Secondary Stroke Prevention in the Era of Carotid Stenting

Update on Recent Trials

Heitham T. Hassoun, MD; Mahmoud B. Malas, MD; Julie A. Freischlag, MD

Stroke is a leading cause of morbidity and mortality worldwide. Traditional therapy for extracranial carotid artery occlusive disease, a significant risk factor for stroke, consists of optimal medical management and selective surgical treatment with carotid endarterectomy (CEA) for stroke risk reduction. Buoyed by the widespread application of percutaneous interventions for the treatment of coronary artery disease, carotid artery stenting (CAS) has steadily developed during the past decade as an alternative to CEA for patients who might benefit from surgical treatment. With greater operator experience have come advances in CAS techniques and patient selection criteria, and several single-center studies and industry-sponsored stent registries have demonstrated excellent results for CAS, especially compared with the landmark randomized CEA trials of the 1980s. Nevertheless, CAS has emerged as one of the most controversial procedures in the era of modern medicine, and recently published randomized trials from Europe have only stoked the fires of controversy. This study reviews the best available data for CAS as an alternative therapy to CEA for stroke risk reduction and gives an overview of eagerly anticipated large randomized trials.

See Invited Critique at end of article

More than 15 years ago, large-scale multicenter randomized controlled trials demonstrated that CEA significantly reduces the risk of ipsilateral stroke in patients with symptomatic (ie, previous transient ischemic attack or stroke) carotid artery stenosis of 50% to 99%. The European Carotid Surgery Trial (ECST) showed a reduction in ipsilateral stroke in surgically treated patients at 3-year follow-up from 21.9% to 9.6% (P<.001) compared with best medical therapy (BMT) alone, and the North American Symptomatic Carotid Endarterectomy Trial (NASCET) showed a reduction from 27.6% to 12.6% at 2-year follow-up (P<.001). Based on these landmark studies and according to guidelines of the American Heart Association, patients with symptomatic carotid artery stenosis greater than 50% and a perioperative stroke and death risk of less than 6% are best treated with a combination of BMT and surgery for stroke prophylaxis.

Large randomized trials have also shown the potential benefit of CEA for stroke risk reduction in select asymptomatic patients. For example, in the Asymptomatic Carotid Atherosclerosis Study...
(ACAS) performed in North America, surgery for asymptomatic carotid stenosis greater than 60% was shown to significantly reduce the overall 5-year risk of ipsilateral stroke or any perioperative stroke or death from 11.0% to 5.1% (P = .004), and the Asymptomatic Carotid Surgery Trial (ACST) performed in Europe similarly demonstrated that CEA significantly reduced the 5-year risk of stroke or death from 11.8% to 6.4% (P = .006). On subset analysis, these trials did not demonstrate significant benefit for surgical treatment in women or diabetic patients. Furthermore, for asymptomatic patients to achieve effective stroke risk reduction, the procedure needs to be performed with exceptionally good results. Therefore, the American Heart Association recommends that CEA should be performed in patients with 60% to 99% asymptomatic carotid artery stenosis if the perioperative stroke or death risk is less than 3% and patient life expectancy is greater than 5 years.9

THE CASE FOR PERCUTANEOUS CAROTID INTERVENTION

Buoyed by the widespread application of percutaneous interventions for the treatment of coronary artery disease, carotid artery stenting (CAS) has steadily developed during the past decade as an alternative to CEA for patients who would benefit from surgical treatment. Percutaneous CAS offers several obvious potential advantages, including the avoidance of (1) general anesthesia, (2) an incision in the neck, and (3) the risk of cranial or cutaneous nerve damage from the surgical incision. Although the large randomized trials in the 1980s and 1990s established class IA indications for the use of CEA in appropriately selected patients, these studies contained strict eligibility criteria and excluded many patients with carotid stenosis commonly found in clinical practice. These exclusion criteria include anatomical and physiologic “high-risk” criteria, such as age, previous surgery, uncontrolled diabetes or hypertension, kidney or liver failure, and heart valve or rhythm disturbance. The presence of such comorbidities has a significant negative effect on outcome after CEA,10-12 and they have served as the basis for subsequent implementation of CAS as an alternative to CEA in clinical practice. Much has been learned in the past decade from carotid stenting registries and clinical trials, which have helped clarify appropriate indications and have led to improved outcomes.

