Secondary Stroke Prevention in the Era of Carotid Stenting

Update on Recent Trials

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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. *Arch Surg. 2010;145(10):928-935*

Stroke, a leading cause of morbidity and mortality worldwide, is the third leading cause of death behind heart disease and cancer, and its survivors place a tremendous burden on society.[1] In fact, the estimated health care expenditure related to stroke in the United States was more than $60 billion in 2007.[2] Extracranial carotid artery occlusive disease accounts for approximately 25% of ischemic strokes, and traditional therapy consists of optimal medical management and selective surgical treatment with carotid endarterectomy (CEA) for stroke risk reduction.

See Invited Critique at end of article

More than 15 years ago, large-scale multicenter randomized controlled trials[3-5] 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% ($P<.01$) 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.[6]

Large randomized trials[7,8] have also shown the potential benefit of CEA for stroke risk reduction in select asymptomatic patients. For example, in the Asymptomatic Carotid Atherosclerosis Study

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(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 treatment 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 studies[13-19] 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 trials[21,22] 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.

Table 1. Early Carotid Artery Stenting Data

Source	Patients, No.	Technical Success, %	MI/Stroke/Death, %
Diethrich et al,[13] 1996	110	99	6.5
Yadav et al,[14] 1997	107	100	8.4
Wholey et al,[15] 1997	108	95	3.6
Henry et al,[16] 1998	163	99	3.0
Teitelbaum et al,[17] 1998	22	100	24.0
Waigand et al,[18] 1998	50	100	4.0
Bergeron et al,[19] 2005	99	97	1.0

Abbreviation: MI, myocardial infarction.

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 trial[24] 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 2. Early Randomized Trials of Carotid Artery Stenting (CAS) vs Carotid Endarterectomy (CEA)

Trial	Patients, No.	Patient Description	Primary End Point	Results (CAS vs CEA), %
Leicester,[20] 1998	17	Low-risk symptomatic	30-d Stroke or death	70 vs 0[a]
Kentucky 1,[21] 2001	104	Low-risk symptomatic	30-d Stroke or death	1.8 vs 1.9
WALLSTENT,[24] 2001	219	Low-risk symptomatic	1-y Stroke or death	12.1 vs 4.5[a]
CAVATAS,[23] 2001	504	Low-risk (a)symptomatic	30-d Stroke or death (3-y stroke)	10.0 vs 9.9
Kentucky 2,[22] 2004	84	Low-risk asymptomatic	30-d Stroke or death	0 vs 0

Abbreviations: CAVATAS, Carotid and Vertebral Artery Transluminal Angioplasty Study.
[a] $P < .05$.

Table 3. Carotid Artery Stenting (CAS) Registries

Registry	Patients, No.	Symptomatic, %	MI/Stroke/Death, %
ARCHeR[25]	581	23.8	8.3
BEACH[26]	480	25.3	5.8
CABERNET[29]	454	NA	3.8
CAPTURE[30]	3500	13.8	5.7
CaRESS[28]	143	31.0	2.1
CREATE[27]	543	17.4	6.2
MAVerIC	498	NA	5.3
SECuRITY	398	21.0	8.5

Abbreviations: ARCHeR, ACCULINK for Revascularization of Carotids in High-Risk patients; CAPTURE, Carotid Acculink/Accunet Post-Approval Trial to Uncover Unanticipated or Rare Events; CaRESS, 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.[1,25-30] 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 Conformité Européene 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.

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.[31,32] 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), Spider (ev3, Plymouth, Minnesota), Emboshield (Abbott Vascular), and Angioguard (Cordis, 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,[33] 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 angulation and calcification of the aortic arch occurs with increased age and is likely a key factor in the reported poor outcomes in octogenarians.[34]

