Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Response to Samuelson et al

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Circulation 2007;116;1602-1610
DOI: 10.1161/CIRCULATIONAHA.106.670034
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CONTROVERSIES IN CARDIOVASCULAR MEDICINE

The Argument to Support Broader Application of Extracranial Carotid Artery Stent Technology

Rodney M. Samuelson, MD; Junichi Yamamoto, MD, PhD; Elad I. Levy, MD; Adnan H. Siddiqui, MD, PhD; L. Nelson Hopkins, MD

As new technology becomes available, the stent technique for the extracranial carotid artery continues to evolve into a safer, more effective therapy for stroke prevention. With the availability of embolic protection, improved stent designs, and added endovascular physician experience, outcomes for carotid artery stenting (CAS) now consistently parallel those for carotid endarterectomy (CEA). Although carotid endarterectomy was established as the gold standard for carotid revascularization, the available scientific evidence must continue to be interpreted in the context of further advancements in nearly all related areas of medicine. One multicenter randomized trial and several nonrandomized registries have successfully established the CAS indications for patients with high surgical risk and have provided evidence to support the use of CAS techniques in patients with low surgical risk. Clinicians must continue to improve their understanding of patient-specific factors and conduct research that will refine indications while optimizing current medical therapy and that will integrate CAS and carotid endarterectomy as complementary treatments.

Response by LoGerfo p 1610

Introduction

The outcomes for CAS have been improving over the past 10 years and now appear nearly equivalent to those for CEA. In fact, many historical similarities are seen in the development of these 2 techniques. Although CEA was established as the gold standard for extracranial carotid revascularization, the available scientific evidence must continue to be interpreted in the context of further advancements in nearly all related areas of medicine. The current research comparing CAS and CEA has not shown a clinically robust and statistically significant difference between the 2 treatments. When differences do exist, clinicians must continue to refine patient-specific indications and to conduct further research to understand these complex risk-benefit analyses in the context of advanced medical treatments and complementary revascularization techniques. The following review details the argument to support implementation of CAS technology for athero-occlusive carotid artery disease beyond the population of patients considered high risk for surgery.

Scientific Evidence for CEA

The surgical outcomes and indications for CEA have been studied more closely than any other surgical procedure. In the 1970s and 1980s, scientific evidence for the efficacy of CEA was lacking. Two randomized trials failed to find a reduction in stroke or death rates among surgically treated patients because of high perioperative morbidity.[1,2] Reported rates for combined stroke and death were as high as 20%.[3–5] In 1982 to 1983, an audit conducted by the Cerebrovascular Section of the American Association of Neurological Surgeons found no consensus for surgical indications, type of operation, or use of intraoperative monitoring.[4] Furthermore, the authors of a large study of CEA among Medicare recipients alleged that

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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(*Circulation.* 2007;116:1602-1610.)

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Circulation is available at http://circ.ahajournals.org DOI: 10.1161/CIRCULATIONAHA.106.670034

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32% of cases were performed for questionable or inappropriate indications.[6]

From this controversial setting grew 4 multicenter, randomized clinical trials: the North American Symptomatic Carotid Endarterectomy Trial (NASCET),[7,8] European Carotid Surgery Trial (ECST),[9,10] Asymptomatic Carotid Atherosclerosis Study (ACAS),[11] and Asymptomatic Carotid Surgery Trial (ACST).[12] At a time when the validity and indications for CEA were in question, these 4 studies established the role for CEA and helped define a new standard for medical research. With publication of the results of NASCET[8] and ECST,[10] performing CEA for symptomatic patients with 70% to 99% (NASCET) carotid stenosis or selected patients with 50% to 69% stenosis became a class IA indication within the American Heart Association guidelines.[13] This means that CEA had demonstrated efficacy on the basis of data derived from multiple randomized clinical trials.

The general population of patients with carotid stenosis is different from those who met the strict NASCET eligibility criteria.[14] NASCET collaborators excluded patients if they were ≥80 years of age or had severe intracranial stenosis; liver, kidney, or lung failure; cardiac valve or rhythm disorder; previous ipsilateral CEA; uncontrolled hypertension or diabetes mellitus; or recent myocardial infarction (MI) or major surgery.[8] For the purposes of the trial, these patients were considered to have confounding risks for perioperative morbidity (high surgical risk). Since NASCET, patients undergoing carotid revascularization often have been divided into low–surgical-risk and high–surgical-risk groups. More recently, classification of patients by their surgical risk has been the foundation of the CAS trials.