EARLY CAS EFFICACY STUDIES

The first carotid artery balloon angioplasty was performed in 1979,1 but it was not until the mid-1990s when several early studies on the safety and feasibility of carotid artery intervention for arterial occlusive disease emerged (Table 1). Many of these studies3-10 were relatively small, single-center experiences with highly variable outcomes and periprocedural stroke rates ranging from 1% to 24%. Stimulated by these early studies, a few randomized clinical trials comparing carotid intervention and CEA were conducted with similarly variable outcomes (Table 2). The Leicester study,20 published in 1998, was the first single-center prospective randomized trial to compare carotid intervention with CEA in low-risk symptomatic patients with greater than 70% stenosis. This trial was stopped after enrolling only 17 patients because of the high rate of adverse neurologic events in the intervention arm. The Kentucky randomized trials21,22 are 2 other single-center trials comparing carotid intervention with CEA in low-risk symptomatic and asymptomatic patients and were published in 2001 and 2004, respectively. These studies reported remarkably low complication rates for CAS and CEA, and the few patients in each group make the results difficult to interpret.

The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) was the first multicenter randomized trial to compare carotid percutaneous transluminal angioplasty and CEA.23 It enrolled 504 symptomatic and asymptomatic patients between 1992 and 1997 at 24 centers in Europe, Australia, and Canada. This study excluded high-risk patients, and stents were used selectively, when available, and in only 26% of cases. The CAVATAS demonstrated no statistically significant difference between endovascular and surgical treatment in the rate of stroke or death within 30 days (10.0% for CAS vs 9.9% for CEA) and no significant difference in the 3-year ipsilateral stroke rate. Although this study was criticized for unusually high stroke rates in both groups, its lasting contribution has been the finding that stent placement reduced carotid restenosis rates after intervention.

The WALLSTENT trial24 was the first multicenter randomized trial designed specifically to evaluate CEA and CAS equivalence. This study enrolled 219 symptomatic patients (of a planned 700) with 60% to 99% stenosis. The 30-day stroke or death rates were 10.2% for CAS vs 3.5% for CEA (P = .049). In addition, 12.1% of patients undergoing CAS experienced ipsilateral stroke, procedure-related death, or vascular death at 1 year vs 4.5% of patients undergoing CEA (P = .02). The trial was halted by the Data Safety and Monitoring Committee after an interim analysis demonstrated worse outcomes for the CAS group. Critical to interpreting these results are the facts that the trial (1) did not use distal embolic protection devices (EPDs), (2) demonstrated a 3-fold increased risk of stroke in procedures performed by less experienced interventionalists (ie, <10 stents performed a priori), and (3) used suboptimal stents designed to be placed in the biliary tract rather than in the carotid artery. This trial was never published or submitted for peer review, which makes it difficult to interpret despite the dismal nature of the CAS outcomes.

Table 1. Early Carotid Artery Stenting Data

<table>
<thead>
<tr>
<th>Source</th>
<th>Patients, No.</th>
<th>Technical Success, %</th>
<th>MI/Stroke/Death, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietrich et al,13 1996</td>
<td>110</td>
<td>99</td>
<td>6.5</td>
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<tr>
<td>Yadav et al,14 1997</td>
<td>107</td>
<td>100</td>
<td>8.4</td>
</tr>
<tr>
<td>Wholey et al,15 1997</td>
<td>108</td>
<td>95</td>
<td>3.6</td>
</tr>
<tr>
<td>Henry et al,16 1998</td>
<td>163</td>
<td>99</td>
<td>3.0</td>
</tr>
<tr>
<td>Teitelbaum et al,17 1998</td>
<td>22</td>
<td>100</td>
<td>24.0</td>
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<tr>
<td>Waigand et al,18 1998</td>
<td>50</td>
<td>100</td>
<td>4.0</td>
</tr>
<tr>
<td>Bergeron et al,19 2005</td>
<td>99</td>
<td>97</td>
<td>1.0</td>
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Abbreviation: MI, myocardial infarction.
ADVANCES IN CAS TECHNIQUE

