Evidence-based treatment of carotid artery stenosis

Kate C. Young, Ph.D., M.P.H., Anunaya Jain, M.B.B.S., M.B.E.M., Minal Jain, M.B.B.S., Robert E. Replogle, M.D., Curtis G. Benesch, M.D., M.P.H., and Babak S. Jahromi, M.D., Ph.D.

Departments of 1Neurology, 2Neurosurgery, and 3Imaging Sciences, University of Rochester Medical Center, Rochester, New York

Carotid atheromatous disease is an important cause of stroke. Carotid endarterectomy (CEA) is a well-established option for reducing the risk of subsequent stroke due to symptomatic stenosis (> 50%). With adequately low perioperative risk (< 3%) and sufficient life expectancy, CEA may be used for asymptomatic stenosis (> 60%). Recently, carotid angioplasty and stent placement (CAS) has emerged as an alternative revascularization technique. Trial design considerations are discussed in relation to trial results to provide an understanding of why some trials were considered positive whereas others were not. This review then addresses both the original randomized studies showing that CEA is superior to best medical management and the newer studies comparing the procedure to stent insertion in both symptomatic and asymptomatic populations. Additionally, recent population-based studies show that improvements in best medical management may be lowering the stroke risk for asymptomatic stenosis. Finally, the choice of revascularization technique is discussed with respect to symptom status. Based on current evidence, CAS should remain limited to specific indications. (DOI: 10.3171/2011.3.FOCUS1143)

KEY WORDS • carotid endarterectomy • carotid angioplasty and stent placement • evidence-based medicine

Strokes accounts for 1 in every 18 deaths in the US, and leaves nearly 30% of those afflicted permanently disabled.3,4 Worldwide, stroke is a leading cause of disability and the third leading cause of death, with 5 million deaths reported annually.7 In the US alone, each year nearly 800,000 individuals suffer a stroke, with one-quarter of those cases being recurrent strokes.8 Despite advances in stroke prevention, imaging, treatment, and rehabilitation, the costs of care continue to increase. In 2008, the costs of stroke care were $65 billion/year.10 The estimated cost of care for patients with stroke in 2010 is $73.7 billion, with overall costs expected to exceed $2 trillion by 2050.99

One of the most important causes of ischemic stroke is carotid atheromatous disease, representing approximately 20% of the total incidence of this type of stroke.31 Severe carotid stenosis is the most important risk factor for recurrent stroke in symptomatic patients with carotid atheromatous disease. Several large randomized trials have shown marked early benefit from CEA. Timely CEA (within 2 weeks from onset of symptoms) results in an absolute risk reduction of 15.6% and a relative risk reduction of 52% over best medical management.4,18,35,37,41 Results of these large-scale trials and their pooled patient-level meta-analyses have made CEA the standard of care in patients with severe (> 70%) symptomatic carotid stenosis, and have provided Level I/A evidence for decisions regarding symptomatic patients with lesser degrees of stenosis by demonstrating modest benefits of CEA for symptomatic 50%–69% stenosis, and no benefit for stenosis < 50%.10,41 In contrast, patients with asymptomatic carotid stenosis have a vastly different natural history, with much lower upfront risks of stroke. Two large-scale randomized controlled trials have demonstrated modest benefits achieved over several years from treatment.18,28

Indeed, significant improvements in stroke prophylaxis achieved by BMT have led to a reappraisal of CEA for asymptomatic stenosis, with current and upcoming trials of carotid revascularization now including an arm for BMT.1,39

