PRESIDENTIAL ADDRESS

From the New England Society for Vascular Surgery

Clinical studies of carotid artery stenting: Why don't they tell us what we need to know?

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Being selected as the 34th President of The New England Society for Vascular Surgery is one of the great honors of my career. My association with this society dates back to meetings at the old Mount Washington Hotel, with 50 or so stalwarts seated on folding chairs in a tiny meeting room with a roll-up screen and a single Kodak carousel projector. In those days, we were a sideshow for the New England Surgical Society. How far we have come! Our growth to independence has mirrored the maturation of our specialty. Witnessing this growth and maturation over the past 25 years has been a great privilege.

The treatment of carotid artery disease, and specifically carotid endarterectomy (CEA), has been my major academic interest in vascular surgery, and so I have been more than a little threatened by the rise of carotid artery stenting (CAS). As I am becoming a late-middle-aged dog, new tricks don't come easily. As I have watched and studied this new procedure, I have become convinced that it has a role in the management of our patients. I simply don't know what role. Unfortunately, the currently available clinical trials don't help me much. Why?

In this presentation, I want to review with you the current trials of CAS, assess their value and their shortcomings, look at their common features, and finally, explore why they fail to define for us the appropriate role for this new procedure.

Any review of the CAS trials should start with a quick history of CEA trials and the evidence basis they provide for the role of endarterectomy in the management of our patients. I will then briefly present the major published registries and trials of CAS. I will summarize the findings of these registries and trials. I will conclude with some reflections on the design of these trials and some recommendations for future trials.

In 1988, there was significant controversy over the safety and efficacy of CEA. The results of CEA, as reported in case series from single institutions, contrasted with the results from regional surveys. A publication from the RAND Corporation suggested that approximately one-third of endarterectomies performed in the United States were performed for "inappropriate" indications.[1] There were no prospective randomized trials demonstrating safety or efficacy in symptomatic or asymptomatic patients.

In 1991, The North American Symptomatic Carotid Endarterectomy Trial (NASCET), along with the parallel European Carotid Surgery Trial (ECST), proved that CEA was highly beneficial for those patients with symptoms who had 70% to 99% carotid stenosis.[2] Those symptomatic patients with 50% to 70% stenosis were later shown to derive statistically significant benefit from surgery.[3] Those with <50% stenosis derived no benefit from surgery.[3] In addition, NASCET gave us a wealth of information on the natural history of medically treated symptomatic carotid disease, which allowed us, based on risk factors and degree of stenosis, to precisely define the patients' risk of stroke[2] (Table I). NASCET allowed us to manage our symptomatic patients using evidence of the highest level.

Similarly, the Asymptomatic Carotid Atherosclerosis Study (ACAS) provided us with a level 1 evidence basis for making treatment recommendations in asymptomatic patients.[4] Asymptomatic patients with ≥60% stenosis derived statistically significant benefit from CEA in the prevention of ipsilateral stroke, as summarized in Table I.

The ACAS data have some issues that limit their usefulness as they are applied to individual patients. The benefit of CEA, although statistically significant, is relatively meager, with an absolute risk reduction of only 6% over 5 years. There was an unexplained sex difference in the benefit of surgery, with men deriving more benefit than women. Finally, there was no increase in the benefit of surgery with increasing severity of disease, a finding clearly at odds with the findings in NASCET.[4] Still, the ACAS data in general support a role for CEA in the management of asymptomatic carotid disease. More recently, the Asymp-

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Table I. A, North American Symptomatic Carotid Endarterectomy Trial and Asymptomatic Carotid Atherosclerosis Study results summarized[2,3,4]

Trial	*Medical therapy, %*	*Medical therapy + CEA, %*	*P*
NASCET			
Ipsilateral stroke			
At 2 y, 70%-99%	26	9	<.001
At 5 y, 50%-70%	22.2	15.7	.045
At 5 y, 30%-50%	18.7	14.9	.16
ACAS			
Ipsilateral stroke			
At 5 y, >60%	11.0	5.1	.004

CEA, Carotid endarterectomy; *NASCET,* North American Symptomatic Carotid Endarterectomy Trial; *ACAS,* Asymptomatic Carotid Atherosclerosis Study.