The early clinical trials and the more recent CAS registry studies have led to greater operator experience and significant improvements in CAS technique. One of the fundamental advances in CAS technique has been the development of EPDs during the past several years. Although no randomized trials have compared CAS with and without EPDs, and there are still those who are not convinced of their efficacy in reducing procedure-related particle emboli and strokes, best available data suggest that EPDs reduce the risk of stroke, and their use has become standard practice in CAS. The 3 approaches used to achieve distal embolic protection are (1) distal balloon occlusion, (2) distal filter placement, and (3) proximal occlusion with flow reversal (Figure 1). Distal balloon occlusion systems are flexible, low-profile systems capable of negotiating rather tortuous vessels and high-grade stenoses. Although these systems generally provide complete capture of released particulate debris, the main disadvantage is the required period of intracerebral flow arrest during balloon angioplasty and stent deployment. The most commonly used EPDs are distal filter devices, and there are 4 devices approved in the United States: AccuNet (Abbott Vascular, Redwood City, California), Emboshield (Abbott Vascular), and Angioguard (Cardis, Warren, New Jersey). The main advantage of the distal filter device is the preservation of antegrade cerebral flow throughout the procedure while providing capture of released embolic particulate debris (Figure 2). However, filter systems tend to be bulkier and more rigid than other classes of EPDs. Flow reversal EPDs, originally described by Parodi et al, are based on the same surgical principle used to measure carotid stump pressures during CEA, whereby in the presence of patent intracranial circulation, proximal occlusion of the common carotid artery and the external carotid artery causes reversal of flow in the internal carotid artery. The obvious advantage of flow reversal EPDs is the ability to gain cerebral embolic protection before crossing the lesion with bulky wires and catheters.

With increased operator experience have also come significant improvements in our understanding of patient selection criteria. In fact, appropriate patient selection is the single most important consideration for successful outcomes in CAS. The 2 most important patient factors are (1) target lesion characteristics and (2) aortic arch anatomy. Target lesion characteristics associated with increased stroke risk include length of the lesion (ie, >1.5 cm), heavily calcified plaques, ulcerated plaques, and tandem lesions in the common carotid ostium. With improved understanding of lesion characteristics has come better EPD and stent selection. For example, short, heavily calcified lesions may be better treated with closed-cell stent designs, which provide greater support than open-cell configurations. Aortic arch anatomy is the most common limiting factor in CAS. Increased annulation and calcification of the aortic arch occurs with increased age and is likely a key factor in the reported poor outcomes in octogenarians.

### Table 2. Early Randomized Trials of Carotid Artery Stenting (CAS) vs Carotid Endarterectomy (CEA)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients, No.</th>
<th>Patient Description</th>
<th>Primary End Point</th>
<th>Results (CAS vs CEA), %</th>
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</thead>
<tbody>
<tr>
<td>ArcHer</td>
<td>581</td>
<td>23.8</td>
<td>30-d Stroke or death</td>
<td>8.3</td>
</tr>
<tr>
<td>beach</td>
<td>480</td>
<td>25.3</td>
<td>30-d Stroke or death</td>
<td>5.8</td>
</tr>
<tr>
<td>capture</td>
<td>454</td>
<td>NA</td>
<td>30-d Stroke or death</td>
<td>3.8</td>
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<tr>
<td>capture</td>
<td>3500</td>
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<td>30-d Stroke or death</td>
<td>5.7</td>
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<td>CaireSS5</td>
<td>143</td>
<td>31.0</td>
<td>30-d Stroke or death</td>
<td>2.1</td>
</tr>
<tr>
<td>create4</td>
<td>543</td>
<td>17.4</td>
<td>30-d Stroke or death</td>
<td>6.2</td>
</tr>
<tr>
<td>MavereIC</td>
<td>498</td>
<td>NA</td>
<td>30-d Stroke or death</td>
<td>5.3</td>
</tr>
<tr>
<td>security</td>
<td>398</td>
<td>21.0</td>
<td>30-d Stroke or death</td>
<td>8.5</td>
</tr>
</tbody>
</table>

