization approach is the “favored treatment strategy.”**
- **This question as currently framed, does not allow the Panel to make the determination that these two treatments are clinically equivalent alternatives that are beneficial for the Medicare population.**
- **We believe that the MEDCAC panel should reframe this question in light of the available evidence so that revascularization techniques may be assessed as “alternative treatment strategies,” rather than “favored treatment strategies.” The evidence does not support a finding that one approach is favored (superior) to the other.**
- **The Panel should have strong confidence (suggested rating: 4 or 5) that these revascularizations strategies are superior to BMT alone, and are reasonable alternatives to one another.**

#### CONSIDERATIONS REGARDING QUESTION 3bi:

For the CREST population most comparable to the landmark NASCET and ACAS study populations (in which patients  $\geq 80$  years of age were excluded), the 30-day death and any stroke event rate for CAS was 5.6% for symptomatics.<sup>48</sup> Therefore, CAS met the target of  $< 6\%$  for symptomatic patients recommended in the current AHA/ASA guidelines for primary and secondary stroke prevention.<sup>49, 50</sup>

Recently published safety results of from the CREST NIH analysis reported no significant differences between CAS and CEA for symptomatic subjects for the primary CREST endpoint [death, stroke or MI (DSMI)].<sup>51</sup>

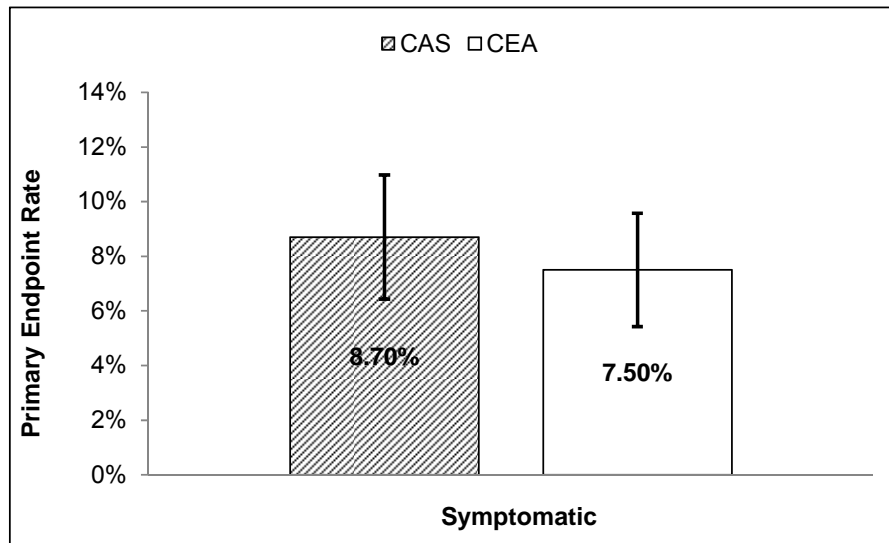
In addition, the CREST protocol and statistical plan included a pre-specified FDA regulatory analysis of the one-year endpoint stratified by symptomatic status.<sup>§</sup> For the symptomatic subgroup, CREST met its endpoint, demonstrating that CAS was statistically non-inferior to CEA in this subgroup (**Figure 2.1**).

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<sup>§</sup> A symptomatic subject was defined by the protocol as having an eligible carotid stenosis with prior symptoms of a transient ischemic attack (TIA), amaurosis fugax, or a minor or non-disabling stroke in the hemisphere supplied by the target vessel within 180 days of the randomization date. An asymptomatic subject must have been free from symptoms in the hemisphere supplied by the target vessel within 180 days of the randomization date.



**Figure 2.1: Primary Composite Endpoint for Symptomatic Subjects (FDA Analysis)**



*Source: Presented to FDA Circulatory System Devices Advisory Panel on January 26, 2011; figure modified to remove asymptomatic population (in response to CMS question).*

**ii. CEA is the favored treatment strategy in this [Symptomatic, Standard Surgical Risk] population?**

- **NASCET demonstrated the superiority of CEA to BMT.**
- **ESCT independently confirmed the superiority of CEA to BMT.**
- **Results of CREST demonstrate that CAS and CEA provide clinically equivalent outcomes. Because the two therapies are comparable alternatives, neither should be viewed as the “favored treatment strategy.” Both CAS and CEA should be made available as treatment options for physicians based on their individual patient needs.**
- **Multiple organizations including the NIH, the FDA, and multi-society guideline authors have advocated a personalized approach to treatment for carotid artery disease. Individual patient circumstances should dictate which revascularization approach is the “favored treatment strategy.”**
- **This question, as currently framed, does not allow the Panel to make the determination that these two treatments are clinically equivalent alternatives that are beneficial for the Medicare population.**
- **We believe that the MEDCAC panel should reframe this question in light of the available evidence, so that revascularization techniques may be assessed as “alternative treatment strategies,” rather than “favored treatment strategies.”**
- **The Panel should have strong confidence (suggested rating of 4 or 5) that both of these revascularizations strategies (CAS and CEA) are superior to BMT alone and reasonable alternatives to each other.**

### CONSIDERATIONS REGARDING QUESTION 3bii:

CEA vs. CAS among Symptomatic Patients - Some might argue that three randomized controlled trials of CAS versus CEA performed in Europe (SPACE, EVA-3S and ICSS) support CEA as the best choice for patients with symptomatic carotid atherosclerosis. We disagree with this assertion, based on the results of CREST that demonstrated equivalence of the two procedures among symptomatic patients, as well as the limitations of the European trials. We discuss these issues below and summarize in **Table 2.1**.

CREST represents the best available evidence with which to compare CEA to CAS, and addressed all the major limitations of European trials.

- CREST is the largest and most rigorous randomized trial of carotid revascularization strategies. The study was sponsored with \$50 million in funding from the NIH, and its design was based on significant input from the NIH, the FDA and CMS within the U.S. Department of Health and Human Services. The CREST protocol was published in advance and it included pre-specified analyses of major endpoints for both the NIH and FDA regulatory analyses.
- CREST is the only randomized trial of CAS versus CEA to involve U.S. physicians (92% of sites) and to study Medicare-age patients (68% of CREST participants).<sup>\*\*</sup>
- CREST is the only trial that required and enforced the use of embolic protection devices, consistent with current safety standards and Medicare national coverage criteria for carotid stenting (EPD used in 98% of all cases).
- CREST included a lead-in phase before randomization to ensure equivalent training and experience between the treatment modalities (referred to as clinical equipoise<sup>52</sup>).
- CREST incorporated modern and rigorous methods to assess myocardial infarction (MI) and account for MI in the composite primary endpoint.

The early randomized studies (SPACE, EVA-3S and ICSS) were criticized for inadequate sample size, sub-optimal interventionalist experience, inconsistent use of anti-platelet medications and incomplete enrollment. In addition, the European trials did not require use of embolic protection devices (a current U.S. standard of care and Medicare coverage requirement) and they allowed for disparate levels of operator experience between the CAS and CEA arms. These trials all had significant design limitations (and this led to early termination of two of the trials).

MI is an important endpoint for carotid revascularization trials. Yet none of the European studies properly captured baseline cardiac markers for MI, despite the accepted use of biomarker levels (e.g., CKMB, troponin<sup>53, 54, 55, 56, 57, 58</sup>) in the detection of MI,<sup>59, 60, 61</sup> and growing evidence showing the relationship between peri-procedural MI and long-term mortality.<sup>62, 63, 64</sup>

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<sup>\*\*</sup> Note, statement refers to completed trials with reported results. The current ACT-I study is U.S.-based and currently enrolling.

MI was included in the composite endpoint of CREST largely because of an improved ability to screen for peri-procedural MI and increasing evidence of its important role as a safety marker. While recently published interim results from ICSS included MI data, none of the European studies actively pursued diagnostics tests for MI (neither biomarkers nor routine ECGs). This resulted in the very low reported 30-day MI rates (0.4% for CAS and 0.8% for CEA in EVA-3S; 0.4% for CAS and 0.6% for CEA in ICSS), especially in comparison to CREST (which reported 1.1% for CAS and 2.3% for CEA).

The European trials only included symptomatic patients. Today, only a minority of patients receiving revascularization procedures in the U.S. are symptomatic; the majority of patients are asymptomatic.<sup>65</sup> Therefore, these three European trials are unable to provide adequate evidence to compare CAS to CEA in asymptomatic patients.

The evidence clearly shows that CAS and CEA are interventions that provide similar benefits and risks among symptomatic patients. We believe that the Panel should have strong confidence that CAS and CEA are reasonable alternative treatment strategies for this population.

**Table 2.1: Summary of CREST and European RCTs Comparing CAS to CEA**

Trial	Country	Size	Symptomatic Status	Follow-up	Primary Endpoint	Outcome	Comments
<b>CREST</b>	U.S.	2,502	Symptomatic and Asymptomatic	Up to 4 years (median: 2.5 yrs.)	Peri-procedural death, stroke, MI or ipsilateral stroke up to 4 years	Composite outcomes in both groups similar	Both symptomatic and asymptomatic patients enrolled to reflect “real world” population  EPD used in 98% of patients  Physicians highly trained  MI included in composite endpoint
<b>SPACE<sup>56</sup></b>	Germany	1,183	Symptomatic only	2 years	Ipsilateral stroke or death within 30-days	Failure to prove non-inferiority of CAS at 30-days	Embolic protection device was not mandated (EPD Use: SPACE – 27% <sup>66</sup> ; EVA-3S – 91.9% <sup>67</sup> )
<b>EVA-3S<sup>55</sup></b>	France	527	Symptomatic only	4 years	Stroke or death within 30-days	Trial stopped early; rates of death or stroke at 1 and 6 months lower with CEA	Questionable training of physicians  MI not included in primary endpoint and did not screen for MI  Premature study termination for safety (EVA-3S) or lack of funding (SPACE) leading to misinterpretation of results <sup>68</sup>
<b>ICSS<sup>112</sup></b>	United Kingdom	1,713	Symptomatic only	120 days	Pre-specified long term fatal or disabling stroke	Interim analysis of composite outcome of peri-procedural stroke or MI showed superiority of CEA	Stenting protocol not standardized  Embolic protection devices not mandated [EPD Use: 71.6% <sup>69</sup> ]  Did not properly screen for MI

***iii. BMT alone is the favored treatment strategy in this [Symptomatic, Standard Surgical Risk] population***

- **Evidence from multiple RCTs of symptomatic patients demonstrates that revascularization is associated with a significant long-term risk reduction of ipsilateral stroke. Best medical therapy alone results in higher rates of ipsilateral stroke and long-term disability when compared to revascularization.**

- Available evidence from RCTs strongly indicates that BMT alone is not the most effective treatment strategy for most symptomatic patients.
- The Panel should have little or no confidence (suggested rating: 1) that BMT alone is the favored treatment strategy for patients with hemodynamically significant carotid stenosis exhibiting symptoms.

**Discussion Questions Related to Q3bi, Q3bii, and Q3biii: *If there is at least intermediate confidence (score  $\geq 2.5$  above) for questions 3.b.i, ii or iii above, please discuss the impact of the following on your conclusions:***

*- Patient age, gender, and racial/ethnic background*

- Pre-specified octogenarian / non-octogenarian analyses showed no statistical differences between CAS and CEA in CREST.
- The age effect reported by CREST researchers was likely a result of significantly lower adverse event rates seen in younger (<60) CAS patients' compared to younger CEA patients.
- CREST data show no significant differences between men and women

#### **IMPACT OF AGE**

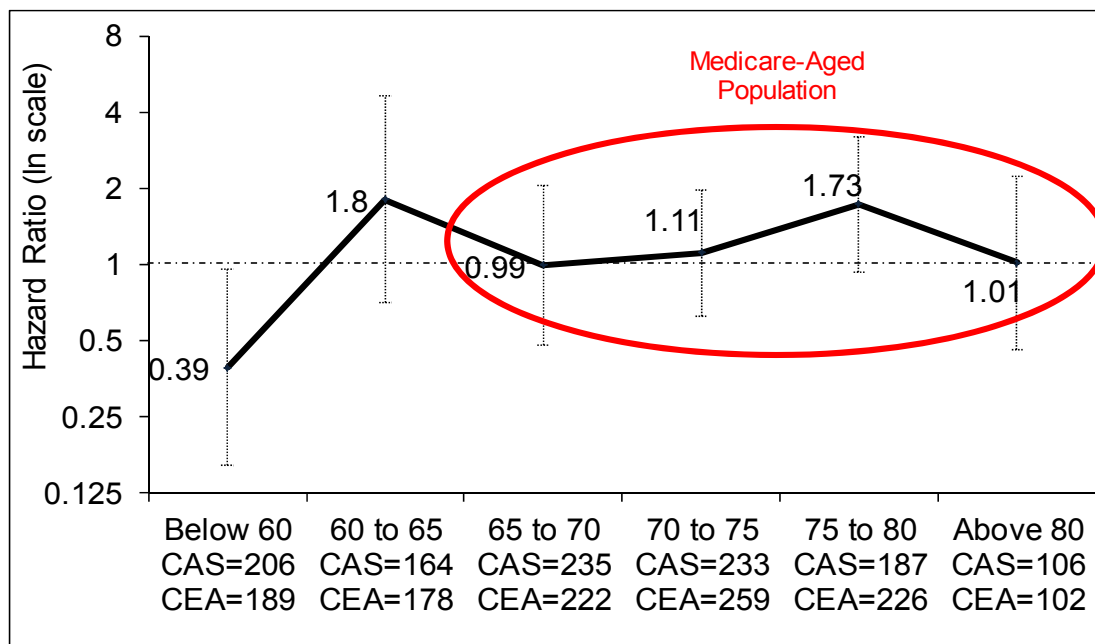
##### *Age Results with Symptomatic and Asymptomatic Patients Combined*

The protocol and statistical plan for the CREST FDA analysis contained a pre-specified non-inferiority hypothesis test for non-octogenarians. In this analysis, CAS was demonstrated to be non-inferior to CEA ( $p=0.02$ ) among non-octogenarians.<sup>70</sup> The CREST FDA statistical plan also included a pre-specified subgroup age analysis by octogenarian status. Results indicate similar outcomes and no significant differences between the CAS and the CEA treatment arms for either the octogenarian or non-octogenarian subgroups.<sup>71</sup>

An additional age analysis was performed and presented by the NIH investigators, suggesting that “CAS tended to show greater efficacy at younger ages, and CEA at older ages.”<sup>72</sup> A recent publication by these investigators is consistent with these statements.<sup>73</sup> However, similar regulatory analyses were performed by the FDA and Abbott Vascular, and neither found statistically significant age interaction.

The FDA performed additional analysis comparing CAS to CEA for the primary endpoint extended to four years on a hazard ratio scale stratified by age groups in five-year increments (**Figure 2.2**). When the HR stratified by age groups is plotted, as is done in **Figure 2.2**, no apparent trend can be observed, with wide 95% confidence intervals overlapping 1.0 for all age categories except for patients under 60 years of age.

**Figure 2.2: Changes in Hazard Ratio by Age Group (FDA Per-protocol)\***



\* Data presented to FDA Circulatory System Devices Advisory Panel on January 26, 2011.<sup>74</sup> Circle and text added for emphasis.

To assess the robustness of this age interaction, Abbott Vascular conducted a sensitivity analysis to determine whether one sub-group had undue influence on the shape of the curve for age interaction published in the NEJM<sup>75</sup>. When patients under age 60 were excluded from the analysis, there was no longer any interaction by age. In other words, the apparent age interaction and its associated curve were statistically driven by the improved outcomes for CAS in patients under 60 years of age (HR = 0.39) and not by any difference in outcomes for elderly patients or patients over 80 (HR = 1.01). Overall, age analysis of the CREST data did not show consistent age-related differences in outcomes between CAS and CEA in the Medicare population.

*Age Results for MEDCAC: Elderly CREST Symptomatic Subjects*  
[Supplemental Abbott Vascular analysis of FDA dataset in symptomatic elderly. For data tables and detailed results, see **Appendix 3.4.**]

To briefly summarize the data and results provided in **Appendix 3.4**, there were no significant differences in event rates for CAS and CEA by age for the primary composite endpoint.<sup>††</sup> Similarly, there were no significant differences in event rates for CAS and CEA by age for peri-procedural MI, although there was a trend (p=0.07) towards more MIs with CEA than CAS among patients  $\geq 80$ . These results were consistent across enrollment periods (entire period of enrollment vs. enrollment during the second half of the trial).

