Centers for Medicare and Medicaid Services conducts a medical evidence development and coverage advisory committee meeting on carotid atherosclerosis

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Publication of the eagerly anticipated Carotid Revascularization Endarterectomy Versus Stenting Trial in May 2010 was anticipated to engender much activity in the realm of interventions for carotid stenosis. Specifically, a variety of professional societies, including the Society for Vascular Surgery (SVS), published updated practice guidelines in the calendar year 2011, timed to include data from large-scale well-conducted clinical trials comparing carotid endarterectomy with carotid artery stenting (CAS). In anticipation of a renewed application to the Centers for Medicare and Medicaid Services (CMS) to reconsider the national coverage determination for CAS, the SVS Board of Directors voted in June 2011 against any change in the national coverage determination for CAS. CMS convened a Medicare evidence development and coverage advisory committee (MEDCAC) meeting to consider fundamental aspects of the treatment of carotid atherosclerosis on January 25, 2012, to allow an unbiased and current deliberation of the state-of-the-art technology and science referable to the management of carotid atherosclerosis. The MEDCAC differs substantially from a reconsideration of coverage determination and, in this case, was built around seven research questions. The MEDCAC consists of a panel of experts who, after reviewing the literature and submitted comments by interested stakeholders, and after hearing testimony from invited speakers and at-large presentations, held a panel vote on the research questions. Given that management of carotid atherosclerosis is a core element of vascular surgical practice, the SVS had a major presence at the MEDCAC in the form of a comprehensive written document individually considering the research questions and a variety of presentations addressing various aspects in carotid disease management. The purpose of this report is to detail the SVS's position on the MEDCAC research questions referable to the management of carotid atherosclerosis and to otherwise detail the proceedings of the MEDCAC. (J Vasc Surg 2012;56:e1-16.)

At the present time, there is a national coverage determination (NCD) restricting reimbursement for carotid angioplasty and stenting (CAS) to specifically defined patient subsets (full details at http://www.cms.gov/medicare-coverage-database/details/medcac-meeting-details.aspx?MEDCACId=62&bc=AAAIAAAAAAAA.). These include symptomatic patients with ≥70% carotid stenosis who are considered at high risk for carotid endarterectomy and/or symptomatic or asymptomatic patients enrolled in U.S. Food and Drug Administration-approved clinical trials or high-risk registries. On a number of different occasions (September 2006-CAG-00853R, February 2007-CAG-0085R3, and March 2008-CAG-00885R6), the Society for Vascular Surgery (SVS) has offered position statements related to the NCD for CAS; typically this has occurred in the context of a reconsideration of the NCD for CAS. Consistent with the position statements related in these communications, at its June 2011 meeting, the SVS Board of Directors, by a vote of 21 to 22, voted against any change in the SVS position referable to the NCD for CAS at this point in time. This was in anticipation of another application for reconsideration of the NCD for CAS in light of the publication of the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST). In fact, the corporate cosponsor of the CREST trial did submit such application but was denied in this regard by the Centers for Medicare and Medicaid Services (CMS).

Instead, CMS decided to convene a medical evidence development and coverage advisory committee meeting (MEDCAC), which is designed (as defined in the CMS Web site) to "review and evaluate the medical literature, technology assessment, and vet public testimony on the evidence available to address the impact of medical items and services on health outcomes in Medicare beneficiaries." The MEDCAC mechanism, established in 1998, is used to supplement CMS's internal expertise and allow an unbiased and current deliberation of the state-of-the-art technology and science. The MEDCAC consists of a pool of 100 appointed members who are recognized authorities in clinical medicine or disciplines, or both, related to clinical trial evidence, such as epidemiology and biostatistics, health

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care management or economics (or both), patient advocacy, or other relevant disciplines.

Participating members in the carotid atherosclerosis MEDCAC of January 25, 2012 are detailed on the CMS Web site, as is the rationale and detail of the seven research questions referable to carotid atherosclerosis constituting the subject matter of this particular MEDCAC. Specific disciplines represented by the 15 sitting or invited guest panel members for the MEDCAC included neurologists (three), general internal medicine (four), health care policy (four), and other disciplines, including nursing (one). An industry representative was also present. Invited guest speakers were allotted 20 minutes to present to the MEDCAC panel, with such speakers clearly intended to represent a spectrum of disciplines and positions and perhaps based on their prior publications. The invited guest speakers at the MEDCAC included (alphabetical order):

1. Anne L. Abbott, MD, PhD, a research neurologist from Australia, whose publications advocate optimal best medical therapy (BMT) alone as sufficient treatment for asymptomatic carotid stenosis.
2. Thomas G. Brott, MD, Professor of Neurology at the Mayo Clinic and National Coprincipal Investigator of the CREST trial, whose presentation largely centered on the rationale for and design of a potential CREST 2 trial whose design would entail randomization of patients with asymptomatic high-grade stenoses to intervention (both CEA and CAS) vs BMT.
3. Mark D. Grant, MD, MPH, Director, Technology Evaluation Center, Blue Cross Blue Shield Association.
4. William A. Gray, MD, Associate Professor of Clinical Medicine, Columbia University College of Physicians and Surgeons. Dr Gray is widely published in the realm of CAS registries and as anticipated advocated extending reimbursement for CAS, based largely or exclusively on CREST data.
5. Wesley S. Moore, MD, Professor and Chief Emeritus, Division of Vascular Surgery, David Geffen School of Medicine at the University of California, Los Angeles. Dr Moore is the surgeon coprincipal investigator of the national CREST trial and a recognized authority in the management of carotid atherosclerosis over a long period of time. Dr Moore was also the 2011 Lifetime Achievement Award winner of the SVS. Dr Moore's testimony, while representing his personal views, was ultimately entirely consistent with that of SVS.

The seven research questions detailed below were published in the Federal Register. The preamble to the seven research questions states:

> The primary focus of the Medicare evidence development and coverage advisory Committee (MEDCAC) meeting is whether or not CAS, CEA, and BMT improve outcomes in symptomatic and asymptomatic persons with carotid atherosclerosis. In discussing the management of such individuals, CMS is most interested in stroke prevention, and the health outcomes of interest are stroke (all stroke) and death (all-cause mortality).

After the presentations and questioning by the panel members (largely confined to the invited speakers), the panel voted on the six voting questions (a question on unmet research needs was not a voting question) along a hierarchal scale (1, low confidence; 5, high confidence) on the adequacy of the *published evidence* referable to the research questions. Panel Chair Clifford Goodman, PhD, repeatedly emphasized that the MEDCAC was interested in the adequacy of evidence rather than in opinion or individual experience.