Table 3. Carotid Artery Stenting (CAS) Registries

<table>
<thead>
<tr>
<th>Registry</th>
<th>Patients, No.</th>
<th>Symptomatic, %</th>
<th>MI/Stroke/Death, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>ArcHer</td>
<td>581</td>
<td>23.8</td>
<td>8.3</td>
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<td>Botch</td>
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</tr>
<tr>
<td>CaireSS5</td>
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<tr>
<td>MavereIC</td>
<td>498</td>
<td>NA</td>
<td>5.3</td>
</tr>
<tr>
<td>SECURITY</td>
<td>398</td>
<td>21.0</td>
<td>8.5</td>
</tr>
</tbody>
</table>

Abbreviations: ARCHeR, ACCULINK for Revascularization of Carotids in High-Risk patients; CAPTURE, Carotid Acculink/Accunet Post-Approval Trial to Uncover Unanticipated or Rare Events; CaireSS, Carotid Revascularization Using Endarterectomy of Stenting Systems; CREATE, Carotid Revascularization With ev3 Arterial Technology Evolution; MI, myocardial infarction; NA, not available.

Prospective Stent Registries

Results of completed industry-sponsored CAS registries have been the strongest and most abundant evidence available in favor of CAS as an alternative treatment for carotid artery stenosis. These prospective registries, with predefined inclusion and exclusion criteria, independent neurologic assessments, and oversight committees, were designed to further assess safety or acquire US Food and Drug Administration or Conformite Europeene approval of CAS with EPDs in high-risk patients. Although these observational studies did not include surgical control groups, the outcomes demonstrated a high level of technical success and 30-day end points of myocardial infarction (MI)/stroke/death ranging from 2.1% to 8.5% (Table 3). A detailed analysis of these stent registries is beyond the scope of this review, and although registries do not provide direct comparison data, these studies have been instrumental in developing our understanding of the real risks related to CAS in high-risk patients.
RECENTLY PUBLISHED RANDOMIZED TRIALS

Three large multicenter randomized trials comparing CAS and CEA have recently been published (Table 4). The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial\(^3\) randomized 334 high-risk (anatomical or physiologic) patients at 29 centers to receive either CEA or CAS with an EPD under the hypothesis that CAS was not inferior to CEA. The study included patients with symptomatic stenosis greater than 50% or asymptomatic stenosis greater than 80%, and the primary end point was the cumulative incidence of major adverse cardiovascular events 30 days and 1 year after the procedure. Consensus agreement by a multidisciplinary team of surgeons, neurologists, and interventionalists was required for a patient’s enrollment into the randomized treatment arm of study, and surgeons and interventionalists had to meet certain procedural criteria to participate. Surgeons were required to have performed an average of 30 CEAs per year, with low corresponding major complication (eg, MI/stroke/death) rates, and interventionalists were required to have performed an average of 64 interventions annually, with similarly low corresponding complication (eg, stroke and transient ischemic attack) rates of less than 2%. The 30-day composite index of the MI/stroke/death rate was 4.8% for CAS and 9.8% for CEA (\(P = .09\)), and results at 1 year (any stroke or death) favored CAS (12.2% vs 20.1%; \(P = .048\)). The study, thus, appropriately concluded that CAS is not inferior to CEA in high-risk patients. The major criticisms of the SAPPHIRE findings are that most MIs were non-Q-wave events identified by means of routine postprocedural laboratory studies and that most patients in the study were asymptomatic. Despite some study design flaws and overstated conclusions, the legacy of the SAPPHIRE trial is that it led to the general acceptance by surgeons, interventionalists, and government agencies of CAS as a viable alternative to CEA in high-risk surgical patients. However, a major point of contention has been the difficulty in defining exactly which patients are indeed high risk and might, therefore, benefit from a particular therapy.