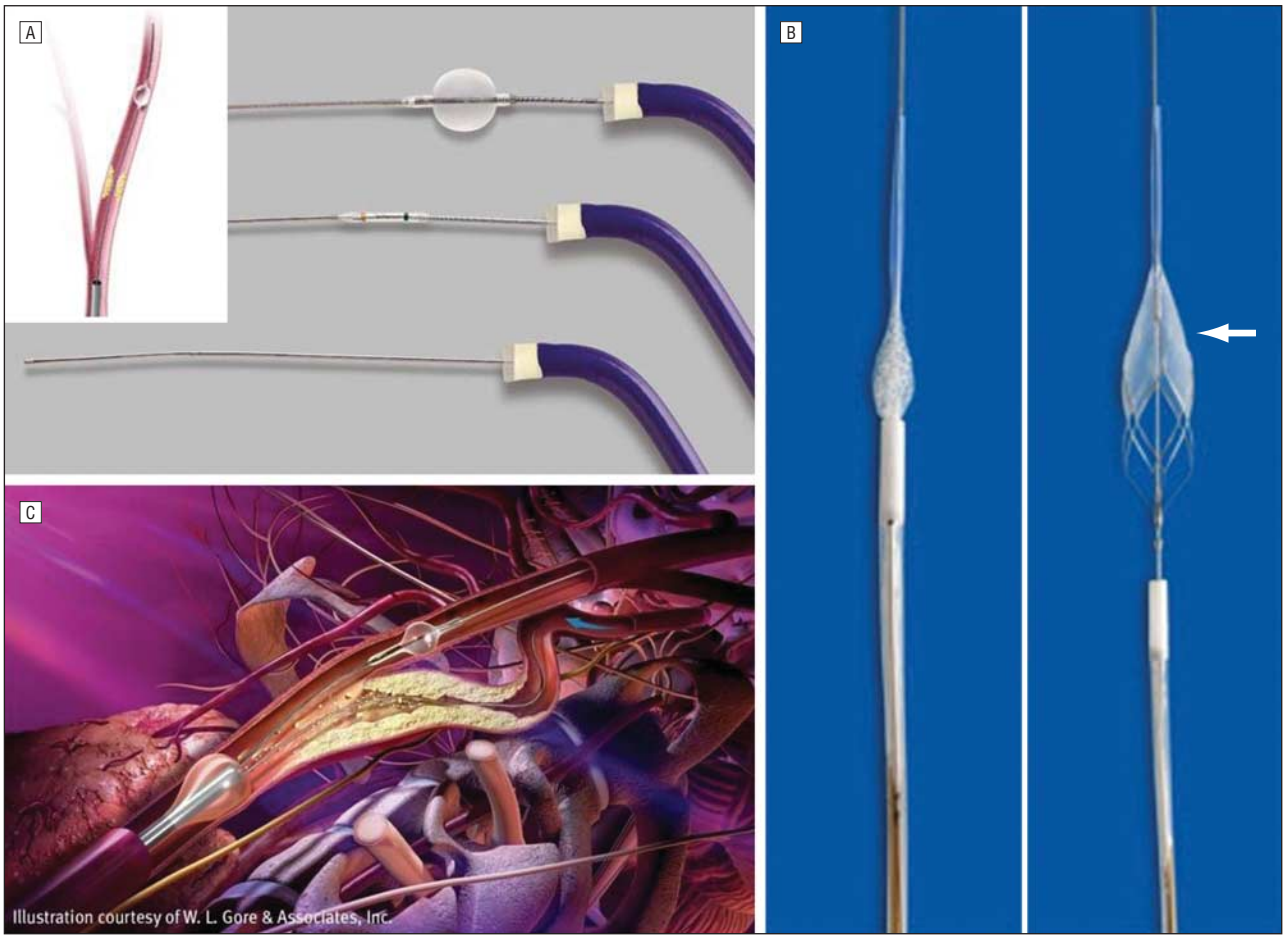

Figure 1. The 3 approaches used to achieve distal embolic protection. A, Depiction of a PercuSurge GuardWire (Medtronic, Santa Rosa, California) distal balloon occlusion system. The balloon is mounted on a 0.014-in wire and has a 0.036-in crossing profile. The stagnant column of blood and debris is aspirated after balloon and stent deployment. This system is not US Food and Drug Administration approved for carotid artery stenting in the United States. B, AccuNet (Abbott Vascular, Redwood City, California) distal filtration type of embolic protection device, which consists of a polyurethane/nitinol filter basket with 120-μm pores (arrow) that is delivered on a 0.014-in wire through a peel-away sheath. C, Depiction of the US Food and Drug Administration–approved GORE flow reversal carotid protection system (WL Gore & Associates Inc, Flagstaff, Arizona). Flow reversal is achieved by selectively occluding common carotid and external carotid artery blood flow, and by establishing an arteriovenous shunt between the femoral artery and vein, blood from collateral vessels via the circle of Willis is redirected to the lower-pressure venous return. Macroemboli and microemboli are continuously directed away from the brain during flow reversal (blue arrow).