"Interested stakeholders" were invited to submit written comments on the research questions or apply to speak publicly at the MEDCAC, or both. Written comments to the MEDCAC were submitted by SVS, as detailed below, the American Heart Association (AHA)/American Stroke Association, the American Academy of Neurology, and the Society of Interventional Radiology. The specific list of public comment speakers is available on the CMS Web site and included a spokesman for the American Academy of Neurology, the American Association of Neurological Surgeons/Congress of Neurological Surgeons, the Society of Neurointerventional Surgery, the American College of Cardiology (ACC), the Society for Cardiovascular Angiography and Intervention, and the Society for Vascular Medicine. The Chief Medical Officer of Abbott Vascular also presented.

All at-large speakers were limited to 4 minutes. SVS speakers comprised six of 14 at-large speakers, all of whom are required to register and submit presentations a month in advance of the MEDCAC. SVS, to augment its extensive written comments and reflect the importance of carotid disease management to its members, offered six presentations, detailed below, delivered in large part by executive committee members, as follows:

1. General comments on management of carotid atherosclerosis (Richard P. Cambria, MD, SVS President);
2. Clinical decision making in asymptomatic patients (John J. Ricotta, MD, SVS Secretary);
3. Real-world results of CEA vs CAS (Robert Zwolak, MD, immediate Past President, SVS);
4. Randomized trial data of CEA vs CAS (Peter Gloviczki, MD, SVS President-Elect);
5. Vascular surgeons as leaders in CAS (Daniel Clair, MD, Chairman, Department of Vascular Surgery, Cleveland Clinic Foundation); and
6. Cost implications of changing the NCD (Julie Freischlag, MD, SVS Vice-President).

Although the MEDCAC was not convened to consider a change in the NCD for CAS, virtually all speakers and professional society representatives voiced position statements on this issue. Predictably, interventional societies (eg, Society of Interventional Radiology and Society for Cardiac Angiography and Intervention) spoke in favor of expanded coverage for CAS, whereas professional societies

concentrating on total patient management, including the SVS, American Association of Neurological Surgeons, and the American Academy of Neurology, voiced position statements against expansion for CAS, in particular in asymptomatic patients. The SVS position is, of course, clearly articulated in the recently published updated SVS practice guidelines referable to extracranial cerebrovascular disease.[1] For purposes of the MEDCAC, the SVS position on the NCD for CAS was also outlined in a cover letter to the CMS coverage group (available on the CMS Web site).

The MEDCAC process involved the panel's review of the available literature and the submitted written comments and testimony of the invited speakers, who were then specifically questioned for a period of time by the panel. The panel clearly gave major consideration to the invited speakers, and accordingly, it is appropriate to summarize briefly the presentations of these invited speakers (see Discussion).

The SVS believes that its members and readers of the *Journal of Vascular Surgery* should be adequately informed about the latest evidence referable to the management of carotid atherosclerosis. Indeed, at a special retreat of its research council, the SVS recently identified management of asymptomatic carotid atherosclerosis as its number 1 clinical research priority. The seven research questions considered by the MEDCAC are detailed individually in what follows, along with the SVS reply and the MEDCAC panel voting results to the individual questions.

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?

THE 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 A REASONABLE, IF IMPERFECT, SURROGATE FOR HIGH RISK. THE SVS AGREES THAT FURTHER RESEARCH IN THIS AREA IS NEEDED.

The degree of carotid bifurcation stenosis has been the most significant factor in determining whether symptomatic and asymptomatic patients were both at risk of subsequent neurologic events. Stenosis was initially determined exclusively by angiography, but as noninvasive 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, Chambers and Norris[2] correlated both the degree of stenosis and the occurrence of plaque progression with stroke risk. Roederer et al[3] monitored patients with cervical bruits and documented a high incidence of symptoms associated with plaque progression (35% at 6 months; 48% at 1 year). These and other observational data were subsequently confirmed by three prospective randomized trials that have shown the utility of stenosis as a predictor of increased stroke risk that can be reduced by CEA:

- The Veterans Affairs (VA) trial[4] randomized 444 asymptomatic patients with hemodynamically significant stenosis by noninvasive testing and a ≥50% angiographic stenosis to CEA or medical therapy. There was a 2.5-fold reduction (8% vs 20.6%) in ipsilateral ischemic events and a twofold reduction in ipsilateral stroke (4.7% vs 9.4%) over a mean 48-month follow-up.
- The Asymptomatic Carotid Atherosclerosis Study (ACAS) trial[5] randomized 1662 asymptomatic patients with ≥60% carotid stenosis between surgery and medical therapy and, again, found a twofold reduction in stroke for CEA vs medical therapy (5.1% vs 11%).
- The largest and most recent trial, the Asymptomatic Carotid Surgery Trial (ACST),[6] randomized 3120 asymptomatic patients, with strikingly similar benefits for CEA over medical therapy (6.4% vs 11.8%) at 5 years. This study was able to identify an increased risk of stroke in patients with "severe" (80%-99%) stenoses compared with (60%-79%) stenosis.

Stenosis has the benefit of being easily and reliably measured by several techniques, but it is a relatively nonspecific indicator of stroke risk because in all of these trials, the annual stroke risk was modest and most patients in the medical arm did not develop neurologic 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 to 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% yearly 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 North American Symptomatic Carotid Endarterectomy Trial (NASCET) and ACAS trials.[8] Echolucent and heterogeneous plaque, as characterized by high-resolution ultrasound imaging, has been found more often in lesions that are symptomatic compared with asymptomatic stenoses.[9,10] Plaque features, such as intraplaque hemorrhage identified on magnetic resonance imaging (MRI), 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 plague imaging or transcranial Doppler (TCD) monitoring for microembolization, or both, may ultimately prove appropriate; further research and cost considerations will be paramount.