In 2006, results were published from 2 European multicenter randomized trials comparing CAS and CEA in...
low- or moderate-risk symptomatic patients: the Stent-Protected Angioplasty vs Carotid Endarterectomy (SPACE) trial and the Endarterectomy Vs Stenting in Patients With Symptomatic Severe Carotid Stenosis (EVA-3S) trial. The SPACE trial set out to demonstrate non-inferiority of CAS to CEA in 1183 randomized patients with symptomatic carotid artery stenosis (≥70% by duplex ultrasonography, ≥50% by NASCET criteria, or ≥70% by ECST criteria) at 33 centers in Germany, Austria, and Switzerland. Unlike the SAPPHIRE trial, the technique used by the interventionalists (type of stent, whether to use a protection device, etc) was not restricted by the protocol. The 30-day primary outcome of ipsilateral stroke or death between randomization and 30 days after treatment was 6.84% for CAS and 6.34% for CEA. Despite the similarity in results, the difference of 0.51% (90% con-
fidence interval, −1.89-2.91) did not allow for a statistical confirmation of the noninferiority hypothesis of CAS vs CEA, likely because the trial was stopped more than 700 patients shy of its target enrollment of 1900 patients. An interim analysis had demonstrated that 2500 patients would need to be enrolled to reach statistical significance, and the steering committee acknowledged a “lack of funds” to expand and, therefore, halted the trial. Besides being underpowered to demonstrate noninferiority, another criticism of the SPACE trial was that embolic protection was not required and was used only in 27% of patients. The EVA-3S trial\(^3\) to assess noninferiority of CAS vs CEA randomized 527 symptomatic patients with greater than 60% stenosis at 30 centers in France. The primary end point was any stroke or death within 30 days after the procedure and was demonstrated to be significantly higher in the CAS group (9.6%) than in the CEA group (3.9%) (P = .01), with a relative risk of 2.5% and an absolute risk of 5.7%. The trial was halted prematurely for safety reasons and has been heavily criticized by proponents of CAS. Early in the trial, the use of embolic protection was not required, and patients treated without protection experienced a 25% risk of stroke or death (5 of 20 patients), thus prompting protocol changes and the requirement for EPDs by the EVA-3S trial safety committee. More important, the EVA-3S trial compared groups of physicians with unequal experience. Surgeons performing CEA had performed at least 25 endarterectomies in the year before trial enrollment. However, interventionalists were certified after completing as few as 5 CAS procedures (5 CASs among ≥35 stent procedures to the supra-aortic vessels or 12 CASs) and were allowed to enroll study patients while simultaneously undergoing training and certification. Although the results of the EVA-3S trial should not be discounted, it is difficult to accept a 30-day stroke/death rate of 9.6% as representative of current CAS standards.