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[35] 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

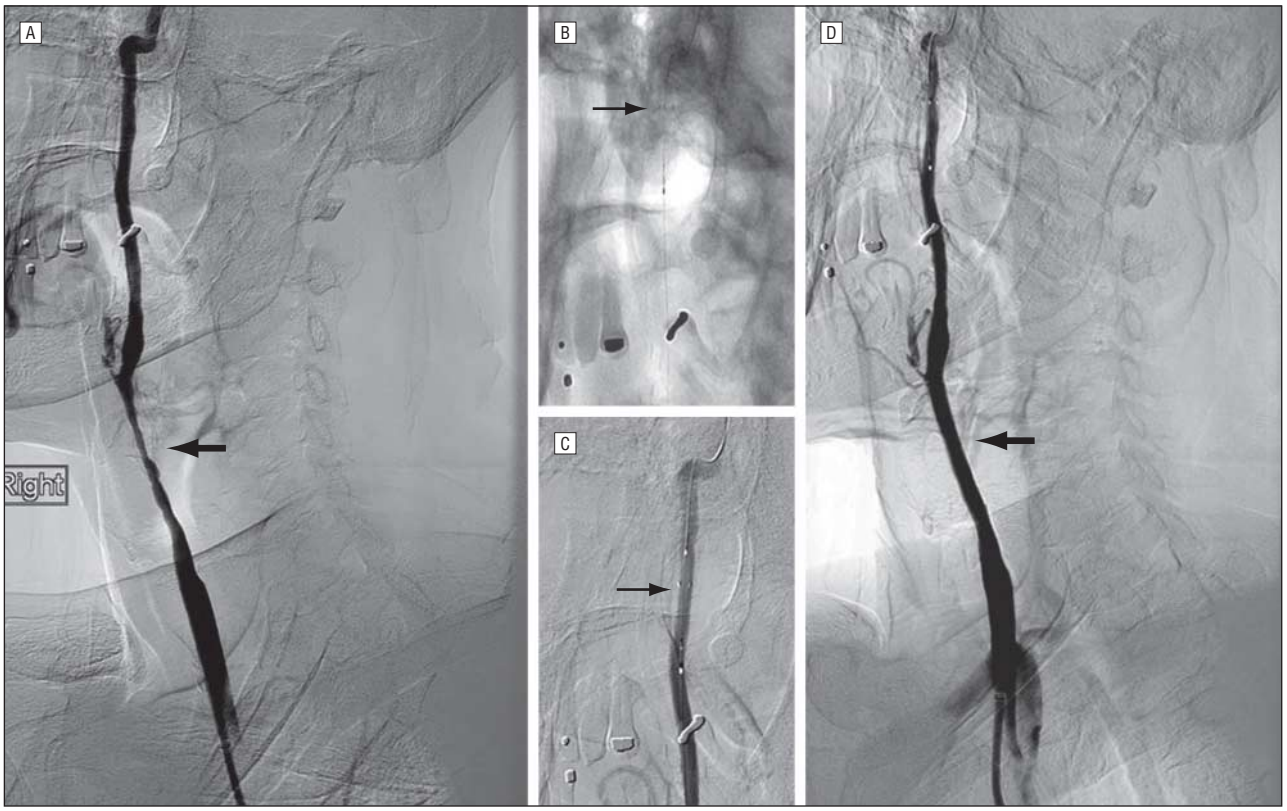

Figure 2. A, Selective carotid arteriogram of a patient with a symptomatic high-grade, radiation-induced carotid stenosis (arrow). B and C, Deployment of a 5.5-mm basket diameter AccuNet (Abbott Vascular, Redwood City, California) embolic protection device with apposition of lateral radiopaque markers to the vessel wall (arrows). D, Completion arteriogram after 8-mm stent deployment and poststent balloon angioplasty, demonstrating less than 10% residual carotid stenosis (arrow).

Table 4. Recent and Ongoing Randomized Trials of Carotid Artery Stenting (CAS) vs Carotid Endarterectomy (CEA)