Over the entire enrollment period of CREST, there were more stroke events<sup>‡‡</sup> in CAS patients than in CEA patients (9.8% vs. 5.9%, respectively) and these

<sup>††</sup> Death, stroke or MI within 30 days and ipsilateral stroke to 4 years.

<sup>‡‡</sup> Any stroke within 30 days, ipsilateral stroke to 4 years.

excess strokes occurred in CAS patients aged 70-80. In the second half of the trial, the rate of stroke events was nearly equal for CAS and CEA (7.0% and 6.0%, respectively) and the differences in stroke rates for CAS and CEA by age group disappeared.

### ***IMPACT OF GENDER***

#### *Gender Results with Symptomatic and Asymptomatic Patients Combined*

Several studies, including an interim analysis from the CREST lead-in phase<sup>76</sup> and recent results from the entire CREST cohort,<sup>77</sup> investigated the impact of gender on revascularization outcomes. These studies have shown no significant differences between men and women or mixed results.<sup>78</sup> It is difficult to interpret these results, especially in light of the recent meta-analysis of individual data from three European-based trials that found no interaction (i.e., death/any stroke rates of 8.5% for women and 9.0% for men and a lower CAS to CEA risk ratio in women than men of 1.22 v 1.68),<sup>79</sup> leading some in the literature to speculate that there is no significant effect of gender on the risks for either CAS or CEA.<sup>80</sup>

#### *Gender Results for MEDCAC: Elderly CREST Symptomatic Subjects*

[Supplemental Abbott Vascular analysis of FDA dataset in symptomatic elderly. For data tables and detailed results, see **Appendix 3.5.**]

There is no evidence of a statistically significant interaction by gender for the primary endpoint, as well as the stroke and MI components of the primary endpoint among symptomatic elderly patients. These results were consistent across enrollment periods (entire period of enrollment vs. enrollment during the second half of the trial).

- ***Time to treatment, e.g., < 2 weeks or > 2 weeks from onset of symptoms***

There is evidence that patients need to be seen and treated within 2 weeks,<sup>81</sup> with important benefit of initiating medical treatment and performing revascularization as soon as possible after the onset of symptoms.<sup>82, 83</sup>

## 2.4 Q4 - Evidence in the Asymptomatic, Standard Surgical Risk Population

**Question 4. For persons with asymptomatic carotid atherosclerosis and carotid narrowing ( $\geq 60\%$  by angiography or  $\geq 70\%$  by ultrasound) who are not generally considered at high risk for adverse events from CEA:**

***a. How confident are you that there is adequate evidence to determine whether or not either CAS or CEA is the favored treatment strategy, as compared to BMT alone, to decrease stroke or death in the Medicare population?***

- **Class IIa and IIb evidence from multiple randomized trials supports the safety and effectiveness of revascularization strategies to decrease stroke and death in the Medicare population (suggested rating: 4), consistent with multi-society guidelines.**
- **Recent observational data estimating the risk of stroke in asymptomatic patients is promising and should be viewed as hypothesis-generating at this time. It is premature to change the current standard of care until additional evidence is available.**

CONSIDERATIONS REGARDING QUESTION 4a: The 2011 AHA/ASA primary prevention guidelines<sup>84</sup> provide a well-accepted benchmark for determining the appropriateness of carotid revascularization versus treatment with medical therapy only. The guidelines, which are based on the results of two randomized controlled trials, ACAS and ACST, recommend carotid revascularization for asymptomatic patients when performed by surgeons with  $< 3\%$  morbidity/mortality rates (30-day death and all stroke).

***b. If there is at least intermediate confidence (score  $b. \geq 2.5$  above), how confident are you that***

***i. CAS is the favored treatment strategy in this [Asymptomatic, Standard Surgical Risk] population?***

- **We believe that the MEDCAC panel should reframe this question in light of the available evidence, so that revascularization techniques may be assessed as “alternative treatment strategies,” rather than “favored treatment strategies.”**
- **We believe that the Panel should have more than intermediate confidence that revascularization (which includes both CAS and CEA) produces favorable results for these asymptomatic patients (suggested rating: 3 or 4). The evidence does not support a finding that one approach is favored (superior) to the other.**

CONSIDERATIONS REGARDING QUESTION 4bi -

Results of CREST demonstrate that CAS and CEA produce equivalent net outcomes in asymptomatic patients and meet the target of  $< 3\%$  30-day death and any stroke rates for such patients<sup>88</sup> as recommended in the current AHA/ASA guidelines for primary stroke prevention.<sup>85</sup>

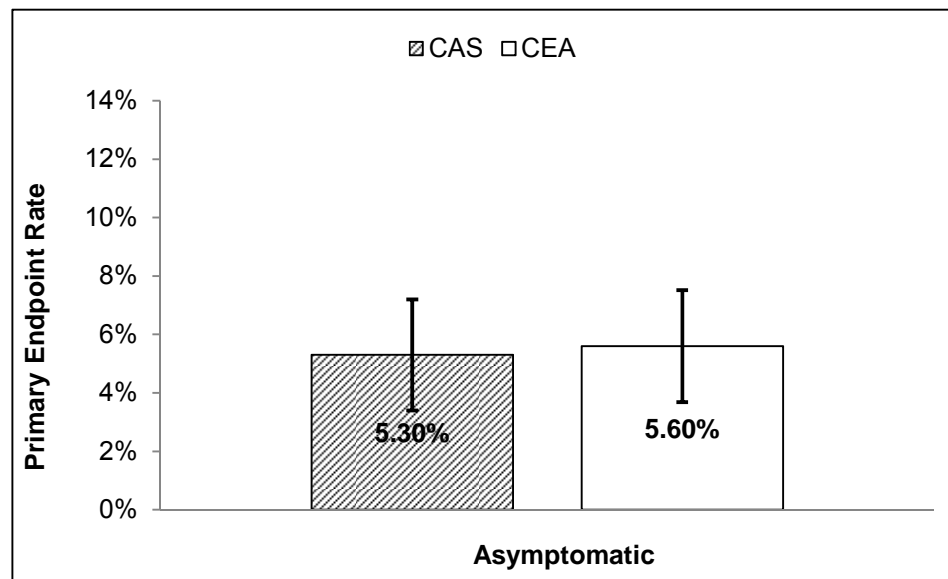
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<sup>88</sup> Asymptomatic patients, octogenarians excluded.



The CREST NIH investigators reported similar and excellent outcomes for CAS and CEA in asymptomatic patients<sup>\*\*\*</sup> with no significant differences [2.4% for CAS and 1.5% for CEA (p=0.27)].<sup>86</sup> As noted in a previous response, the CREST protocol also included a pre-specified FDA regulatory analysis of the one-year endpoint stratified by symptomatic status.<sup>†††, 87</sup> As with symptomatic patients, this analysis showed that CAS was statistically non-inferior to CEA in the asymptomatic subgroup<sup>‡‡‡</sup> (**Figure 2.3**). Finally, the most recent PROTECT data in a largely asymptomatic (high-risk) patient population found the lowest event rate for CAS to date, 1.8% all stroke and death rate at 30 days.<sup>88</sup>

**Figure 2.3: Primary Composite Endpoint for Asymptomatic Subjects (FDA Analysis)**



Source: Presented to FDA Circulatory System Devices Advisory Panel on January 26, 2011; figure modified to remove symptomatic population (in response to CMS question).<sup>88</sup>

**ii. CEA is the favored treatment strategy in this [Asymptomatic, Standard Surgical Risk] population:**

- We believe that the MEDCAC panel should reframe this question in light of the available evidence, so that revascularization techniques may be assessed as “alternative treatment strategies,” rather than “favored treatment strategies.”
- We believe that the Panel should have more than intermediate confidence that revascularization (which includes both CAS and CEA) produces favorable results for these asymptomatic patients (suggested rating: 3 or 4). The evidence does not support a finding that one approach is favored (superior) to the other.

<sup>\*\*\*</sup> Asymptomatic patients, octogenarians excluded.

<sup>†††</sup> A symptomatic subject was defined by the protocol as having an eligible carotid stenosis with prior symptoms of a transient ischemic attack (TIA), amaurosis fugax, or a minor or non-disabling stroke in the hemisphere supplied by the target vessel within 180 days of the randomization date. An asymptomatic subject must have been free from symptoms in the hemisphere supplied by the target vessel within 180 days of the randomization date.

<sup>‡‡‡</sup> All asymptomatic patients, octogenarians included.

CONSIDERATIONS REGARDING QUESTION 4bii

As shown below, ACAS and ACST demonstrated a clear benefit for revascularization with CEA, compared to BMT in asymptomatic patients.<sup>89, 90</sup> In addition, both studies reported low peri-procedural stroke and death rates (which would become the reference for the AHA/ASA guidelines of 3.0% in asymptomatic patients). Finally, the two studies demonstrated remarkably similar annual stroke and death rates of ~2% for the best medical therapy arms whereas the CEA + best medical therapy arms had an annualized rate of ~1%.

**Table 2.2: Benefits of Revascularization**

Study	Treatment Arm	Peri-procedure Stroke and Death	5-year Ipsilateral Stroke and Death	5-year All Stroke and Death
ACAS <sup>91</sup> (1987-1993)	CEA + BMT	2.3%	5.1%	-
	BMT	N/A	11.0%	-
ACST <sup>92</sup> (1999-2003)	Immediate CEA	3.1%	-	6.4%
	Deferred	N/A	-	11.8%

$\Delta = 5.9$  (bracketed between ACAS rows)  
 $\Delta = 5.4$  (bracketed between ACST rows)

Overall, revascularization was effective in reducing the long-term stroke and death rate by approximately 50% and resulted in a 4% to 6% absolute reduction in stroke and death at five years.

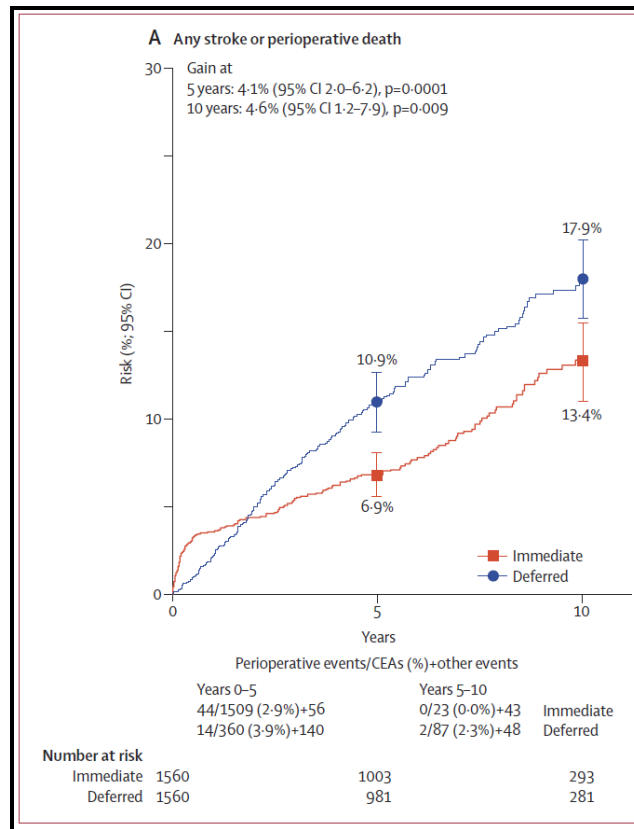
Number Needed to Treat (NNT) is commonly used to compare interventions. Based on results from ACAS, the NNT with CEA to prevent a single stroke or death in asymptomatic patients with hemodynamically significant stenosis is 22 over a four-year time horizon (inverse of the 4.5% absolute risk reduction). This figure compares favorably to other primary stroke prevention therapies, including statins (NNT range of 40-70), anti-hypertensives of both the diuretic and  $\beta$ -blocker variety (NNT range of 80-160), and aspirin (NNT range >300).<sup>93</sup>

The ACST study is particularly informative because it continued to follow patients beyond five years. In 2010, the ACST Collaborative Group reported 10-year ACST results, providing the most rigorous long-term comparison of immediate versus deferred revascularization plus medical therapy.<sup>94</sup> By the end of the study, more than 80% of subjects were on lipid lowering drugs, 88% of subjects were on anti-hypertensives, and 88-89% of patients were on anti-platelet medications. Patients followed to 2009 were on intensive and well accepted medical therapy regimens with revascularization continuing to show statistically significant benefit out to 10-years for patients who underwent immediate CEA vs. deferred CEA.

As shown in Figure 2.4, the 10-year risk of any stroke or peri-operative death in ACST was 13.4% for the immediate CEA group versus 17.9% for the deferred group (p=0.009), an absolute gain of 4.6% at 10-years. These long-

term rates demonstrate that patient benefits from revascularization have been maintained out to ten years. In fact, the absolute reduction in any stroke or peri-operative death actually increased slightly from 4.1% at five years to 4.6% at ten years.

**Figure 2.4 - ACST 10-year Any Stroke or Peri-operative Death**



Source: Halliday A, Harrison M, Hayter E, Kong X, Mansfield A, Marro J, Pan H, Peto R, Potter J, Rahimi K, Rau A, Robertson S, Streifler J, Thomas D, for the Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomized trial. *Lancet* 2010;376:1074-84.

The results of these two landmark RCTs, ACAS and ACST, represent the best available evidence to date, supporting a clear role for revascularization in stroke risk reduction for asymptomatic carotid stenosis. The recent multi-society guidelines continued use of these studies in setting their recommendations for peri-procedural safety attest to the longevity of their findings.

The only published evidence comparing CAS to CEA for this patient population (Asymptomatic, Standard Surgical Risk) comes from CREST. These results, discussed in detail above, provide the most rigorous evidence to date that CAS and CEA are equivalent treatment strategies.

**iii. BMT alone is the favored treatment strategy in this [Asymptomatic, Standard Surgical Risk] population:**

- **To date, the only evidence supporting this position is observational, with no support from randomized trials. Therefore, the Panel should have little or no confidence (suggested rating: 1 or 2) that BMT is the favored treatment strategy for this population group.**

CONSIDERATIONS REGARDING QUESTION 4biii - Some observers have expressed concern that the AHA/ASA guidelines may be outdated due to advancements in medical therapy for stroke prevention.<sup>95</sup> Recent reports showing an improved efficacy for medical management should be viewed as hypothesis-generating at this time. Additional testing in randomized trials is needed.

There currently is insufficient evidence to justify changes to longstanding treatment guidelines that support revascularization. These guidelines are based on data from multiple randomized controlled trials, and they should continue to serve as the primary benchmark for evaluating the appropriateness of both CAS and CEA.

Discussion re Q4: If there is at least intermediate confidence (score  $\geq 2.5$  above), please discuss the impact of the following on your conclusions:

***i. Patient age, gender, and racial/ethnic background (for questions 4.b.i,ii or iii)***

Please refer to the sections entitled *Age and Gender Results with Symptomatic and Asymptomatic Patients Combined* under Question 3 for age and gender analyses that include both symptomatic and asymptomatic patients. For brevity, we do not repeat this information here. Below, we discuss results of supplemental analyses of the CREST FDA dataset by Abbott Vascular. As in Question 3, we limit these analyses to elderly (65+) CREST patients and provide results by symptomatic status.

*Age Results for MEDCAC: Elderly CREST Asymptomatic Subjects* [For data tables and detailed results, see **Appendix 3.6**]

There were no significant differences in event rates for CAS and CEA by age for the primary composite endpoint<sup>§§§</sup> among asymptomatic elderly patients in CREST. Similarly, there were no significant differences in event rates for CAS and CEA by age for peri-procedural MI. These results were consistent across enrollment periods (entire period of enrollment vs. enrollment during the second half of the trial).

*Gender Results for MEDCAC: Elderly CREST Asymptomatic Subjects* [For data tables and detailed results, see **Appendix 3.7**]

There is no evidence of a statistically significant interaction by gender for the primary endpoint, as well as MI components of the primary endpoint among asymptomatic elderly patients. These results were consistent across enrollment periods (entire period of enrollment vs. enrollment during the second half of the trial).

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<sup>§§§</sup> Death, stroke or MI within 30 days and ipsilateral stroke to 4 years.