In a study of 821 asymptomatic patients with 60% to 99% carotid stenosis, Kakkos et al[12] identified asymptom-

atic ipsilateral cortical infarcts in 17.8%. Patients with asymptomatic ipsilateral cortical infarctions had double the annual neurologic event rate (4.8% vs 2.4%), irrespective of whether the stenosis was "moderate" (60%-79%) or "severe" (80%-99%). The Asymptomatic Carotid Stenosis and Risk of Stroke (ASCRS) trial[10] monitored 1121 patients with asymptomatic stenoses of 50% to 99% for an average of 48 months. Information on the degree of stenosis, clinical conditions, and plaque character was obtained at entry. Factors associated with an increased risk of ipsilateral ischemic events, in addition to degree of stenosis, included age, hypertension, smoking >10 packs/year, renal insufficiency, contralateral transient ischemic attack (TIA), plaque size, and plaque character. Cerebrovascular risk scores were developed from these data that allowed the investigators to define four categories of 5-year stroke risk that varied from <5% to >20%.[10] These data remain to be validated by further studies; yet in the ASCRS study, the overall event (TIA/stroke) rates in patients who harbored asymptomatic stenoses *of a degree wherein CEA would be recommended by SVS guidelines* was an impressive 10% at just 3 years of follow-up.

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 size, and evidence of ipsilateral cortical infarction are also likely factors that increase the risk of neurologic symptoms. However, further research is needed to determine the relative importance of these factors and whether they can be reproducibly used as part of an algorithm to reliably identify patients who can be treated with medical therapy alone. At present, Level 1 data from >5000 patients show that selecting patients for intervention by degree of stenosis alone, although not ideal, is sufficient to significantly reduce stroke risk with CEA.

Although BMT has been shown to reduce stroke risk in the last decade,[13,14] it does not follow that this has obviated the additional benefit of CEA demonstrated by multiple controlled trials. In particular, the 10-year data from the ACST trial demonstrated that the net gain in stroke protection for CEA vs BMT, although greater in patients *not* taking statin mediations, was still highly significant, even in those who were receiving such medical therapy.[15] Given that one-third of strokes occur without warning, and one-half of TIAs are ignored or misdiagnosed, coupled with the economic, physical, and psychologic impact of stroke, there remains a continued need to treat carotid stenosis in a presymptomatic state. It would be ideal to have more reliable discriminating markers of stroke risk in the future. Identification of risk factors in addition to the 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.

MEDCAC panel voting results. Six of 13 voting members recorded a level 4 vote (ie, identical to the SVS position and between intermediate and high confidence). One "1" vote dropped the overall average score to 3.15; thus, the MEDCAC panel had a net intermediate level of confidence in question 1.

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?*

THE 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 BMT[5,6,15,16] excluded a number of patients who are often treated by CEA. In many cases, the 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. Although 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,[17] these results were clearly within thresholds of the AHA recommendations.[18] Therefore, although 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.

The definition of "high medical risk" is imprecise and not supported by robust data. Multiple single-center studies demonstrated that about one-third of CEA patients would have been eligible for "high-risk" CAS studies and that there was no difference in outcomes in these patients and in those who did not have these "high-risk" characteristics.[19-21] Stroke and death rates in single-center reports of "high-risk" patients range from 1.6% to 3.6%. Outcomes from the National Surgical Quality Improvement Program (NSQIP) database were similar.[22] In the latter study, 30% of 3949 CEAs in the NSQIP database met "high risk," as defined in criterion from the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE). 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-neurologic source of morbidity and mortality with CEA is cardiac. The most recent randomized trial data comparing CAS and CEA show that CEA is associated with an increased incidence of cardiac events and a decreased risk of stroke and death compared with CAS.[23-25]

It is intuitively logical 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 carotid 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 somewhat less import, although there is evidence that it does increase the risk of both CEA and CAS.[26] This is therefore an important factor to consider, particularly in the neurologically asymptomatic patient. Alternatively, the large Asymptomatic Carotid Stenosis and Risk of Stroke (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 uncommonly encountered in clinical practice, and when CEA is indicated, such patients are often managed without a general anesthetic, namely, with a cervical plexus block.

Definition of "anatomic high risk" is generally more straightforward. The 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 the SVS. These are situations in which local factors would increase risks of cranial nerve injury or wound infection, such as fibrosis or scarring of the neck, 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, or a lesion that extends above the level of the second cervical vertebra or below the clavicle.[1] It is important to note, however, that the mere history of radiation or 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.[27-29] Furthermore, lesions in many patients associated with prior endarterectomy are fibrous in nature and are likely to remain asymptomatic for long periods of time.[30] Data on the effect of contralateral carotid occlusion are mixed. Although NASCET identified patients with contralateral carotid occlusion as having increased risk of stroke after intervention,[31] 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.[32-34]

In summary, the exclusion criterion from ACAS and NASCET do not of themselves define a "high-risk" group for CEA. Data sets from single-center series and the NSQIP 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 asymptomatic patients and is likely the reason that these reported series[18-22] contrast favorably with the results of CEA in the SAPPHIRE trial,[35] where the combined risk of stroke and death was 7.3% even though 70% 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. These conditions, as well as hypertension and diabetes, should be optimally managed in neurologically symptomatic patients before surgery. This is almost always possible within a few days. Asymptomatic patients with these conditions should not be subjected to any intervention because the long-term benefit of intervention is low. Occult coronary ischemia should be identified and treated before 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, whereas the decision between CAS and medical management for asymptomatic patients at anatomic high risk for CEA remains unresolved at present.

MEDCAC panel voting results. Eight of 13 voting members recorded a level 4 vote, identical to the SVS position. The panel average score was 3.56, indicating a higher than intermediate level of confidence in question 2.

Question 3: For persons with symptomatic carotid atherosclerosis and carotid narrowing (≥50% by angiography or ≥70% by ultrasound imaging) 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, compared with *BMT alone*, to decrease stroke or death *in the Medicare population?***
b. **If there is at least intermediate confidence (score ≥2.5), how confident are you that**
   i. ***CAS* is the favored treatment strategy in this population?**
   ii. ***CEA* is the favored treatment strategy in this population?**
   iii. ***BMT alone* is the favored treatment strategy in this population?**

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

The data conclusively support use of CEA as the primary treatment in such patients, and this is reflected in several practice guidelines (including that of SVS) published in 2011.[1] The NASCET and European Carotid Symptomatic Trial (ECST) demonstrated the benefit of CEA in neurologically symptomatic patients with carotid stenosis >50%.[36,37] There was a 7% incidence of fatal and nonfatal strokes in the surgical group in contrast to 24% in the medically treated group ($P < .001$) 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 ($P < .01$), 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% to 69%

stenosis but not for those with <50% stenosis.[36] Results from ECST corroborated these data, even though a slightly different method was used for measuring the degree of stenosis. ECST demonstrated that the perioperative (for CEA) risk of stroke and death was 7.5%, yet CEA still resulted in a significant reduction in subsequent stroke at the 3-year interval ($P < .0001$). This, in turn, was related to a 26.5% stroke risk in the medical treatment with CEA, resulting in an absolute risk reduction of 14.9%.[37]