Table I. B, North American Symptomatic Carotid Endarterectomy Trial risk factors for stroke at 2 years in patients managed without surgery

Factor	*Stroke risk at 2 years*	*%*
Age >70	Risk by factors	
SBP >160 mm Hg	0-5 factors	17
DBP >90 mm Hg	6 factors	23
Recent CVA	>6 factors	39
Stenosis>80%		
Ulceration on arteriogram	Risk by carotid stenosis	
History of tobacco use	70%-79%	12
Diabetes	80%-89%	18
Claudication	90%-99%	26
Hyperlipidemia		

SBP, systolic blood pressure; *DBP,* diastolic blood pressure; *CVA,* cerebrovascular accident.

tomatic Carotid Surgery Trial, a very large international trial, confirmed the ACAS conclusion that endarterectomy plus medical management was more beneficial than medical management alone in the prevention of stroke in patients with asymptomatic carotid stenosis.[5]

Critics of NASCET and ACAS, and those generally skeptical of the benefits of CEA, have pointed to the ACAS and NASCET exclusion criteria in suggesting that the data from these studies apply to only a select group of patients. These skeptics conclude (erroneously in my mind) that the excluded patients will not benefit from CEA because of increased operative risk or limited longevity. They argue that the excluded patients a priori won't benefit from CEA but that they may benefit from stenting. I would argue that many of these exclusion criteria, such as disabling stroke, uncontrolled hypertension, and severe intracranial disease, apply equally to endarterectomy and stenting; that others, such as cardiac rhythm or valvular disorders, were used simply to allow clear attribution of end point causation; whereas still others, such as age and recent contralateral CEA, were poorly thought out and probably unnecessary.

Other clinical investigators, though, have found that medical risk factors really cannot define a group at high risk for adverse outcomes from CEA. A study by Gasparis et al[6] failed to show a significant CEA outcome difference when outcomes in patients with established "high-risk" comorbidities were compared with outcomes in usual-risk patients.[6]

So, just as we got comfortable with the application of the ACAS and NASCET findings in our individual practices, we began to learn of CAS as an alternative to CEA, and the appeal of this minimally invasive, catheter-based approach was undeniable. Early reports with the usual remarkable "before and after" pictures revealing beautiful results fueled early enthusiasm. The ease of performing the procedure in high-anatomic-risk settings was undeniable. Early registry results were encouraging. The early appeal of CAS led to speculation about its potential role in the management of anatomically and medically high-risk patients and ultimately to speculation that it might replace CEA as the default treatment for all patients with severe carotid disease.

As experience with CAS increased nationally and internationally, publications of case series appeared, followed quickly by several nonrandomized and then randomized trials comparing stenting and endarterectomy (Table II).[7-17] I will now review these.

Roubin et al[7] published a large multihospital registry illustrating the safety and efficacy of CAS in which the 30-day stroke/death rate was 7.4% and the 3-year freedom from ipsilateral or fatal stroke was 92%.[7] In 2004, the German Societies of Angiology and Radiology published the largest registry of CAS, again suggesting a high level of safety and technical success, with a combined stroke and death rate of only 2.8% despite very significant variability in equipment and technique.[8]

Three registries—Medtonics AVE Self-Expanding Carotid Stent System with Distal Protection in the Treatment of Carotid Stenosis (MAVERiC), Carotid Stenting With the Nexstent and Distal Protection With the FilterWire EX in High Risk Patients (CABERNET), and Boston Scientific EPI: A Carotid Stenting Trial for High-Risk Surgical Patients (BEACH)—were industry-sponsored attempts to demonstrate safety and efficacy for United States Food and Drug Administration approval for selected combinations of stents, delivery systems, and cerebral protection devices. MAVERiC evaluated the Medtronic carotid stent system and found a major adverse event rate of 5% and a "procedural success" rate of 90%.[9] CABERNET evaluated the Boston Scientific Filter wire used with the Nex-Stent stent and delivery systems and found reasonable safety, with 30-day and 1-year adverse event rates of 3.9% and 11.9%, respectively.[10] In the BEACH registry, which evaluated use of the Wallstent and Filterwire EX or EZ, the major adverse event rate at 30 days was 5.8% and the procedural success rate was 98%.[11]

The final registry I will discuss, ACCULINK for Revascularization of Carotids in High-Risk Patients (ARCHeR), is both the most compelling and at the same time, the most misleading of these industry-sponsored trials.[12] This regis-

try evaluated the performance of the Guidant stent and cerebral protection systems. By design, this was a large registry of high-risk patients that incorporated well-documented eligibility criteria. The results are credible, although not as promising as those of prior registries, with an overall 30-day stroke/death/myocardial infarction (MI) rate of 13% in symptomatic patients, 6.8% in asymptomatic patients, and 8.3% overall. However, the credibility of this study ends when the authors introduce their "control group," a historical series of high-risk CEA patients including patients undergoing combined coronary artery bypass grafting/CEA. The authors calculate a control group composite adverse event rate of >14%, which makes the composite adverse event rate in the stent group (8.3% overall but 13% in symptomatic patients) look favorable.