Over the entire enrollment period, asymptomatic elderly women had similar outcomes after CAS and CEA across all endpoints analyzed. For asymptomatic elderly men, there were more strokes and fewer MIs after CAS compared to CEA, and results improved in both arms during the second half of the trial

ii. Concurrent BMT (for questions 4.b.i or ii)

Concurrent best medical therapy is the standard of care for patients with hemodynamically significant carotid atherosclerosis that are candidates for revascularization. While treatment advances, including new drug therapies, may have impacted the underlying stroke risk for some patients, it is unclear to what degree, especially in light of recent studies indicating patient compliance may be limited in real-world settings.<sup>96</sup>

## 2.5 Q5- Evidence in the Asymptomatic, Non-High Risk for Stroke Population

5. For persons with asymptomatic carotid atherosclerosis who are not generally considered at high risk for stroke in either cerebral hemisphere:

a. How confident are you that there is adequate evidence to determine whether or not CAS or CEA or BMT alone is the favored treatment strategy to decrease stroke or death in the Medicare population?

- We believe that the Panel should find that the available evidence is not adequate to make this determination (suggested rating: 1).

CONSIDERATIONS REGARDING QUESTION 5a - Among patients with asymptomatic carotid atherosclerosis without hemodynamically significant stenosis or other known risk factors (e.g., cardiovascular disease), there is insufficient evidence to recommend any interventions. Because all interventions carry some degree of risk, treatments should be reserved for those patients determined to be at elevated risk.

b. If there is at least intermediate confidence (score  $\geq 2.5$  above), how confident are you that

i. CAS is the favored treatment strategy in this population?

- N/A because the evidence is insufficient.

ii. CEA is the favored treatment strategy in this population?

- N/A because the evidence is insufficient.

iii. BMT alone is the favored treatment strategy in this population?

- N/A because the evidence is insufficient.

*Discussion for Q5: If there is at least intermediate confidence (score  $\geq 2.5$  above), please discuss the impact of the following on your conclusions:*

i. Patient age, gender, and racial/ethnic background (for questions 5.b.i,ii or iii)

- N/A because the evidence is insufficient.

ii. Concurrent BMT (for questions 5.b.i or ii)

- N/A because the evidence is insufficient.

## 2.6 Q6- Determination of Screening in Asymptomatic Population

### 6. In the general Medicare population:

*a. How confident are you that there is adequate evidence to determine whether or not carotid artery screening of asymptomatic persons decreases stroke or death?*

- **There is inadequate evidence to determine if general population screening of asymptomatic patients decreases stroke or death. Therefore, the Panel should have little to no confidence (suggested rating: 1 or 2).**

#### CONSIDERATIONS REGARDING QUESTION 6a

Carotid screening studies to date have been focused on identifying carotid stenosis and characterizing hemodynamically significant lesions.<sup>97 98</sup> Few RCTs exist on actual screening of the general population. Therefore, there is insufficient evidence to determine whether screening of otherwise undifferentiated asymptomatic patients decreases stroke and death.

The prevalence of asymptomatic carotid stenosis is not insignificant, with a general population prevalence estimate of 2-8%.<sup>99</sup> Among the Medicare population (patients 65+), the U.S. Preventive Services Task Force estimates that approximately 1% of the elderly population have hemodynamically significant lesions of 60% to 99% stenosis.<sup>100</sup> Once hemodynamically significant carotid atherosclerosis is identified, it is possible to estimate therapeutic outcomes based upon data from randomized controlled trials in this population. However, it would be logistically challenging to complete a randomized trial of screening to determine the impact on outcomes in the asymptomatic population due to the large sample size that would be needed.

Based on a U.S. community-based cohort study, the presence of a carotid bruit represents a 25% likelihood the patient has a hemodynamically significant lesion.<sup>101</sup> However, the presence of carotid bruit has been shown to have low specificity and sensitivity as an indicator for hemodynamically significant carotid lesions, as well as being associated with a significant false negative rate.<sup>102, 103, 104</sup> Given these limitations, and the assumption of limited resources, a more sound strategy would be to favor duplex ultrasonographic evaluation for patients with risk factors for atherosclerosis and carotid disease. Duplex ultrasound is relatively inexpensive and has been recommended as the preferred non-invasive method for screening asymptomatic patients at risk for carotid atherosclerosis; it is not recommended to screen the general asymptomatic population.<sup>105</sup>

Identifying asymptomatic patients at high risk for vascular disease and screening for hemodynamically significant carotid atherosclerosis yields an ability to reduce death and stroke in this high risk population.

*b. If there is at least intermediate confidence (score  $\geq 2.5$  above), how confident are you that carotid artery screening of asymptomatic persons decreases stroke or death?*

- **N/A, because of insufficient data.**

## 2.7 Q7- Additional Research and Diagnostic Tools

7. *What unmet research needs, specific to the following issues, are important to consider and explore further?*

*a. Should future stroke prevention trials*

*i. Be powered to evaluate only symptomatic or asymptomatic patients?*

- While cognizant of the trade-offs between trial feasibility and costs with study power, we believe that both symptomatic and asymptomatic patients should be evaluated in future studies to further stratify which risk factors and carotid disease characteristics increase patient risk for stroke. This will improve the ability to improve patient selection.

*ii. Be powered to draw conclusions regarding gender?*

- We believe that future studies should be robustly powered to investigate the possible presence of a gender interaction that can be further subdivided by symptomatic status, age and other important clinical parameters.

*iii. Evaluate outcomes for more racially/ethnically diverse patient populations?*

- We believe that enrollment of diverse racial and ethnic populations should be an important focus for ongoing clinical research. While previous trials have demonstrated relatively low event rates in these sub-populations, recent work published by the Multi-Ethnic Study of Atherosclerosis (MESA) illustrates recognition of these factors in possible risk stratification.<sup>106</sup>

*b. So as to help delineate those who require carotid revascularization from those who do not, how should future trials best utilize and validate for the Medicare population the following tools to identify persons with asymptomatic carotid atherosclerosis who are at high risk for stroke?*

- New diagnostic tests and advanced imaging techniques show great promise. Eventually, physicians may be able to more accurately risk stratify their asymptomatic patients.
- Currently-available evidence does not support broad or mandated use of these technologies among asymptomatic patients with hemodynamically significant stenosis.
- Additional methodologically rigorous studies are needed before these tests and techniques can be considered a standard of care for the management of asymptomatic carotid atherosclerosis.

*i. Advanced imaging, such as 3D ultrasound, for plaque morphology*

Ultrasound is the initial imaging modality of choice in evaluating carotid artery stenosis,<sup>107</sup> and it is widely used in measurement of intima media thickness. While thickness of the intima media is a marker of wider systemic



radiographic sequelae,<sup>124</sup> a recent substudy from the International Carotid Stenting Study (ICSS) has reported that almost three times more patients in the stenting group than in the endarterectomy group had new ischemic lesions on DW-MRI post-treatment scans.<sup>125</sup> While the clinical significance of the lesions from the ICSS sub-study remains to be seen, this modality may not have predictive value in risk stratification.

#### ***iv. Risk assessment tools and predictive stroke models***

Serum biomarkers reflecting the molecular processes such as inflammation, lipid accumulation, apoptosis, proteolysis and thrombosis associated with the presence of vulnerable carotid artery plaques such as C-reactive protein, IL-6, S-100B, MMP-9, MMP-2, and tissue inhibitors of metalloproteinases (TIMP)-1 and -2, may represent a noninvasive way to identify high-risk patients for carotid surgery.<sup>126, 127</sup> Use of a combination of biomarkers with radiological findings (i.e., enhanced fluoro-deoxyglucose uptake by PET/CT scanning) may provide valuable insights into plaque stability.<sup>128, 129, 130</sup> Studies investigating these tools, combined with other risk assessment methodologies, such as those of the Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) Study Group, represent promising areas of continuing research in stroke risk stratification.<sup>131</sup>

atherosclerosis and coronary artery disease, it is not recommended for treatment guidance.<sup>108</sup>

NASCET showed that plaque ulceration on angiography was associated with a greater risk of stroke,<sup>109</sup> and it was later shown that three-dimensional ultrasound (3D US) can reliably detect ulcerations in the carotid artery.<sup>110</sup> While the Asymptomatic Carotid Emboli Study (ACES) supports a promising role for transcranial doppler in risk stratification (see **7.b.ii**, below), a recent report demonstrates the presence of two or more ulcers on 3D US in asymptomatic patients predicted a significantly greater risk of microemboli, stroke in three years, and stroke, death, or TIA in three years.<sup>111</sup> While the authors note that their observational findings have limited feasibility for broader use in the U.S. (due to the considerable training and experience to be able to detect ulceration reliably), their results are indeed promising and warrant further research.

### ***ii. Transcranial Doppler (TCD) for cerebral microembolization***

Transcranial Doppler (TCD) can be used to evaluate the presence of microembolic signals in patients with carotid artery stenosis. Embolic signals may independently predict stroke risk, recurrence during acute stroke, symptomatic carotid lesions and postoperatively after carotid CEA. Embolic signals are consistently found to be more frequent in patients with large artery disease, less frequent in cardioembolic stroke, and minimal or absent in patients with lacunar stroke.<sup>112</sup>

The Asymptomatic Carotid Emboli Study (ACES) recently concluded that embolic signals on TCD in asymptomatic carotid stenosis were independently predictive of two-year stroke and TIA risk.<sup>113, 114</sup> The ACES recording protocol would likely be viewed as onerous in a community setting (two recordings each lasting one hour, separated by one week). However, other studies suggest shorter recording protocols would have similar predictive value,<sup>115</sup> and together provide support for a role for TCD in stroke risk stratification.<sup>116</sup> A recent meta-analysis classifies this Level I evidence and calls for continued research into the use of TCD in risk stratification.<sup>117</sup>

### ***iii. Pre- and post-procedure diffusion weighted MRI (DW-MRI) for silent infarcts***

High-resolution MRI has been widely used to evaluate characteristics of atherosclerosis, including *in vivo* MRI depiction of carotid plaque hemorrhage, lipid-rich necrotic core, and thinning of the overlying fibrous cap (with histologic correlation).<sup>118, 119, 120</sup> These features make the plaque prone to rupture with subsequent thromboembolic ischemic events.<sup>121</sup> The clinical significance of these MR images has been confirmed in prospective studies of asymptomatic patients with moderate stenosis that led to subsequent strokes or TIA.<sup>122, 123</sup>

While a previous analysis of carotid interventions using diffusion-weighted MRI concluded that the majority of microemboli do not have long-term

### 3 Appendices

#### 3.1 Summary: Carotid Artery Disease Treatments & FDA Approval of Carotid Stent Systems

##### Medical Management

Medical therapy is the foundation of stroke risk factor management for all patients with carotid artery disease. Treatments may include anti-hypertensive agents to maintain normal blood pressure, statins for control of hyperlipidemia, antiplatelet therapy for prevention of cardiovascular events and glucose lowering medications for patients with diabetes mellitus.<sup>132, 133</sup> These therapies are intended to modify vascular risk factors and to stabilize and prevent the advancement of the carotid atherosclerotic disease.

##### Carotid Endarterectomy (CEA)

Carotid endarterectomy is a surgical treatment involving a neck incision to access and excise the atherosclerotic plaque. CEA has been performed for almost 60 years<sup>134, 135</sup> and multiple randomized controlled trials have demonstrated substantial improvements in the procedure safety and proven clinical effectiveness.<sup>136, 137, 138, 139, 140, 141, 142, 143, 144</sup> These randomized controlled trials are the basis for clinical practice guidelines recommending CEA as a proven treatment option with a low risk-adjusted operative mortality for symptomatic and asymptomatic patients.<sup>145, 146, 147, 148, 149</sup> As a result, CEA has become a common vascular procedure, with roughly 79,000 Medicare inpatient discharges in 2009.<sup>150</sup>

##### Carotid Artery Stenting (CAS) with Embolic Protection

Carotid artery stenting is a catheter-based treatment involving stent placement to unblock a narrowing (or stenosis) of the carotid artery lumen. Introduced in 1989, the first CAS procedures utilized stents designed for coronary or other vascular lesions. CAS has since undergone considerable improvements in procedural technique, patient selection, carotid-specific technology design and operator experience.<sup>151</sup> Consistent with the results of CREST, multi-society guidelines and stroke prevention guidelines have incorporated CAS and recommend its use.<sup>152, 153, 154</sup> In 2009, there were roughly 11,000 Medicare inpatient discharges for CAS largely in the high surgical risk population and those enrolled in prospective clinical trials.<sup>155</sup>

The primary objective of CAS is to reduce the risk of embolization and stroke by trapping the atheromatous plaque against the vessel wall and improving blood flow to the brain. The first publication of a multicenter study of CAS occurred in 1995.<sup>156</sup> Over the last 10 years, considerable improvements in procedural technique, including the introduction of embolic protection devices (EPDs), patient selection, stent design, and operator experience have contributed to substantial improvements in the safety and efficacy of CAS procedures.<sup>157, 158</sup>

The major risk of carotid stent procedures is embolization of atherosclerotic material into the cerebral circulation, resulting in stroke. There is a substantial body of evidence supporting the use of embolic protection devices (EPDs) during CAS, in order to reduce adverse event rates and improve outcomes.<sup>159, 160, 161, 162, 163, 164, 165, 166, 167, 168</sup> The effectiveness of distal EPD has been discussed in the literature<sup>169, 170, 171, 172, 173</sup> and has gained wide acceptance in the United States. The current Medicare national coverage policy requires embolic protection during the procedure as a condition of coverage.<sup>174</sup> There is also new evidence and interest regarding the potential for *proximal* embolic protection to further improve outcomes for patients.<sup>175, 176, 177</sup>

To perform CAS procedures, physicians must have an in-depth understanding of carotid artery disease, carotid and vascular cerebral anatomy, and specialized training in diagnostic imaging and endovascular treatment strategies, percutaneous transluminal angioplasty and stenting procedures with embolic protection.<sup>178, 179</sup> Evidence demonstrates that physician and facility experience is positively correlated with improved patient outcomes.<sup>180, 181, 182, 183, 184</sup>

### FDA Approval of Carotid Stent Systems

Since 2004, the FDA has approved a number carotid stent systems for **high surgical risk** patients, including six (**Table 3.1**) that are commercially available today. On May 6, 2011 the FDA approved the RX Acculink<sup>®</sup> Carotid Stent System (Acculink) used in conjunction with the RX Accunet<sup>®</sup> Embolic Protection System (Accunet) for expanded use in patients at **standard surgical risk** for CEA surgery. This FDA approval was based on the results of CREST, the largest randomized study comparing CAS and CEA in standard surgical risk symptomatic or asymptomatic patients.<sup>185</sup>

The additional five high risk carotid stent FDA approvals were based on the results of the SAPPHIRE randomized controlled trial<sup>186</sup> or other prospective single arm clinical trials. The FDA-approved carotid artery stent systems are summarized in **Table 3.1**.