The practice of CEA also is quite different now, nearly 20 years after NASCET began. Continued advances have molded surgical technique. These include the timing of surgery after neurological symptom onset, synthetic patch grafts, new shunt designs, new antiplatelet medications, and differing methods of perioperative management.[15–18] As these new methods of CEA were introduced into clinical use, very few were reestablished with class IA evidence.

For asymptomatic lesions, the degree of benefit is not as large, and the indications for surgical revascularization are still debated. Although the first 3 randomized trials in asymptomatic patients failed to identify a reduction in stroke or death for CEA,[19–21] in ACAS and ACST, a 5.4% to 5.9% absolute risk reduction was identified over 5 years.[11,12] The risks of surgery and angiography detract from the potential benefit, and a perioperative morbidity of >3% minimizes any benefit. However, since ACAS was published, nearly 75% of CEAs in the United States are performed on asymptomatic patients (versus 34% in 1981).[22]

In the major clinical trials, carefully selected patients with low surgical risk were operated on by highly experienced surgeons at high-volume medical centers. Other studies have shown that the low complication rates seen in NASCET and ACAS are not always obtained within the general population. Reported perioperative stroke and death rates range from 0%[23] to 11.1%[24] for symptomatic patients and 0%[25] to 5.5%[24] for asymptomatic patients.

Use of 1992 to 1993 mortality data from 113 000 Medicare recipients showed that patients treated in hospitals participating in NASCET or ACAS had a 1.4% perioperative mortality.[14] This rate compares with 0.6% reported in NASCET and 0.1% reported in ACAS.[8,11] In this Medicare population–based study, CEA-related mortality rates were higher (2.5%) for low-volume hospitals[14] (although other reports have found only small differences in mortality based on hospital volume [0.2%]).[26]

Numerous factors have been shown to influence the combined stroke and death rates for patients undergoing CEA. Common medical comorbidities and their associated rates for perioperative stroke and death include the following: congestive heart failure, 8.6%[27,28]; age >75 years, 7.5%[27,28]; postendarterectomy restenosis, 10.8%[29]; ipsilateral carotid siphon stenosis, 13.9%[27]; intraluminal thrombus, 10.7% to 17.9%[27,30]; contralateral carotid occlusion, 14.3%[31]; and CEA combined with coronary artery bypass grafting, 16.4% to 26.2%.[32,33] However, in these cases, the natural history of the carotid disease also is less favorable. Therefore, the decision for surgical treatment is heavily dependent on patient-specific factors, including medical/surgical history, anatomic characteristics, and institutional experience.

In the Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) "natural history" study, the mean duration of follow-up for 1115 patients with asymptomatic internal carotid artery stenosis treated with medical therapy alone was 37.1 months.[34] This trial has identified subgroups of patients having asymptomatic carotid stenosis with increased risk for stroke and death. The group with the highest risk (82% to 99% stenosis by NASCET criteria,[8] history of contralateral transient ischemic attack, and serum creatinine level >0.085 mmol/L) had a 4.3% annual ipsilateral stroke rate compared with 0.7% in the group with the lowest risk.[34,35] However, at this time, the data are insufficient to tell us the true natural history of patients with severe asymptomatic carotid stenosis and significant medical comorbidities. This population of patients is likely at substantially higher risk for stroke than the low-surgical-risk patients studied in all of the major CEA trials.[36]

Several medical societies have set standards for complication rates in their CEA guidelines. Among them, the guidelines for the AHA[13] and the Canadian Neurosurgical Society[37] establish a 6% limit for surgical risk in symptomatic patients[13] and 3% limit for surgical risk in asymptomatic patients, assuming >5-year life expectancy.[33] Other medical societies such as the Canadian Stroke Consortium do not endorse CEA for asymptomatic patients at all.[38]

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Medical Treatment for Cerebrovascular and Extracranial Carotid Artery Atherosclerotic Disease

The indications for extracranial carotid revascularization and the acceptable rates for periprocedural complications were based on the risk of treating the disease without surgery. However, since the major randomized trials of CEA were initiated, the treatments that constitute best medical therapy also have continued to improve.

