

# Current Management of Extracranial Carotid Occlusive Disease

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Stroke continues to be a major public health concern, with more than 750,000 strokes occurring per year in the United States, making it the third most common cause of death and the leading neurologic cause of long-term disability.<sup>1</sup> The majority of strokes are ischemic in nature, and up to 20% of ischemic strokes are a result of carotid artery atherosclerotic disease. Treatment of carotid artery stenosis is aimed at preventing ischemic events caused by embolization of components of the atherosclerotic plaque, and less commonly, by hemodynamic compromise secondary to progression to occlusion of a previously narrowed but patent internal carotid artery.

Management of carotid occlusive disease continues to evolve today. Carotid endarterectomy (CEA), first introduced in the 1950s, was established as the gold standard for treatment of carotid stenosis by several landmark trials in the 1990s.<sup>2-8</sup> More recently, carotid angioplasty and stenting (CAS) emerged as a minimally invasive alternative, and several trials ensued to determine its safety and efficacy, and the indications for its use. Although CAS has proved feasible and relatively safe, the appropriate clinical setting for its preferential use over CEA remains unclear and continues to be the subject of many ongoing clinical trials. The purpose of this article is to review the literature on treatment of carotid occlusive disease, and to attempt to elucidate the current status of CAS and its proper place and indication in the therapeutic management of stroke associated with carotid artery stenosis.

## Carotid endarterectomy

Early landmark CEA trials sought primarily to evaluate the efficacy of CEA as compared with medical management, identify the appropriate patient population that would derive benefit from CEA, and establish an acceptable complication rate for the procedure.

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## Symptomatic carotid stenosis

The North American Symptomatic Carotid Endarterectomy Trial (NASCET)<sup>2,3</sup> and the European Carotid Surgery Trial (ECST)<sup>4</sup> addressed the use of CEA in symptomatic patients. Patients who had experienced a recent transient ischemic attack or nondisabling hemispheric stroke secondary to stenosis of the internal carotid artery were randomized to CEA or best medical management. Although NASCET and ECST used slightly different methods to calculate lesion severity, they both demonstrated substantial benefit for patients with significant stenosis. The NASCET method, which uses the normal distal internal carotid artery, tends to underestimate the degree of stenosis as compared with the ECST method, which uses an estimate of the original carotid artery width at the point of maximal narrowing. The more commonly cited findings from NASCET reflected an impressive decrease in the rate of ipsilateral stroke at 2-year followup for symptomatic patients with high-grade stenosis (70% to 99%) from 26% in the medical group to 9% in the CEA group, yielding an absolute risk reduction of 17% ( $p < 0.001$ ). Patients with moderate stenosis were further subdivided into two subsets: 50% to 69% and 30% to 49%. Although patients with  $<50\%$  stenosis did not derive any significant benefit from CEA, with nearly equivalent 5-year ipsilateral stroke risk of 18.7% in the medical group versus 14.9% in the CEA group, patients with 50% to 69% stenosis were found to derive modest benefit from CEA, as illustrated by a 5-year ipsilateral stroke risk of 22.2% in the medical group versus 15.7% in the CEA group (absolute risk reduction of 6.5%,  $p = 0.045$ ). Surgical complication rates reported from NASCET were low, with the risk of permanent disabling stroke and death at 90 days of 2.0%, and the benefits from revascularization were found to be durable over the longterm.<sup>5</sup>

## Asymptomatic carotid stenosis

The Asymptomatic Carotid Arteriosclerosis Study (ACAS), Asymptomatic Carotid Surgery Trial (ACST), and Veterans Affairs Cooperative Trial were designed to examine whether CEA may be appropriate in the treatment of asymptomatic patients with hemodynamically significant lesions of greater than 60% stenosis as identified by duplex ultrasound. ACST was the largest trial, randomizing 3,120 asymptomatic patients equally between immediate CEA

**Abbreviations and Acronyms**

ACAS	= Asymptomatic Carotid Arteriosclerosis Study
ACST	= Asymptomatic Carotid Surgery Trial
CAS	= carotid angioplasty and stenting
CEA	= carotid endarterectomy
ECST	= European Carotid Surgery Trial
EPD	= embolic protection device
EVA-3S	= Endarterectomy Versus Stenting in Patients with Symptomatic Severe Carotid Stenosis
NASCET	= North American Symptomatic Carotid Endarterectomy Trial
SAPPHIRE	= Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy
SPACE	= Stent-Protected Angioplasty versus Carotid Endarterectomy

and indefinite deferral of CEA. With a 30-day perioperative stroke and death risk of 3.1%, the findings from ACST demonstrated a significant net reduction in 5-year stroke risk from 11.8% to 6.4%, producing a 5.4% absolute risk reduction for patients undergoing immediate CEA ( $p < 0.0001$ ).<sup>6</sup> The ACAS was a smaller study, which randomized a total of 1,662 asymptomatic patients to CEA or medical management, and produced similar results, with estimated 5-year risk of ipsilateral stroke and any perioperative stroke or death of 11.0% for the medical group and 5.1% for the surgical group ( $p = 0.004$ ). Of note, the perioperative complication rate in ACAS was extremely low, at 2.3%, which included a 1.2% risk associated with mandatory preoperative arteriography for all patients randomized to the surgical arm, indicating that only one-half of perioperative strokes were related to the actual surgical procedure itself.<sup>7</sup> Finally, although its sample size was modest ( $n = 444$ ), the Veterans Affairs study also demonstrated that CEA reduced the incidence of ipsilateral neurologic events in a select group of asymptomatic male patients with carotid stenosis.<sup>8</sup>