Abbreviations used in this paper: ACAS = Asymptomatic Carotid Atherosclerosis Study; ACST = Asymptomatic Carotid Surgery Trial; BMT = best medical treatment; CAS = carotid angioplasty and stent placement; CEA = carotid endarterectomy; CREST = Carotid Revascularization Endarterectomy versus Stenting Trial; DWI = diffusion-weighted imaging; ECST = European Carotid Surgery Trial; EVA-3S = Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis; ICSS = International Carotid Stenting Study; MI = myocardial infarction; NASCET = North American Symptomatic Carotid Endarterectomy Trial; SAPPHIRE = Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy; SPACE = Stent-Protected Percutaneous Angioplasty of the Carotid artery versus Endarterectomy.
Over the past decade, CAS has emerged as a potential alternative to CEA. The appeal of CAS has been driven in part by patient, physician, and hospital preferences for less invasive procedures, with underlying assumptions that this would lead to a reduction in complications, length of stay, and cost, although the latter 2 appear to not be borne out in practice.\textsuperscript{25,28,38,51} The choice between CEA and CAS has therefore been primarily centered around which technique provides better clinical outcomes. Multiple CAS case series and registries have emerged, of mixed quality and with conflicting data, which will not be reviewed here. Unfortunately, large-scale randomized controlled trials comparing the 2 revascularization techniques have proven controversial, and have not convincingly identified a superior technique.\textsuperscript{11,17,22,26,33,40,50} The most recent trial, CREST, was designed to avoid prior pitfalls and to reach definitive conclusions regarding choice of revascularization technique for carotid stenosis, although interpretation of its results has not been free of controversy either.\textsuperscript{2,5}

Health care is undergoing a radical transformation. The economic environment has challenged health care organizations to deliver optimal services in the face of compromised cash flows, reduced resources, and declining margins. There is an overwhelming need for health care policy makers to audit current practices to ensure incorporation of cost-effective guidelines without compromising quality and outcomes of care. Our objective in this review of trials comparing CEA, CAS, and BMT in patients with carotid artery stenosis was to analyze existing evidence and cite comparative measures to consider while making such treatment decisions.

**Trial Design**

The trials of CEA compared with BMT were designed as superiority trials, whereas some of the recent trials comparing CAS to CEA were designed as noninferiority trials. As an example, NASCET, ACST, and ACAS tested the proportion of stroke following CEA ($P_{\text{CEA}}$) and BMT ($P_{\text{BMT}}$) to show that one treatment is superior to the other. In this case, the null hypothesis was defined as $H_0$: $P_{\text{CEA}} = P_{\text{BMT}}$. The 2-sided alternate hypothesis was defined as $H_A$: $P_{\text{CEA}} \neq P_{\text{BMT}}$. The data analysis would either 1) reject the null hypothesis (the proportions are different), or 2) fail to reject the null hypothesis. Although there is an equal sign in the null hypothesis, equivalence cannot be proven when the null hypothesis is not rejected. It can only be said that there is not enough evidence to show a difference.

Instead of testing for superiority, several trials of CEA and CAS have used a noninferiority design. The SAPPHIRE, EVA-3S, and SPACE trials tested whether the upper limit of the CI for the difference between $P_{\text{CEA}}$ and the proportion of stroke following CAS ($P_{\text{CAS}}$) is within a prespecified margin ($\delta$).\textsuperscript{32,40,50} The null hypothesis is $H_0$: upper limit of the CI ($P_{\text{CEA}} - P_{\text{CAS}}$) $\geq \delta$, whereas the alternate hypothesis is $H_A$: upper limit of the CI ($P_{\text{CEA}} - P_{\text{CAS}}$) $< \delta$.

Examples using superiority and noninferiority are illustrated in Fig. 1. The prespecified $\delta$ margin for noninferiority for each trial is indicated (dashed line). In EVA-3S, the 95% CI exceeds 2%; thus, it cannot reject the null hypothesis for noninferiority. The 95% CI does not include zero, therefore demonstrating superiority of CEA over CAS. The SPACE trial failed to show noninferiority and it failed to show superiority; the CI crosses the 2.5% $\delta$ margin (fails to show noninferiority) and contains zero (failing to show superiority). The SAPPHIRE (noninferiority design), CREST (superiority design), and ICSS (superiority design) trials are presented for comparison.