In NASCET, the primary medical intervention was 1300 mg/d aspirin.[8] This dose of aspirin is no longer used because lower doses have proved equally efficacious with fewer gastrointestinal side effects.[39–41] Aspirin alternatives such as clopidogrel and ticlopidine are available,[15,18] and the aspirin-dipyridamole combination was shown to be more effective than aspirin alone.[42]

Methods for blood pressure control were not specified in NASCET, and at the time, blood pressure goals were more loosely defined. Today, it is understood that blood pressures <120 to 130/70 mm Hg are optimum for cardiovascular risk reduction in patients with medical comorbidities.[13,43,44] For primary stroke prevention, a large meta-analysis found that regardless of the agent used, a 10-mm Hg reduction in systolic blood pressure produced a 31% relative risk reduction for stroke.[45] Often, a carefully balanced combination of medications is required for optimum blood pressure control.[45] For secondary stroke prevention, proven agents include angiotensin-converting enzyme inhibitors[43,46] and the combination of a thiazide diuretic with angiotensin-converting enzyme inhibitor.[46] Diabetes mellitus and tobacco use also are known risk factors, but achieving proof of benefit with specific treatments has been more elusive.[13,47–51]

Over the past 10 years, statins have assumed a prominent role in cerebrovascular and cardiovascular risk modification.[52–56] In a recent review of 180 patients undergoing CAS, a significantly higher 30-day rate of stroke, MI, or death was identified among patients who were not receiving preprocedural statin therapy.[57] A similar result was obtained for symptomatic patients undergoing CEA.[58] In a third study of patients receiving medical treatment for severe carotid artery disease, statin use was associated with significantly lower rates of stroke, MI, or death.[59]

Although the medical treatments for carotid atherosclerotic disease and related comorbidities have advanced considerably over the past 20 years, comprehensive evaluations that prove the additive benefit of combination therapy are lacking, and use of these adjunctive treatments is low. For example, a study published in 2004 analyzed private insurance data of prescriptions filled after CEA from 1999 to 2001.[60] Prescriptions were supplied to 1049 patients at the following rates throughout the first postoperative year: statins, 38%; β-blockers, 24%; calcium channel blockers, 19%; angiotensin-converting enzyme inhibitors, 19%; diuretics, 13%; angiotensin receptor blockers, 6%; and nonaspirin antiplatelets, 5%. Therefore, medical treatment outcomes and guidelines for surgical intervention may depend on periodic reevaluation and adjustment of the risk-to-benefit analysis.

Carotid Artery Angioplasty and Stent Placement

Into this sophisticated and evolving medical landscape, CAS was introduced as a means to revascularize diseased vessels while minimizing the risks from open surgery or general anesthesia. NASCET-like evidence of benefit and safety of CAS has been required before its widespread use. This is due, in part, to the proven efficacy of CEA and to the earlier shortcomings of surgical revascularization.

The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) was the first randomized trial that compared endovascular and surgical treatments for patients with carotid stenosis.[61] A total of 504 patients were enrolled in the trial between 1992 and 1997; the results were published in 2001. The trial was designed to compare balloon angioplasty with CEA. When stents became available, they were incorporated into the trial (26% of cases).

The trial involved 24 centers in Europe, Australia, and Canada. Like previous trials of CEA, high-risk surgical patients were excluded from enrollment. This included patients with recent MI, poorly controlled hypertension or diabetes mellitus, renal disease, respiratory failure, inaccessible carotid stenosis, or severe cervical spondylosis.

The results showed no statistically significant difference between endovascular and surgical treatment in the rate of disabling stroke or death within 30 days (6.4% CAS versus 5.9% CEA). No significant difference in ipsilateral stroke existed during 3 years of follow-up. Significant restenosis (70% to 99%) occurred in 14% of the endovascular group and 4% of the surgical group, but surgical patients had a higher incidence of neck hematoma and cranial nerve injury. Because these early results showed very similar outcomes (0.5% difference), they generated significant interest in the technique and helped support further investigation.