Trial	Design	Patients, No.	Patient Description	Primary End Point	Results (CAS vs CEA), %
SAPPHIRE,[35] 2004	Prospective, randomized, multicenter noninferiority trial	334	High-risk (a)symptomatic	1-y MI, stroke, or death	12.2 vs 20.1
SPACE,[36] 2006	Prospective, randomized, multicenter noninferiority trial	1183	Low-risk symptomatic	30-d Stroke or death	6.8 vs 6.3
EVA-3S,[37] 2006	Prospective, randomized, multicenter noninferiority trial	527	Low-risk symptomatic	30-d Stroke or death	9.6 vs 3.9[a]
CREST,[38] 2004	Prospective, randomized, multicenter trial	2500	Low-risk (a)symptomatic	30-d MI, stroke, or death (4-y stroke)	Completed enrollment
ICSS,[39] 2004	Prospective, randomized, multicenter trial	1500	Low-risk symptomatic	30-d MI, stroke, or death (3-y stroke)	Active enrollment
ACT I	Prospective, randomized, multicenter trial	1540	Low-risk (a)symptomatic	30-d MI, stroke, or death (1-y stroke)	Active enrollment
TACIT	Prospective, randomized, multicenter trial	2400	Low- and high-risk (a)symptomatic	Stroke or death at 3 y	Planned enrollment

Abbreviations: ACT I, Asymptomatic Carotid Trial; CREST, Carotid Revascularization Endarterectomy vs Stent Trial; EVA-3S, Endarterectomy vs stenting in Patients with Symptomatic Severe Carotid Stenosis; ICSS, International Carotid Stenting Study; MI, myocardial infarction; SAPPHIRE, Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy; SPACE, Stent-Protected Angioplasty vs Carotid Endarterectomy; TACIT, Transatlantic Asymptomatic Carotid Intervention Trial.

[a] $P \leq .05$.

low- or moderate-risk symptomatic patients: the Stent-Protected Angioplasty vs Carotid Endarterectomy (SPACE) trial[36] and the Endarterectomy Vs Stenting in Patients With Symptomatic Severe Carotid Stenosis (EVA-3S) trial.[37] The SPACE trial set out to demonstrate noninferiority 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 35 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[37] 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.[38] A lead-in phase was designed to provide a credentialing period, requiring up to 20 monitored CAS procedures using a standardized protocol of neuroprotection and stent use (RX AccuNet and RX Acculink [Abbott Vascular]). The CAS results during this nonrandomized lead-in phase compare favorably with results from the NASCET (30-day stroke and death rates: 5.7% vs 5.8%) and ACAS (30-day stroke and death rates: 3.5% vs 2.3%). The main finding during this lead-in phase was increasing risk with age, especially in octogenarians, who demonstrated a 12.1% 30-day risk of stroke or death. Results of the CREST are eagerly anticipated in the near future.

The International Carotid Stenting Study,[39] also known as the CAVATAS-2, is an international, multicenter, randomized, controlled clinical trial comparing CEA and CAS in patients with symptomatic stenosis greater than 50%. This study has made improvements from the previous published randomized trials and has implemented a more standardized protocol. For example, before enrollment, surgeons and interventionalists must provide documentary evidence of their experience, which is then assessed by an accreditation committee. Surgeons are expected to have performed a minimum of 50 CEAs with an annual rate of at least 10 cases. Interventionalists are expected to have performed a minimum of 50 stenting procedures, of which 10 should be CAS. Surgeons and interventionalists are expected to show a 30-day stroke and death rate consistent with data from the ECST (7.0%; 95% confidence interval, 5.8%-8.3%).[5] Stents and other devices are chosen for use at the discretion of the interventionalists but must be Conformité Européene marked and approved by the devices committee. The protocol recommends that an EPD be used whenever the operator thinks that one can be safely deployed. Premedication is discretionary, but the combination treatment of aspirin and clopidogrel is recommended as good practice to cover stenting procedures.

Two additional ongoing studies are the Asymptomatic Carotid Trial and the Transatlantic Asymptomatic Carotid Intervention Trial (TACIT). The Asymptomatic Carotid Trial is an industry-sponsored randomized trial at multiple centers across North America comparing CAS and CEA in low-risk patients with asymptomatic 80% to 99% carotid stenosis. The primary outcomes will be 30-day MI, stroke, and death rates and 5-year stroke-free survival. The TACIT is an interesting study that plans to randomize standard- and high-risk patients with asymptomatic carotid stenosis into 1 of 3 treatment arms: optimal medical therapy only, optimal medical therapy plus CEA, or optimal medical therapy plus CAS with embolic protection. Planned enrollment is 2400 patients with a primary end point of stroke and death occurrence at 3 years. Secondary end points include rates of transient ischemic attack and MI, economic cost, quality-of-life analysis, neurocognitive function, and carotid restenosis.[40] The TACIT will add importance as the first trial to compare any procedure with contemporary BMT in the new millennium.