**Symptomatic Carotid Stenosis: CEA Versus BMT**

Three key trials have compared the effectiveness of CEA (combined with BMT) versus BMT alone for symptomatic carotid stenosis: NASCET, Veteran’s Affairs, and ECST.\textsuperscript{4,18,35,37} The first pivotal results of NASCET, examining 659 patients with >70% stenosis, found an absolute risk reduction of 16.5% and a relative risk reduction of 51% in any stroke or perioperative death after CEA at 2 years.\textsuperscript{37} Similar results were observed in the other 2 trials, despite differences between them regarding aspirin dosage, time from symptoms to CEA, sex, degree of stenosis, and its measurement. Because of the overall similarity between the 3 trials and the availability of individualized patient-level data, a meta-analysis incorporating uniform (NASCET) criteria for stenosis measurement and outcomes was performed (6092 total patients).\textsuperscript{41} This meta-analysis validated NASCET’s results for CEA based on degree of stenosis (Table 1), with no benefit in stenosis <50%, modest benefit in stenosis 50%–69%, high benefit for stenosis 70%–99%, and a trend toward benefit for near-occlusion at the 2-year but not at the 5-year follow-up.\textsuperscript{18,35,37,40}
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TABLE 1: Benefit of CEA for symptomatic carotid artery stenosis*

<table>
<thead>
<tr>
<th>Degree of Stenosis</th>
<th>% ARR</th>
<th>p Value</th>
<th>FU (yrs)</th>
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<tbody>
<tr>
<td>near occlusion</td>
<td>5.6/−1.7†</td>
<td>0.19/0.9†</td>
<td>2/5</td>
</tr>
<tr>
<td>70%–99%</td>
<td>16.0</td>
<td>&lt;0.001</td>
<td>5</td>
</tr>
<tr>
<td>50%–69%</td>
<td>4.6</td>
<td>0.04</td>
<td>5</td>
</tr>
<tr>
<td>30%–49%</td>
<td>3.2</td>
<td>0.6</td>
<td>5</td>
</tr>
<tr>
<td>&lt;30%</td>
<td>−2.2</td>
<td>0.05</td>
<td>5</td>
</tr>
</tbody>
</table>

* Pooled results of ECST, NASCET, and Veteran’s Affairs trials (Rothwell et al., 2003; trial #8008), demonstrating reduction in ipsilateral carotid stroke or any perioperative stroke/death after CEA for each stenosis category. Abbreviations: ARR = absolute risk reduction; FU = follow-up.
† Data are given as the 2-year/5-year results.

The added power of pooled CEA data has permitted subgroup analyses to demonstrate a significant differential benefit in certain groups of patients: men, patients ≥ 75 years of age, and those presenting with stroke rather than transient ischemic attack derive greater benefit from CEA for symptomatic stenosis > 50%.3 Two other large-scale trials comparing CEA with CAS, the SAPPHIRE trial, and the CREST trial, demonstrated little evidence of a treatment effect in patients who were asymptomatic and who might have been most effectively treated with BMT rather than CAS or CEA; 3) use of dual antiplatelet agents in CAS versus a single antiplatelet agent in CEA; 4) the fact that > 22% of each group had restenosis after prior CEA (a much higher risk for repeat CEA); and 5) high prevalence of contralateral occlusion (> 25% of patients treated with CEA and > 23% of patients treated with CAS), which doubled the risk related to CEA in NASCET.11,12,20,36

Two other large-scale noninferiority trials of CAS compared with CEA have taken place since SAPPHIRE, attempting to answer these criticisms by more specific selection criteria, in particular restricting entry to symptomatic patients (Table 2). First, the EVA-3S trial and the SPACE trial showed that CEA was superior to CAS in the 30-day periprocedural period (see Fig. 1).33 The SPACE trial failed to show noninferiority during the periprocedural period at their prespecified δ margin of 2.5%.40 Subsequent criticisms of these trials include the following: 1) premature stoppage at 1200 patients (SPACE trial) due to futility; 2) relative operator inexperience (particularly in the CAS group); and 3) nonuniform use of embolic protection devices.