CAS Before Embolic Protection

The early trials with CAS did not include embolic protection. Many of the major neurological complications of CAS are due to embolization of atheromatous material from the aortic arch or the carotid plaque.[62–65] Devices that capture the embolic debris released during CAS have significantly improved procedural safety.[62,65–69] Before implementation of embolic protection, the randomized CAS trials had unfavorable results caused by a high rate of perioperative morbidity. In this way, early CAS trials reflected the early results with CEA trials because both treatments had initially high rates of perioperative morbidity.

The Wallstent trial was the first multicenter randomized trial designed to evaluate the equivalence of CEA and CAS.[70,71] A total of 219 symptomatic patients with 60% to 99% stenosis were enrolled. The 30-day rates for any stroke or death were 12.1% with CAS and 4.5% with CEA

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(P=0.049). The primary end point of ipsilateral stroke, procedure-related death, or vascular death at 1 year was reached by 12.1% of those randomized to CAS and 3.6% of those randomized to CEA (P=0.022). The trial was terminated by the Data Safety and Monitoring Committee after an interim analysis as a result of worse outcomes for the CAS group.

CAS After Introduction of Embolic Protection

The Carotid Revascularization Using Endarterectomy or Stenting Systems (CaRESS) trial was one of the first trials to use embolic protection.[72,73] It was a multicenter, nonrandomized, prospective study comparing CAS with embolic protection (n=143) and CEA (n=254). Patients were both symptomatic (32%) and asymptomatic (68%) with low and high surgical risk. A key feature of this trial was the nonrandomized treatment assignment. The type of procedure was chosen by the treating physician and the patient. A prespecified algorithm for treatment selection was not used. Although this may have allowed selection bias, the CaRESS trial represented a more generalized perspective on carotid revascularization and more closely represents a "real-world" approach in which each patient gets the operation best suited to his or her clinical and anatomic substrate in the opinion of the operator.

The baseline characteristics of the groups were similar, except those with prior carotid intervention were more often assigned to CAS. The results showed no statistically significant difference between CAS and CEA for death or stroke at 30 days (2.1% CAS versus 3.6% CEA) or 1 year (10.0% CAS versus 13.6% CEA). There also was no significant difference for rates of restenosis, residual stenosis, repeat angiography, and need for carotid revascularization. The overall morbidity and mortality rate approached the standards set by NASCET[7,8] and ACAS[11] and represents the lowest rates among the major CAS trials to date. Some attribute the low stroke and death rates to the treating physicians' ability to consider patient-specific factors and to successfully assign patients to the safer therapy on that basis.

CAS for Patients With High Surgical Risk

The Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial successfully established the CAS indication for patients with high surgical risk.[36] SAPPHIRE (n=344) was a randomized, multicenter trial designed to demonstrate the statistical noninferiority of CAS. Enrolled patients had symptomatic stenosis of at least 50% or asymptomatic stenosis of at least 80%.

Combined rates of MI, stroke, and death within 30 days were 4.8% for CAS and 9.8% for CEA (P=0.09). This difference in perioperative outcomes is due partly to a greater number of MIs in the CEA group (P=NS). Although not reported together in SAPPHIRE, the 30-day rate of stroke plus death was ≈4.8% in the CAS group and ≈5.6% in the CEA group.

At 1 year, 12.2% of patients undergoing CAS had reached the primary end point compared with 20.1% with CEA (noninferiority analysis: P=0.004; superiority analysis: intention to treat, P=0.053; as treated, P=0.048). CAS was superior to CEA with respect to MI (2.5% versus 8.1%; P=0.03) and major ipsilateral stroke (0% versus 3.5%; P=0.02).

At 3 years, the major event rate was 25.5% for CAS and 30.3% for CEA (P=0.20) (J.S. Yadav, MD; unpublished data; 2005). The incidences of death, ipsilateral stroke, and target lesion revascularization all favored CAS over CEA but were not statistically significant.