Subgroup analysis in the previously mentioned studies was limited but offered some insight pertaining to the influence of age and severity of stenosis. With respect to age, findings from ACST suggested no benefit from CEA for patients older than age 75; roughly half of these patients died within the subsequent 5 years from unrelated causes, obviating any durable benefit secondary to a shortened life expectancy.<sup>6</sup> Although ACAS and ACST did not specifically address the impact of degree of stenosis, the ECST study, in the investigation of stroke risk in asymptomatic disease, was able to shed some light on the topic. Of their 2,295 patients, they found that although the overall 3-year risk of stroke was 2.1% in medically treated patients, this rate increased to 5.7% for patients with 70% to 99% stenosis, 9.8% for patients with 80% to 89% stenosis, and

14.4% for those with 90% to 99% stenosis, implying that patients with severe stenosis may comprise a subgroup in whom CEA provides greater benefit.<sup>9</sup>

**Indications for carotid endarterectomy**

Based on the major landmark CEA trials discussed earlier, the American Heart Association issued treatment recommendations. Symptomatic patients with >50% to 99% stenosis are best treated by CEA if the risk of perioperative stroke or death is <6%, with greatest benefit in those with severe stenosis (>70% to 99%). For asymptomatic patients, the criteria are more stringent, recommending CEA for those with 60% to 99% stenosis if the perioperative risk of stroke or death is <3% and if the patient has a life expectancy greater than 5 years.<sup>10,11</sup>

In practice, few surgeons doubt the benefit of CEA in symptomatic patients with high-grade stenosis, but they are understandably more cautious when evaluating asymptomatic patients or symptomatic patients with only moderate degrees of stenosis. There is a great deal of complexity about risk assessment in these latter groups of patients. So the decision to operate is often made only after careful consideration of patient characteristics and comorbidities reveals reasonable life expectancy, higher risk of stroke with medical management alone, and acceptable perioperative risk. To further complicate matters, medical management has changed considerably since the early CEA trials, perhaps indicating that the stroke risk reduction benefit from operative therapy may be overstated. For example, ACAS used lone aspirin therapy, and ACST, the most recent trial, reported a significant increase in the number of patients on lipid lowering agents who were randomized between 1993 and 1996 (17%) and between 2000 and 2003 (58%).<sup>6,7</sup>

In addition, treatment recommendations as outlined by the American Heart Association are often considered inadequate because they pertain to only a carefully selected subgroup of low-risk patients as defined by study exclusion criteria. For example, NASCET exclusion criteria included, but were not limited to age greater than 80 years, failure of the kidney, liver, or lung, cancer judged likely to cause death within 5 years, and presence of cardiac valvular or rhythm disorder. Patients were also temporarily ineligible if they had uncontrolled hypertension or diabetes mellitus, unstable angina, myocardial infarction within the previous 6 months, and recent major surgery.<sup>2</sup> Based on similar exclusion criteria, patients were also deemed ineligible from ACAS, necessitating the screening of 25 patients for every 1 randomized.<sup>7</sup> As a result, there is valid concern that the general population of patients with carotid stenosis has significantly different demographics than those patients who met strict eligibility criteria in the randomized trials, and in fact, it has been noted that the general popu-

lation with carotid stenosis is likely older and less healthy, with higher perioperative morbidity and mortality.<sup>12</sup>

Although the trials mentioned earlier established CEA as the gold standard in treatment of carotid artery stenosis, several issues remained specifically with respect to the utility of CEA in high-risk subsets of patients who were excluded from the studies. Amid this controversy, endovascular techniques were being developed, and subsequently these high-risk patients became the focus of several trials evaluating carotid angioplasty and stenting as a potential mode of intervention for carotid disease.

### **Carotid angioplasty and stenting**

Balloon angioplasty of the carotid artery was first described in the late 1970s as a proposed intervention for carotid artery stenosis.<sup>13</sup> Initially it was promoted as a potentially safer alternative to CEA in medically high-risk patients and those with hostile neck anatomy. Early trials involving carotid angioplasty demonstrated feasibility of the technique but were not widely accepted because of small study size, relatively high complication rates, and random use of stenting, to name a few. Enthusiasm was further curtailed by the concern for embolic complications associated with the procedure. Gradually, however, CAS evolved to its current form with improvements in equipment and technique, increased operator experience, and the standard use of stenting and cerebral protection.

### **Cerebral protection**

The use of embolic protection devices (EPDs) for cerebral protection became standard practice in CAS trials after several articles suggested decreased risk of embolic complications with their use.<sup>14</sup> These devices are based on three different approaches: distal filter placement, distal balloon occlusion, and proximal protection with flow reversal.