The CREST and ICSS are the 2 most recent large-scale trials comparing CEA with CAS for carotid stenosis. They were in part designed to answer criticisms of prior CEA versus CAS trials.11,26 Both trials reported data separately for asymptomatic versus symptomatic patients (CREST) or only included symptomatic patients (ICSS); both had rigorous selection of proceduralists based on operator experience (verified during a lead-in phase in CREST); both mandated (CREST) or recommended (ICSS) use of embolic protection devices; and both presented traditional (stroke/death) as well as composite (stroke/death/MI) end points (Table 2).

The primary end point of CREST, in a population of asymptomatic and symptomatic patients, was stroke, MI, or death during the periprocedural period, or any ipsilateral stroke within 4 years after randomization. There was no difference in the composite primary end point for CAS (7.2%) versus CEA (6.8%, HR 1.11 for stenting, 95% CI 0.81–1.51). However, the difference in the 4-year stroke or death rate did reach statistical significance for CAS (6.4%) versus CEA (4.7%, HR 1.5, 95% CI 1.05–2.15). Patients who underwent CEA were less likely to have a stroke (4.1% for CAS vs 2.3% for CEA, p = 0.01) or die (0.7% vs 0.3%, respectively; p = 0.18), but more likely to have an MI (1.1% vs 2.3%, respectively; p = 0.03). The SAPPHIRE study also reported excess MI after CEA, although more recent results from ICSS contradict these findings.23

The long-term effects of MI and stroke were different in CREST. At 1 year postprocedure, quality of life was significantly impacted by stroke but not by MI. The increased rate of MI in patients treated with CEA has been ascribed to the following factors: 1) the more frequent use of general rather than local anesthesia in patients undergoing CEA (although choice of anesthesia failed to play a part in post-CEA MI in the General Anaesthesia Versus Local Anaesthesia for carotid surgery [GALA] trial); and 2) use of dual (aspirin and clopidogrel) rather than single antiplatelet agents in patients undergoing CAS.30

The CREST investigation did not show a difference in composite primary end points for symptomatic revascularization compared with asymptomatic revascularization. However, the natural history and acceptable periop-
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<tr>
<td>Yadav et al., 2004; Gurm et al., 2008</td>
<td>167</td>
<td>9.3</td>
<td>2.1</td>
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<td>21.7</td>
<td>32.0</td>
<td>ND</td>
<td>3 yrs</td>
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<tr>
<td>Mas et al., 2006; Mas et al., 2008</td>
<td>259</td>
<td>3.9</td>
<td>9.6</td>
<td>0.01</td>
<td>21.6</td>
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<tr>
<td>Ringleb et al., 2006; Eckstein, 2008 SPACE‡</td>
<td>599</td>
<td>6.16</td>
<td>7.51</td>
<td>NS</td>
<td>9.7</td>
<td>10.5</td>
<td>0.14</td>
<td>2 yrs</td>
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<td>CREST§</td>
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<td>6.0</td>
<td>0.02</td>
<td>5.4</td>
<td>6.7</td>
<td>0.30</td>
<td>4 yrs</td>
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<td>ICSS¶</td>
<td>858</td>
<td>3.4</td>
<td>7.4</td>
<td>0.0004</td>
<td>4.0</td>
<td>7.4</td>
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<td>120 days</td>
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*In SAPPHIRE, long-term follow-up events were defined as death or ipsilateral stroke only.
†In CREST, long-term follow-up events were defined as any periprocedural stroke, MI, or death, or postprocedural ipsilateral stroke.
‡In the SPACE study, long-term follow-up events were defined as ipsilateral stroke or vascular death.
§In CREST, long-term follow-up events were defined as periprocedural stroke or death, plus any ipsilateral stroke. Long-term stroke/death/MI is defined as any periprocedural stroke, MI, or death, or postprocedural ipsilateral stroke.
¶In ICSS, 30-day data were per-protocol, not intention-to-treat results. The long-term events were defined as stroke, death, or periprocedural MI.