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 twofold increased compared to CREST. This was a grade 1 recommendation with a level of evidence B in the SVS updated guidelines.[1]

More recently, data from CREST and International Carotid Stenting Study (ICSS) have been further scrutinized.[23,38] In CREST at 30 days, the rate of stroke was significantly higher with stenting, at 4.1% vs 2.3% with surgery (hazard ratio [HR], 1.9; $P = .005$), when all patients were considered, with such differences being more pronounced in symptomatic patients (CAS 6.0% ± 0.9% vs CEA 3.2% ± 0.7%; HR, 1.9, $P = .02$).[25] CEA demonstrated HRs of 1.74 ipsilaterally and 1.89 for any procedural stroke or death, favoring CEA over CAS.[23,25] In ICSS, risk of stroke, death, or procedural myocardial infarction was higher in the stenting group than in the CEA group, with a 30-day risk of 7.7% vs 4.0%, with a risk ratio (RR) of 1.83 ($P = .003$) and a risk difference of 3.3%.[38] These two large prospective randomized studies favored CEA over CAS for treatment of symptomatic patients.

This led internationally respected 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."[23] Similarly, in a commentary accompanying publication of the ICSS results in *The Lancet*, Peter M. Rothwell, MD,[39] a noted Oxford neurologist and participant in multiple carotid disease trials, noted an excess of acute ischemic embolic lesions on diffusion-weighted MRI after CAS (46%) compared with CEA (14%; $P < .0001$). Thus, enforcing the conclusion from the ICSS[40] 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."[38,41]

The most recent meta-analysis of all randomized trials conducted at the Health Policy Research Institute of Mayo Clinic compared CEA with CAS and 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).[24] 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% confidence interval [CI], 1.35-2.45) and periprocedural mortality (RR, 2.53; 95% CI, 1.27-5.08) for CAS vs CEA; CAS had a nonsignificant reduction in periprocedural myocardial infarction compared with CEA.

The European trials were often criticized for using less experienced carotid interventionists as well as not universally using cerebral protection devices.[41,42] Martin M. Brown, Principal Investigator of ICSS, and Warner Hacke, Principal Investigator of the Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE) trial, brought up a very interesting question, when asked about the Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis (EVA-3S), SPACE, and ICSS results, 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 interventionist 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 trials, the data indicate that the stroke/death rate in ICSS (7.4%) for CAS is not statistically different than that for symptomatic patients treated with CAS in CREST (6.0%).

The data on upfront stroke/death risk apparently indicate a minimum of a twofold-increased risk for such complication for CAS compared with 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, the data indicate that for symptomatic patients, CEA is the favored treatment strategy in virtually all populations. CAS should be reserved as an alternative only for 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. In addition, BMT alone would only be a logical treatment alternative in patients with comorbid conditions expected to limit their longevity to <1 year.

Although the SVS knows of no data to indicate that specific sex 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,[23] has associated

increasing patient age with inferior outcomes of CAS compared with CEA. In virtually all CAS trials, the highest complication rates were in symptomatic octogenarians, often reaching levels that most vascular surgeons would consider unacceptable. The inflection point in CREST for significantly worse outcomes for CAS occurred at about age 75 years. There are also data available indicating unacceptable complication rates for CAS when performed within 14 days of neurologic events. Analysis of the combined Carotid Acculink/Accunet Post-Approval Trial to Uncover Unanticipated or Rare Events (CAPTURE) and Emboshield and Xact Post Approval Carotid Stent Trial (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.

MEDCAC panel voting results. Six of 13 voting members recorded a level 4 or 5 vote, swinging the overall panel average to 3.46 (ie, in between intermediate and high confidence for this question). As noted above, in the presence of at least intermediate confidence to the principle research question, derivative questions were then voted on. There was low confidence (score, 1.85) that CAS and nearly high confidence (score, 3.62) that CEA was the favored treatment in symptomatic patients. Similarly, there was low confidence (score, 1.69) that BMT was the favored treatment in these patients.

Question 4: For persons with *asymptomatic* carotid atherosclerosis (≥60% by angiography or ≥70% by ultrasound imaging) 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*?
b. If there is at least intermediate confidence (score ≥2.5), how confident are you that
  i. *CAS* is the favored treatment strategy in this population?
  ii. *CEA* is the favored treatment strategy in this population?
  iii. *BMT alone* is the favored treatment strategy in this population?

SVS IS HIGHLY CONFIDENT (SCORE 5) THAT FOR PERSONS WITH ASYMPTOMATIC, SEVERE (>60% BY ULTRASOUND OR OTHER IMAGINING STUDIES BY NASCET CRITERIA) CAROTID STENOSIS, THERE IS ADEQUATE EVIDENCE IN THE FORM OF LEVEL 1 DATA FROM LARGE, RANDOMIZED TRIALS SUPPORTING CEA AS AN EFFECTIVE TREATMENT STRATEGY (COMPARED WITH BMT) TO DECREASE STROKE OR DEATH IN THE MEDICARE POPULATION. THE SUPPORTING EVIDENCE COMES IN THE FORM OF (1) DATA FROM WELL-CONDUCTED, LARGE, RANDOMIZED TRIALS AND (2) AVAILABLE NATURAL HISTORY DATA OF STROKE RISK RELATED TO HIGH-GRADE, ASYMPTOMATIC CAROTID STENOSIS.

Consistent with not only the SVS updated practice guidelines[1] but also practice recommendations from at least four other international practice guidelines published during calendar year 2011,[43-46] CEA is supported as an effective stroke-reduction strategy in *appropriately selected* patients with severe asymptomatic carotid stenosis. On the basis of the available trial data, the designation of appropriate patients are those with an acceptable operative risk and an anticipated life expectancy of minimum of 3 to 5 years and those with high-grade (≥60% NASCET criteria) stenosis, because 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:

The VA study. The VA cooperative, asymptomatic, carotid surgery study[4] was conducted in Veterans Administration hospitals and, accordingly, limited to men. Its criteria for entry were a ≥50% (by angiography) asymptomatic stenosis, and 444 patients were randomized to CEA vs available medical therapy, which at that point was 650 mg acetylsalicylic acid. The study was published in 1993, and the perioperative stroke/death rate after CEA was 4.3%. The primary outcome measure was combined ipsilateral neurologic event (TIA or stroke, or both) and death, which occurred in 8% of CEA patients vs 20.6% of the medically treated cohort (RR reduction, 38%; $P < .0002$). In consideration of stroke alone, the respective figures (4.7% vs 9.4%) were insignificant related to the small study cohort. There was no survival benefit to CEA related to an overall excessive (>10% yearly) mortality in the entire study cohort. Despite the small sample size and inclusion of patients with a moderate degree of stenosis, the data favored CEA as a more effective stroke-reducing strategy.