Filters are the most commonly used EPD and are positioned in the internal carotid artery distal to the target lesion. Antegrade cerebral flow is maintained through the filter during CAS. The embolic debris dislodged during the procedure is captured within the filter, and then subsequently removed with retraction of the device. The filters typically retain fragments larger than their pore size, approximately 100  $\mu\text{m}$ , but do allow passage of smaller particles. Filters are advantageous because they allow continued cerebral perfusion, particularly in patients who have inadequate collateral circulation to permit temporary carotid occlusion. Currently, several filters are FDA-approved for use in the United States and include AccUNET (Abbott Laboratories), Emboshield (Abbot Laboratories), FilterWire EZ (Boston Scientific Corporation), SpiderFx (EV3), and Angioguard XP (Cordis-Johnson & Johnson).<sup>15-18</sup>

In addition to filters, distal balloon occlusion can be used for embolic protection. The PercuSurge occlusion bal-

loon (Medtronic)<sup>19</sup> is a component of an angiographic wire that is passed through the stenotic area and inflated in the distal internal carotid artery. After the CAS procedure, the standing column of blood containing particulate matter is aspirated. The balloon is then deflated and flow is restored to the cerebral circulation. Compared with filters, distal occlusion balloons have a lower device-crossing profile, but are disadvantageous in that they require temporary interruption of cerebral perfusion while the inflated balloon captures embolic debris. It was reported in one study that up to 23% of patients had temporary neurologic intolerance to balloon occlusion, with a significant number of these patients exhibiting symptoms immediately after initial balloon inflation. Of note, however, is that all neurologic deficits were completely reversible with restoration of antegrade flow, and did not recur with balloon reinflation.<sup>20</sup>

Unlike both distal filters and balloons, proximal protection devices with flow reversal, such as the MOMA device (Invatec)<sup>21</sup> and the Parodi Anti-Embolic System (Gore)<sup>22</sup> are beneficial because they do not require crossing of the stenosis. Such devices are under active investigation and provide protection by occluding the common and external carotid arteries, after which collateral flow through the circle of Willis creates a back-pressure that prevents antegrade flow into the internal carotid artery.

Despite the fact that EPDs likely provide additional cerebral protection, there is still a risk of stroke associated with CAS secondary to particle embolization from the aortic arch. In addition, EPDs have inherent risks and complications of their own, such as inability to cross the target lesion, failure to capture emboli through filter pores, and vasospasm or injury to the vessel wall.<sup>23</sup> In addition, it is still debatable whether the routine use of EPDs is required at all. A recent single-center randomized study found no demonstrable reduction of microemboli, as detected by diffusion-weighted MRI, as might be expected with filter use.<sup>24</sup> But there are no large randomized trials to date that compare CAS with and without EPDs, and most data rely on historical comparison of results before widespread EPD usage. So EPD use has become standard and is currently mandated by the Centers for Medicare and Medicaid Services.

### **Carotid artery stenting trials**

CAS trial data stems from industry-sponsored registry trials and randomized trials. Registry trials are nonrandomized outcomes trials evaluating the safety and efficacy of specific stents and EPDs in a predominantly asymptomatic population of patients who are all considered to be at high risk for conventional CEA. Most registries are conducted to acquire initial device approval, or as part of a required postapproval evaluation in a larger group of patients. Tech-

**Table 1.** Carotid Artery Stenting Registry Trials

Registry trial	n	Symptomatic, %	30-d Stroke, %	30-d Death, %	30-d MI, %	30-d Combined,* %
Beach <sup>25</sup>	480	25	4.4	1.5	1.0	5.8
Archer <sup>26†</sup>	581	24	5.5	2.1	2.4	8.3
Cabernet <sup>27†</sup>	454	24	3.6	0.5	0.5	4.0
Maveric <sup>28</sup>	498	NR	3.6	1.0	1.8	5.2
Caress <sup>29</sup>	143	31	2.1	0.0	0.0	2.1
Security <sup>30†</sup>	305	NR	6.9	0.0	0.3	7.2
Priamus <sup>31</sup>	416	63	4.1	0.5	0.0	4.6
Create <sup>32†</sup>	419	17	3.3	1.9	1.0	6.2
Capture <sup>33</sup>	3,500	14	4.8	1.8	0.9	6.3
Moma <sup>34</sup>	157	NR	5.1	0.6	0.0	5.7
Pascal <sup>35</sup>	113	NR	NR	NR	NR	8.0
Exact <sup>36</sup>	1500	10	3.9	1.0	0.2	4.6
Cases-PMS <sup>37</sup>	1493	22	3.8	1.0	0.8	5.0
Cristallo <sup>38</sup>	124	24	1.6	2.4	0.8	4.0

\*30-d Combined = death, stroke, or myocardial infarction. Not always additive because some individuals experienced multiple events.

†Resulted in FDA device approval.

MI, myocardial infarction; NR, not reported.

nical success was achieved in >97% of patients in most studies. The combined incidence at 30 days of myocardial infarction, stroke, or death varied between 2.1% and 8.3%, and stroke rate at 30 days ranged from 1.6% to 6.9%<sup>25-38</sup> (Table 1).

Although registry trials are invaluable in providing information pertaining to risks and adverse events associated with CAS, they are unable to offer level 1 comparative data between CAS and CEA. To date, randomized controlled data are limited to five completed trials,<sup>39-42</sup> and four other trials,<sup>43-46</sup> which were all terminated before study completion (Table 2).