**Table 3.1: FDA Approved Carotid Artery Stent Systems (Commercially Available in U.S.)**

Manufacturer	Product	Reference Study	High Surgical Risk Indication	Standard Surgical Risk Indication
Abbott Vascular	Acculink <sup>®</sup>	ARCher <sup>187</sup> & CREST <sup>188</sup>	X	X
Abbott Vascular	XACT <sup>®</sup>	SECURITY <sup>189</sup>	X	
Boston Scientific	Wallstent <sup>®</sup>	BEACH <sup>190</sup>	X	
eV3	Protégé <sup>®</sup>	CREATE <sup>191</sup>	X	
Cordis	PRECISE <sup>®</sup>	SAPPHIRE <sup>192</sup>	X	
Medtronic	Exponent <sup>®</sup>	MAVERIC <sup>193</sup>	X	

### 3.2 Classification of Recommendations & Level of Evidence \*\*\*\*

		SIZE OF TREATMENT EFFECT →				
		CLASS I <i>Benefit &gt;&gt;&gt; Risk</i> Procedure/Treatment <b>SHOULD</b> be performed/administered	CLASS IIa <i>Benefit &gt;&gt; Risk</i> Additional studies with <i>focused objectives needed</i> <b>IT IS REASONABLE</b> to perform procedure/administer treatment	CLASS IIb <i>Benefit ≥ Risk</i> Additional studies with <i>broad objectives needed; additional registry data would be helpful</i> Procedure/Treatment <b>MAY BE CONSIDERED</b>	CLASS III <i>No Benefit</i> or CLASS III <i>Harm</i>	
ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is useful/effective</li> <li>Sufficient evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation in favor of treatment or procedure being useful/effective</li> <li>Some conflicting evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation's usefulness/efficacy less well established</li> <li>Greater conflicting evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is not useful/effective and may be harmful</li> <li>Sufficient evidence from multiple randomized trials or meta-analyses</li> </ul>	
	LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is useful/effective</li> <li>Evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation in favor of treatment or procedure being useful/effective</li> <li>Some conflicting evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation's usefulness/efficacy less well established</li> <li>Greater conflicting evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is not useful/effective and may be harmful</li> <li>Evidence from single randomized trial or nonrandomized studies</li> </ul>	
	LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is useful/effective</li> <li>Only expert opinion, case studies, or standard of care</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation in favor of treatment or procedure being useful/effective</li> <li>Only diverging expert opinion, case studies, or standard of care</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation's usefulness/efficacy less well established</li> <li>Only diverging expert opinion, case studies, or standard of care</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is not useful/effective and may be harmful</li> <li>Only expert opinion, case studies, or standard of care</li> </ul>	
Suggested phrases for writing recommendations <sup>†</sup>		should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit is not recommended is not indicated should not be done is not useful/ beneficial/ effective	COR III: Harm potentially harmful causes harm associated with excess morbidity/mortality should not be done
Comparative effectiveness phrases <sup>†</sup>		treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B			

\*\*\*\* Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, Cates CU, Creager MA, Fowler SB, Friday G, Hertzberg VS, McIff EB, Moore WS, Panagos PD, Riles TS, Rosenwasser RH, Raylor AJ. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Neuro-Interventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. *J Am Coll Cardiol* 2011; 57:e16-94.

### 3.3 Summary: Multi-Society Guidelines for Screening of Asymptomatic Patients<sup>††††</sup>

- For asymptomatic patients with known or suspected carotid stenosis, duplex ultrasonography is recommended as the initial diagnostic test to detect hemodynamically significant carotid stenosis (Class I, Level of Evidence: C, See **Appendix 3.2** for a description of the Classes and Levels of Evidence).
- For asymptomatic patients with carotid bruit, it is reasonable to perform duplex ultrasonography to detect hemodynamically significant carotid stenosis in (Class IIa, Level of Evidence: C).
- For asymptomatic patients with symptomatic PAD, coronary artery disease (CAD), or atherosclerotic aortic aneurysm, duplex ultrasonography to detect hemodynamically significant carotid stenosis may be considered. However, because such patients already have an indication for medical therapy to prevent ischemic symptoms, it is unclear whether establishing the additional diagnosis of extracranial carotid and cerebral artery disease (ECVD) in those without carotid bruit would justify actions that affect clinical outcomes (Class IIb, Level of Evidence: C).
- For asymptomatic patients without clinical evidence of atherosclerosis but with 2 or more risk factors (hypertension, hyperlipidemia, tobacco smoking, a family history in a first degree relative of atherosclerosis manifested before age 60 years, or a family history of ischemic stroke), duplex ultrasonography might be considered to detect carotid stenosis. However, it is unclear whether establishing a diagnosis of ECVD would justify actions that affect clinical outcomes (Class IIb, Level of Evidence: C).

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<sup>††††</sup> Note, the multi-society guidelines also include a recommendation for ultrasound among asymptomatic patients with atherosclerosis who have had stenosis greater than 50% detected previously, as a mechanism to assess disease progression or response to therapy (Class IIa, Level of Evidence: C). Since this patient population does not appear to be relevant to the question proposed by CMS, we do not include it above but mention it here for completeness.

### 3.4 Supplemental Analyses: Age - Symptomatic Elderly Patients

#### Death, Stroke and MI to 30 days, Ipsilateral Stroke to 4 Years By 5-Yr Age Groups Symptomatic Elderly (65+) Patients

All Symptomatic Patients (N= 795)				Symptomatic Patients Enrolled in Second Half (N= 385)			
DSMI + ipsilateral stroke to 4 years	CAS Count (%)	CEA Count (%)	p	DSMI + ipsilateral stroke to 4 years	CAS Count (%)	CEA Count (%)	p
65-70	8 (9.0)	9 (11.8)	0.57	65-70	3 (5.4)	1 (3.9)	0.41
70-75	18 (17.1)	12 (9.8)	0.10	70-75	6 (11.3)	7 (12.4)	0.94
75-80	13 (13.4)	9 (7.7)	0.20	75-80	4 (8.2)	6 (9.5)	0.84
≥ 80	8 (11.8)	10 (16.3)	0.42	≥ 80	3 (11.9)	5 (23.0)	0.31
total	47 (12.1)	40 (9.9)		total	16 (8.6)	19 (9.5)	

Table notes: Primary Endpoint outcomes by age groups in Symptomatic patients ≥ 65 years old. P values computed on HR, after adjustment for gender; unadjusted for multiple comparisons.

In the population of symptomatic elderly patients, there were slightly more primary endpoint events for CAS over CEA (12.1% vs. 9.9%, *All Symptomatic Patients* above), although no significant differences were detected in any of the age categories. In the second half of CREST, there was a decrease in primary endpoint events in the CAS treatment arm (expected: ~ 24 events; actual: 16), and a lower primary composite endpoint event rate for CAS than CEA (8.6% vs. 9.5%).

During the entire enrollment period of CREST, the p-value for interaction by age for this endpoint was p= 0.72, indicating a lack of a statistically significant differential effect of CAS and CEA by age in symptomatic elderly patients for the primary composite endpoint. In the second half of CREST, the event rate for CAS trended lower but was not significant (p=0.39).

#### All Stroke to 30 days, Ipsilateral Stroke to 4 Years By 5-Yr Age Groups Symptomatic Elderly (65+) Patients

All Symptomatic Patients (N= 795)				Symptomatic Patients Enrolled in Second Half (N= 385)			
Stroke + ipsilateral stroke to 4 years	CAS Count (%)	CEA Count (%)	p	Stroke + ipsilateral stroke to 4 years	CAS Count (%)	CEA Count (%)	p
65-70	6 (7.2)	6 (8.7)	0.74	65-70	2 (5.4)	1 (3.9)	0.59
70-75	14 (13.5)	8 (6.7)	0.08	70-75	4 (11.3)	5 (12.4)	0.94
75-80	10 (10.4)	3 (2.6)	0.03	75-80	4 (8.2)	2 (9.5)	0.22
≥ 80	8 (12.0)	7 (11.7)	0.97	≥ 80	3 (11.9)	4 (23.0)	0.52
total	38 (9.8)	24 (5.9)		Total	13 (7.0)	12 (6.0)	

Table notes: Primary Endpoint outcomes by age groups in Symptomatic patients ≥ 65 years old. P values computed on HR, after adjustment for gender; unadjusted for multiple comparisons.

In the population of symptomatic elderly patients, there was a higher stroke event rate for CAS than CEA (9.8% vs. 5.9%, *All Symptomatic Patients* above). This trend was seen in the 70-75 and the 75-80 age groups, but absent in the age groups at the two extremes: 65-70 and  $\geq 80$  years old. In the second half of CREST, there was a decrease of in the stroke event rate in the CAS treatment arm (expected: 19 events; actual: 13), and a similar stroke event rate for CAS and CEA (7.0% vs. 6.0%).

During the entire enrollment period of CREST, the p-value for interaction by age for this endpoint was  $p=0.74$ , indicating the lack of a statistically significant differential effect of CAS and CEA by age in symptomatic elderly patients for stroke and ipsilateral stroke to 4 years. In the second half of CREST, the p-value for interaction was also not significant ( $p=0.99$ ).

### Peri-Procedural (to 30 days) MI By 5-Yr Age Groups Symptomatic Elderly (65+) Patients

All Symptomatic Patients (N= 795)				Symptomatic Patients Enrolled in Second Half (N= 385)			
Peri-procedural MI	CAS Count (%)	CEA Count (%)	p	Peri-procedural MI	CAS Count (%)	CEA Count (%)	p
65-70	2 (1.8)	3 (3.1)	0.58	65-70	1 (1.7)	0 (0.0)	NA
70-75	6 (5.6)	4 (3.1)	0.36	70-75	3 (5.7)	2 (3.2)	0.50
75-80	3 (3.0)	6 (5.1)	0.44	75-80	1 (2.0)	4 (6.3)	0.29
$\geq 80$	1 (1.4)	6 (9.5)	0.07	$\geq 80$	0 (0.0)	3 (13.6)	NA
total	12 (3.1)	19 (4.7)		total	5 (2.7)	9 (4.5)	

Table notes: Primary Endpoint outcomes by age groups in Symptomatic patients  $\geq 65$  years old. P values computed on HR, after adjustment for gender; unadjusted for multiple comparisons.

In the population of symptomatic elderly patients, there was a non-significant trend of higher peri-procedural MI events for CEA over CAS (4.7% vs. 3.1%, *All Symptomatic Patients* above). This was most pronounced among patients  $\geq 80$  years old, albeit not reaching statistical significance, likely due to the small number of events (6 vs. 1).

In the second half of CREST, there continued to be more peri-procedural MIs in the CEA arm (4.5% vs. 2.7%). This was more pronounced in patients 75-80 years old and in patients  $\geq 80$  years old. As above, the small number of events results in non-significant differences in MIs for CAS and CEA by age group.

During the entire enrollment period of CREST, the p-value for interaction by age for this endpoint was  $p=0.17$ , indicating a lack of a statistically significant differential effect of CAS and CEA by age in symptomatic elderly patients for peri-procedural MI. In the second half of CREST, the interaction was significant ( $p=0.04$ ), likely a result of MIs being more common after CEA than after CAS for patients 75 years and older.



### 3.5 Supplemental Analyses: Gender - Symptomatic Elderly Patients

#### Multiple Endpoints By Gender in Symptomatic Elderly (65+) Patients

All Symptomatic Patients (N= 795)					Symptomatic Patients Enrolled in Second Half (N= 385)				
DSMI + ipsilateral stroke to 4 years	CAS Count (%)	CEA Count (%)	P	P <sub>i</sub>	DSMI + ipsilateral stroke to 4 years	CAS count (%)	CEA Count (%)	p	P <sub>i</sub>
Men	24 (9.9)	24 (10.0)	0.81	0.35	Men	8 (7.0)	10 (8.9)	0.69	0.86
Women	23 (18.1)	16 (12.0)	0.22		Women	8 (11.7)	9 (13.1)	0.95	
Stroke + ipsilateral stroke to 4 years	CAS Count (%)	CEA Count (%)	P	P <sub>i</sub>	Stroke + ipsilateral stroke to 4 years	CAS Count (%)	CEA Count (%)	p	P <sub>i</sub>
Men	19 (7.9)	13 (5.9)	0.18	0.31	Men	7 (6.1)	5 (5.0)	0.49	0.53
Women	19 (15.3)	11 (2.4)	0.12		Women	6 (8.8)	7 (10.4)	0.89	
DSMI	CAS Count (%)	CEA Count (%)	P	P <sub>i</sub>	DSMI	CAS Count (%)	CEA Count (%)	p	P <sub>i</sub>
Men	20 (8.0)	19 (7.1)	0.72	0.86	Men	7 (6.0)	8 (6.3)	0.86	0.69
Women	19 (13.7)	10 (7.1)	0.10		Women	7 (10.1)	6 (8.2)	0.67	
Peri-procedural MI	CAS Count (%)	CEA Count (%)	P	P <sub>i</sub>	Peri-procedural MI	CAS Count (%)	CEA Count (%)	p	P <sub>i</sub>
Men	7 (2.8)	13 (4.9)	0.23	0.63	Men	3 (2.6)	6 (4.7)	0.32	0.78
Women	5 (3.6)	6 (4.3)	0.72		Women	2 (2.9)	3 (4.1)	0.71	

Table Notes: Primary endpoint and components for Symptomatic patients  $\geq 65$  years old (Medicare population). P values computed on HR; unadjusted for multiple comparisons.

There was no evidence of a statistically significant interaction by gender for the primary endpoint and in various components of the primary endpoint (stroke plus ipsilateral stroke to 4 years, DSMI, peri-procedural MI) in this population of symptomatic elderly patients.

There was a trend towards more strokes in symptomatic elderly women undergoing CAS, which also was reflected for the the primary endpoint, in DSMI and in the stroke endpoint. However, in the second half of CREST, this numerical advantage disappeared and CAS and CEA were comparable for symptomatic elderly women.

During the entire enrollment period, there were more strokes after CAS for symptomatic elderly men, balanced by more MIs after CEA. However, in the second half of the trial, the higher MI rate persisted, whereas difference in strokes disappeared, resulting in a slight (non-significant) advantage for CAS over CEA.

### 3.6 Supplemental Analyses: Age - Asymptomatic Elderly Patients

#### Death, Stroke and MI to 30 days, Ipsilateral Stroke to 4 Years By 5-Yr Age Groups Asymptomatic Elderly (65+) Patients

All Asymptomatic Patients (N= 775)				Asymptomatic Patients Enrolled in Second Half (N= 381)			
DSMI + ipsilateral stroke to 4 years	CAS Count (%)	CEA Count (%)	p	DSMI + ipsilateral stroke to 4 years	CAS Count (%)	CEA Count (%)	p
65-70	7 (6.0)	5 (4.08)	0.56	65-70	3 (5.3)	1 (1.7)	0.31
70-75	5 (4.0)	12 (10.0)	0.16	70-75	3 (4.3)	6 (10.3)	0.20
75-80	11 (13.4)	8 (7.5)	0.21	75-80	4 (10.1)	6 (10.3)	0.92
≥ 80	5 (15.2)	2 (5.2)	0.17	≥ 80	2 (12.5)	1 (5.6)	0.47
total	28 (6.9)	27 (7.3)		Total	12 (6.4)	19 (9.8)	

Table Notes: Primary Endpoint outcomes by age groups in asymptomatic patients ≥ 65 years old. P-values computed on HR, after adjustment for gender; unadjusted for multiple comparisons.

In the population of asymptomatic elderly patients, there is no difference overall between CAS and CEA in the rate of primary composite endpoint events (6.9% vs. 7.3%, *All Asymptomatic Patients* above), and no evidence of a statistically significant difference in any of the age categories. In the second half of CREST, there is a slight advantage in the relative rates of primary composite endpoint events between CAS and CEA, in favor of CAS (6.4% vs. 9.8%, respectively)

During the entire enrollment period of CREST, the p-value for interaction was p= 0.18, indicating a lack of a statistically significant differential effect of CAS and CEA by age in asymptomatic elderly patients for the primary composite endpoint. In the second half of CREST, the p-value for interaction by age was also not significant (p=0.82).

#### Any Stroke to 30 Days and Ipsilateral Stroke to 4 Years By 5-Yr Age Groups Asymptomatic Elderly (65+) Patients

All Asymptomatic Patients (N= 775)				Asymptomatic Patients Enrolled in Second Half (N= 381)			
Stroke + ipsilateral stroke to 4 years	CAS Count (%)	CEA Count (%)	p	Stroke + ipsilateral stroke to 4 years	CAS Count (%)	CEA Count (%)	p
65-70	6 (5.2)	3 (2.4)	0.32	65-70	2 (3.5)	1 (1.7)	0.53
70-75	3 (2.4)	6 (5.4)	0.36	70-75	2 (2.9)	3 (5.2)	0.51
75-80	10 (12.3)	3 (2.8)	0.03	75-80	4 (10.1)	2 (3.4)	0.26
≥ 80	4 (12.4)	1 (2.7)	0.13	≥ 80	2 (12.5)	0 (0.0)	NA
total	23 (5.7)	13 (3.5)		total	10 (5.3)	6 (3.1)	

Table Notes: Post-hoc endpoint of Stroke plus ipsi-lateral stroke by age groups in Asymptomatic patients ≥ 65 years old. P values computed on HR, after adjustment for gender; unadjusted for multiple comparisons.

In the population of asymptomatic elderly patients, there was a non-significant increase in stroke events for CAS over CEA. This increase is more pronounced in the 75-80 and in the  $\geq 80$  years old groups, but is also present in the 65-70 years old category. In the second half of CREST, a similar trend is observed, but is attenuated by the lower event rates observed after CAS.