The ACAS study. The larger ACAS study (published in 1995) was conducted at 39 North American community and academic centers, with 117 surgeons participating.[5] ACAS randomized 1662 patients with 60% stenosis (NASCET method, angiography mandated before CEA) to CEA or medical therapy consisting of 325 mg acetylsalicylic acid and telephone-monitored risk factor reduction counseling. Study end points were any stroke/death, and median follow-up was 2.7 years. Aggregate 5-year stroke/death occurred in 5.1% of CEA patients vs 11.0% of the medically treated cohort (RR reduction, 53%; $P = .004$). 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 <10% of CEA patients were being evaluated with invasive angiography by the year 2000.[47]

ACST trial. This was the most recent and largest randomized, prospective study of CEA vs BMT, which was conducted in 30 countries and at 128 hospitals. ACST randomized 3120 patients beginning in 1993, and the final patients were enrolled in 2003. The initial publication of the actuarial 5-year stroke risk showed a highly significant reduction in ipsilateral disabling strokes and in all strokes in patients treated with CEA vs BMT (RR, 6.4% vs 11.8%; net gain, 5.4%; $P < .0001$).[6] Important to point out with respect to the data analysis is that nearly 50% of patients actually completed 5 years of follow-up at the time that the study was initially published in 2004. Although analysis was on an intention-to-treat basis, the crossover rate from the medical arm to CEA was 17% 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, because 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 2 years, which was the interval required for the BMT group to "catch up" to the upfront morbidity of surgery. The data indicate that the annual risk of stroke in patients with BMT was in the 2% range, essentially doubled the rate of the surgically treated cohort. Long-term data from the ASCT trial, out to 10 years, have now been published.[15] 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 BMT alone. In the latter years of the trial, lipid-lowering therapy and antiplatelet therapy were used in >80% of patients. Although the proportionate gain of CEA vs medical therapy was larger in patients not receiving lipid-lowering therapy before stroke, the net gain at both 5 and 10 years remained highly significant for the surgically treated patients vs 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."[15]

It is unfair, in a sense, to compare the protective effect of CEA in stroke prevention with that of CAS because CAS has not been adequately evaluated in this regard. At the moment, there are 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 was 1.9% among nearly 25,000 CAS procedures performed in Medicare beneficiaries between 2005 and 2007.[48] SVS clinical practice guidelines state that CEA is the preferred treatment in these patients, and the ACC/AHA multispecialty guidelines indicate, has 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.)[1,43] International practice guidelines indicate that CAS should only be performed in asymptomatic patients in the context of well-conducted prospective clinical trials.[45,46] Accordingly, when intervention is appropriate in asymptomatic carotid stenosis, the SVS supports CEA as the preferred therapy.

With respect to concurrent BMT in patients who are candidates for intervention for high-grade asymptomatic stenosis, the current guideline with respect to processes of care for CEA indicates that all patients who are under observation for asymptomatic carotid stenosis, and especially patients who are being potentially treated with CEA, should be on combined antiplatelet and statin therapy.[1,49] A prior Medicare database study[50] and a regional quality registry[51] 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.[52] Furthermore, at least one report has correlated a significant reduction in the risk of restenosis after CEA in patients being treated with lipid-lowering therapy.[53] The SVS knows of no reliable data suggesting that individual racial or ethnic backgrounds have variable results with complications from CEA or long-term stroke protection after CEA. Furthermore, the above-cited trial results are applicable to the Medicare population because <15% of ACAS patients were aged <60 years, and two-thirds of ACST patients were aged ≥65 years 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 after CEA. The roll-in phase of CREST noted a 12% periprocedural risk of stroke and death in octogenarians, significantly higher than the 5% risk in those aged <80 years.[54] 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 vs endarterectomy with the infection point at age ~75 years.[23] However, the converse with respect to patient age and anticipated complications of CEA appears disproven by the best available current evidence. A recently reported NSQIP study that specifically focused on high-risk variables documented an overall 30-day (nurse-reviewer adjudicated) stroke/death rate of 2.2% after CEA.[22] In this study, 19% of some 3949 patients treated with CEA in private sector hospitals were aged >80 years, but perioperative complications were no different in octogenarians vs those aged <80 years.

BMT ALONE FOR HIGH-GRADE ASYMPTOMATIC STENOSIS

1. The 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. The SVS supports the position that all patients under observation with carotid stenosis or being 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. The 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 question 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.[2,10,56]
4. The contention that modern medical therapy is adequate treatment to control or prevent stroke (or both) from asymptomatic high-grade carotid stenosis is unsubstantiated.

A comment on the flawed literature making this claim is in order.[13] In assessing stroke risk of asymptomatic carotid stenosis, most clinicians have used data from the NASCET study (specifically, those examining the fate of a high-grade asymptomatic stenosis contralateral to the index artery for entry into the trial),[56] the original studies of Chambers and Norris,[2] and more recently, the medically treated patients in the ACST trial and the ACSRS prospective study of asymptomatic carotid stenosis.[6,10,15,55]

These studies in aggregate indicated that the annual risk of unheralded stroke from high-grade asymptomatic stenosis was at least 2% per year (the event rate was doubled if TIA was included) and also showed that the first neurologic event was as likely (or even more likely) to be stroke rather than a 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 unproved. A widely quoted 2009 meta-analysis concluded that modern drug therapy alone is now the best prevention for stroke in such patients.[13] This meta-analysis included data from two modestly sized prospective studies[57,58] and one large prospective study.[56] This meta-analysis claimed that the annual risk of stroke of asymptomatic "severe" carotid stenosis was now in the range of 0.5% per year.

The Second Manifestations of Arterial Disease (SMART) study, however, included only 221 patients, 7% of whom crossed over to surgical intervention during a nearly 4-year follow-up interval and only half of the patients had high-grade stenosis (NASCET, 70%-99%), wherein prophylactic CEA would typically be offered.[57] The Oxford vascular study[58] concluded that the risk of ipsilateral stroke was only 0.34% per year with BMT, but contained only 101 patients with >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 BMT alone as adequate treatment for asymptomatic carotid stenosis is seriously flawed by the inclusion of many patients with only moderate degrees of stenosis, such that they would not be offered an intervention by current guidelines.

