Carotid Artery Stenting Versus Carotid Endarterectomy: Current Status

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KEYWORDS

- Carotid stenosis
- Carotid angiogplasty and stenting
- Carotid endarterectomy • Stroke prevention
- Carotid disease management

COMMENTARY

Since the original publication of this article two years ago, several clinical trials comparing the efficacy of carotid endarterectomy (CEA) to carotid angioplasty and stenting (CAS) for stroke prevention in carotid occlusive disease have been completed. This is exciting and encouraging. The initial results from two European studies and the long-term follow-up data from a previously published study have added to the growing body of knowledge regarding CAS. The recent completion of a large North American study promises to further advance our current understanding of the merits and indications for these two treatments. While much of the material in this article remains relevant, the purpose of this commentary is to highlight the results of studies published since the original article, provide the clinician with up-to-date references, and to summarize current management strategies for carotid occlusive disease.

The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy trial (SAPPHIRE) has reported 3-year results which found no difference between CAS and CEA for the prespecified composite outcome of death, stroke, or MI within 30 days of the procedure or death or ipsilateral stroke between 31 days and 3 years.[1] The absence of an increased risk of repeat revascularization within 3 years of treatment supports the durability of CAS. The Endarterectomy versus Stenting in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) study was terminated early after a statistically significant increase in the rate of stroke and death was found in patients undergoing carotid stenting.[2] The Stent-supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE) trial was stopped after meeting futility criteria and exhaustion of funding sources. SPACE failed to prove non-inferiority of CAS compared with CEA.[3] EVA-3S and SPACE enrolled symptomatic patients without medical conditions or anatomic features perceived to increase surgical risk. Methodological concerns, including the use of low-volume centers, the lack of stringent credentialing of CAS proceduralists, and variable use of embolic protection devices, have led to cautious interpretation of the EVA-3S and SPACE results. Still, neither of these trials produced definitive data to support the

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use of CAS in conventional risk patients with carotid stenosis.

The prospective, multicenter North American Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) completed enrollment in July 2008. The results of this study are eagerly anticipated and may better define the role of CAS in patients with low surgical risk. The Asymptomatic Carotid Stenosis Stenting vs. Endarterectomy Trial (ACTI) is enrolling patients with asymptomatic stenosis >70% to CAS with distal protection or CEA in a 3:1 ratio. The primary safety outcome will be the 30-day risk of stroke, MI, or death and ipsilateral stroke risk between 31 days and 1 year.[4] Approximately 575 patients have been enrolled at the time of this writing with an estimated completion date of 2014.

In addition to data from clinical trials, carotid stent registries have provided a valuable means of collecting standardized safety and efficacy data for evolving stent and embolic protection device technology. The short-term efficacy and safety outcomes for several registries have been published[5,6,7] and summarized in a recent review.[8] These registries included symptomatic and asymptomatic patients who were perceived to be high-risk surgical candidates. The short-term safety and efficacy outcomes for CAS have generally proved comparable to historical cohorts of CEA. Other industry-sponsored registries continue to enroll high-risk patients and the results of interim analyses have led to FDA approval of several carotid stent systems. The Carotid Artery Revascularization and Endarterectomy (CARE) registry is an ongoing national collaborative effort to collect clinical data and patient outcomes in order to improve carotid revascularization and to meet minimum standards for reimbursement purposes.[9]

Evidence-based decision making in selection of treatment of carotid disease has become complex. Despite a growing understanding and acceptance of CAS, translation of the emerging safety and efficacy data into routine clinical practice remains challenging. We offer the following summary recommendations:

For symptomatic and asymptomatic patients with the conventional risk factors of the cohorts studied in NASCET, ECST, ACAS, ACST, SPACE, and EVA-3S the indications for CEA are relatively well defined:

- Symptomatic patients, age $\leq$80, with $\geq$50% carotid stenosis if surgical risk for stroke and death is $\leq$6–7%.
- Asymptomatic patients, age $\leq$80, with $\geq$60% carotid stenosis if surgical risk for stroke and death is $\leq$3%

For these patients, carotid artery stenting should *not* be recommended as standard of care. Whether or not this recommendation can be changed in the future will depend on the long term results of SPACE and EVA-3S and the results of CREST, CAVATAS II, and other appropriately designed randomized controlled clinical trials.