The results of early, randomized controlled trials were mixed. The first randomized trial comparing endovascular and surgical treatments for carotid artery stenosis, Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS), was designed to compare balloon angioplasty alone without embolic protection to CEA in symptomatic patients. Stents were incorporated once they became available, but were used in only 26% of patients in the endovascular arm. For the 504 patients enrolled, there was no significant difference found in the composite stroke or death rate at 30 days (10.0% endovascular group versus 9.9% CEA group) or at 3 years (14.3% endovascular group versus 14.2% CEA group).<sup>39</sup> But this study was criticized for a number of reasons. To name a few, the lack of embolic protection and 26% stent usage are in contrast to current standard practice, and the substantially higher stroke rate of 9.9% in the CEA arm make comparison with other reports difficult. The Wallstent trial followed; it was the first multicenter randomized trial designed to compare CAS and CEA equivalence, but was stopped early after

interim analysis revealed worse outcomes in the CAS arm with combined risk of stroke or death at 30 days of 12.1% in the CAS group versus 4.5% in the CEA group.<sup>44</sup> Notably, cerebral protection was not used, and this was thought to contribute in part to the high risk associated with CAS in this study. More encouraging were the results of the Kentucky trials, the first of which was published in 2001 and involved symptomatic patients, and the second of which was published in 2004 and involved asymptomatic patients.<sup>40,41</sup> Extremely low complication rates were observed in both arms, and the results of both trials suggested equivalence of CAS to CEA, but enthusiasm was appropriately guarded because these were small, single institution studies carried out by a highly select experienced team.

The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial demonstrated great promise for CAS. It was the first randomized trial to use mandatory distal embolic protection, and it was designed to demonstrate noninferiority of CAS in a group of patients who were at high risk for conventional endarterectomy, and who turned out to be largely asymptomatic (>70% asymptomatic, <30% symptomatic). The 30-day combined periprocedural adverse event rates were 4.8% for CAS patients and 9.8% for CEA patients ( $p = 0.09$ ). At 1 year, the combined major adverse event rates were 12.2% for CAS patients and 20.1% for CEA patients ( $p = 0.004$  for noninferiority analysis,  $p = 0.05$  for intention-to-treat analysis).<sup>42</sup> These data strongly suggested noninferiority of CAS for high-risk, largely asymptomatic patients. But a few things must be noted. First, the differences in event rates between CAS and CEA were, in part, from the greater association of CEA

**Table 2.** Randomized Carotid Artery Stenting Trials

Trial or first author	n	CAS pts, n	CEA pts, n	Year	Neurologic symptoms	30-d Stroke, %		30-d Death, %		30-d MI, %		Primary endpoint, *		Notes
						CAS	CEA	CAS	CEA	CAS	CEA	CAS	CEA	
Naylor <sup>43</sup>	17	7	10	1998	S	71.0	0.0	—	—	—	—	—	—	Single institution study. Trial ended prematurely after 5 of 7 patients in CAS arm experienced stroke at 30 days.
Alberts <sup>44</sup>	219	107	112	2001	S	12.1	3.6	—	—	—	—	12.1	3.6	Trial ended prematurely after interim analysis revealed worse outcome in CAS arm.
Kentucky 1 <sup>40</sup>	104	53	51	2001	S	0.0	0.0	0.0	2.0	—	—	—	—	Single institution study. No EPD use.
CAVATAS <sup>39</sup>	504	251	253	2001	S, AS	8.0	8.0	3.0	2.0	—	—	10.0	9.9	Only 26% patients in CAS arm received stents. No EPD use.
SAPPHIRE <sup>42</sup>	334	167	167	2004	S, AS	3.6	3.1	1.2	2.5	2.4	6.1	12.2	20.1	High-risk, largely asymptomatic patients. Mandatory EPD use. Demonstrated noninferiority of CAS to CEA.
Kentucky 2 <sup>41</sup>	86	44	42	2004	AS	0.0	0.0	0.0	0.0	—	—	—	—	Single institution study. No EPD use.
SPACE <sup>45</sup>	1,183	599	584	2006	S	7.5	6.2	0.7	0.9	—	—	6.8	6.3	Noninferiority trial ended prematurely for reasons of futility. EPD use not required.
EVA-3S <sup>46</sup>	520	261	259	2006	S	8.8	2.7	0.8	1.2	0.4	0.8	9.6	3.9	Noninferiority trial ended prematurely for safety reasons. EPD use not initially required.
CREST <sup>50,51</sup>	2,500				S, AS									CAS versus CEA. Lead-in phase results demonstrated overall 4.4% 30-day stroke and death rate for CAS, with increased adverse event risk in octogenarians. Target enrollment completed 2008.
ICSS <sup>52†</sup>	1,500				S									CAS vs CEA. Target enrollment projected 2008.
ACT I <sup>53†</sup>	1,858				AS									CAS vs CEA in standard-risk patients.
ACST 2 <sup>54†</sup>	5,000				AS									CAS vs CEA in standard-risk patients.
TACIT <sup>53†</sup>	3,700				AS									3-arm trial comparing CAS, CEA, and best medical management.
Vienna <sup>55†</sup>	300				AS									CAS vs best medical management.