During the entire enrollment period of CREST, the p-value for interaction is  $p=0.20$ , indicating a lack of a statistically significant differential effect of CAS and CEA by age in symptomatic elderly patients for stroke events. In the second half of CREST, the interaction by age also was not significant ( $p=0.33$ ).

**Peri-Procedural MI (to 30 Days) By 5-Yr Age Groups  
Asymptomatic Elderly (65+) Patient**

All Asymptomatic Patients (N= 775)				Asymptomatic Patients Enrolled in Second Half (N= 381)			
Peri-procedural MI	CAS Count (%)	CEA Count (%)	p	Peri-procedural MI	CAS Count (%)	CEA Count (%)	p
65-70	1 (0.8)	2 (1.6)	0.57	65-70	1 (1.7)	0 (0.0)	NA
70-75	2 (1.6)	6 (4.6)	0.19	70-75	1 (1.4)	3 (5.2)	0.50
75-80	3 (3.5)	5 (4.6)	0.77	75-80	1 (2.4)	4 (6.9)	0.29
$\geq 80$	1 (2.8)	1 (2.5)	0.97	$\geq 80$	0 (0.0)	1 (5.6)	NA
total	7 (1.7)	14 (3.8)		total	3 (1.6)	8 (4.1)	

Table Notes: Post-hoc endpoint of Peri-procedural MI by age groups in Symptomatic patients  $\geq 65$  years old. P values computed on HR, after adjustment for gender; unadjusted for multiple comparisons.

In the population of asymptomatic elderly patients, the rate of MI events after CAS was less than half the rate after CEA (1.7% vs. 3.8%, *All Asymptomatic Patients* above). In the second half of CREST, this trend persisted (1.6% vs. 4.1%). The increase is particularly pronounced in patients  $\geq 75$  years old, albeit not reaching statistical significance, due to the small number of events (5 vs. 1 for CEA and CAS, respectively).

During the entire enrollment period of CREST, the p-value for interaction is  $p=0.40$ , indicating a lack of statistically significant differential effect of CAS and CEA by age for peri-procedural MI in asymptomatic elderly patients. In the second half of CREST, the p-value for interaction also was not significant ( $p=0.39$ ).

### 3.7 Supplemental Analyses: Gender - Asymptomatic Elderly Patients

#### Multiple Endpoints (see Table)

#### By Gender

#### Asymptomatic Elderly (65+) Patients

All Asymptomatic Patients (N= 775)					Asymptomatic Patients Enrolled in Second Half (N= 381)				
DSMI + ipsilateral stroke to 4 years	CAS Count (%)	CEA Count (%)	P	P <sub>i</sub>	DSMI + ipsilateral stroke to 4 years	CAS Count (%)	CEA Count (%)	p	P <sub>i</sub>
Men	21 (9.2)	18 (7.1)	0.32	0.35	Men	8 (6.6)	9 (7.0)	0.90	0.98
Women	7 (5.7)	9 (6.8)	0.64		Women	4 (7.0)	5 (7.8)	0.86	
Stroke + ipsilateral stroke to 4 years	CAS Count (%)	CEA Count (%)	P	P <sub>i</sub>	Stroke + ipsilateral stroke to 4 years	CAS Count (%)	CEA Count (%)	p	P <sub>i</sub>
Men	17 (7.6)	8 (3.4)	0.03	0.31	Men	6 (5.0)	3 (2.3)	0.27	0.74
Women	6 (4.9)	5 (3.8)	0.73		Women	4 (7.0)	3 (4.7)	0.60	
DSMI	CAS Count (%)	CEA Count (%)	P	P <sub>i</sub>	DSMI	CAS Count (%)	CEA Count (%)	p	P <sub>i</sub>
Men	10 (4.1)	12 (4.4)	0.96	0.86	Men	5 (3.9)	8 (6.2)	0.48	0.57
Women	5 (3.9)	6 (4.5)	0.80		Women	3 (5.2)	3 (4.6)	0.88	
Peri-procedural MI	CAS Count (%)	CEA Count (%)	p	P <sub>i</sub>	Peri-procedural MI	CAS Count (%)	CEA Count (%)	p	P <sub>i</sub>
Men	5 (2.0)	10 (3.7)	0.32	0.90	Men	2 (1.6)	6 (4.7)	0.20	0.74
Women	2 (1.6)	4 (3.0)	0.44		Women	1 (1.7)	2 (3.1)	0.63	

Table Notes: Primary endpoint and components for Asymptomatic patients  $\geq 65$  years old (Medicare population). P values computed on HR; unadjusted for multiple comparisons.

There was no statistically significant interaction by gender for the primary composite endpoint and in various components of the primary composite endpoint (stroke plus ipsilateral stroke to 4 years, DSMI, peri-procedural MI) in this population of asymptomatic elderly patients. There were more strokes and fewer MIs for asymptomatic elderly men undergoing CAS, resulting in a similar number of primary composite endpoint events.

In the second half of CREST, excess stroke events among asymptomatic elderly men, while still present, are reduced, and become non-statistically significant. Similarly, more stroke events after CAS are balanced by more MI events after CEA for these same elderly male

patients, resulting in a similar number of primary composite endpoint events for CAS and CEA in the second half as well.

Asymptomatic elderly women had similar outcomes after CAS and CEA across all endpoints analyzed.

## 4 References

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- <sup>1</sup> Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, Cates CU, Creager MA, Fowler SB, Friday G, Hertzberg VS, McIff EB, Moore WS, Panagos PD, Riles TS, Rosenwasser RH, Raylor AJ. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Neuro-Interventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. *J Am Coll Cardiol* 2011; 57:e16-94.
- <sup>2</sup> Rosamond W, Flegal K, Furie K, et al.. Heart disease and stroke statistics – 2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2008;117:e25-146.
- <sup>3</sup> Heron MP, Hoyert DL, Murphy SL, Xu JQ, Kochanek KD, Tejada-Vera B. Deaths: Final data for 2006, National Vital Statistics Reports; 57(14). Hyattsville, MD: National Center for Health Statistics. 2009
- <sup>4</sup> Sacco RL, Kargman DE, et al.. Race-Ethnicity and Determinants of Intracranial Atherosclerotic Cerebral Infarction. The Northern Manhattan Stroke Study. *Stroke*. 1995;26:14-20.
- <sup>5</sup> Wityk RJ, Lehman D, Klag M, et al.. Race and sex differences in the distribution of cerebral atherosclerosis. *Stroke*. 1996;27:1974-80.
- <sup>6</sup> Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, Cates CU, Creager MA, Fowler SB, Friday G, Hertzberg VS, McIff EB, Moore WS, Panagos PD, Riles TS, Rosenwasser RH, Raylor AJ. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Neuro-Interventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. *J Am Coll Cardiol* 2011; 57:e16-94.
- <sup>7</sup> Sitzer M, Puac D, Buehler A, Steckel DA, von Kegler S, Markus HS, Steinmetz H. Internal carotid artery angle of origin: a novel risk factor for early carotid atherosclerosis. *Stroke* 2003;34:950-955.
- <sup>8</sup> Milner, JS, Moore JA, Rutt BK, Steinman DA. Hemodynamics of human carotid artery bifurcations: Computational studies with models reconstructed from magnetic resonance imaging of normal subjects. *J Vasc Surg* 1998;27:143-56.
- <sup>9</sup> Markl M, Wegent F, Zech T, Bauer S, Strecker C, Schumacher M, Weiller C, Hennig J, Harloff A. In vivo wall shear stress distribution in the carotid artery: effect of bifurcation geometry, internal carotid artery stenosis, and recanalization therapy. *Circ Cardiovasc Imaging* 2010;3:647-655.
- <sup>10</sup> Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, Cates CU, Creager MA, Fowler SB, Friday G, Hertzberg VS, McIff EB, Moore WS, Panagos PD, Riles TS, Rosenwasser RH, Raylor AJ. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Neuro-Interventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. *J Am Coll Cardiol* 2011; 57:e16-94.
- <sup>11</sup> Hobson RW, Brott T, Ferguson R, Roubin G, Moore W, Kuntz R, Howard G, Ferguson J. CREST: Carotid Revascularization Endarterectomy versus Stent Trial. *Cardiovascular Surgery* 1997; 5; 457-458.
- <sup>12</sup> Chaturvedi S, Bruno A, Feasby T, et al.. Carotid Endarterectomy- An evidence-based review: Report of the the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2005;65;794

- 
- <sup>13</sup> Furie KL, Kasner SE, Adams RJ, Albers GW, Bush RL, Fagan SC, Halperin JL, Johnston SC, Katzan I, Kernan WN, Mitchell PH, Ovbiagele B, Palesch YY, Sacco RL, Schwamm LH, Wassertheil-Smolter S, Turan TN, Wentworth D, and on behalf of the Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Interdisciplinary Council on Quality of Care and Outcomes Research, Guidelines for the Prevention of Stroke in Patients With Stroke or Transient Stroke: A Guideline for Healthcare Professionals From the American Guidelines for the Prevention of Stroke in Patients With Stroke or Transient Stroke. *Stroke* 2011;42:227-276.
- <sup>14</sup> National Coverage Determination (NCD) for Percutaneous Transluminal ANGIOPLASTY (PTA) (20.7) <https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=201&ncdver=9&CoverageSelection=National&Keyword=angioplasty&KeywordLookup=Title&KeywordSearchType=And&bc=gAAAABAAAA&>
- <sup>15</sup> National Coverage Determination (NCD) for Percutaneous Transluminal ANGIOPLASTY (PTA) (20.7) <https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=201&ncdver=9&CoverageSelection=National&Keyword=angioplasty&KeywordLookup=Title&KeywordSearchType=And&bc=gAAAABAAAA&>
- <sup>16</sup> ICACSF STANDARDS FOR THE ACCREDITATION OF CAROTID STENTING FACILITIES [http://www.icacsf.org/icacsf/seeking/icacsf\\_standards.htm](http://www.icacsf.org/icacsf/seeking/icacsf_standards.htm) accessed June 20, 2011.
- <sup>17</sup> ACE Standards 2010 for Carotid Artery Stenting Accreditation <http://www.cvexcel.org/CAS.aspx> accessed June 20, 2011.
- <sup>18</sup> White CJ, Anderson HV, Brindis RG, Cates CU, Cohen DJ, Ho K, Hopkins LN, Jaff MR, Koroshetz WJ, Rosenfield KA. The Carotid Artery Revascularization and Endarterectomy (CARE) Registry: Objectives, Design and Implications. *Cath Cardiovasc Interv* 2008;71:721-725.
- <sup>19</sup> Anderson HV, Rosenfield KA, White CJ, Ho KKL, Spertus JA, Jones PG, Tang F, Cates CU, Jaff MR, Koroshetz WJ, Katzan IL, Hopkins LN, Rumsfeld JS, Brindis RG. Clinical Features and Outcomes of Carotid Artery Stenting by Clinical Expert Consensus Criteria: A Report from the CARE Registry. *Cath Cardiovasc Interv* 2010;75:519-525.
- <sup>20</sup> Sidawy AN, Zwolak RM, White RA, Siami FS, Schermerhorn ML, Sicard GA, for the Outcomes Committee for the Society for Vascular Surgery. Risk-adjusted 30-day outcomes of carotid stenting and endarterectomy: Results from the SVS Vascular Registry. *J Vasc Surg* 2009;49:71-9.
- <sup>21</sup> Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, Cates CU, Creager MA, Fowler SB, Friday G, Hertzberg VS, McIff EB, Moore WS, Panagos PD, Riles TS, Rosenwasser RH, Raylor AJ. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Neuro-Interventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. *J Am Coll Cardiol* 2011; 57:e16-94.
- <sup>22</sup> Wolff T, Guirguis-Blake J, Miller T, Gillespie M, Harris R. Screening for Carotid Artery Stenosis: An Update of the Evidence for the U.S. Preventive Services Task Force. *Ann Int Med* 2007;147:860-870.
- <sup>23</sup> Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, Cates CU, Creager MA, Fowler SB, Friday G, Hertzberg VS, McIff EB, Moore WS, Panagos PD, Riles TS, Rosenwasser RH, Raylor AJ. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Neuro-Interventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. *J Am Coll Cardiol* 2011; 57:e16-94.
- <sup>24</sup> Hobson RW, Weiss DG, Fields WS, et al.. Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. The Veterans Affairs Cooperative Study Group. *N Engl J Med* 1993;328:221-7.
- <sup>25</sup> Barnett HJM, Taylor DW, Haynes RB, Sackett DL, Peerless SJ, Ferguson GG, Fox AJ, Rankin RN, Hachinski VC, Wiebers DO, Eliasziw M, for the North American Symptomatic Carotid Endarterectomy

---

(NASCET) Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med* 1991;325: 445–53.

<sup>26</sup> European Carotid Surgery Trialists' (ECST) Collaborative Group. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70–99%) or with mild (0–29%) carotid stenosis. *Lancet* 1991;337:1235–43.

<sup>27</sup> Gray WA, Hopkins LN, Yadav S, Davis T, Wholey M, Atkinson R, Cremonesi A, Fairman R, Walker G, Verta P, Popma J, Virmani R, Cohen DJ; ARCHEr Trial Collaborators. Protected carotid stenting in high-surgical-risk patients: the ARCHEr results. *J Vasc Surg*. 2006 Aug;44(2):258-68. Erratum in: *J Vasc Surg*. 2007 Jan;45(1):226.

<sup>28</sup> Gray WA. A Cardiologist in the Carotids. *J Am Coll Cardiol* 2004;43(9):1602-5.

<sup>29</sup> White CJ, Iyer SS, Hopkins LN, et al.. Carotid stenting with distal protection in high surgical risk patients: the BEACH trial 30-day results. *Catheter Cardiovasc Interv*. 2006;67:503–12.

<sup>30</sup> Iyer SS, White CJ, Hopkins LN, Katzen BT, Safian R, Wholey MH, Gray WA, Ciocca R, Bachinsky WB, Ansel G, Joye JD, Russell ME, for the BEACH Pivotal Group. Carotid artery revascularization in high-surgical-risk patients using the Carotid WALLSTENT and FilterWire EX/EZ: one-year outcomes in the BEACH Pivotal Group. *J Am Coll Cardiol* 2008;51(4):427-34.

<sup>31</sup> Safian RD, Jaff MR, Bresnahan JF, Foster M, Bacharach JM, Yadav J, Joye J, Myla S, Kassab E, Mann JT, Ansel GM, for the CREATE SpideRX Trial Investigators. Protected carotid stenting in high-risk patients: results of the SpideRX arm of the carotid revascularization with ev3 arterial technology evolution trial. *J Interv Cardiol* 2010;23(5):491-8.

<sup>32</sup> Gray WA, Yadav JS, Verta P, et al.. The CAPTURE registry: predictors of outcomes in carotid artery stenting with embolic protection for high surgical risk patients in the early post-approval setting. *Catheter Cardiovasc Interv* 2007;70:1025–33.

<sup>33</sup> Gray WM, Rosenfield KA, Jaff MR, Chaturvedi S, Peng L, Verta P. Influence of Site and Operator Characteristics on Carotid Artery Stent Outcomes Analysis of the CAPTURE 2 Clinical Study. *JACC: Cardiol Intv* 2011;4:235-46.

<sup>34</sup> PROTECT manuscript, accepted for publication to *J Vasc Surg*, May 26, 2011.

<sup>35</sup> Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ, Bajwa TK, Whitlow P, Strickman NE, Jaff MR, Popma JJ, Snead DB, Cutlip DE, Firth BG, Ouriel K, for the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy Investigators (SAPPHIRE). Protected Carotid-Artery Stenting Versus Endarterectomy In High-Risk Patients. *N Engl J Med* 2004;351:1493–501.

<sup>36</sup> Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, Cates CU, Creager MA, Fowler SB, Friday G, Hertzberg VS, McIff EB, Moore WS, Panagos PD, Riles TS, Rosenwasser RH, Raylor AJ. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Neuro-Interventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. *J Am Coll Cardiol* 2011; 57:e16-94.

<sup>37</sup> Jordan WE Jr, Alcocer F, Wirthlin DJ, et al. High-risk carotid endarterectomy: challenges for carotid stent protocols. *J Vasc Surg* 2002;35:16-21.