A meta-analysis of patient-level data from EVA-3S, SPACE, and ICSS showed that overall CAS had a 30-day risk of stroke or death of 8.9%, whereas CEA had a 30-day risk of 5.8% (p < 0.001). This meta-analysis did show that the 120-day risk following CAS for patients ≥ 70 years of age was 12%, whereas the 120-day risk for this population following CEA was 5.9%. This risk ratio of 2.04 (95% CI 1.48–2.82) was significant and consistent with the CREST data, showing that CAS, where possible, should be avoided in patients ≥ 70 years of age. A more recent meta-analysis, adding CREST to the prior 3 trials (excluding asymptomatic patients), found a relative risk of 1.77 (95% CI 1.38–2.26) for any stroke or death in patients undergoing CAS. Neither meta-analysis nor CREST showed a difference in outcomes based on sex. Such analyses cannot address whether revascularization or timing of the intervention is the appropriate choice for females; the analysis only suggests that sex may not be an important determinant of technique.
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For the most part CAS demonstrates higher 30-day risks than CEA. One must place these results within the context of acceptable risks. As outlined above, the American Heart Association/American Academy of Neurology guideline for 30-day stroke or death following CEA for symptomatic stenosis is 6%.10 With respect to the guidelines, the above-mentioned trials suggest that the risk in patients treated with CAS for revascularization of symptomatic stenosis may be too high (EVA-3S, SPACE, ICSS) or borderline (CREST). The cost-effectiveness and economics of CAS and CEA have been reported. Although many studies have shown that the initial hospitalization costs for CAS exceed the cost of CEA, further evidence suggests that CEA has greater benefit per dollar spent than CAS over the long term.25,27,28,38,51 The higher initial costs of CAS could be offset by a decrease in the length of hospital stay for the procedure.21 However, considering total length of stay over a lifetime, the marginal savings for the initial hospital stay could be offset by avoiding hospitalization for future events. In fact, CEA appears to be the dominant (preferred) treatment option because it has lower lifetime costs while also having increased quality-adjusted life-years—CEA will continue to be preferred as long as it is less expensive and has comparable or slightly better outcomes than CAS.51

Asymptomatic Carotid Stenosis: CEA Versus BMT

Two key trials, ACAS and ACST (Table 4), randomized asymptomatic patients with angiographically confirmed stenosis > 60% (ACAS) or stenosis > 50% on ultrasonography studies (ACST) to an upfront CEA versus a BMT group (or BMT/deferred CEA in the case of ACST).19,21,23 Despite slight differences in entry criteria and analysis, overall outcomes were fairly similar, with a slightly less than 5% decrease in stroke/death over 5 years. The larger number of patients enrolled into ACST and its longer follow-up period provide a much more specific understanding of the modest gains of CEA versus BMT, as follows: 1) of the 4.1% absolute reduction in stroke/death over 5 years, only half of this benefit came from preventing disabling strokes/death (a net gain < 0.5%/year); 2) after 5 years, no further benefit accrues, with a net gain of only 4.6% at 10 years (CEA vs BMT lines parallel each other after 5 years); 3) no benefit exists for patients older than 75 years; 4) women derive less benefit (reaching statistical significance only at 10 years); and 5) patients on a regimen of lipid-lowering agents have less benefit. Given the underwhelming gains achieved by CEA in asymptomatic patients relative to symptomatic patients, benefit was critically dependent on an extremely low perioperative complication rate, with 3% set as the threshold margin for perio-