\*Primary endpoint = 30-d stroke and/or death (Alberts, CAVATAS, SPACE, EVA-3S) or composite of 30-d stroke/death/ myocardial infarction and ipsilateral stroke or death at 1 year (SAPPHIRE).

†Trials currently enrolling.

ACST2, Asymptomatic Carotid Surgery Trial 2; ACT I, Asymptomatic Carotid Trial; AS, asymptomatic; CAS, carotid artery stenting; CAVATAS, Carotid and Vertebral Artery Transluminal Angioplasty Study; CEA, carotid endarterectomy; CREST, Carotid Revascularization Endarterectomy versus Stent Trial; EPD, embolic protection device; EVA-3S, Endarterectomy Versus Stenting in Patients with Symptomatic Severe Carotid Stenosis; ICSS, International Carotid Stenting Study; MI, myocardial infarction; S, symptomatic; SAPPHIRE, Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy; SPACE, Stent-Protected Angioplasty versus Carotid Endarterectomy; TACIT, Transatlantic Asymptomatic Carotid Intervention Trial.

with non-Q-wave myocardial infarction, which is notably a nontraditional surgical endpoint. Excluding myocardial infarction, there was no significant difference found between CAS (5.5%) and CEA (8.4%) patients. Second, the high event rate noted in both groups casts serious doubt as to the appropriateness or durability of any intervention in the high-risk, asymptomatic population. This concern was supported by longterm followup data at 3 years, which revealed a substantial cumulative incidence in death from cardiac and non-neurologic causes (18.6% CAS versus 21.0% CEA).<sup>47</sup> Third, the possibility of inherent bias in any industry-sponsored trial warrants cautious interpretation. Nevertheless, SAPHIRE was subsequently viewed as the trial that proved the noninferiority of CAS in high-risk patients.

Because SAPHIRE demonstrated noninferiority in high-risk patients, two recently published multicenter, randomized European trials, Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) and Endarterectomy Versus Stenting in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S), sought to establish noninferiority in standard risk, symptomatic patients.<sup>45,46</sup> In SPACE, the primary endpoint was ipsilateral stroke or death at 30 days. A variety of different stents were used and embolic protection was not mandated. The initial aim of the study was to enroll 950 patients per group to achieve a power of 80%. The final analysis in the SPACE trial comprised 1,183 patients and reported a primary event rate of 6.84% in the CAS group versus 6.34% in the CEA group, ( $p = 0.09$  for noninferiority analysis).<sup>45</sup> SPACE CAS patients were treated variably with embolic protection, but there were no significant differences found between those who were treated with and without. In addition, in most endpoints there seemed to be a favorable trend toward the surgical arm, although none were statistically significant. After this interim analysis, the steering committee decided to terminate the study on the basis of both futility and financial constraints because it was revealed that 2,500 patients would be needed to adequately power the study to achieve trial endpoints. So, SPACE failed to prove noninferiority of CAS compared with CEA, and the authors concluded that CEA should remain the preferred treatment for patients with symptomatic stenosis because evidence was lacking to support equivalent or superior endovascular treatment. Subsequent subgroup analysis from SPACE revealed that this was particularly true for older patients, in whom CAS was associated with a worse outcome. Investigators found that the risk of ipsilateral stroke or death increased significantly with age in the CAS group ( $p = 0.001$ ) but not in the CEA group ( $p = 0.534$ ).<sup>48</sup>

Similarly, the EVA-3S trial also failed to demonstrate noninferiority of CAS in symptomatic patients. The primary endpoint was defined as a composite of any stroke or

death occurring within 30 days after treatment. The goal was to enroll 872 patients per group to achieve a power of 80%. A variety of different stents were used at different centers, and cerebral protection was initially not required until the safety committee instituted a protocol change as a result of a 25% 30-day rate of stroke or death in patients treated without EPDs.<sup>49</sup> The study randomized 527 patients and was subsequently ended prematurely for safety reasons after interim analysis revealed a significantly higher 30-day event rate in the CAS group (9.6%) compared with the CEA group (3.9%;  $p = 0.01$ ). These results persisted at 6 months, with an event rate of 11.7% in the CAS arm versus 6.1% in the CEA group ( $p = 0.02$ ).<sup>46</sup>

The EVA-3S results have been widely criticized for the significantly higher 30-day stroke rate observed in the CAS arm of the study as compared with other recently published results, namely from the SAPHIRE trial (9.2% EVA-3S versus 3.6% in SAPHIRE).<sup>42,46</sup> In addition to the lack of initial EPD use in EVA-3S, the difference in reported stroke rate was also attributed to the overwhelming number of patients with asymptomatic stenosis in the SAPHIRE trial, which carries a lower risk of stroke during carotid repair than does symptomatic stenosis. Criticism for EVA-3S has also been directed at the fact that the trial did not compare groups of physicians with equal experience. The surgeons performing CEA had done at least 25 endarterectomies within 1 year before trial entry, but interventionalists were certified after performing less than half that number and were allowed to enroll study participants while completing their training and certification, a factor that could also theoretically increase stroke risk in the CAS arm. Despite these claims, however, subgroup analysis failed to show any statistically significant difference between operators based on level of experience.<sup>46</sup> The conclusion from the EVA-3S authors essentially supported the notion that CEA remains an excellent option for symptomatic carotid stenosis with low complication rates that are currently not matched or bested by CAS.