**RECENTLY COMPLETED AND CURRENT TRIALS**

Despite obvious study design flaws, the results of the SPACE and EVA-3S trials cannot be discounted, and although their results have certainly dampened some of the recent enthusiasm for CAS in patients at low or moderate surgical risk, results of more comprehensive and contemporary randomized trials remain eagerly anticipated (Table 4). The Carotid Revascularization Endarterectomy vs Stent Trial (CREST) is a National Institutes of Health–funded, multicenter, randomized trial in North America that recently completed its target enrollment of approximately 2500 patients with greater than 50% symptomatic carotid stenosis or greater than 70% asymptomatic stenosis randomized to undergo CEA or CAS. Primary end points included MI, stroke, or death at 30 days and ipsilateral stroke within the study follow-up period. The protocol calls for all patients to receive aspirin and clopidogrel before and 30 days after the procedure and for a structured assessment by a neurologist before the procedure and 24 hours and 30 days after the procedure. The CREST maintained rigorous credentialing criteria for its interventionalists.\(^3\) A lead-in phase was designed to provide a creden-
therapy have steadily developed during the past decade, making CAS a potential alternative treatment for this disease. However, CAS has emerged as one of the most controversial procedures in the era of modern medicine. Some specialties have openly embraced this technology with many questions to be answered. In its most recent clinical practice guidelines, the Society for Vascular Surgery has included CAS as a potential alternative treatment to CEA only in symptomatic patients with severe (>50%) stenosis and high perioperative risk. To date, a few randomized trials comparing CAS and CEA for stroke prevention have been published but have done little but stoke the fires of controversy. Although the results of the ongoing CREST and International Carotid Stenting Study are eagerly awaited, the most likely future scenario will be that CAS, CEA, and BMT are all complementary in the fight against stroke. Physicians will hopefully think about the best treatment for this patient and advance beyond global concepts of gold standard therapies.

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Correspondence: Heitham T. Hassoun, MD, The Methodist Hospital Physician Organization & DeBakey Heart and Vascular Center, 6550 Fannin St, Ste 1401, Houston, TX 77030 (hhassoun@tmhs.org).

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Drafting of the manuscript: Hassoun. Critical revision of the manuscript for important intellectual content: Hassoun, Malas, and Freischlag. Administrative, technical, and material support: Hassoun and Malas. Study supervision: Hassoun and Freischlag.

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REFERENCES

Carotid stenting has become the “procedure du jour”; however, multiple studies and articles tout both its advantages and failures. With the rapid advancement and public acceptance of catheter-based technology, expansion into the realm of carotid revascularization was just a matter of time. The initial justification for CAS was based on the results of multiple randomized trials (the NASCET, ECST, ACAS, and ACST) that evaluated CEA with BMT. Patients who were excluded from the CEA trials as “high risk” may possibly benefit from CAS.

Hassoun et al provide a thorough review of the literature to support CAS. They describe the acceptance of CAS after the incorporation and validation of the use of neuroprotection devices, required for procedure reimbursement by Medicare and other third-party payers. Spurring the widespread acceptance of CAS are 3 recent prospective randomized trials. Only 1 trial, the United States–based SAPPHIRE trial, was completed. The European trials, EVA-3S and SPACE, were prematurely stopped for safety and monetary reasons, respectively. Thus, only 1 trial has been brought to completion for this controversial procedure.

CREST, funded by the National Institutes of Health, showed basically equivalent outcomes with CAS and CEA, and the findings were recently published.1 CREST, the largest prospective randomized trial to date, enrolled 2502 patients from 117 US and Canadian centers. For the composite primary end point (stroke, MI, or death), stenting was associated with a 7.2% rate of these events vs 6.8% with surgery (P>0.05). However, at 30 days, the higher rate of stroke was significant with stenting and, conversely, MI was significantly higher with CEA. Similar to the SAPPHIRE trial, CREST allows for only 1 stent (a criterion that plays into patient selection and provider bias), and it is limited by the industry-associated neuroprotection device that must be used. Furthermore, the CREST is missing the comparison with BMT. Despite these limitations, the CREST should provide real-world data from experienced interventionalists. In addition, the field of vascular surgery needs a trial comparing CAS and CEA without industry bias and incorporating a third arm comparing CEA and CAS with BMT. Several investigators have applied for funding through the Department of Veterans Affairs for this important and necessary trial.

Ruth L. Bush, MD, MPH

Author Affiliation: Division of Vascular Surgery, Scott and White Hospital, Texas A & M Health Science Center College of Medicine, Temple.

Correspondence: Dr Bush, Division of Vascular Surgery, Scott and White Hospital, Texas A & M Health Science Center College of Medicine, Temple, TX 76508 (rbush@swmail.sw.org).

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