CONCLUSIONS

In summary, extracranial carotid artery occlusive disease is a significant cause of stroke worldwide. New advances in BMT and cardiovascular interventional

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, and others have seen a tremendous rift among its ranks regarding this procedure. CAS is an emerging 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.[41] 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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REFERENCES

1. van der Vaart MG, Meerwaldt R, Reijnen MM, Tio RA, Zeebregts CJ. Endarterectomy or carotid artery stenting: the quest continues. *Am J Surg*. 2008;195(2):259-269.
2. Rosamond W, Flegal K, Friday G, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee (published correction appears in *Circulation*. 2010;122[1]:e9). *Circulation*. 2007;115(5):e69-e171. doi:10.1161/CIRCULATIONAHA.106.179918.
3. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med*. 1991;325(7):445-453.
4. Mayberg MR, Wilson SE, Yatsu F, et al; Veterans Affairs Cooperative Studies Program 309 Trialist Group. Carotid endarterectomy and prevention of cerebral ischemia in symptomatic carotid stenosis. *JAMA*. 1991;266(23):3289-3294.
5. European Carotid Surgery Trialists' Collaborative Group. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet*. 1998;351(9113):1379-1387.
6. Moore WS. The American Heart Association Consensus Statement on guidelines for carotid endarterectomy. *Semin Vasc Surg*. 1995;8(1):77-81.
7. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. *JAMA*. 1995;273(18):1421-1428.
8. Halliday A, Mansfield A, Marro J, et al; MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet*. 2004;363(9420):1491-1502.
9. Moore WS, Barnett HJ, Beebe HG, et al. Guidelines for carotid endarterectomy. A multidisciplinary consensus statement from the Ad Hoc Committee, American Heart Association. *Circulation*. 1995;91(2):566-579.
10. Goldstein LB, McCrory DC, Landsman PB, et al. Multicenter review of preoperative risk factors for carotid endarterectomy in patients with ipsilateral symptoms. *Stroke*. 1994;25(6):1116-1121.
11. Meyer FB, Piepgras DG, Fode NC. Surgical treatment of recurrent carotid artery stenosis. *J Neurosurg*. 1994;80(5):781-787.
12. Gasecki AP, Eliasziw M, Ferguson GG, Hachinski V, Barnett HJ; North American Symptomatic Carotid Endarterectomy Trial (NASCET) Group. Long-term prognosis and effect of endarterectomy in patients with symptomatic severe carotid stenosis and contralateral carotid stenosis or occlusion: results from NASCET. *J Neurosurg*. 1995;83(5):778-782.
13. Diethrich EB, Ndiaye M, Reid DB. Stenting in the carotid artery: initial experience in 110 patients. *J Endovasc Surg*. 1996;3(1):42-62.
14. Yadav JS, Roubin GS, Iyer S, et al. Elective stenting of the extracranial carotid arteries. *Circulation*. 1997;95(2):376-381.
15. Wholey MH, Wholey MH, Jarmolowski CR, Eles G, Levy D, Buecthel J. Endovascular stents for carotid artery occlusive disease. *J Endovasc Surg*. 1997;4(4):326-338.
16. Henry M, Amor M, Masson I, et al. Angioplasty and stenting of the extracranial carotid arteries. *J Endovasc Surg*. 1998;5(4):293-304.
17. Teitelbaum GP, Lefkowitz MA, Giannotta SL. Carotid angioplasty and stenting in high-risk patients. *Surg Neurol*. 1998;50(4):300-312.
18. Waigand J, Gross CM, Uhlich F, et al. Elective stenting of carotid artery stenosis in patients with severe coronary artery disease. *Eur Heart J*. 1998;19(9):1365-1370.
19. Bergeron P, Roux M, Khanoyan P, Douillez V, Bras J, Gay J. Long-term results of carotid stenting are competitive with surgery. *J Vasc Surg*. 2005;41(2):213-222.
20. Naylor AR, Bolia A, Abbott RJ, et al. Randomized study of carotid angioplasty and stenting versus carotid endarterectomy: a stopped trial. *J Vasc Surg*. 1998;28(2):326-334.
21. Brooks WH, McClure RR, Jones MR, Coleman TC, Breathitt L. Carotid angioplasty and stenting versus carotid endarterectomy: randomized trial in a community hospital. *J Am Coll Cardiol*. 2001;38(6):1589-1595.
22. Brooks WH, McClure RR, Jones MR, Coleman TL, Breathitt L. Carotid angioplasty and stenting versus carotid endarterectomy for treatment of asymptomatic carotid stenosis: a randomized trial in a community hospital. *Neurosurgery*. 2004;54(2):318-325.
23. CAVATAS Investigators. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. *Lancet*. 2001;357(9270):1729-1737.
24. Alberts MJ; Publications Committee of WALLSTENT. Results of a multicenter prospective randomized trial of carotid artery stenting vs. carotid endarterectomy. *Stroke*. 2001;32:300-384.
25. Gray WA, Hopkins LN, Yadav S, et al; ARCHeR Trial Collaborators. Protected carotid stenting in high-surgical-risk patients: the ARCHeR results. *J Vasc Surg*. 2006;44(2):258-268.
26. White CJ, Iyer SS, Hopkins LN, Katzen BT, Russell ME; BEACH Trial Investigators. Carotid stenting with distal protection in high surgical risk patients: the BEACH trial 30 day results. *Catheter Cardiovasc Interv*. 2006;67(4):503-512.
27. Safian RD, Bacharach JM, Ansel GM, Criado FJ. Carotid stenting with a new system for distal embolic protection and stenting in high-risk patients: the Carotid Revascularization With EV3 Arterial Technology Evolution (CREATE) feasibility trial. *Catheter Cardiovasc Interv*. 2004;63(1):1-6.
28. CaRESS Steering Committee. Carotid Revascularization Using Endarterectomy or Stenting Systems (CaRESS) phase I clinical trial: 1-year results. *J Vasc Surg*. 2005;42(2):213-219.
29. Hopkins LN, Myla S, Grube E, et al. Carotid artery revascularization in high surgical risk patients with the NexStent and the Filterwire EX/EZ: 1-year results in the CABERNET trial. *Catheter Cardiovasc Interv*. 2008;71(7):950-960.
30. Gray WA, Yadav JS, Verta P, et al. The CAPTURE registry: results of carotid stenting with embolic protection in the post approval setting. *Catheter Cardiovasc Interv*. 2007;69(3):341-348.
31. Kastrup A, Gröschel K, Krapf H, Brehm BR, Dichgans J, Schulz JB. Early outcome of carotid angioplasty and stenting with and without cerebral protection devices: a systematic review of the literature. *Stroke*. 2003;34(3):813-819.
32. Eskandari MK. Cerebral embolic protection. *Semin Vasc Surg*. 2005;18(2):95-100.
33. Parodi JC, Ferreira LM, Sicard G, La Mura R, Fernandez S. Cerebral protection during carotid stenting using flow reversal. *J Vasc Surg*. 2005;41(3):416-422.
34. Hobson RW II, Howard VJ, Roubin GS, et al; CREST Investigators. Carotid artery stenting is associated with increased complications in octogenarians: 30-day stroke and death rates in the CREST lead-in phase. *J Vasc Surg*. 2004;40(6):1106-1111.