Where in the literature in the past 20 years have we seen any study of carotid surgery in which the 30-day adverse event rate was 14%? To my mind, the publication of this article with inclusion of the historical composite control group was a failure of the *Journal of Vascular Surgery* editorial process. The inclusion of this control group is even more egregious given potential conflict of interest in this study because most authors were Guidant employees or consultants. In addition, 76% of the patients entered were asymptomatic. With a periprocedural adverse event rate of 6.8%, the asymptomatic patients might well have fared better with medical therapy alone.

Now I will move from registries to comparative trials. The Carotid Revascularization using Endarterectomy or Stenting Systems (CaRESS) trial was an industry-sponsored (Boston Scientific and Medtronic) nonrandomized comparative trial.[13] Patients received CEA or CAS on the basis of recommendations by their physicians or their own preference. The results revealed no significant differences in 30-day or 1-year outcomes, although there was a nonstatistically significant trend toward better outcomes in the stent group.

Of course, in this industry-sponsored nonrandomized study, the potential for selection bias is very real, and the findings, therefore, are difficult to interpret. Still, it would appear from these data that CAS represents a reasonably safe procedure that has a significant role in the management of some patients with carotid disease. Still, because patients were assigned to treatments on the basis of some combination of the recommendations of their physicians and on their preference, we can never know which patients are better served by stenting and which by endarterectomy.

Prospective randomized trials usually provide the highest level of evidence and should allow for truly evidence-based decision making. Unfortunately, the peculiar characteristics of the existing randomized trials comparing CEA and CAS do not really permit generalizable conclusions regarding their relative merits. The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) was the first randomized trial, but included both carotid and vertebral disease patients, plain old balloon angioplasty with little use of stents, no cerebral protection device use, and had high morbidity and mortality rates in both the surgical and interventional arms.[14] This trial is of little relevance today.

Perhaps the stent vs endarterectomy trial that caused the biggest splash, at least initially, was the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial.[15] This randomized trial, sponsored by Cordis, compared the outcomes of CEA and stenting in patients at high risk for CEA. Without peer review, the initial results were published in *USA Today* and were widely misinterpreted. The primary end point for the SAPPHIRE trial, after peer review and publication in the *New England Journal of Medicine*, was an amalgam of short- and intermediate-term results (periprocedural stroke, MI, or death and 1-year ipsilateral stroke or death). Analyzed in this way, the results for stenting were statistically significantly superior to those of CEA ($P = .05$). However, there was no statistically significant difference in outcome in any individual end point of death, stroke, or MI. Furthermore, 15 of 17 MIs encountered overall and 10 of 12 MIs in the CEA group were non-Q-wave events of doubtful significance.

Perhaps most importantly, this trial may not reflect real-world decision making. Less than 30% of these "high-risk" patients had symptomatic carotid disease. In most practices, many of these asymptomatic patients would have been followed conservatively, probably with a very low incidence of stroke. The failure of the SAPPHIRE group to include a medical management arm makes their overall results largely irrelevant to current practice and hints at the true motivation behind this study. I will offer more of my thoughts on this motivation in a moment.

Randomized controlled trials comparing patients equally eligible for either CEA or CAS would seem, at least to me, to be the best way to evaluate the relative merits of these two treatments. A large enough trial might even have the statistical power to permit subgroup analysis so we could really learn something about who is likely to benefit most from CEA and who is likely to benefit most from CAS. Recently, two European trials have been published in which results of CEA and CAS in patients equally eligible for these alternative treatments were compared.

First, the Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis (EVA-3S) trial compared the outcome of CEA and CAS in 527 patients with severe symptomatic carotid stenosis.[16] The 30-day results revealed stroke/death rates of 3.9% in the CEA group and 9.6% in the stent group ($P = .01$), and the 6-month results revealed stroke death rates of 6.1% in the CEA group and 11.7% in the CAS group ($P = .02$). Critics of this study point to several flaws, including the inclusion of 20 patients done without cerebral protection in whom there was a 25% stroke incidence, the diversity of stents and cerebral protection devices used, and differences in the experience levels of the surgeons and interventionalists.