It has been challenging to collectively interpret the results of the randomized trials to date because they reached different conclusions about the safety and efficacy of CAS versus CEA. So the question still remains whether CAS offers an advantage or is even equivalent to CEA, and which subgroup of patients, if any, would derive the most benefit from CAS. Current data probably suggest better outcomes for CAS with certain high-risk, asymptomatic patients as compared with standard-risk, symptomatic patients. The answer, however, awaits completion of several ongoing large, multicenter randomized trials<sup>50-55</sup> (Table 2).

### **Carotid angioplasty and stenting: evolving indications**

Although CAS has proved a feasible and effective technique in the management of carotid artery stenosis, the appropriate clinical setting for its preferential use over CEA has yet to be clearly defined by the results of randomized trials. Initially CAS was proposed as a good alternative to CEA in loosely defined categories of high-risk patients. Later, CAS was even touted by some proponents as an acceptable substitute and universal replacement for CEA in all patients. Subsequently, however, certain subgroups of patients have been identified as inappropriate for CAS and preferably treated by CEA, so indications for CAS continue to be in a state of flux.

#### **High-risk for carotid endarterectomy**

CAS was initially promoted as a preferred intervention for high-risk patients. Patients considered to be high risk from an anatomic standpoint are rare, constituting less than 5% of CEA patients,<sup>56</sup> and include those who have had previous neck surgery (carotid and noncarotid), history of neck radiation, high surgically inaccessible lesions, the presence of tracheostomy, contralateral recurrent laryngeal nerve palsy, or spinal immobility. On the other hand, medical or physiologic high-risk patients are much more common in the CEA population, and this category has typically included patients with advanced age, contralateral occlusion, and cardiac and other medical comorbidities.

Exclusion from early landmark trials sought to identify individuals at greater than average risk for CEA, and by default identified a subgroup of patients in whom CEA was not of proven benefit over medical management. This triggered multiple studies, which together almost uniformly concluded that in fact, CEA could be performed in most of these trial ineligible high-risk patients, with low mortality and morbidity. Lepore and colleagues<sup>57</sup> reviewed 366 CEAs and divided them into NASCET/ACAS eligible and ineligible groups, finding no significant difference in stroke or death rate between them (3.6% ineligible versus 1.5% eligible,  $p = 0.17$ ). More recently, Mozes and associates<sup>58</sup> performed a retrospective analysis of 776 CEAs and stratified patients into high- and low-risk categories according to identical inclusion criteria used in the SAPPHERE trial; they also found no significant difference in stroke or death rates between the two groups. Similarly, another analysis of 788 CEAs revealed no difference in stroke and death rates between high- and normal-risk patients (1.3% and 1.1%, respectively), and not only refuted the idea that CEA was associated with unacceptable complication rates in the high-risk subgroup, but questioned the existence of a significant high-risk CEA group at all.<sup>56</sup>

The notion that risk of stroke or death associated with CEA is higher in all patients excluded from NASCET and

ACAS is clearly not supported. But there are circumstances under which most would agree that CAS offers a safe and reasonable alternative. Anatomically, those with a tracheostomy, spinal immobility, surgically inaccessible lesions, or contralateral recurrent laryngeal nerve palsy complicate CEA because of difficult exposure and maintenance of sterility, risk of airway compromise, and inability to use cervical block anesthesia, all of which are nonissues with CAS. A history of cervical irradiation, although rare, is cause for concern with CEA as compared with CAS primarily because of loss of native tissue planes and poor tissue healing, leading to increased incidence of cranial nerve injury and wound complications, respectively. For example, one study noted a 25% incidence of cranial nerve injury in previously irradiated necks with CEA,<sup>59</sup> unsurprisingly, recent trials have noted a 0% incidence of cranial nerve injuries with CAS.<sup>39</sup> Cranial nerve injury is also an important consideration in the reoperative neck for similar reasons. Despite the fact that several recent reports have suggested that patients with reoperative CEAs should not be considered a high-risk subgroup in which surgery should be avoided,<sup>60</sup> this category of patients has traditionally experienced a higher incidence of complications than patients undergoing primary CEAs, making CAS a sensible alternative. This is especially true in light of recent work that suggests that minor complications after CEA, such as cranial nerve palsy, are associated with a three- to fourfold increase in risk of perioperative stroke or combined risk of stroke and death ( $p < 0.0001$ ).<sup>61</sup>

On the other hand, physiologic risk factors that have been thought to increase risk associated with CEA include advanced age, contralateral occlusion, and medical comorbidities. Advanced age is the most common, yet most widely disputed and often inappropriate preferential indication for CAS. Numerous studies have demonstrated that patients older than 80 years are perfectly suitable candidates for CEA.<sup>62,63</sup> In addition, it has also been shown consistently that advanced age is actually predictive of worse outcomes with CAS.<sup>51</sup>