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Study</th>
<th>Stenosis Category</th>
<th>No. of Patients</th>
<th>% 30-Day Stroke/Death</th>
<th>% LT Stroke/Death</th>
<th>p Value</th>
<th>LT FU Period</th>
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<tr>
<td>ICSS Investigators, 2010</td>
<td>symptomatic</td>
<td>17.0</td>
<td>107</td>
<td>50.0</td>
<td>124</td>
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<td>Schofer et al., 2008</td>
<td>symptomatic</td>
<td>ND</td>
<td>ND</td>
<td>63.0</td>
<td>8</td>
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<td>Capoccia et al., 2010</td>
<td>asymptomatic</td>
<td>0.0</td>
<td>20</td>
<td>22.0</td>
<td>23</td>
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<td>Schnaudigel et al., 2008</td>
<td>mixed</td>
<td>10.0</td>
<td>754</td>
<td>37.0</td>
<td>1363</td>
<td>&lt;0.01</td>
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<tr>
<td>Skjelland et al., 2009</td>
<td>mixed</td>
<td>6.7</td>
<td>30</td>
<td>21.4</td>
<td>28</td>
<td>0.103</td>
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<td>Zhou et al., 2009</td>
<td>mixed</td>
<td>12.0</td>
<td>100</td>
<td>46.3</td>
<td>68</td>
<td>&lt;0.05</td>
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<tr>
<td>Leal et al., 2010</td>
<td>mixed</td>
<td>ND</td>
<td>ND</td>
<td>12.5</td>
<td>31</td>
<td></td>
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</table>

* All references are primary material, with the exception of Schnaudigel et al. (meta-analysis).

TABLE 4: Literature review of asymptomatic carotid stenosis: CEA versus BMT

* Ex Comm = Executive Committee; OXVASC = Oxford Vascular Study.
† ACAS calculated 5-year risks from a median follow-up of 2.7 years; 5-year risks are for any stroke or perioperative death.
‡ ACST 30-day stroke or death rates are given with respect to the 30 days after CEA, even when the CEA was deferred. Long-term stroke/death is defined as any stroke or perioperative death.
§ Data are given as the 5-year/10-year results.
However, significant improvements in BMT have occurred over time, especially in the use of lipid-lowering drugs such as statins, which were used in only 10% of patients in the ACST at trial initiation and in 80% at 10-year follow-up. More recent data from the Oxford Vascular Study (OXVASC) demonstrates a stroke risk of only 0.3%/year attributable to ipsilateral asymptomatic carotid stenosis treated with BMT alone. It is important to emphasize that selection of asymptomatic patients for carotid revascularization should include careful consideration of life expectancy, age, sex, and comorbidities. The benefit of surgery may now be less than anticipated on the basis of earlier randomized trials, and the cited 3% complication rate should be interpreted in the context of interim advances in medical therapy.10

Asymptomatic Carotid Stenosis: CEA Versus CAS

The CREST and SAPPHIRE studies are 2 randomized trials comparing CEA and CAS in patients with asymptomatic carotid artery stenosis (Table 5). In the SAPPHIRE study, the 30-day risk of MI, stroke, or death was 5.4% for CAS, and 10.2% for CEA (not significantly different). Of note, these complication rates are higher for asymptomatic individuals compared with symptomatic participants within the same trial, and probably exceed the threshold of 3%. For this reason, a persistent criticism of this trial remains that the enrolled patients should not have undergone revascularization at all, given the trial’s perioperative complication rates.36

In CREST, the 4-year rate of stroke or death in asymptomatic patients was 4.5% for CAS and 2.7% for CEA (HR 1.86, 95% CI 0.95–3.6; p = 0.07). Although the null hypothesis cannot be rejected at the 5% level, it is appropriate to conclude that, with a 7% chance of being incorrect, CEA was superior to CAS. The peri-procedural risk of stroke or death was 2.5% in the CAS group and 1.4% in the CEA group (HR 1.88, 95% CI 0.79–4.49; p = 0.15). It is reassuring that the 30-day complication rates from CREST for asymptomatic revascularization are within the recommended 3% benchmarks. However, neither the SAPPHIRE nor the CREST investigations address the question now posed by improvements in BMT, namely whether patients with asymptomatic carotid stenosis should undergo any revascularization procedure. Future trials of CEA versus CAS in asymptomatic stenosis may include a third arm for BMT (Table 6).9