The carotid registries are nonrandomized outcome records for symptomatic and asymptomatic CAS patients with high surgical risk. Although they do not provide direct comparison with CEA, they do help to establish the adverse event rates among a population of high-surgical-risk patients. The Carotid Artery Revascularization Using the Boston Scientific FilterWire EX/EZ and the EndoTex NexStent (CABERNET) collaborators found a 3.9% 30-day rate of stroke or death.[74] The investigators of ACCULINK for Revascularization of Carotids in High-Risk Patients (ARCHeR; n=581 patients) found a 30-day stroke or death rate of 6.9%.[75] The 1-year composite outcome was 9.6% (30-day rate of MI, stroke, or death plus the 1-year rate of ipsilateral stroke). Carotid Revascularization With ev3 Arterial Technology Evolution (CREATE; n=419 patients) showed a 6.2% rate of MI, stroke, and death within 30 days.[76] Independent predictors of death or stroke included the duration of filter deployment, preoperative neurological symptoms, and renal insufficiency. The investigators of Boston Scientific EPI: A Carotid Stenting Trial for High-Risk Surgical Patients (BEACH; n=747 patients) found a 30-day MI, stroke, or death rate of 5.8%.[77] The German Arbeitsgemeinschaft Leitende Kardiologische Krankenhausarzte (ALKK) registry (n=1888 patients) included patients with standard surgical risk.[78] The in-hospital rate of death and stroke was 3.8% and improved from 6.3% in 1996 to 1.9% in 2004 (P=0.021).

CAS for Patients With Standard Surgical Risk

The Stent-Supported Percutaneous Angioplasty of the Carotid Artery Versus Endarterectomy (SPACE) trial[79] evaluated outcomes between CAS and CEA for patients with low surgical risk. Conducted at multiple centers in Europe, SPACE compared the safety and efficacy of CAS against CEA in patients with symptomatic carotid artery stenosis (≥70% by duplex ultrasonography, ≥50% by NASCET criteria,[8] or ≥70% by ECST criteria[9]).

Among 1183 randomized patients, the 30-day rate of ipsilateral stroke or death was 6.84% for CAS and 6.34% for CEA.[79] This 0.51% difference was not statistically significant. Embolic protection was not required; it was used in only 27% of cases. Subgroup analysis showed the 30-day rate of

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ipsilateral stroke or death was 7.3% with and 6.7% without embolic protection.

Because of a prespecified analysis for noninferiority, the trial authors concluded, "SPACE failed to prove the non-inferiority of carotid-artery stenting. . .." In this analysis for noninferiority, the authors reasoned that an arbitrary cutoff of 2.5% difference in primary outcome could separate inferiority from noninferiority. That is, CAS is noninferior to CEA only if the 90% confidence interval (CI) of the absolute difference does not exceed 2.5%. SPACE had a 90% CI of −1.89% to 2.91%. However, the clinical relevance of 2.5%, rather than 2.91%, at the outer limit of the CI has not been established.

Furthermore, the CI varies with the size of the study population and the frequency of outcome events. When the SPACE planning committee placed the limit of noninferiority at 2.5%, they also intended to enroll 1900 patients and estimated that the rate of primary outcome events would be ≈5%. No provision was made to modify the 2.5% cutoff if the trial ended early or if the outcome events occurred at a higher rate. The authors also noted in their discussion that they underestimated their enrollment needs. Given the results at the interim analysis, >2500 patients would have been needed to achieve an 80% power. Because of this need to significantly increase the size of the trial and a "lack of funds,"[79] the steering committee elected to close the trial early, leaving the prespecified analysis for noninferiority in limbo. Therefore, the SPACE authors based their conclusions on an underpowered analysis for noninferiority. The 0.51% difference in perioperative stroke or death was not statistically significant and is well within the published differences between individuals, institutions, and variations of CEA. In addition, the lack of standardized use of embolic protection devices confounds the interpretation of the study.

Endarterectomy Versus Angioplasty in Patients With Severe Symptomatic Carotid Stenosis (EVA-3S) was designed as a multicenter, noninferiority randomized trial to compare the efficacy of CAS versus CEA for the secondary prevention of ischemic stroke.[80] A total of 527 patients with >60% stenosis were enrolled. The trial was ended after an interim analysis showed that the 30-day rate of any stroke or death was significantly higher in the CAS group (9.6%) than the CEA group (3.9%; $P=0.01$).

Early in the trial, use of embolic protection was not required. However, patients treated without embolic protection experienced a 25% rate of stroke or death within 30 days (5 of 20 patients). These results prompted a protocol change by the EVA-3S safety committee, and this complication rate clearly does not represent the practice of CAS in other regions.