For higher risk patients, those who would not fit the inclusion criteria of SPACE and EVA-3S, only SAPPHIRE provides randomized clinical trial data. These data and the CEA and CAS registry and case series results suggest the following:

- CEA and CAS may be comparable with regard to 30-day morbidity and durability.
- CEA would be favored where anatomic features make safe deployment of the embolic protection device or carotid stent technically difficult.
- CAS would be favored when a consensus exists that general or local anesthesia and a surgical procedure would pose excess risk.
- CAS would be favored in situations in which anatomic characteristics put the patient at higher risk for CEA
- The SAPPHIRE and ARCHeR 30-day results and the CAPTURE 30-day results for symptomatic patients are not ideal. These results raise the question as to whether medical therapy alone may be superior to carotid revascularization in high-risk patients, whether CEA or CAS. Except for NASCET, the number-needed-to-treat for symptomatic and asymptomatic patients in all the large randomized trials is modest in the moderate risk patients. For high-risk patients, higher periprocedural morbidity, concurrent illness, and higher stroke risk outside the territory of the treated carotid could counter-balance or even exceed the benefits of revascularization.

Finally, reimbursement for CAS remains a contentious topic. The Center for Medicare and Medicaid Services (CMS) provides coverage for CAS when performed on patients at high risk for CEA with symptomatic carotid stenosis $\geq$70% only when performed in a CMS approved facility for CAS with FDA-approved carotid artery stenting systems and embolic protection devices. For asymptomatic patients, CMS coverage is available only when beneficiaries are enrolled in FDA-approved or FDA-acknowledged trials. Recently, CMS declined a request to expand coverage for anatomically high-risk asymptomatic patients outside the setting of investigational trials. The decision is open for public comment over a 30-day period with the final coverage decision for this cohort expected in October 2008.

Approximately 700,000 new and recurrent strokes occur in the United States each year.[10] Atherosclerotic narrowing of the extracranial internal carotid artery (ICA) is estimated to be causative in more than 10% of cases.[11] The results of large, prospective, randomized controlled trials (RCTs) demonstrate the superiority of carotid endarterectomy (CEA) plus medical therapy over medical management alone for prevention of ipsilateral stroke in patients who are symptomatic and those who are asymptomatic.[12–16] The advent of minimally invasive endovascular approaches to treatment of extracranial carotid occlusive disease has generated interest in these techniques as alternatives to surgical revascularization. The potential of balloon angioplasty and stenting of the carotid artery to reduce patient discomfort and postprocedural complications has made this therapeutic alternative attractive to patients and physicians. Randomized trials of carotid angioplasty and stenting (CAS) are underway in North America and Europe. This article highlights the pivotal data demonstrating the effectiveness of CEA and focuses on evidence from completed and ongoing trials of CAS as a treatment alternative for carotid atherosclerosis. Related issues, including safety, durability, and cost-effectiveness, also are discussed.

CLINICAL TRIALS OF CAROTID ENDARTERECTOMY

The North American Symptomatic Carotid Endarterectomy Trial (NASCET), European Carotid Surgery Trial (ECST), and Veterans Affairs Cooperative Study Program were the pivotal trials demonstrating the effectiveness of surgical revascularization for the treatment of symptomatic carotid occlusive disease.[12,17,18] Patients included in these studies had transient ischemic attack (TIA) or nondisabling stroke within the preceding 6 months and ipsilateral high-grade carotid stenosis. The major difference between NASCET and ECST was the method used to measure the degree of carotid stenosis. Percent stenosis was calculated by comparison of the residual lumen diameter at the point of maximal stenosis to the diameter of the distal ICA in NASCET, whereas comparison to the estimated normal carotid bulb diameter was used in ECST. In NASCET, the life-table estimate of any ipsilateral stroke at 2 years for 659 patients was 26% in the medical arm (n = 331) and 9% in the surgical arm (n = 328) with an absolute risk reduction (ARR) of 17% (P<.001). The number needed to treat (NNT) to prevent one stroke annually was 12. In ECST, the risk of any ipsilateral stroke at 3 years for 778 patients was 16.8% in the medical arm (n = 323) and 2.8% in the surgical arm (n = 455), with an ARR of 14% (P<.0001). The NNT to prevent one stroke annually was 21. Based on these results, the American Stroke Association (ASA) recommends that CEA be performed by surgeons who have perioperative morbidity and mortality of less than 6% in symptomatic patients who have greater than 70% stenosis (class I, level A evidence).[19] No benefit of surgery is demonstrated in patients who have carotid stenosis less than 50%. Medical therapy alone is recommended in this patient population.