<sup>38</sup> Gasparis AP, Ricotta L, Cuadra SA, et al. High-risk carotid endarterectomy: fact or fiction. *J Vasc Surg* 2003;37:40-6.

<sup>39</sup> Halm EA, Hannan EL, Rojas M, et al. Clinical and operative predictors of outcomes of carotid endarterectomy. *J Vasc Surg* 2005;42:420-8.

<sup>40</sup> Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, Cates CU, Creager MA, Fowler SB, Friday G, Hertzberg VS, McIff EB, Moore WS, Panagos PD, Riles TS, Rosenwasser RH, Raylor AJ. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological



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Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Neuro-Interventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. *J Am Coll Cardiol* 2011; 57:e16-94.

<sup>41</sup> Barnett HJM, Taylor DW, Haynes RB, Sackett DL, Peerless SJ, Ferguson GG, Fox AJ, Rankin RN, Hachinski VC, Wiebers DO, Eliasziw M, for the North American Symptomatic Carotid Endarterectomy (NASCET) Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med* 1991;325: 445–53.

<sup>42</sup> European Carotid Surgery Trialists' (ECST) Collaborative Group. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70–99%) or with mild (0–29%) carotid stenosis. *Lancet* 1991;337:1235–43.

<sup>43</sup> Mayberg MR, Wilson SE, Yatsu F, et al.. Carotid endarterectomy and prevention of cerebral ischemia in symptomatic carotid stenosis. Veterans Affairs Cooperative Studies Program 309 Trialist Group. *JAMA* 1991;266:3289–94.

<sup>44</sup> Barnett HJM, Taylor DW, Haynes RB, Sackett DL, Peerless SJ, Ferguson GG, Fox AJ, Rankin RN, Hachinski VC, Wiebers DO, Eliasziw M, for the North American Symptomatic Carotid Endarterectomy (NASCET) Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med* 1991;325: 445–53.

<sup>45</sup> European Carotid Surgery Trialists' (ECST) Collaborative Group. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70–99%) or with mild (0–29%) carotid stenosis. *Lancet* 1991;337:1235–43.

<sup>46</sup> Mayberg MR, Wilson SE, Yatsu F, et al.. Carotid endarterectomy and prevention of cerebral ischemia in symptomatic carotid stenosis. Veterans Affairs Cooperative Studies Program 309 Trialist Group. *JAMA* 1991;266:3289–94.

<sup>47</sup> Rothwell PM, Eliasziw M, Gutnikov SA, Fox AJ, Taylor DW, Mayberg MR, Warlow CP, Barnett HJM, for the Carotid Endarterectomy Trialists' Collaboration. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet* 2003;361:107-16.

<sup>48</sup> Silver FL, Mackey A, et al. for the CREST Investigators. Safety of Stenting and Endarterectomy by Symptomatic Status in the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST). *Stroke* 2011;42:675-680.

<sup>49</sup> Goldstein LB, Bushnell CD, Adams RJ, et al.. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011 Feb;42(2):517-84.

<sup>50</sup> Furie KL, Kasner SE, Adams RJ, Albers GW, Bush RL, Fagan SC, Halperin JL, Jonston SC, Katzan I, Kernan WN, Mitchell PH, Ovbiagele B, Palesch YY, Sacco RL, Schwamm LH, Wassertheil-Smoller S, Turan TN, Wentworth D. Guidelines for the prevention of stroke in patients with a stroke or transient ischemic attack. A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2010 Oct 21 (pub ahead of print).

<sup>51</sup> Silver FL, Mackey A, et al. for the CREST Investigators. Safety of Stenting and Endarterectomy by Symptomatic Status in the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST). *Stroke* 2011;42:675-680.

<sup>52</sup> Miller FG, and Joffe S. Equipoise and the Dilemma of Randomized Clinical Trials. *N Engl J Med* 2011;364:476-480.

<sup>53</sup> Nienhuis, MB, Ottervanger JP, Bilo HJ, Dikkeschei BD, Zijlstra F. Prognostic value of troponin after elective percutaneous coronary intervention: A meta-analysis. *Cath Cardiovasc Interv* 2008;71(3):318-24.

<sup>54</sup> Kim LJ, Martinez EA, Faraday N, et al. Cardiac troponin I predicts short-term mortality in vascular surgery patients. *Circulation* 2002.

<sup>55</sup> Landesberg G, Shatz V, Akopnik I, et al. Association of cardiac troponin, CK-MB, and postoperative survival after major vascular surgery. *J Am Coll Cardiol* 2003.

<sup>56</sup> Oscarsson A, Eintrei C, Anskar S, et al. Troponin T-values provide long-term prognosis in elderly patients undergoing non-cardiac surgery. *Acta Anaesth Scand* 2004.

<sup>57</sup> Yadav JS, Wholey MH, et al. Protected carotid-artery stenting versus endarterectomy in high risk patients. *N Engl J Med* 2004.

- <sup>58</sup> Bursi F, Babuin L, Barbieri A, et al. Vascular surgery patients: perioperative and long-term risk according to the Acc/AHA guidelines, the additive roles of post-operative troponin elevation. *Eur Heart J* 2005.
- <sup>59</sup> Bursi F, Babuin L, Barbieri A, Politi L, Zennaro M, Grimaldi T, Rumolo A, Gargiulo M, Stella A, Modena MG, Jaffe AS. Vascular surgery patients: perioperative and long-term risk according to the ACC/AHA guidelines, the additive roles of post-operative troponin elevation. *Eur Heart J* 2005;26(22):2358-60.
- <sup>60</sup> Cavallini C, Rugolotto M, Savonitto S. Prognostic significance of creatine kinase release after PCI. *Ital Heart J* 2005;6(6):522-9.
- <sup>61</sup> Prasad A, Singh M, Lerman A, Lennon RJ, Holmes DR Jr., Rihal CS. Isolated elevation in troponin T after percutaneous coronary intervention is associated with higher long-term mortality. *J Am Coll Cardiol* 2006;48(9):1765-70.
- <sup>62</sup> Thygesen K, Alpert JS, White HD, for the Joint European Society of Cardiology / American College of Cardiology Foundation / American Heart Association / World Heart Federation. Universal Definition of Myocardial Infarction. *Circulation* 2007;116:2634-2653.
- <sup>63</sup> Landesberg G, Shatz V, Akopnik I, Wolf RG, Mayer M, Berlatzky Y, Weissman C, Mosseri M. Association of cardiac troponin, CK-MB, and postoperative myocardial ischemia with long-term survival after major vascular surgery. *J Am Coll Cardiol* 2003;42(9):1547-54.
- <sup>63</sup> Lopez-Jimenez F, Goldman L, Sacks DB, Thomas EJ, Johnson PA, Cook EF, Lee TH. Prognostic value of cardiac troponin T after noncardiac surgery: six-month follow-up data. *J Am Coll Cardiol* 1997;29(6):1241-5.
- <sup>64</sup> Kertai MD, Boersma E, Klein J, Van Urk H, Bax JJ, Poldermans D. Long-term prognostic value of asymptomatic cardiac troponin T elevations in patients after major vascular surgery. *Eur J Vasc Endovasc Surg* 2004;28(1):59-66.
- <sup>65</sup> McPhee JT, Hill JS, Ciocca RG, Messina LM, Eslami MH. Carotid endarterectomy was performed with lower stroke and death rates than carotid artery stenting in the United States in 2003 and 2004. *J Vasc Surg* 2007;46:1112-8.e1.
- <sup>66</sup> Ringleb PA, Allenberg J, Bruckmann H, Eckstein HH, Fraedrich G, Hartmann M, Hennerici M, Jansen O, Klein G, Kunze A, Marx P, Niederkorn K, Schmiedt W, Solymosi L, Stingele R, Zeumet H, Hacke W for the SPACE Collaborative Group. 30-day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. *Lancet* 2006;368:1239-1247. Erratum 368:1238.
- <sup>67</sup> Mas JL, Chatellier G, Beyssen B, Branchereau A, Moulin T, Becquemin JP, Larrue V, Lievre M, Leys D, Bonneville JF, Watelet J, Pruvo JP, Albucher JF, Viguier A, Piquet P, Garneir P, Viader F, Touze E, Giroud M, Hosseini H, Pillet JC, Favrole P, Neau JP, Ducrocq X, for the EVA-3S Investigators. Endarterectomy versus Stenting in Patients with Symptomatic Severe Carotid Stenosis. *N Engl J Med* 2006; 355: 1660-71. [Note, overall cerebral protection rate was 91.9%; 78.4% before the Safety Committee recommendation and 97.7% after.]
- <sup>68</sup> Montori VM, Devereaux PJ, Adhikari NKJ, Burns KEA, Eggert CH, Briel M, Lacchetti C, Lwung TW, Darling E, Bryant DM, Bucher HC, Schunemann HJ, Meade MO, Cook CJ, Erwin PH, Sood A, Sood R, Lo B, Thompson CA, Zhou Q, Mills E, Guyatt GH. Randomized Trials Stopped Early for Benefit – A Systematic Review. *JAMA* 2005;294:2203-2209.
- <sup>69</sup> Ederle J, Dobson J, Featherstone RL, Bonati LH, van der Worp HB, de Borst GJ, Lo TH, Gaines P, Dorman PH, Macdonald S, Lyrer PA, Hendriks JM, McCollum C, Nederkoorn PH, Brown MM, Writing Committee for the International Carotid Stenting Study (ICSS) investigators. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (ICSS): an interim analysis of a randomized controlled trial. *Lancet* 2010;375:985-97. [Note, embolic protection was known to have been used in 593 of 828 patients (71.6%); 208 patients did not receive embolic protection and it was not known whether EPD was used in 27 patients.]
- <sup>70</sup> FDA Executive Summary. Circulatory System Devices Panel- Meeting Materials FDA-Generated. January 26, 2011. <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/ucm240575.htm> accessed July 27, 2011.
- <sup>71</sup> FDA Executive Summary. Circulatory System Devices Panel- Meeting Materials FDA-Generated. January 26, 2011. <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/ucm240575.htm> accessed July 27, 2011.

- 
- <sup>72</sup> FDA Executive Summary. Circulatory System Devices Panel- Meeting Materials FDA-Generated. January 26, 2011.  
<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/ucm240575.htm> accessed July 27, 2011.
- <sup>73</sup> Voeks JH, Howard G, Roubin GS, Malas MB, Cohen DJ, Sternbergh WC 3rd, Aronow HD, Eskandari MK, Sheffet AJ, Lal BK, Meschia JF, Brott TG; for the CREST Investigators. Age and Outcomes After Carotid Stenting and Endarterectomy: The Carotid Revascularization Endarterectomy Versus Stenting Trial. *Stroke*. 2011 Dec;42(12):3484-3490. Epub 2011 Oct 6.
- <sup>74</sup> Abbott Vascular Presentation to FDA Circulatory System Devices Advisory Panel, Jan. 26, 2011, available at:  
<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM248647.pdf> accessed on July 7, 2011.
- <sup>75</sup> Brott TG, Hobson RW 2nd, Howard G, Roubin GS, Clark WM, Brooks W, Mackey A, Hill MD, Leimgruber PP, Sheffet AJ, Howard VJ, Moore WS, Voeks JH, Hopkins LN, Cutlip DE, Cohen DJ, Popma JJ, Ferguson RD, Cohen SN, Blackshear JL, Silver FL, Mohr JP, Lal BK, Meschia JF; CREST Investigators. Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med*. 2010 Jul 1;363(1):11-23.
- <sup>76</sup> Howard VJ, Voeks JH, Lutsep HL, Mackey A, Milot G, Sam AD 2<sup>nd</sup>, Rom M, Hughes SE, Sheffet AJ, Longbottom M, Avery JB, Robson RW 2<sup>nd</sup>, Brott TG.. Does Sex Matter? Thirty-day Stroke and Death Rates Following Carotid Artery Stenting in Women vs. Men: Results from CREST Lead-In Phase. *Stroke* 2009;40(4):1140-7.
- <sup>77</sup> Bonati LH, Dobson J, Algra A, Branchereau A, Chatellier G, Fraedrich G, Mali WP, Zeumer H, Brown MM, Mas JL, Ringleb PA, for the Carotid Stenting Trialists' Collaboration. Short-term outcome after stenting versus endarterectomy for symptomatic carotid stenosis: a preplanned meta-analysis of individual patient data. *Lancet* 2010;376:1062-73.
- <sup>78</sup> Howard VJ, Lutsep HL, Mackey A, Demaerschalk BM, Sam AD 2<sup>nd</sup>, Gonzales NR, Sheffet AJ, Voeks JH, Meschia JF, Brott TG, for the CREST Investigators. Influence of sex on outcomes of stenting versus endarterectomy: Results from CREST. *Lancet Neurology*, Published online May 9, 2011, DOI:10.1016/S1474-4422(11)70080-1.
- <sup>79</sup> Bonati LH, Dobson J, Algra A, Branchereau A, Chatellier G, Fraedrich G, Mali WP, Zeumer H, Brown MM, Mas JL, Ringleb PA, for the Carotid Stenting Trialists' Collaboration. Short-term outcome after stenting versus endarterectomy for symptomatic carotid stenosis: a preplanned meta-analysis of individual patient data. *Lancet* 2010;376:1062-73.
- <sup>80</sup> Brown MM, Raine R. Should sex influence the choice between carotid stenting and carotid endarterectomy?, *Lancet Neurol* 2011; 4422:e1-3.
- <sup>81</sup> Rothwell PM, Giles MF, Chandratheva A, Marquardt L, Geraghty O, Redgrave JN, Lovelock CE, Binney LE, Bull LM, Cuthbertson FC, Welch SJ, Bosch S, Alexander FC, Silver LE, Gutnikov SA, Mehta Z. Early use of Existing Preventive Strategies for Stroke (EXPRESS) study. Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. *Lancet* 2007;370:1432-1442.
- <sup>82</sup> Luengo-Fernandez R, Gray AM, Rothwell PM. Effect of urgent treatment for transient ischaemic attack and minor stroke on disability and hospital costs (EXPRESS study): a prospective population-based sequential comparison. *Lancet Neurol* 2009;8:235-43.
- <sup>83</sup> Naylor AR. The importance of initiating 'best medical therapy' and intervening as soon as possible in patients with symptomatic carotid artery disease: time for a radical rethink of practice. *J Cardiovasc Surg (Torino)* 2009;50:773-782.
- <sup>84</sup> Goldstein LB, Bushnell CD, Adams RJ, Appel LJ, Braun LT, Chaturvedi S, Creager MA, Culebras A, Eckel RH, Hart RG, Hinchey JA, Howard VJ, Jauch EC, Levine SR, Meschia JF, Moore WS, Nixon JV, Pearson TA, on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Epidemiology and Prevention, Council for High Blood Pressure Research, Council on Peripheral Vascular Disease, and Interdisciplinary Council on Quality of Care and Outcomes Research. Guidelines for the Primary Prevention of Stroke: A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association. *Stroke* 2011;42:517-584
- <sup>85</sup> Goldstein LB, Bushnell CD, Adams RJ, Appel LJ, Braun LT, Chaturvedi S, Creager MA, Culebras A, Eckel RH, Hart RG, Hinchey JA, Howard VJ, Jauch EC, Levine SR, Meschia JF, Moore WS, Nixon JV, Pearson TA,

---

on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Epidemiology and Prevention, Council for High Blood Pressure Research, Council on Peripheral Vascular Disease, and Interdisciplinary Council on Quality of Care and Outcomes Research. Guidelines for the Primary Prevention of Stroke: A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association. *Stroke* 2011;42:517-584

<sup>86</sup> Silver FL, Mackey A, Clark WM, Brooks W, Timaran CH, Chiu D, Goldstein LB, Meschia JF, Ferguson RD, Moore WS, Howard G, Brott TG, for the CREST Investigators. Safety of Stenting and Endarterectomy by Symptomatic Status in the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST). *Stroke* 2011;42:675-680.

<sup>87</sup> Supplementary Appendix to: Brott TG, Hobson RW II, Howard G, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med* 2010;363:11-23. DOI: 10.1056/NEJMoa0912321. [http://www.nejm.org/doi/suppl/10.1056/NEJMoa0912321/suppl\\_file/nejmoa0912321\\_appendix.pdf](http://www.nejm.org/doi/suppl/10.1056/NEJMoa0912321/suppl_file/nejmoa0912321_appendix.pdf)

<sup>88</sup> Matsumura JS, Gray W, Chaturvedi S, Yamanouchi D, Peng L, Verta P. Results of Carotid Artery Stenting with Distal Embolic Protection with Improved Systems (PROTECT). Accepted for publication to *J Vasc Surg*, on Oct. 17, 2011.