Similarly, the Stent-Protected Percutaneous Angioplasty Versus Carotid Endarterectomy (SPACE) trial compared outcomes in 1185 symptomatic patients randomized to CAS or CEA.[17] This trial, which was designed as a

Table II. Representative clinical studies of carotid artery stenting

Registries
• Roubin, et al[7]
• Pro-CAS[8]
• MAVErIC[9]
• CABERNET[10]
• BEACH[11]
• ARCHER[12]
Nonrandomized comparative trials
• CaRESS[13]
Randomized comparative trials
• CAVATAS[14]
• CREST[18]
• SAPPHIRE[15]
• EVA-3S[16]
• SPACE[17]

MAVEriC, Medtronic AVE Self- Expanding Carotid Stent System with Distal Protection in the Treatment of Carotid Stenosis; *CABERNET,* Carotid Artery Revascularization Using the Boston Scientific EPI FilterWire EX/EZ and the EndoTex NexStent; *BEACH,* Boston Scientific EPI: A Carotid Stenting Trial for High Risk Surgical Patients; *ARCHeR,* ACCULINK for Revascularization of Carotids in High-Risk Patients; *CARESS,* Carotid Revascularization using Endarterectomy or Stenting Systems; *CAVATAS,* Carotid and Vertebral Artery Transluminal Angioplasty Study; *SAPPHIRE,* Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy; *EVA-3S,* Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis; *SPACE,* Stent-Protected Percutaneous Angioplasty Versus Carotid Endarterectomy.

"noninferiority" study, failed to prove the noninferiority of CAS compared with CEA in these patients. SPACE is criticized for the use of cerebral protection in only 27% of the CAS patients. Of interest, the entire outcome difference was confined to the subgroup of patients aged >75 years old. Those aged <75 fared equally with CEA and CAS.

Perhaps the most awaited trial results since those of NASCET and ACAS are the results eagerly anticipated from the Carotid Revascularization Endarterectomy vs. Stent Trial (CREST), a randomized trial comparing stenting and endarterectomy in 2500 subjects deemed equally eligible for either treatment. The results of the lead-in phase of this trial suggest that age plays a significant role in outcome of CAS, with older patients having much worse CAS outcomes than younger patients.[18] These results are consistent with the findings of the SPACE trial.

One additional study deserves mention because it represents a good faith effort to identify subgroups of patients for whom stenting might be the preferred treatment and others for whom endarterectomy might be the preferred treatment. The Imaging in Carotid Angioplasty and Risk of Stroke (ICAROS) trial analyzed stent outcomes according to gray-scale median (GSM) measurements.[19] GSM represents a measure of plaque echogenicity. Low GSM plaques are those with a large lipid core or intraplaque hemorrhage, whereas higher GSM plaques are those with predominantly fibrous or calcific composition. In this study, patients with GSM of ≤25 had a periprocedural stroke risk of 7.1%, whereas those with GSM >25 had a periprocedural stroke risk of only 1.5%. Of note is that cerebral protection seemed ineffective in patients with very low GSM.

Table III. Currently accepted indications for carotid stenting

• Early recurrent stenosis
• Hostile heck (radiation, radical neck dissection, tracheostomy, infection)
• Surgically inaccessible lesion
• Fibromuscular dysplasia
• Inclusion in approved randomized controlled trial
• Extreme medical risk (hard to define precisely)

So, where does this leave us? The situations in which CAS was initially deemed intuitively appropriate in the management for carotid disease are summarized in Table III. I would submit to you that despite all of the trials we have reviewed (and a few more which time did not permit us to review), our appreciation of the role of CAS now is no more sophisticated than it was 5 years ago. Why?

What we have learned is that CAS is both feasible and reasonably safe, yielding satisfactory short- and intermediate-term results. In addition, although not covered in this talk in detail, restenosis rates seem acceptable at an intermediate term of 1 to 3 years. On the other hand, what we have yet to learn is much more important. In which patients is stenting preferred over endarterectomy? In which patients is endarterectomy preferred over stenting? And, perhaps most importantly, what is the impact of newer drugs, especially statins and clopidogrel, on the role of intervention and on the indications for medical management? Why have we not yet learned which treatment is best in which patient?

Current trials have really been designed to tell us whether endarterectomy or stenting is superior in large groups of patients with rather broadly defined risk criteria and other characteristics. They have not been designed to explore potentially complementary roles for stenting, endarterectomy, and medical treatment. Because it is virtually certain that some patients will be best served by endarterectomy, others by stenting, and still others by medical therapy alone, why are there no trials specifically designed to promote the development of rational treatment guidelines or standards?

I believe that the answer to this question lies in the economics of carotid disease treatment. First, it is clear that device manufacturers have spent very large amounts of money to engineer, manufacture, and study stents, delivery systems, and protection devices. For them, having CAS turn out to be a niche treatment for only a select subset of carotid disease patients would be a disaster. To recoup their investment, they need for stenting to be the default in carotid disease management.