Symptomatic patients who had moderate degrees of carotid stenosis (50%–69%) also were studied in the context of NASCET and ECST. The reduction in stroke risk achieved with CEA in patients who had moderate stenosis was less robust when compared with the risk reduction in patients who had high-grade stenosis. In NASCET, the 5-year ipsilateral stroke rate was 22.2% in the medical arm and 15.7% in the surgical arm. The ARR was 6.5% (1.3%/year) and the NNT was 15 to prevent one stroke over a 5-year period (NNT = 77 at 1 year).[14] Patient characteristics and existence of comorbid conditions modified the beneficial effects of surgery. Men had a greater reduction in stroke risk than women, as did patients ages 75 years old and older, those who had stroke as the qualifying event (rather than TIA), and those who had hemispheric symptoms (rather than retinal ischemic symptoms). The ASA recommends CEA for patients who have had recent TIA or stroke and carotid stenosis 50% to 69% depending on patient-specific factors, such as age, gender, comorbidities, and severity of initial symptoms (class I, level A).[19]

The Asymptomatic Carotid Atherosclerosis Study (ACAS) and Asymptomatic Carotid Surgery Trial (ACST) are the largest RCTs to evaluate the efficacy of endarterectomy for patients who have asymptomatic disease. ACAS randomized 1662 patients who had 60% or greater stenosis by cerebral arteriography or by duplex ultrasonography to surgical intervention plus medical therapy or medical therapy alone.[15] Results were published after a median follow-up of 2.7 years. The aggregate risk over 5 years for ipsilateral stroke and any perioperative stroke or death was 11.0% in the medical arm and 5.1% in the surgical arm. The ARR was 5% (1.2%/year) and the NNT to prevent 1 event was 17 (NNT = 83 at 1 year) within 5 years. An exceedingly low perioperative complication rate (<3%) was achieved by trial surgeons. The benefits of surgery were greater for men than women (66% versus 17% risk reduction) and perioperative complications were higher among women than men (3.6% versus 1.7%). Guidelines published by the Stroke Council of the American Heart Association recommend surgical treatment for patients who have asymptomatic carotid stenosis greater than 60% given a perioperative risk less than 3% and life expectancy of at least 5 years (grade A).[20] ACST randomized 3120 patients over a 10-year study period to either surgery or medical therapy.[16] Patients had carotid stenosis greater than 60% by ultrasound and no referable symptoms within the preceding 6 months. The surgical group had a net 5-year risk of combined perioperative events and nonoperative strokes of 6.4% and the medical group had a net 5-year risk of 11.8% for the same outcome. The ARR and NNT were almost identical to those achieved in ACAS. Subgroup analyses suggested a benefit for women (n = 1076); however, the benefit was not suggested for patients 75 years old and older; the analyses as presented, however, did not balance the 30-day morbidity and mortality of the surgery. The principle methodologic difference between ACAS and ACST was the primary endpoint; ACAS used ipsilateral stroke in contrast to ACST, which included all strokes (ipsilateral, contralateral, and vertebrobasilar territory).

A recent Cochrane systematic review sought to determine the effects of CEA in asymptomatic patients.[21] Three large trials met the study inclusion criteria and found an overall net excess of operation-related perioperative stroke or death in 5223 patients to be 2.9%. The primary outcome measure of perioperative stroke or death or any subsequent stroke favored the surgically treated patients (relative risk [RR] 0.69; 95% CI, 0.57–0.83). Similarly, the outcome of perioperative stroke or death or ipsilateral stroke favored the group of patients randomized to surgery (RR 0.71; 95% CI, 0.55–0.91). The investigators conclude that CEA for asymptomatic

Table 1
Absolute risk reduction and number needed to treat for event prevention by medical and surgical therapy

Study	Intervention	Recruits	Absolute Risk Reduction (%)	Number Needed toTreat to Prevent One Stroke Annually
CAPRIE	75 mg clopidogrel versus 325 mg aspirin	Stroke	0.9 at 2 years	222
BHP	40 mg simvastatin versus placebo	All CVD	1.4 at 5 years	355
PROGRESS	4 mg perindopril versus placebo	TIA/CVA	2.3 at 4 years	172
UKPDS	HT Rx in type II DM	HT Rx + DM	3.7 at 8 years	216
ACST	Immediate CEA versus BMT (deferred CEA in 13%)	Asymptomatic carotid stenosis	5.3 at 5 years	95
ACAS	Immediate CEA versus BMT	Asymptomatic carotid stenosis	5.9 at 5 years	85
NASCET 70%–99%	Immediate CEA versus BMT	TIA/stroke and carotid stenosis	17.0 at 2 years	12

Abbreviations: BHP, British Heart Protection Study; BMT, best medical therapy; CAPRIE, Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events; CVA, stroke; CVD, cardiovascular disease; DM, type 2 diabetics; HT Rx, hypertensive therapy; PROGRESS, Perindopril Protection Against Recurrent Stroke Study; UKPDS, UK Prospective Diabetes Study.

carotid stenosis reduces the risk of any stroke and ipsilateral stroke by approximately 30% over 3 years. The investigators note that the per annum ARR was less than 1% per year but might be higher with longer follow-up periods.