In summary, the 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 2011 Practice Guidelines would support CAS in this setting. The contention that modern BMT in this setting would provide stroke prevention equivalent to CEA is unsubstantiated.

MEDCAC panel voting results. Nine of 13 voting panel members voted level 1 or 2 scores, such that the overall panel score was 2.15 (ie, low confidence that intervention vs BMT is the best treatment strategy). Given the low confidence vote, the panel did not vote on the derivative questions.

Question 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*? SVS level of confidence: intermediate to high (score 4)
b. If there is at least intermediate confidence (score ≥2.5), how confident are you that
  i. *CAS* is the favored treatment strategy in this population? SVS level of confidence: low (score 1)
  ii. *CEA* is the favored treatment strategy in this population? SVS level of confidence: intermediate to high (score 4; see below)
  iii. *BMT alone* is the favored treatment strategy in this population? SVS level of confidence: low to intermediate (score 2; see below)

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) PERTAINS. THE SVS RECOMMENDS BMT 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 at high or low risk of stroke with carotid atherosclerosis. Level 1 evidence currently 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)[4-6] that included 5223 patients with asymptomatic carotid artery disease with internal carotid artery stenosis of 50% to 99% or 60% to 99%, confirmed the *degree of stenosis* is a predictor of increased risk of stroke that could be effectively decreased by CEA. The absolute risk reduction is small, however, and in these RTCs, performed in the years

1983 to 2003, CEA resulted in an annual decrease of stroke risk of 0.5% to 1.0% vs BMT alone.

Considering the very low risk of stroke or death due to mild or moderate asymptomatic carotid atherosclerosis (<60% carotid stenosis), there is an *intermediate to high level of confidence*[1] 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[1] that asymptomatic patients with stenosis <60% diameter reduction should receive BMT is a Level 1 recommendation with intermediate supporting evidence. This conservative strategy is well supported, even in symptomatic patients with data of the ECST, where BMT alone was recommended for carotid stenosis of 0% to 29%. Results were inconclusive for stenosis between 30% and 69%, with clear benefit of surgery in those with a stenosis of 70% to 99%.[37] In consideration of asymptomatic severe carotid atherosclerosis (ie, NASCET 60% to 99% stenosis), the level of evidence to further stratify risk within this group is *low*.

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 found that increasing stenosis, plaque characterization by ultrasound imaging, 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) from a low-risk (0.7%) group.[10] Silent embolic infarcts, contralateral carotid occlusion, plaque morphology, plaque echolucency on ultrasound imaging and embolic signals on transcranial Doppler ultrasound imaging, and MRI characterization have all been proposed to predict a higher risk of stroke in asymptomatic patients.[12,59-63]

Most importantly, no RCT to date has investigated the effect of CAS, CEA, and BMT comparing low-stroke risk vs high-stroke risk patients with severe (>60% NASCET) asymptomatic lesions. 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,[2] 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. As a consequence, the level of confidence to define best therapy for low-risk patients with moderate to severe carotid atherosclerosis remains *low*.

Patient age, sex, and racial/ethnic background. The meta-analysis of Murad et al[24] examined the effect of age and sex on outcomes of patients who underwent CAS or CEA. The meta-analysis concurred with other data, including an individual patient-pooled analysis,[63] CREST,[23,64] and also the SPACE trial,[41,42] that younger patients did better with CAS than those aged ≥70 years. These data support CEA over CAS as intervention in the Medicare population. The meta-analysis failed to reveal any significant treatment interactions based on sex. Howard et al[65] recently reported on the influence of sex in the CREST trial that enrolled 872 women (34.9%). There was no difference in primary end points between different sexes (interaction $P = .34$). Although there was a trend to an increased rate of periprocedural events in women after CAS vs CEA (6.8% vs 3.8%; $P = .064$), this difference was not statistically significant. In a recent review of a national database, Rockman et al[66] found that outcome among women for perioperative stroke favored CEA over CAS, particularly in asymptomatic patients. 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 BMT have greatly improved in recent years and include complex risk factor modification in addition to treatment of hyperlipidemia and therapy with statins, antihypertensive, and antiplatelet medications.[13,14] The CAS patients in CREST received combined antiplatelet therapy, including aspirin and clopidogrel or ticlopidine, in the periprocedural period and for at least 30 days after. Similar antiplatelet therapy was also used for patients who underwent CEA. New prospective, well-designed randomized studies should include not only a treatment arm with BMT, but also BMT in addition to CEA and CAS. Results of both CEA and CAS are expected to improve in the future when best prevention and medical treatment are used concurrent to interventions.

MEDCAC panel voting results. Of 13 voting panel members, there was wide discrepancy of opinion; six members voted 1 or 2 (low confidence) and seven voted 4 or 5 (high confidence), for a net score of 3.15. The derivative questions perhaps clarified the issue because the panel voted low confidence (unanimous scores of 1 for both CEA and CAS) for interventions but voted 4.38 that BMT was the favored approach.

Question 6a: What is the confidence relative to adequate evidence to determine if carotid artery screening of asymptomatic persons decreases stroke or death?

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

THE SVS MAINTAINS A FAIRLY CONFIDENT POSITION (SCORE 4) THAT SCREENING ONLY *AT-RISK POPULATIONS* IS BENEFICIAL.

Stroke is the third leading cause of death and is the leading cause of disability in the United States and in 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 the stroke, and waiting until symptoms occur is neither safe nor ethical because natural history studies of asymptomatic high-grade carotid stenosis indicate that the first event is likely to be a stroke rather than a TIA. Therefore, screening with duplex ultrasound imaging to detect "stroke-prone" carotid bifurcation plaque and identify a high-risk patient likely to benefit from therapy is designed to reduce stroke risk.