<sup>89</sup> Halliday A, Harrison M, Hayter E, Kong X, Mansfield A, Marro J, Pan H, Peto R, Potter J, Rahimi K, Rau A, Robertson S, Streifler J, Thomas D, for the Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomised trial. *Lancet* 2010; 376: 1074-1084.

<sup>90</sup> Toole JF, Baker WH, Castaldo JE, Chambless LE, Moore WS, Robertson JT, Young B, Howard VJ, Executive Committee for the Asymptomatic Carotid Atherosclerosis Study (ACAS). Endarterectomy for asymptomatic carotid artery stenosis. *JAMA* 1995;273:1421- 8.

<sup>91</sup> Toole JF, Baker WH, Castaldo JE, Chambless LE, Moore WS, Robertson JT, Young B, Howard VJ, Executive Committee for the Asymptomatic Carotid Atherosclerosis Study (ACAS). Endarterectomy for asymptomatic carotid artery stenosis. *JAMA* 1995;273:1421- 8.

<sup>92</sup> Halliday A, Harrison M, Hayter E, Kong X, Mansfield A, Marro J, Pan H, Peto R, Potter J, Rahimi K, Rau A, Robertson S, Streifler J, Thomas D, for the Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomized trial. *Lancet* 2010;376:1074-84.

<sup>93</sup> Ridker PM, MacFadyen JG, Fonseca FAH, Genest J, Gotto AM, Kastelein JJP, Koenig W, Libby P, Lorenzatti AJ, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ, for the JUPITER Study Group. Number Needed to Treat with Rosuvastatin to Prevent First Cardiovascular Events and Death Among Men and Women With Low Low-Density Lipoprotein Cholesterol and Elevated High-Sensitivity C-Reactive Protein. *Circ Cardiovasc Qual Outcomes* 2009;2:616-623.

<sup>94</sup> Halliday A, Harrison M, Hayter E, Kong X, Mansfield A, Marro J, Pan H, Peto R, Potter J, Rahimi K, Rau A, Robertson S, Streifler J, Thomas D, for the Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomized trial. *Lancet* 2010;376:1074-84.

<sup>95</sup> Marquardt L, Geraghty OC, Mehta Z, Rothwell PM. Low Risk of Ipsilateral Stroke in Patients with Asymptomatic Carotid Stenosis on Best Medical Treatment: A Prospective, Population-Based Study. *Stroke* 2010;41:e11-e17.

<sup>96</sup> Choudhry NK, Avorn J, Glynn RJ, Antman EM, Schneeweiss S, Toscano M, Reisman L, Fernandes J, Spettell C, Lee JL, Levin R, Brennan T, Shrank WH, for the Post-Myocardial Infarction Free Rx Event and Economic Evaluation (MI FREEE) Trial. Full Coverage for Preventive Medications after Myocardial Infarction. *New Engl J Med* 2011;365:2088-97.

<sup>97</sup> Ratchford EV, Jin Z, Di Tullio MR, Salameh MJ, Homma S, Gan R, Boden-Albala B, Sacco RL, Rundek T. Carotid bruit for detection of hemodynamically significant carotid stenosis: the Northern Manhattan Study. *Neurol Res.* 2009 Sep;31(7):748-52. Epub 2009 Jan 7.

<sup>98</sup> Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, Cates CU, Creager MA, Fowler SB, Friday G, Hertzberg VS, McIff EB, Moore WS, Panagos PD, Riles TS, Rosenwasser RH, Taylor AJ. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS Guideline On The Management Of Patients With Extracranial Carotid And Vertebral Artery Disease: A Report Of The American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of

---

Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Neuro-Interventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. *J Am Coll Cardiol* 2011; 57:e16-94.

<sup>99</sup> Goldstein, et al. Guidelines for the Primary Prevention of Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. 2011; 42: 517-584.

<sup>100</sup> U.S. Preventive Services Task Force. Screening for carotid artery stenosis: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2007;147:854-859

<sup>101</sup> Ratchford EV, Jin Z, Di Tullio MR, Salameh MJ, Homma S, Gan R, Boden-Albala B, Sacco RL, Rundek T. Carotid bruit for detection of hemodynamically significant carotid stenosis: the Northern Manhattan Study. *Neurol Res* 2009 Sep;31(7):748-52. Epub 2009 Jan 7.

<sup>102</sup> Goldstein, et al. Guidelines for the Primary Prevention of Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. 2011; 42: 517-584.

<sup>103</sup> Ziegler DK, Zileli T, Dick A, Sebaugh JL. Correlation of bruits over the carotid artery with angiographically demonstrated lesions. *Neurology*. 1971 Aug;21(8):860-5.

<sup>104</sup> A David TE, Humphries AW, Young JR, Beven EG. correlation of neck bruits and arteriosclerotic carotid arteries. *Arch Surg*. 1973 Nov;107(5):729-31.

<sup>105</sup> Wolff et al. Screening For Asymptomatic Carotid Artery Stenosis Evidence Syntheses, No. 50 Rockville (MD): Agency for Healthcare Research and Quality (US); December 2007.

<sup>106</sup> Polak JF, Jencina MJ, O'Leary DH, D'Agostino RB. Common Carotid Artery Intima-Media Thickness Progression as a Predictor of Stroke in Multi-Ethnic Study of Atherosclerosis. *Stroke* 2011;42:3017-21.

<sup>107</sup> Gompels GM. High-definition imaging of carotid arteries using a standard commercial ultrasound 'B' scanner. *Br J Radiol* 1979;52(620):608-619.

<sup>108</sup> Sramek A, Bosch JG, Reiber JH, Van Oostayen JA, Rosendaal FR. Ultrasound assessment of atherosclerotic vessel wall changes: reproducibility of intima-media thickness measurements in carotid and femoral arteries. *Invest Radiol* 2000;35(12):699-706.

<sup>109</sup> Eliasziw M, Streifler JY, Fox AJ, Hachinski VC, Ferguson GG, Barnett HJ. Significance of plaque ulceration in symptomatic patients with high-grade carotid stenosis: North American Symptomatic Carotid Endarterectomy Trial. *Stroke* 1994;25:304-8.

<sup>110</sup> Schminke U, Motsch L, Hilker L, Kessler C. Three-dimensional ultrasound observation of carotid artery plaque ulceration. *Stroke* 2000;31:1651-5.

<sup>111</sup> Madani A, Beletsky V, Tamayo A, Munoz C, Spence JD. High-risk asymptomatic carotid stenosis: Ulceration on 3D ultrasound vs TCD microemboli. *Neurology* 2011;77:744-750.

<sup>112</sup> Kaposzta Z, Young E, Bath PM, Markus HS. Clinical application of asymptomatic embolic signal detection in acute stroke: a prospective study. *Stroke* 1999;30(9):1814-18.

<sup>113</sup> Markus HS, King A, Shipley M et al. Asymptomatic Embolization for prediction of stroke in the Asymptomatic Carotid Emboli Study (ACES): a prospective observational study. *Lancet Neurol* 2010;9:663-671. .

<sup>114</sup> Topakian R, King A, Kwon SU, Schaafsma A, Shipley M, Markus HS, for the ACES Investigators. Ultrasonic plaque echolucency and emboli signals predict stroke in asymptomatic carotid stenosis. *Neurology* 2011;77:751-8.

<sup>115</sup> Abbott AL, Chambers BR, Stork JL, Levi CR, Bladin CF, Donnan GA. Embolic signals and prediction of ipsilateral stroke or transient ischemic attack in asymptomatic carotid stenosis: A multicenter prospective cohort study. *Stroke* 2005;36:1128-1133.

<sup>116</sup> King A, Shipley M, Markus H, for the ACES Investigators. Optimizing Protocols for Risk Prediction in Asymptomatic Carotid Stenosis Using Embolic Signal Detection: The Asymptomatic Carotid Emboli Study. *Stroke* 2011;42:2819-24.

<sup>117</sup> Jayasooriya G, Thapar A, Chalhoub J, Davies AH. Silent cerebral events in asymptomatic carotid stenosis. *J Vasc Surg* 2011;54(1):227-36.

<sup>118</sup> Cai J, Hatsukami TS, Ferguson MS et al. *In vivo* quantitative measurement of intact fibrous cap and lipid-rich necrotic core size in atherosclerotic carotid plaque : comparison of high-resolution, contrast-enhanced magnetic resonance imaging and histology. *Circulation* 2005;112(22):3437-3444.

- <sup>119</sup> Ota H, Yarnykh VL, Ferguson MS et al. Carotid intraplaque hemorrhage imaging at 3.0-T MR imaging: comparison of the diagnostic performance of three T1-weighted sequences. *Radiology* 2011;254(2):551-563.
- <sup>120</sup> Saam T, Cai JM, Cai YQ et al. Quantitative evaluation of carotid plaque composition by *in vivo* MRI. *Arterioscler Thromb Vasc Biol* 2005;25(3):234-9.
- <sup>121</sup> Virmani R, Burke AP, Farb A, Kolodgie FD. Pathology of the vulnerable plaque. *JACC* 2006;47(8 Suppl):C13-C18.
- <sup>122</sup> Singh N, Moody AR, Gladstone DJ et al. Moderate carotid artery stenosis: MR imaging-depicted intraplaque hemorrhage predicts risk of cerebrovascular ischemic events in asymptomatic men. *Radiology* 2009;252(2):502-8.
- <sup>123</sup> Takaya N, Uyan C, Chu B et al. Association between carotid plaque characteristics and subsequent ischemic Cerebrovascular events: a prospective assessment with MRI: initial results. *Stroke* 2006;37(3):818-23.
- <sup>124</sup> Zhou W, Dinishak D, Lane B, Hernandez-Boussard T, Bech F, Rosen A. Long-term radiographic outcomes of microemboli following carotid interventions. *J Vasc Surg* 2009;50:1314-9.
- <sup>125</sup> Bonati LH, Jongen LM, Saller S, Flach HZ, Dobson J, Nederkoorn PJ, Macdonald S, Gaines PA, Waaijer A, Stierli P, Rolf HJ, Lyrer PA, Kappelle LJ, Wetzel SG, van der Lugt A, Mali WP, Brown MM, van der Worp HB, Engelter ST, for the ICSS MRI study group. New ischaemic brain lesions on MRI after stenting or endarterectomy for symptomatic carotid stenosis: a substudy of the International Carotid Stenting Study (ICSS). *Lancet Neurol* 2010;9:353-62.
- <sup>126</sup> Hermus L, Lefrandt JD, Tio RA, Breek JC, Zeebregts CJ. Carotid plaque formation and serum biomarkers. *Atherosclerosis* 2010;213(1):21-29.
- <sup>127</sup> Scarcello E, Morrone F, Piro P, Tarsitano S, Intrieri F, Vaccarella S, Guerra E, Serra R, de Franciscis S. Protein S-100B as Biochemical Marker of Brain Ischemic Damage After Treatment of Carotid Stenosis. *Ann Vasc Surg* 2011;25:975-978.
- <sup>128</sup> Aziz K, Berger K, Claycombe K, Huang R, Patel R, Abela GS. Noninvasive detection and localization of vulnerable plaque and arterial thrombosis with computed tomography angiography/positron emission tomography. *Circulation* 2008;117(16):2061-2070.
- <sup>129</sup> Rudd JH, Warburton EA, Fryer TD et al. Imaging atherosclerotic plaque inflammation with [18-F]-fluorodeoxyglucose positron emission tomography. *Circulation* 2002;105(23):2708-2711.
- <sup>130</sup> Tawakol A, Migrino RQ, Hoffmann U et al. Noninvasive *in vivo* measurement of vascular inflammation with F-18 fluorodeoxyglucose positron emission tomography. *J Nucl Cardiol* 2005;12(3):294-301.
- <sup>131</sup> Nicolaides AN, Kakkos SK, Kyriacou E, Griffin M, Sabetai M, Thomas DJ, Tegos T, Geroulakos G, Labropoulos N, Dore CJ, Morris TP, Naylor R, Abbott AL, for the Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) Study Group. Asymptomatic internal carotid artery stenosis and cerebrovascular risk stratification. *J Vasc Surg* 2010;52:1486-96.
- <sup>132</sup> Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, Cates CU, Creager MA, Fowler SB, Friday G, Hertzberg VS, McIff EB, Moore WS, Panagos PD, Riles TS, Rosenwasser RH, Raylor AJ. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Neuro-Interventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. *J Am Coll Cardiol* 2011; 57:e16-94.
- <sup>133</sup> Goldstein LB, Bushnell CD, Adams RJ, Appel LJ, Braun LT, Chaturvedi S, Creager MA, Culebras A, Eckel RH, Hart RG, Hinchey JA, Howard RJ, Jauch EC, Levine SR, Meschia JF, Moore WS, Nixon JV, Pearson TA and on behalf of the Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, Council for High Blood Pressure Research, Council on Peripheral Vascular Disease and Interdisciplinary Council on Quality of Care and Outcomes Research Guidelines for the Primary Prevention of Stroke: A guideline for Healthcare Professionals from the American Heart Association/American Stroke Association, *Stroke* 2011;42:517-584.
- <sup>134</sup> DeBakey ME. Successful carotid endarterectomy for cerebrovascular insufficiency. Nineteen-year follow-up. *JAMA* 1975;233:1083-5.

- 
- <sup>135</sup> Eastcott HH, Pickering GW, Rob CG. Reconstruction of internal carotid artery in a patient with intermittent attacks of hemiplegia. *Lancet* 1954;267:994–6.
- <sup>136</sup> Bates ER, Babb JD, Casey DE, Cates CU, Duckwiler GR, Feldman TE, Gray WA, Ouriel K, Peterson ED, Rosenfield K, Rundback JH, Safian RD, Sloan MA, White CJ. ACCF/SCAI/SVMB/SIR/ASITN 2007 clinical expert consensus document on carotid stenting: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents (ACCF/SCAI/SVMB/SIR/ASITN Clinical Expert Consensus Document Committee on Carotid Stenting). *J Am Coll Cardiol* 2007;49:126–70.
- <sup>137</sup> Barnett HJM, Taylor DW, Haynes RB, Sackett DL, Peerless SJ, Ferguson GG, Fox AJ, Rankin RN, Hachinski VC, Wiebers DO, Eliasziw M, for the North American Symptomatic Carotid Endarterectomy (NASCET) Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med* 1991;325: 445–53.
- <sup>138</sup> Barnett HJ, Taylor DW, Eliasziw M, Fox AJ, Ferguson GG, Haynes RB, Rankin RN, Clagett GP, Hachinski VC, Sackett DL, Thorpe KE, Meldrum HE, for the North American Symptomatic Carotid Endarterectomy (NASCET) Trial Collaborators. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. *N Engl J Med* 1998;339:1415–25.
- <sup>139</sup> Toole JF, Baker WH, Castaldo JE, Chambless LE, Moore WS, Robertson JT, Young B, Howard VJ, Executive Committee for the Asymptomatic Carotid Atherosclerosis Study (ACAS). Endarterectomy for asymptomatic carotid artery stenosis. *JAMA* 1995;273:1421–8.
- <sup>140</sup> Halliday A, Mansfield A, Marro J, Peto C, Peto R, Potter J, Thomas D, for the ACST Collaborative Group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet* 2004;363:1491–502.
- <sup>141</sup> European Carotid Surgery Trialists' (ECST) Collaborative Group. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70–99%) or with mild (0–29%) carotid stenosis. *Lancet* 1991;337:1235–43.
- <sup>142</sup> Farrell B, Fraser A, Sandercock P, Slattery J, Warlow CP, Writing Committee for the European Carotid Surgery Trial (ECST). Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial. *Lancet* 1998;351:1379–87.
- <sup>143</sup> Mayberg MR, Wilson SE, Yatsu F, et al.. Carotid endarterectomy and prevention of cerebral ischemia in symptomatic carotid stenosis. Veterans Affairs Cooperative Studies Program 309 Trialist Group. *JAMA* 1991;266:3289–94.
- <sup>144</sup> Hobson RW, Weiss DG, Fields WS, et al.. Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. The Veterans Affairs Cooperative Study Group. *N Engl J Med* 1993;328:221–7.
- <sup>145</sup> Chaturvedi S, Bruno A, Feasby T, et al.. Carotid Endarterectomy- An evidence-based review: Report of the the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2005;65:794
- <sup>146</sup> Goldstein LB, Bushnell CD, Adams RJ, Appel LJ, Braun LT, Chaturvedi S, Creager MA, Culebras A, Eckel RH, Hart RG, Hinchey JA, Howard RJ, Jauch EC, Levine SR, Meschia JF, Moore WS, Nixon JV, Pearson TA and on behalf of the Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, Council for High Blood Pressure Research, Council on Peripheral Vascular Disease and Interdisciplinary Council on Quality of Care and Outcomes Research Guidelines for the Primary Prevention of Stroke: A guideline for Healthcare Professionals from the American Heart Association/American Stroke Association, *Stroke* 2011;42:517-584.
- <sup>147</sup> Furie KL, Kasner SE, Adams RJ, Albers GW, Bush RL, Fagan SC, Halperin JL, Johnston SC, Katzan I, Kernan WN, Mitchell PH, Ovbiagele B, Palesch YY, Sacco RL, Schwamm LH, Wassertheil-Smoller S, Turan TN, Wentworth D, and on behalf of the Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Interdisciplinary Council on Quality of Care and Outcomes Research, Guidelines for the Prevention of Stroke in Patients With Stroke or Transient Stroke: A Guideline for Healthcare Professionals From the American Guidelines for the Prevention of Stroke in Patients With Stroke or Transient Stroke. *Stroke* 2011;42:227-276.
- <sup>148</sup> Lal BK and Hobson RW. Treatment of Carotid Artery Disease: Stenting or Surgery? *Curr Neurol Neurosci Rep.* 2007 Jan;7(1):49-53.
- <sup>149</sup> Finks JF, Osborne NH, Birkmeyer JD. Trends in Hospital Volume and Operative Mortality for High-Risk Surgery. *N Engl J Med.* 2011;364:2128-37.