Current practice of CAS and CEA in the US for asymptomatic stenosis was recently examined, and in-hospital complication rates were presented, and CAS was associated with increased odds of stroke or death (OR 1.28, 95% CI 1.03–1.58). However, CAS was not associated with increased odds of stroke, death, or cardiac complications (OR 1.12, 95% CI 0.99–1.27; p < 0.14). The inhospital complication rates for stroke or death for age ≥ 80 years were 1.5% following CEA and 2.7% following CAS, although this did not reach statistical significance at the 5% level (p < 0.07). Nonetheless, the 30-day complication rates would be equal to or greater than the in-hospital rates. Because the complication rate following

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Trial</th>
<th>No. of Pts</th>
<th>% 30-Day Stroke/Death (guidelines: &lt;3%)</th>
<th>% 30-Day Stroke/Death/MI (guidelines: none)</th>
<th>% LT Stroke/Death</th>
<th>% LT Stroke/Death/MI</th>
<th>% LT FU Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yadav et al., 2004; Gurm et al., 2008</td>
<td>SAPPHIRE†</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>10.2</td>
<td>5.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Brott et al., 2010</td>
<td>CREST‡</td>
<td>1262</td>
<td>1240</td>
<td>1.4</td>
<td>2.5</td>
<td>0.15</td>
<td>3.6</td>
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* In most of the comparisons the p value is for the hazard ratio; for SAPPHIRE it is the p value for the absolute difference in the event rate. Abbreviation: NA = not available.
† In SAPPHIRE long-term events were defined as death or ipsilateral stroke, or death plus any ipsilateral stroke.
‡ In CREST long-term follow-up events were defined as death or ipsilateral stroke.
CAS was rapidly approaching the 3% 30-day benchmark, CAS should be considered with extreme caution in this age group.

**Current/Ongoing Trials**

There are several ongoing or planned trials examining the best treatment for carotid stenosis; these are summarized in Table 6.** Most current work is examining CEA versus CAS in asymptomatic patients. Fortunately, at least one trial (SPACE-2) also includes a third arm for BMT.

**Summary**

Patients with symptomatic stenosis > 70% should undergo carotid revascularization. There is clear evidence that CEA is superior to BMT for such a group, with an absolute risk reduction of 15.6%. The benefits of CEA for 50%–69% stenosis, although significant, were modest compared with those in patients with 70% stenosis. Therefore, revascularization is recommended for 50%–69% symptomatic stenosis, with the understanding that aggressive lipid management and other antplatelet agents have been added to the BMT regimen since NASCET and ECST were conducted, and may be useful in this population. Based on meta-analysis and recent data, CEA remains the procedure of choice for revascularization of symptomatic stenosis ≥ 50%; however, CAS is a potential alternative for patients with specific high-risk factors for CEA (for example, contralateral occlusion, radiation therapy, restenosis). Also, CAS has other, less well-defined indications, such as severe chronic obstructive pulmonary disease or the somewhat ambiguous “high risk” criteria.

We found that CEA has a modest benefit for asymptomatic stenosis, given at least a 3–5 year life expectancy after surgery. In contrast, CAS has a dubious benefit for asymptomatic stenosis; procedural morbidity and mortality rates approach or exceed 3%, whereas the procedural risks with CEA remain much lower. With the declining incidence of stroke due to asymptomatic lesions and the current natural history, SPACE-2 and other trials are well justified to compare BMT against CAS or CEA. The CAS procedure for asymptomatic stenosis should remain relegated to clinical trials, which should also include an arm for BMT.

**Disclosure**

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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*Address correspondence to:* Babak S. Jahromi, M.D., Ph.D., 575 Elmwood Avenue, Box 670, Rochester, New York 14620. email: babak_jahromi@urmc.rochester.edu.