Second, vascular surgeons, a small and underrepresented group, and our patients are really the only stakeholders in carotid disease management that can afford to be objective and to look at stenting as an interesting and potentially complementary treatment preferred for some yet to be defined segment of the carotid disease population. We, as vascular surgeons, can offer endarterectomy, carotid stenting, and medical ther-

Table IV. One potential carotid treatment algorithm for comparison with alternative algorithms in future clinical trials

Carotid endarterectomy (+ medical management)	*Carotid stenting (+ medical management)*	*Medical management alone*
Age >80	Hostile neck	Limited life expectancy
Low or very high gray-scale median	Recurrent stenosis	Age >90
Extreme tortuosity	High lesion	Asymptomatic patient on dialysis
Difficult arterial access	Specified cardiac risk	Defined extreme medical risk
Contrast allergy or renal issue	Contralateral cranial nerve palsy	
Clopidogrel and ticlopidine contraindicated	History of malignant hyperthermia or other anesthetic issue	
Significant arch disease		

apy to our patients and, therefore, we should be most objective in assessing the relative merits of each of these treatments in each individual patient. Interventional cardiologists can offer only medical therapy or stenting, and interventional radiologists only stenting. When your only tool is a hammer, the whole world looks like a nail, or in the immortal words of a former partner "Go to Midas, get a muffler!"

All the evidence I need in support of my interpretation of the motivation for carotid stent trial design is seen in this headline from the November 2006 issue of *Vascular News.* This headline "Setback For Carotid Stenting?" followed publication of the EVA-3S and SPACE trials in which stenting came out second best compared with endarterectomy. If the editors of this publication were interested in furthering our understanding of the optimal management of patients with carotid disease, the headline would have been very different, perhaps something like: "Are EVA-3S and SPACE Results Valid?" or "EVA-3S and SPACE: Should They Influence Carotid Disease Management?" In the chosen headline, the editors decided to interpret the results of EVA-3S and SPACE as potential threats to carotid stenting and to those whose interests are aligned with carotid stenting, rather than as potential advances in patient management. The primacy of economic concern over concern for scientific merit or patient welfare is evident.

Where do we go, then, with trial design in assessing the future roles of medical management, carotid stenting, and carotid endarterectomy? I believe that all future trials should be designed with the assumption that some patients will be best managed medically, some with medical therapy plus stenting, and some with medical therapy plus endarterectomy. These treatments are complementary and not competing. Varying treatment algorithms including more or less liberal use of each modality can be designed, patients randomly assigned to one of the algorithms, and their results compared. For example, if we use experience as our guide, we might come up with a management algorithm that looks something like Table IV. At present, such an algorithm lacks evidentiary support. We could, however, randomly assign large numbers of patients to be managed according to this paradigm and compare their outcomes with patients randomized to alternative schemes that include more liberal or conservative use of stenting, of medical management, or of endarterectomy. In this way over time, we could develop a much more robust understanding of the appropriate place of our three potential treatments for carotid disease.

I would like to close with a cautionary note. At present, the needs of industry and of other self-interested parties are framing the way in which we evaluate carotid artery stenting and compare it with medical management and with carotid endarterectomy. Their interests have not only biased the reports of these evaluations, but in fact, have also dictated the very questions that are being asked about these treatments. No one is protecting the interests of our patients because no one is asking the question, "What treatment program is optimal?" We are only asking the question, "Is stenting better than endarterectomy?" because in the answer to this question lies the greatest potential to further industrial and other interests. In 1961, the 34th President of the United States, Dwight Eisenhower, gave his farewell address and warned against the rising power of the military-industrial complex, who by feeding off of the public's general xenophobia and paranoia regarding communism, threatened to define our military's needs in a way that would both empower the military and further fatten the wallets of those in the defense industry. He stated, "In the councils of government, we must guard against the acquisition of unwarranted influence, whether sought or unsought, by the military-industrial complex. The potential for the disastrous rise of misplaced power exists and will persist."[20]

I would submit that this quotation is highly relevant to the current situation with carotid stenting if we substitute the words "practice of surgery" for the words "councils of government" and the word "medical" for the word "military." My revised cautionary note would then read: "*In the practice of surgery, we must guard against the acquisition of unwarranted influence, whether sought or unsought, by the* **medical-industrial complex**. The potential for the disastrous rise of misplaced power exists and will persist."

Our patients deserve an unbiased evaluation of the currently available options for the treatment of carotid disease. We must protect their interests by taking the lead in such studies. I thank you for your attention and for the privilege of serving as your president.

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