With respect to contralateral occlusion, the data are more conflicting. In theory, there is the potential for profound cerebral ischemia when flow in the lone carotid artery is interrupted during cross clamping, although many argue that this is temporized by the routine use of intraoperative shunting. Much of the concern stems from the posthoc analysis of the NASCET data, which demonstrated a 2.2-fold increase in perioperative stroke and death in the presence of contralateral occlusion.<sup>2</sup> Additionally, in a retrospective review of 1,370 endarterectomies, Reed and coauthors<sup>64</sup> found contralateral occlusion to be a significant predictor of adverse outcomes and reduced longterm

survival. On the contrary, Rockman and colleagues<sup>65</sup> did not find this to increase the perioperative risk of neurologic events associated with CEA, with a rate of 3.0% in patients with contralateral occlusion, versus 2.1% in those without ( $p = 0.34$ ). Despite this, CAS may prove to be a preferable choice in this subgroup because the technique obviates the risk associated with clamping, allowing antegrade flow with only brief interruptions during balloon inflation that are well tolerated. In addition, CAS has been shown to be safe and effective in this subgroup of patients without increased risk for neurologic events.<sup>66</sup>

The other physiologic risk factors purportedly increasing the risk of CEA include the presence of significant cardiac and noncardiac medical comorbidities. Ouriel and associates<sup>67</sup> identified a high-risk subgroup among 3,061 endarterectomies performed at a single institution by the presence of severe coronary artery disease, chronic obstructive pulmonary disease, or renal insufficiency. The authors found a significant increase in the combined perioperative risk of stroke, death, or myocardial infarction of 7.4% in the high-risk group as compared with 2.9% in the low risk group ( $p < 0.0005$ ). But many believe that true medical contraindications to CEA are rare, and those with significant cardiopulmonary disease precluding the use of general anesthesia can safely undergo CEA using regional block, which has been shown by some to reduce the risk of perioperative complications.<sup>68,69</sup>

### **High-risk for carotid artery stenting**

Only recently has attention focused on identification of patients who may be at high risk for complications during and after CAS. The literature includes data for octogenarians, the presence of specific vascular anatomic and lesion characteristics, and symptomatic patients. So far, there seems to be consensus about at least one high-risk category of patients: those with advanced age. Several studies have demonstrated increased rates of stroke and death among octogenarians. The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) lead-in phase reported a 30-day stroke and death rate of 12.1% for octogenarians compared with 3.2% among nonoctogenarians ( $p < 0.0001$ ), prompting the study investigators to exclude patients more than 80 years of age from the study.<sup>51</sup> Similarly, results from Stanziale and associates<sup>70</sup> indicated that CAS in octogenarians was associated with a statistically significant higher rate of adverse events at 30 days and at 1-year followup. Subgroup analysis of the SPACE trial also found that the rate of complications was significantly associated with age in the CAS group; patients in the CEA group had homogenous event rates across all age groups.<sup>48</sup> Collectively, the results indicate that CAS should be cautiously considered in the elderly population.

The etiology of increased adverse event risk for CAS procedures in the elderly remains incompletely understood. It has been suggested that adverse vascular anatomy and lesion characteristics that have the potential to increase the technical complexity of CAS may account for this finding because recent studies have suggested that some of these complex anatomic features seem to be more prevalent among older patients.<sup>71-73</sup> Lin and coworkers<sup>71</sup> found that aortic arch calcification, common carotid and innominate artery stenosis, and tortuosity of the common and internal carotid arteries were significantly more severe in patients greater than 80 years old. Likewise, in addition to the features mentioned earlier, others have also found unfavorable arch elongation, severe lesion stenosis greater than 85%, and plaque ulceration to be significantly more common among patients age 80 years and older.<sup>72,73</sup> Recent work has also sought to determine the impact of these anatomic characteristics on outcomes after CAS. Some variables that have been associated with increased risk of adverse events include abnormal arch anatomy,<sup>74</sup> vessel tortuosity,<sup>75</sup> long stenotic lesions ( $>15$  mm), involvement of the internal carotid ostium,<sup>76</sup> and plaque echolucency.<sup>77</sup> It is important to note that although these anatomic and lesion characteristics are thought to be more common in the elderly population, younger patients may also have similar unfavorable risk factors. For example, Sayeed and colleagues<sup>76</sup> reported that long stenosis and ostial involvement were associated with increased risk of stroke independent of octogenarian status. So, the presence of certain anatomic factors that preclude safe passage or proper positioning of stents and EPDs must be considered high risk at any age, and this could possibly delineate a new group of patients who, in addition to the elderly, also may not be appropriate candidates for CAS.

Controversy also exists surrounding the role of CAS in managing symptomatic patients. Favorable CAS results to date from SAPHIRE and registry trials have been achieved in populations of predominantly asymptomatic patients, and despite some evidence to the contrary based on retrospective data,<sup>78</sup> many believe that symptomatic patients comprise a high-risk category for CAS.<sup>26,33</sup> As mentioned in previous discussion, two recent randomized trials comparing CEA and CAS in exclusively symptomatic patients, SPACE and EVA-3S, were both terminated prematurely because of futility and safety concerns in the CAS arm.<sup>45,46</sup> Further, the CAPTURE (Carotid Acculink/Accunet Postapproval Trial to Uncover Rare Events) post-marketing trial reported a significant increase in risk of the primary composite outcomes of stroke, myocardial infarction, or death at 30 days among symptomatic patients (12.1%) when compared with asymptomatic patients (5.4%). Even more sobering are the numbers reported in symptomatic octogenarians, who suffered a 17.1% inci-

dence of perioperative stroke, myocardial infarction, or death, which is in stark contrast to the 4.6% reported risk in asymptomatic nonoctogenarians.<sup>33</sup> The rationale behind the observed increased risk with CAS in symptomatic patients remains speculative and unknown, but many would advocate cautious application of CAS in this population at the current time.