35. Yadav JS, Wholey MH, Kuntz RE, et al; Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy Investigators. Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med.* 2004; 351(15):1493-1501.
36. Ringleb PA, Allenberg J, Brückmann H, et al; SPACE Collaborative Group. 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. *Lancet.* 2006;368(9543):1239-1247.
37. Mas JL, Chatellier G, Beyssen B, et al; EVA-3S Investigators. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. *N Engl J Med.* 2006;355(16):1660-1671.
38. Hobson RW II, Howard VJ, Roubin GS, et al; CREST. Credentialing of surgeons as interventionalists for carotid artery stenting: experience from the lead-in phase of CREST. *J Vasc Surg.* 2004;40(5):952-957.
39. Featherstone RL, Brown MM, Coward LJ; ICSS Investigators. International Carotid Stenting Study: protocol for a randomised clinical trial comparing carotid stenting with endarterectomy in symptomatic carotid artery stenosis. *Cerebrovasc Dis.* 2004;18(1):69-74.
40. Rundback J. Update on the TACIT trial. *Endovascular Today.* August 2006:93-94.
41. Hobson RW II, Mackey WC, Ascher E, et al; Society for Vascular Surgery. Management of atherosclerotic carotid artery disease: clinical practice guidelines of the Society for Vascular Surgery. *J Vasc Surg.* 2008;48(2):480-486.

INVITED CRITIQUE

To Stent or Not to Stent

The Question Remains Unanswered

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 ($P>.05$). 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.

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1. Brott TG, Hobson RW II, Howard G, et al; CREST Investigators. Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med.* 2010; 363(1):11-23.