EVA-3S compared groups of physicians with unequal experience. The surgeons who performed CEA were fully trained and had performed at least 25 endarterectomies in the year before trial entry. However, the endovascular physicians were certified after completing as few as 5 to 12 carotid stent placements (5 carotid stents among at least 35 stent procedures to supra-aortic vessels or 12 carotid stents). Other endovascular physicians were allowed to enroll study patients while simultaneously undergoing training and certification. The resulting 9.6% rate of stroke and death overall is higher than in other randomized trials.

A subgroup analysis based on the experience of the CAS physicians showed a 12.3% stroke and death rate among established endovascular physicians who were tutored in CAS during the trial.[80] This compares with 7.1% among those tutored in CAS during their endovascular training and 10.5% among experienced CAS physicians. Although the authors note that the differences between groups of endovascular physicians were not statistically significant, EVA-3S was not powered for this analysis. Therefore, this trial may have identified a group of "high-risk" endovascular physicians, and further research is needed.

EVA-3S does serve an important function by highlighting the importance of embolic protection and rigorous training and credentialing for CAS physicians. However, EVA-3S should not be used to judge the overall safety and effectiveness of CAS for treating carotid artery disease.

Ongoing Trials

The Carotid Revascularization Endarterectomy Versus Stent Trial (CREST) is ongoing. Enrollment criteria include >50% symptomatic carotid stenosis or >70% asymptomatic stenosis. Primary end points include death, stroke, or MI at 30 days and ipsilateral stroke within 60 days. Multiple centers in North America are enrolling patients, with a final goal of 2500.

CREST included a rigorous credentialing phase for CAS providers.[81] Endovascular physicians are required to perform up to 20 monitored procedures. CREST has shown a 4.6% 30-day stroke and death rate during the lead-in phase. Rates of MI, stroke, and death were 5.7% for symptomatic patients and 3.5% for asymptomatic patients. These rates are similar to the published guidelines for CEA.[13] Similar stroke and death rates were observed for both men and women[82] and for those treated with or without embolic protection.[83] For patients ≥80 years of age,[84,85] the 30-day stroke and death rate was 12.1%. This is significantly higher than for patients 60 to 69 years of age (1.3%) and 70 to 79 years of age (5.3%; $P=0.0006$).[84]

Other ongoing trials include the International Carotid Stenting Study (ICSS), the Asymptomatic Carotid Stenosis, Stenting Versus Endarterectomy Trial (ACT I), ACST-2, and the Transatlantic Asymptomatic Carotid Intervention Trial (TACIT). The favorable results of CAVATAS and the finding of higher restenosis rates in the carotid angioplasty arm resulted in the initiation of ICSS, also known as CAVATAS-2.[86] This multinational trial randomizes symptomatic patients who are equally suited for CAS or CEA. Embolic protection is recommended.

ACT I is randomizing low-surgical-risk patients with asymptomatic carotid stenosis (80% to 99%) at multiple

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centers in North America.[87,88] The primary analysis will include rates of MI, stroke, and death within 30 days of treatment and 5-year stroke-free survival.

TACIT is in the development stage. Both standard-risk and high-surgical-risk patients with asymptomatic carotid stenosis will be randomized into 1 of 3 treatment arms.[89,90] The first arm will be optimal medical therapy only (antiplatelet, antilipidemic, antihypertensive, strict diabetes control, and smoking cessation). The second and third arms will be optimal medical therapy plus CEA or CAS with embolic protection. Planned enrollment is 2400 patients. The primary end point is the 3-year rate of all stroke and death. Secondary end points include rates of transient ischemic attach and MI, economic cost, quality-of-life analysis, neurocognitive function, and carotid restenosis.

Conclusions

The CAS technique continues to evolve into a safer and more effective treatment as new technology becomes available. However, CAS is now at a point in its development in which the focus of future clinical research should change. With the availability of embolic protection, improved stent designs, and added endovascular physician experience, outcomes for CAS now consistently parallel those for CEA.