- 
- <sup>150</sup> Weighted national estimate for Medicare as a primary payer from HCUP Nationwide Inpatient Sample (NIS), Agency for Healthcare Research and Quality (AHRQ), based on data collected by individual States and provided to AHRQ by the States. Downloaded July 25, 2011 from <http://hcupnet.ahrq.gov/> for ICD-9-CM principle procedure code 38.12 – *Endarterectomy; other vessels of head and neck*.
- <sup>151</sup> Al-Mubarak N, Roubin G, Iyer S, Vitek J, *Carotid Artery Stenting* Lippincott Williams & Wilkins, 2004.
- <sup>152</sup> Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, Cates CU, Creager MA, Fowler SB, Friday G, Hertzberg VS, McIff EB, Moore WS, Panagos PD, Riles TS, Rosenwasser RH, Raylor AJ. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Neuro-Interventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. *J Am Coll Cardiol* 2011; 57:e16-94.
- <sup>153</sup> Goldstein LB, Bushnell CD, Adams RJ, Appel LJ, Braun LT, Chaturvedi S, Creager MA, Culebras A, Eckel RH, Hart RG, Hinchey JA, Howard RJ, Jauch EC, Levine SR, Meschia JF, Moore WS, Nixon JV, Pearson TA and on behalf of the Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, Council for High Blood Pressure Research, Council on Peripheral Vascular Disease and Interdisciplinary Council on Quality of Care and Outcomes Research Guidelines for the Primary Prevention of Stroke: A guideline for Healthcare Professionals from the American Heart Association/American Stroke Association, *Stroke* 2011;42;517-584.
- <sup>154</sup> Furie KL, Kasner SE, Adams RJ, Albers GW, Bush RL, Fagan SC, Halperin JL, Johnston SC, Katzan I, Kernan WN, Mitchell PH, Ovbiagele B, Palesch YY, Sacco RL, Schwamm LH, Wassertheil-Smoller S, Turan TN, Wentworth D, and on behalf of the Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Interdisciplinary Council on Quality of Care and Outcomes Research, Guidelines for the Prevention of Stroke in Patients With Stroke or Transient Stroke: A Guideline for Healthcare Professionals From the American Guidelines for the Prevention of Stroke in Patients With Stroke or Transient Stroke. *Stroke* 2011;42;227-276
- <sup>155</sup> Medicare Provider and Analysis Review (MedPAR) file for FY 2009, MS- DRGs 034, 035 and 036 (Carotid Artery Stenting Procedure, with Major Complications and Comorbidities (w/ MCC), with Complications and Comorbidities (w/ CC), without CC/MCC, respectively). Downloaded July 25, 2011 from [http://www.cms.gov/MedicareFeeForSvcPartsAB/03\\_MEDPAR.asp](http://www.cms.gov/MedicareFeeForSvcPartsAB/03_MEDPAR.asp).
- <sup>156</sup> NACPTAR Investigators. Update of the immediate angiographic results and in-hospital central nervous system complications of cerebral percutaneous transluminal angioplasty. *Circulation* 1995;92:383.
- <sup>157</sup> Lal BK and Hobson RW. Treatment of Carotid Artery Disease: Stenting or Surgery? *Curr Neurol Neurosci Rep*. 2007 Jan;7(1):49-53.
- <sup>158</sup> Al-Mubarak N, Roubin G, Iyer S, Vitek J, *Carotid Artery Stenting* Lippincott Williams & Wilkins, 2004.
- <sup>159</sup> Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, Cates CU, Creager MA, Fowler SB, Friday G, Hertzberg VS, McIff EB, Moore WS, Panagos PD, Riles TS, Rosenwasser RH, Raylor AJ. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Neuro-Interventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. *J Am Coll Cardiol* 2011; 57:e16-94.
- <sup>160</sup> Wholey MH, Al-Mubarek N, Wholey MH. Updated review of the global carotid artery stent registry. *Catheter Cardiovasc Interv*. 2003;60:259–66.
- <sup>161</sup> Theiss W, Hermanek P, Mathias K, et al.. Pro-CAS: a prospective registry of carotid angioplasty and stenting. *Stroke*. 2004;35:2134 –9.
- <sup>162</sup> Kastrup A, Groschel K, Krapf H, et al.. Early outcome of carotid angioplasty and stenting with and without cerebral protection devices: a systematic review of the literature. *Stroke*. 2003;34:813–9.



- <sup>163</sup> Roubin GS, New G, Iyer SS, et al.. Immediate and late clinical outcomes of carotid artery stenting in patients with symptomatic and asymptomatic carotid artery stenosis: a five-year prospective analysis. *Circulation*. 2001;103:532–7.
- <sup>164</sup> Gurm HS, Yadav JS, Fayad P, et al.. Long-term results of carotid stenting versus endarterectomy in high-risk patients. *N Engl J Med*. 2008;358:1572–9.
- <sup>165</sup> Safian RD, Bresnahan JF, Jaff MR, et al.. Protected carotid stenting in high-risk patients with severe carotid artery stenosis. *J Am Coll Cardiol*. 2006;47:2384–9.
- <sup>166</sup> Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ, Bajwa TK, Whitlow P, Strickman NE, Jaff MR, Popma JJ, Snead DB, Cutlip DE, Firth BG, Ouriel K, for the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy Investigators (SAPPHIRE). Protected Carotid-Artery Stenting Versus Endarterectomy In High-Risk Patients. *N Engl J Med* 2004;351:1493–501.
- <sup>167</sup> White CJ, Iyer SS, Hopkins LN, et al.. Carotid stenting with distal protection in high surgical risk patients: the BEACH trial 30-day results. *Catheter Cardiovasc Interv*. 2006;67:503–12.
- <sup>168</sup> Garg N, Karagiorgos N, Pisimisis GT, et al.. Cerebral protection devices reduce peri-procedural strokes during carotid angioplasty and stenting: a systematic review of the current literature. *J Endovasc Ther*. 2009;16:412–27.
- <sup>169</sup> Barbato JE, Dillavou E, Horowitz MB, Jovin TG, Kanal E, David S, Makaroun MS. A randomized trial of carotid artery stenting with and without cerebral protection. *J Vasc Surg* 2008;47:760-765.
- <sup>170</sup> Cloft HJ. Distal protection: Maybe less than you think. *Am J Neuroradiol* 2008;29:407-8.
- <sup>171</sup> Atkins MD, Bush RL. Embolic protection devices for carotid artery stenting: Have they made a significant difference in outcomes? *Semin Vasc Surg* 2007;20:244-51.
- <sup>172</sup> Vos JA, van den Berg JC, Ernst SM, Suttorp MJ, Overtoom TT, Mauser HW, Vogels OJ, van Heesewijk HP, Moll FL, van der Graaf Y, Mali WP, Ackerstaff RG. Carotid angioplasty and stent placement; Comparison of transcranial Doppler US data and clinical outcome with and without filtering cerebral protection devices in 509 patients. *Radiology* 2005;234:493-499.
- <sup>173</sup> Henry M, Polydorou A, Henry I, Polydorou AD, Hugel M. Carotid angioplasty and stenting under protection; Advantages and drawbacks. *Expert Rev Med Devices* 2008;5:591-603.
- <sup>174</sup> National Coverage Determination (NCD) for Percutaneous Transluminal Angioplasty (PTA) (20.7) Transmittal 115. CR6839. <http://www.cms.gov/transmittals/downloads/R115NCD.pdf>, accessed March 5, 2010.
- <sup>175</sup> Brewster LP, Beaulieu R, Corriere MA, Veeraswamy R, Niazi KA, Robertson G, Dodson TF, Kasirajan K. Carotid revascularization outcomes comparing distal filters, flow reversal, and endarterectomy. *J Vasc Surg* 2011 Oct;54(4):1000-4.
- <sup>176</sup> Stabile E, Salemme L, Sorropago G, Tesorio T, Nammias W, Miranda M, Popusoi G, Cioppa A, Ambrosini V, Cota L, Petroni G, Della Pietra G, Ausania A, Fontanelli A, Biamino G, Rubino P. Proximal Endovascular Occlusion for Carotid Artery Stenting: Results from a Prospective Registry of 1,300 Patients. *J Am Coll Cardiol* 2010;55:1661-7.
- <sup>177</sup> Pinter L, Ribo M, Loh C, Lane B, Roberts T, Chou TM, Kolvenback RR. Safety and feasibility of a novel transcervical access neuroprotection system for carotid artery stenting in the PROOF study. *J Vasc Surg* 2011;54:1317-23.
- <sup>178</sup> Connors J, Sacks D, et al.. (2005) Training, competency, and credentialing standards for diagnostic cervicocerebral angiography, carotid stenting, and cerebrovascular intervention. A Joint Statement from the American Academy of Neurology, the American Association of Neurological Surgeons, the American Society of Interventional and Therapeutic Neuroradiology, the American Society of Neuroradiology, the Congress of Neurological Surgeons, the AANS/CNS Cerebrovascular Section, and the Society of Interventional Radiology. *Neurology* 64:190-198.
- <sup>179</sup> Sacks D, Connors J. (2009) Carotid Stenting, Stroke Prevention, and Training. *J Vasc Interv Radiol* 2009; 20(7S): S302-S305.
- <sup>180</sup> Gray WM, Rosenfield KA, Jaff MR, Chaturvedi S, Peng L, Verta P. Influence of Site and Operator Characteristics on Carotid Artery Stent Outcomes Analysis of the CAPTURE 2 Clinical Study. *JACC: Cardiol Intv* 2011;4:235-46.
- <sup>181</sup> Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, Cates CU, Creager MA, Fowler SB, Friday G, Hertzberg VS, McIff EB, Moore WS, Panagos PD, Riles TS, Rosenwasser RH, Raylor AJ. 2011

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ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Neuro-Interventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. *J Am Coll Cardiol* 2011; 57:e16-94.

<sup>182</sup> Brown MM, Rogers J, Bland JM, for the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS). Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. *Lancet*. 2001;357: 1729–37.

<sup>183</sup> Mas JL, Chatellier G, Beyssen B, Branchereau A, Moulin T, Becquemin JP, Larrue V, Lievre M, Leys D, Bonneville JF, Watelet J, Pruvo JP, Albucher JF, Viguier A, Piquet P, Garneir P, Viader F, Touze E, Giroud M, hosseini H, Pillet JC, Favrole P, Neau JP, Ducrocq X, for the EVA-3S Investigators. Endarterectomy versus Stenting in Patients with Symptomatic Severe Carotid Stenosis. *N Engl J Med* 2006; 355: 1660-71.

<sup>184</sup> Ringleb PA, Allenberg J, Bruckmann H, et al.. 30-day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial [published correction appears in *Lancet*. 2006;368:1238]. *Lancet*. 2006;368:1239–47.

<sup>185</sup> Brott TG, Hobson RW 2nd, Howard G, Roubin GS, Clark WM, Brooks W, Mackey A, Hill MD, Leimgruber PP, Sheffet AJ, Howard VJ, Moore WS, Voeks JH, Hopkins LN, Cutlip DE, Cohen DJ, Popma JJ, Ferguson RD, Cohen SN, Blackshear JL, Silver FL, Mohr JP, Lal BK, Meschia JF; CREST Investigators. Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med*. 2010 Jul 1;363(1):11-23. Epub 2010 May 26.

<sup>186</sup> Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ, Bajwa TK, Whitlow P, Strickman NE, Jaff MR, Popma JJ, Snead DB, Cutlip DE, Firth BG, Ouriel K, for the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy Investigators (SAPPHIRE). Protected Carotid-Artery Stenting Versus Endarterectomy In High-Risk Patients. *N Engl J Med* 2004;351:1493–501.

<sup>187</sup> Gray WA, Hopkins LN, Yadav S, Davis T, Wholey M, Atkinson R, Cremonesi A, Fairman R, Walker G, Verta P, Popma J, Virmani R, Cohen DJ; ARChER Trial Collaborators. Protected carotid stenting in high-surgical-risk patients: the ARChER results. *J Vasc Surg*. 2006 Aug;44(2):258-68. Erratum in: *J Vasc Surg*. 2007 Jan;45(1):226.

<sup>188</sup> Brott TG, Hobson RW 2nd, Howard G, Roubin GS, Clark WM, Brooks W, Mackey A, Hill MD, Leimgruber PP, Sheffet AJ, Howard VJ, Moore WS, Voeks JH, Hopkins LN, Cutlip DE, Cohen DJ, Popma JJ, Ferguson RD, Cohen SN, Blackshear JL, Silver FL, Mohr JP, Lal BK, Meschia JF; CREST Investigators. Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med*. 2010 Jul 1;363(1):11-23.

<sup>189</sup> Gray WA. A Cardiologist in the Carotids. *J Am Coll Cardiol* 2004;43(9):1602-5.

<sup>190</sup> Iyer SS, White CJ, Hopkins LN, Katzen BT, Safian R, Wholey MH, Gray WA, Ciocca R, Bachinsky WB, Ansel G, Joye JD, Russell ME, for the BEACH Pivotal Group. Carotid artery revascularization in high-surgical-risk patients using the Carotid WALLSTENT and FilterWire EX/EZ: one-year outcomes in the BEACH Pivotal Group. *J Am Coll Cardiol* 2008;51(4):427-34.

<sup>191</sup> Safian RD, Jaff MR, Bresnahan JF, Foster M, Bacharach JM, Yadav J, Joye J, Myla S, Kassab E, Mann JT, Ansel GM, for the CREATE SpideRX Trial Investigators. Protected carotid stenting in high-risk patients: results of the SpideRX arm of the carotid revascularization with ev3 arterial technology evolution trial. *J Interv Cardiol* 2010;23(5):491-8.

<sup>192</sup> Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ, Bajwa TK, Whitlow P, Strickman NE, Jaff MR, Popma JJ, Snead DB, Cutlip DE, Firth BG, Ouriel K, for the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy Investigators (SAPPHIRE). Protected Carotid-Artery Stenting Versus Endarterectomy In High-Risk Patients. *N Engl J Med* 2004;351:1493–501.

<sup>193</sup> Higashida RT, Popma JJ, Apruzzese P, Zimetbaum P, on behalf of the MAVERiC I and II Investigators. Evaluation of the Medtronic Exponent Self-Expanding Carotid Stent System with the Medtronic Guardwire Temporary Occlusion and Aspiration System in the Treatment of Carotid Stenosis. *Stroke* 2010;41(2):e102-9.