Indications for carotid screening in neurologically asymptomatic patients. Evaluation and treatment of patients who are asymptomatic is controversial. The benefit of CEA for stenosis >60%, although statistically significant in large trials, is much less than for neurologically symptomatic individuals and rests on available natural history data and the premise that intervention (ie, CEA) can be performed with minimal morbidity and mortality.[6]

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.[67] When the prevalence of stenosis was ≥20%, screening reduced the risk of stroke in a cost-effective manner, with an intermediate prevalence of between 5% and 20%, 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, including the Canadian Stroke Consortium,[68] the National Stroke Association,[69] and the U.S. Preventive Services Task Force.[70] The American Stroke Association/AHA Stroke Council[71] 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 SVS guidelines and a multispecialty expert consensus document both 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.[1,72]

Screening patients with asymptomatic carotid bruits. Ratchford et al[73] 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.[74] 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 compared with available medical therapy.[6]

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[75] 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: coronary artery disease (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[76] identified the following variables associated with ≥60% asymptomatic carotid stenosis: hypercholesterolemia (odds ratio [OR], 1.9), current smoking (OR, 2), CAD (OR, 2.4), and age >65 years (OR, 4.1). Patients undergoing coronary revascularization are another group with an increased prevalence of carotid stenosis of 2% to 27%.[77] 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.[78] The ACC/AHA and SVS guidelines both note that carotid screening before CABG is probably indicated in the subset of patients aged >65 years, with left main coronary stenosis, a history of smoking, a history of TIA/stroke or carotid bruit, and PAD.[1,79] Several studies have also suggested that the prevalence of ≥60% carotid artery stenosis among patients with symptomatic PAD is >20%, regardless of the patient's age.

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 otherwise appropriate for carotid intervention if a significant stenosis is detected: patients with evidence of clinically significant peripheral vascular disease, regardless of age, and patients aged ≥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 those aged >65 years who have left main disease or a history of peripheral vascular disease.[1,79]

MEDCAC panel voting results. Six of 13 voting panel members expressed high confidence relative to question 6a (ie, the available evidence), such that the overall panel score was 3.54. Yet, the derivative question about panel confidence in the value of screening scored poorly, at 1.33. This may relate to the context of the question, which considered only "asymptomatic persons."

Question 7 (nonvoting question): 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. 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. TCD for cerebral microembolization

iii. Preprocedure and postprocedure diffusion-weighted MRI (DW-MRI) for silent infarcts

iv. Risk assessment tools and predictive stroke models

FOR QUESTION 7.A.I., THE SVS MAINTAINS IT IS IMPERATIVE THAT ALL FUTURE STROKE PREVENTION TRIALS SHOULD BE POWERED TO EVALUATE *SEPARATELY* SYMPTOMATIC VS 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 NASCET (symptomatic trial), medical management of 70% to 99% symptomatic stenosis was associated with a 2-year stroke risk of 26%, whereas the medical management of 50% to 69% symptomatic stenosis was associated with a 5-year stroke risk of 22%.[16] In the ACAS (asymptomatic trial), the medical management of asymptomatic ≥60% stenosis was associated with a 5-year stroke risk of only 11%.[5] Likewise, in the more recent ACST trial, medical management of ≥70% asymptomatic stenosis was associated with a 5-year stroke risk of only 11.8%.[6]

THE SVS POSITION FOR QUESTION 7.A.II IS THAT GENDER DIFFERENCES IN TREATMENT OUTCOMES ARE REAL BUT SEEM INSUFFICIENT TO JUSTIFY POWERING STUDIES TO DETECT GENDER-SPECIFIC DIFFERENCES IN RESPONSE TO TREATMENT.

Although in ACAS the RR 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 in many case series published since ACAS, sex-related differences in operative risk appear negligible. Large prospective database instruments have shown that female sex is not associated with increased risk for adverse outcomes after CEA.[22,51] In ACST, CEA was statistically significantly beneficial in both men and women, although surgical risk in women remained higher. Finally in the 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 in a recommendation that the threshold degree of stenosis warranting surgery be set higher for women than for men.[37] In these major randomized CEA vs medical management trials, sex-related treatment effects were real but did not negate the benefit of intervention for symptomatic or asymptomatic disease in men or women.

There are currently little data indicating a sex effect on outcome in CAS, at least compared with CEA. In CREST, the outcome difference attributable to sex was insignificant ($P = .34$).[23,65] There are no data exploring sex effects in medical management vs stenting trials.

THE SVS POSITION FOR QUESTION 7.A.III IS THAT 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 symptomatic or asymptomatic carotid disease.

THE SVS POSITION FOR QUESTION 7.B.I IS THAT PLAQUE MORPHOLOGY COULD EVENTUALLY BE PROVEN TO BE AS IMPORTANT AS THE DEGREE OF STENOSIS IN DETERMINING THE PROGNOSIS OF ASYMPTOMATIC CAROTID LESIONS.

High-resolution 3D ultrasound imaging with computer-enhanced plaque analyses can detect plaque characteristics that may be more important than the degree of stenosis in determining stroke risk in asymptomatic patients. The ACSRS trial offers the most compelling data in support of plaque morphologic features as prime determinants of prognosis in asymptomatic patients.[10] In this study, 1121 patients with asymptomatic 50% to 99% carotid stenoses underwent plaque characterization using a duplex ultrasound imaging protocol and then were monitored. This protocol showed that severity of stenosis, grayscale median (a measure of plaque echodensity), total plaque area, and plaque heterogeneity, as measured by the presence of noncalcified discrete white areas, predicted a wide range of clinical outcomes.

On the basis of 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% to 80% stenosis, these same criteria identify subgroups with 5-year stroke risks ranging from 1.3% to 70.4%.[10]

These data offer compelling evidence that duplex ultrasound-identifiable plaque characteristics other than stenosis are potentially important determinants of plaque behavior and, therefore, of prognosis in asymptomatic carotid disease patients. Furthermore, significant emerging evidence indicates that plaque morphology has a significant affect on stroke risk associated with CAS. Future clinical trials should evaluate ultrasound-determined plaque morphologic characteristics apart from stenosis as reliable pre-

dictors of prognosis and of outcome under surgical, interventional, and medical management.

THE SVS POSITION FOR QUESTION 7.B.II IS THAT TCD CAN DETECT MICROEMBOLIC EVENTS AND INCREASED FREQUENCY OF THESE EVENTS IS ASSOCIATED WITH THE PRESENCE OF UNSTABLE PLAQUES.

Although the data are not uniform,[62] a recent review of the available information indicated that TCD-detected microemboli are indeed correlated with degree of stenosis, presence of silent cerebral infarcts, and increased risk of neurologic symptom advent.[61] This concept has not been tested in clinical trials, and logistic considerations of availability and cost may constrain its widespread use.

THE SVS POSITION FOR QUESTION 7.B.III IS THAT MRI SEEMS PROMISING IN THE ANALYSIS OF PLAQUE MORPHOLOGY AND IN ANALYSIS OF TREATMENT RESULTS.