### Summary of carotid angioplasty and stenting indications

The literature to date seems to support the use of CAS as a reasonable alternative to CEA in patients with anatomic risk factors, in addition to patients with contralateral occlusion and severe, multiple medical comorbidities. Conversely, many would agree that CAS is best avoided in patients older than 80 years of age, those with complex vascular anatomy and specific unfavorable lesion characteristics, and possibly those with symptomatic disease. Using the previously mentioned criteria, a recent retrospective analysis compared high-risk patients treated with CAS to standard-risk patients treated with CEA.<sup>79</sup> The investigators reported comparable perioperative outcomes between the two groups, concluding that a properly selected patient population can be treated with CAS while achieving complication rates equivalent to CEA, reinforcing the critical importance of appropriate patient selection for CAS success.

It should be noted, however, that to date, the approved indications for reimbursement of CAS as defined by the Centers for Medicare and Medicaid Services has not been modified to reflect recent work and continues to support use of CAS in only high-risk, symptomatic patients with severe stenosis.<sup>80</sup> This is problematic because a number of these high-risk categories have been challenged by several reports as being poorly predictive of adverse outcomes with CEA, and evidence is mounting that symptomatic patients may actually fare worse after CAS than CEA. Additionally, the cost-efficacy of CAS versus CEA will necessitate further exploration. At present, CAS is at best noninferior to CEA in terms of clinical outcomes and offers no financial advantage secondary to high material costs, an issue that bears significant implications for its future application and reimbursement.<sup>81</sup>

Finally, it should be emphasized that for many high-risk patients, and asymptomatic patients, the decision to perform any form of revascularization in favor of conservative management is far more important than the choice of technique. This decision has been complicated by the fact that best medical management has improved considerably since the early landmark trials were undertaken more than a decade ago. Lone aspirin therapy has now been supplemented with newer antiplatelet agents, antihypertensive therapy, angiotensin-converting-enzyme inhibitors, and

statin therapy, which collectively serve to reduce all vascular sources of morbidity and mortality.<sup>9</sup> So, when considering any intervention, it is critical to determine whether the immediate risks attendant to the procedure are indeed significantly less than the risks associated with the natural history of the disease process, and whether or not this is durable over the longterm. It is possible that many high-risk or asymptomatic patients will ultimately be best served with modern medical management, a conclusion that awaits the completion of ongoing and future clinical trials.

### Future directions

The challenge for the future will continue to evolve around optimizing patient selection for CEA, CAS, or medical management alone. Ongoing prospective randomized trials will provide invaluable data on this front, but so will examination of CEA versus CAS in the "real world" setting. At the most recent Society for Vascular Surgery annual meeting, several abstracts were presented in support of this notion, and addressed the frequently cited criticism that trial data are often not applicable to the general population (Vascular Annual Meeting, 2008, San Diego, CA). The Society for Vascular Surgery Vascular Registry was developed in response to the Centers for Medicare and Medicaid Services National Coverage Decision on CAS, but was designed to include data for both CAS and CEA to allow comparison of outcomes. At the 2008 Vascular Annual Meeting, Sidawy and colleagues<sup>82</sup> reported data on 6,403 procedures entered from 287 providers at 56 centers from July 2005 to December 2007. Risk-adjusted logistic regression analysis of the data demonstrated significantly better outcomes in terms of 30-day complications after CEA as compared with CAS. Similarly, other investigators using the Nationwide Inpatient Sample database examined data from 2001 through 2005 and found substantially increased stroke and death rates after CAS when compared with CEA.<sup>82-84</sup> Continued use of resources such as the Society for Vascular Surgery Vascular Registry and the Nationwide Inpatient Sample will broaden our knowledge by serving as an outcomes assessment tool for CAS and CEA in a "real-world" setting, which supplements information provided by randomized trial data.

In conclusion, although CEA has remained the gold standard for carotid revascularization, CAS has experienced tremendous growth over the last decade. Now a routinely performed procedure in academic and community settings, the CAS annual volume is on the rise while CAS-related stroke and death rates continue to decline. As longterm data reflecting the durability of CAS begin to accumulate, greater operator experience is acquired, and new stenting technology develops, the application of CAS will continue to mature. Currently,

however, the choice of CEA versus CAS remains largely based on individual practitioner experience. This will be better defined by ongoing investigations and the emergence of societal guidelines. The Society for Vascular Surgery recently published evidence-based guidelines for management of carotid disease, but the indications for CAS as a potential alternative to CEA in patients with high operative risk were weakly recommended based on low quality evidence.<sup>85</sup> Ultimately, the benefit of either procedure in terms of stroke prevention will depend to a significant degree on institutional outcomes with both techniques. So, for the clinician confronted with a patient in need of revascularization, it is best to view CAS and CEA as complementary techniques that, when taken together, strengthen our ability to offer optimal therapy for patients with carotid artery occlusive disease.

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