Just as surgeons have learned over the years which patients should not be offered CEA, endovascular physicians are learning clinical and anatomic features that predict elevated risk for CAS. Therefore, endovascular physicians must rigorously apply the lessons learned in the CAS trials to avoid treating patients who are clearly at higher risk for complications with endovascular stenting. Patient-specific factors and individual clinician variability are critically important for outcome, but this is underemphasized among large randomized trials. A greater need exists to reduce morbidity and mortality by integrating CAS and CEA as complementary therapies while optimizing current medical treatments.

Future trials should refine indications within a multimodality, comprehensive treatment protocol for groups of unselected patients. Evaluating treatment within these protocols will aim to improve patient outcomes overall, regardless of the specific treatments used. This paradigm more closely models the real clinical environment and is in line with the current NIH Roadmap for Interdisciplinary Research.[91] The TACIT trial may be a step in this direction by clarifying outcomes between revascularization and modern best medical therapy.

Further analysis of the ACSRS study also may clarify the stroke risk for patients receiving optimal medical therapy. This may identify "high-risk" groups with asymptomatic lesions who will benefit most from carotid revascularization.

Additional trials such as CaRESS,[72,73] in which the physician teams tailor the therapy rather than randomly assigning patients to treatment arms, may demonstrate reductions in perioperative complications and may allow further refinements in stroke risk analysis. However, thorough descriptions of the treatment selection algorithms are necessary to allow broader application of the results within clinical practice.

By integrating CEA and CAS as complementary therapies, we can improve patient outcomes. To accomplish this integration, appropriately credentialed endovascular physicians should be given full access to the CAS technique. They should be allowed to offer CAS to their patients according to their professional discretion. As with any surgical or interventional procedure, endovascular physicians know that their outcomes must meet society expectations. The medical regulatory agencies, health insurance carriers, patients, and physicians everywhere are watching.

Acknowledgments

Thanks go to Mary Ann Kedron, PhD, MBA (University at Buffalo Neurosurgery), and Chester Fox, MD, for their critical review of this manuscript.

Disclosures

Dr Hopkins reports receiving industry grant support from Boston Scientific, Cordis, and Micrus; honoraria from Bard, Boston Scientific, Cordis, and Medsn; and consultant fees from Abbott, Bard, Boston Scientific, Cordis, EndoTex, and Micrus. Dr Hopkins is a stockholder or shareholder of Boston Scientific, EndoTex, APW Holding Inc, and Micrus and serves on the board, as a trustee, or in an officer position for Access Closure, marketRx, and Micrus. Dr Levy reports receiving industry grant support and honoraria from Boston Scientific and Cordis; serving as an expert witness for multiple legal depositions and as a consultant for a malpractice case; receiving patent royalties from Zimmer Spine; and receiving support from Abbott Vascular and ev3 for cartid stent training. Dr Siddiqui reports receiving a local University at Buffalo grant and honoraria from the American Association of Neurological Surgeons' Course and Emergency Medicine Conference. Drs Samuelson and Yamamoto report no conflicts.

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Response to Samuelson et al

Frank W. LoGerfo, MD

The heart of this controversy is embodied in these 2 perspectives. Dr Hopkins views the Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial and the US Food and Drug Administration approval of carotid stenting as entirely legitimate and goes further to argue in favor of expanded indications for stenting. My view is that the SAPPHIRE trial is scientifically unsound, with flaws in design, conduct, and data analysis, a view corroborated by the Food and Drug Administration statistician and staff reviewers. My explanation for Food and Drug Administration approval is the pervasive influence of industry on every aspect of clinical science. How can readers sort this out? My suggestion is to focus on the SAPPHIRE trial and decide whether or not it meets the level of scientific conduct appropriate to making a major policy decision, especially one in which the risk to the public is stroke. As for the various other trials, it is the usual conduct of these debates to pick apart each of them so that the argument becomes diluted by a "he said, she said" atmosphere. Rather than engage in this conduct, it was my decision to concentrate on the data and circumstances surrounding Food and Drug Administration approval to best illustrate the magnitude of the flaws in our system. Readers should assume a highly critical and demanding posture whenever a clinical study favors approval of a new high-revenue device. In the end, the only protector of the patients' welfare is our commitment as physicians to caring for our patients. This is true whether we act on behalf of individual patients or on behalf of public health.

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