The ICSS study, in particular, focused attention on the significant incidence of clinically silent, yet DW-MRI visualized new brain lesions after carotid interventions in symptomatic patients. Such lesions were found in some 50% of CAS-treated patients vs 17% of CEA patients (OR, 5.1; $P < .0001$).[40] The long-term sequela of such periprocedural emboli are unknown, yet appropriately feared. Also, postprocedure DW-MRI–detected brain infarcts can serve as end points in future clinical trials.

A different issue relates to the use of high-resolution MRI to characterize the at-risk plaque in asymptomatic patients.[60] In a recent prospective study of 154 asymptomatic patients presenting with 50% to 79% (ie, moderate) stenosis and monitored for a mean of 38.2 months, Takaya et al[11] noted 12 cerebrovascular events. MRI findings at study entry of thin or ruptured fibrous cap (OR, 17.2; $P < .001$), intraplaque hemorrhage (OR, 5.2; $P = .005$), larger area of intraplaque hemorrhage (OR for 10 mm^2, 2.6; $P = .006$), larger lipid-rich or necrotic core (OR 10% increase, 1.6; $P = .004$), and greater maximal wall thickness (OR for 1-mm increase, 1.6; $P = .008$) predicted clinical outcome. Interestingly, in this study, incidence of TIA/stroke was 9% at 38 months of follow-up, and 65% of the patients were maintained on statin therapy. Thus, high-resolution MRI imaging has the potential to characterize at-risk plaques; however, cost considerations will likely constrain its widespread application.

THE SVS POSITION FOR QUESTION 7.B.IV IS THAT IT IS INCONCEIVABLE THAT ANY MODEL PREDICTING STROKE RISK IN PATIENTS WITH ASYMPTOMATIC CAROTID DISEASE WOULD NOT USE CAROTID STENOSIS SEVERITY AS ITS MAIN RISK INDICATOR.

We therefore believe that research efforts should be focused on detection of plaque characteristics predictive of stroke. Predictive models incorporating other patient clinical characteristics should be combined with more reliable noninvasive means for predicting plaque behavior.[10] Perhaps the best predictive model for symptomatic patients was developed from the medical arm of the NASCET, and this model incorporated degree of stenosis as well as the presence of plaque ulceration. Furthermore in this study, the degree of stenosis alone was a strong predictor of outcome for medically managed patients.[56] Although the degree of stenosis is presently the best available surrogate for risk prediction in asymptomatic patients, as seen in the answers to questions 7.b.i and 7.b.iii, it appears that other measurable plaque characteristics will be major determinants of prognosis as well as response to treatment.

MEDCAC panel voting results. This was a nonvoting question.

COMMENTARY

As detailed herein, the SVS position statements to the CMS MEDCAC have largely been derived from our recently updated carotid disease practice guidelines,[1] and the position statements on the research questions are entirely consistent with same. Similar to the posture of the MEDCAC panel, the SVS practice guidelines reflect best available evidence rather than personal experience, or for example, claims about the adequacy of medical therapy that are derived from literature projections rather than from high-quality clinical trials. It was repeatedly emphasized to the MEDCAC panel members, and to the presenters, that the consideration was to the available evidence rather than clinician experience.

The MEDCAC panel votes were concordant with the SVS position statements and practice guidelines in the important questions related to the natural history and stroke risk of asymptomatic (severe) carotid stenoses and in the prediction of adverse events after CEA. Both of these considerations are fundamental to clinical decision making. Perhaps the most striking concordance between the SVS position and the MEDCAC panel vote related to the treatment of symptomatic carotid stenoses, where the panel had more than an intermediate level of confidence that CEA is the favorite treatment strategy for such patients. The panel scores for CAS and BMT in these patients were both in the low-confidence realm. No doubt, most clinicians (possibly excepting vociferous advocates of CAS) would respond with "of course." It is important, once again, to emphasize that the best available trial data (CREST) and the most recent meta-analysis of all available trial data continue to demonstrate a twofold increase in the risk of stroke/death when CAS is used rather than CEA to treat symptomatic patients.[23-25] Despite the criticism referable to CAS operator expertise leveled at the European trials, CREST has shown that even in the hands of the highly selected and admittedly expert interventionalists, CAS has a twofold increased stroke risk compared with CEA in the treatment of symptomatic carotid stenoses.

In the realm of asymptomatic patients, the research questions were influenced (in terms of panel voting) by parsing them in consideration of procedural risk (ie, for CEA) and qualifying patients by whether they were at high risk for stroke. There was low confidence, in the panel's view, that intervention of any kind vs BMT was the favored approach to asymptomatic stenoses. If asymptomatic carotid atherosclerosis were characterized as not being at high risk for stroke, then there was a high level of confidence that BMT is the appropriate treatment. This is, of course, consistent with the SVS position, although clinicians at the

present time have continued to rely on the degree of carotid stenosis as the single best surrogate for stroke risk in patients with asymptomatic lesions. As reviewed herein, although this is an imperfect surrogate, it is in fact reliable and useful, based on the best available natural history data.[10,56]

That fact notwithstanding, the SVS has identified investigation in the realm of asymptomatic carotid stenoses as its number one clinical research priority. The further characterization of asymptomatic plaques with a variety of imaging modalities is likely to add valuable information to the degree of stenosis in clinical decision making. The SVS supports the position that future trials in asymptomatic patients should include an optimal medical therapy arm. However, as reviewed herein, the contention that modern medical therapy has obviated the need for intervention in asymptomatic patients is unsubstantiated.

The further course, utilization, and outcomes of the CMS MEDCAC are not clearly defined at the moment. Obviously, it will be a repository of information should CMS choose to reopen the issue of the NCD for CAS.

Contributing to this article or the MEDCAC, or both, were Richard P. Cambria, MD, SVS President; Peter Glovickzi, MD, SVS President-Elect; Julie Frieschlaig, MD, SVS Vice-President; John Ricotta, MD, SVS Secretary; R. Clement Darling, III, MD, SVS Treasurer; Kimberly Hansen, MD, Chair SVS Fellows Council; Robert Zwolak, MD, SVS immediate Past-President; Daniel Clair, MD, Chairman, Department of Vascular Surgery, Cleveland Clinic Foundation; William Mackey, MD, Chairman, Department of Surgery, Tufts Medical Center, Boston; and Ali AbuRhama, MD, Chief Vascular Surgery, University of West Virginia.

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