Medical therapy has evolved since publication of the early trials demonstrating a greater benefit of CEA compared with best medical management. The introduction of newer antiplatelet agents, such as clopidogrel and combination extended-release dypridamole/aspirin;[22,23] the use of statins to reduce cholesterol and LDL;[24] and more aggressive control of blood pressure[25] have contributed to reductions in stroke risk in patients who have atherosclerotic disease. Despite these advances, the ARR for modern medical therapy remains low and the benefits are borne only in patients who are compliant after prolonged periods of medication use.[26] Studies comparing CEA to present-day medical management are lacking. The high NNT for event prevention with medical therapy alone, however, is unlikely to offset the benefit of surgery, even in patients who are symptomatic and who have moderate stenosis or patients who are asymptomatic in whom the beneficial effect of surgery is modest (**Table 1**).

CAROTID ANGIOPLASTY AND STENTING TECHNIQUE

Endovascular approaches to treat arteries narrowed by atherosclerosis have been used in the coronary circulation and other peripheral vascular beds for many years. In the extracranial carotid artery, an intraluminal balloon-tipped catheter can be advanced across a focal stenosis and lumen diameter re-established with balloon dilatation. Deployment of a mechanical stent after angioplasty has the theoretic advantage of decreasing the risk of vessel recoil and recurrent stenosis.[27] **Fig. 1** illustrates the angiographic appearance of the ICA pre- and post-CAS. The metallic stent surface may have the additional advantage of serving as a regular surface for future endoluminal modeling as opposed to the irregular, thrombogenic vessel wall created after balloon angioplasty.[27] Patients who have femoral or iliac access problems, patients who have marked toruosity of the common carotid artery and ICA, or those who have contraindications to antiplatelet therapy commonly prescribed to prevent postprocedure thrombotic complications may not be suitable candidates for endovascular therapy. Acute and delayed complications associated with CAS are listed in **Box 1**. Stimulation of baroreceptors in the carotid sinus during balloon angioplasty and stent deployment may precipitate clinically significant hemodynamic changes. The resultant increase in parasympathetic discharge may result in slowing of heart rate and diminished arterial smooth muscle tone. One retrospective series of 471 patients undergoing CAS without distal protection finds severe hypotension (systolic blood pressure < 80 mm Hg) or bradycardia (heart rate < 50) to occur in 7% of patients (n = 34).[28] Other series report rates of hemodynamic instability occurring in up to 33% of patients during CAS.[29–31] Preadministration of atropine and maintenence of adequate

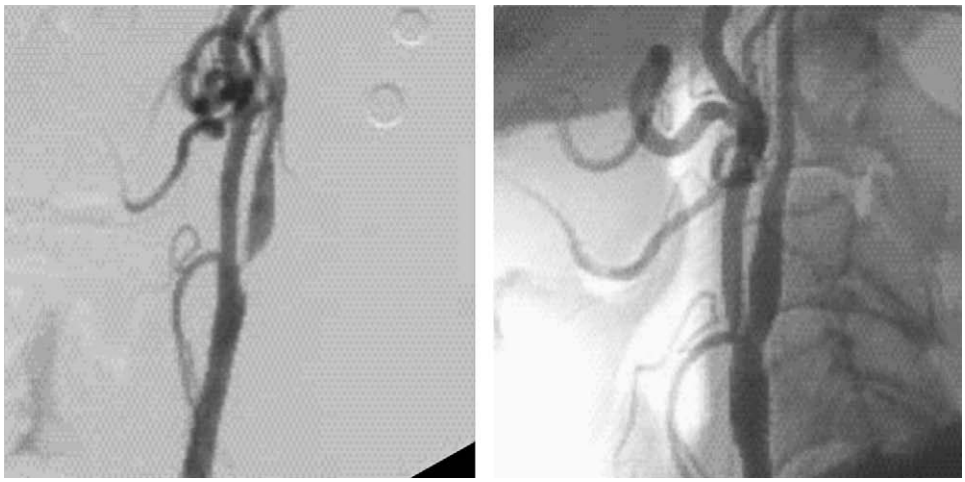

Fig. 1. (*Left*) Conventional angiogram with stenotic ICA before stent placement. (*Right*) Angiogram with dilation of the ICA after angioplasty and stent deployment. (*From* Brott TG, Brown RD, Meyer FB, et al. Carotid revascularization for prevention of stroke: carotid endarterectomy and carotid artery stenting. Mayo Clin Proc 2004;79:1197–208; with permission.)

Box 1
Complications of carotid angioplasty and stenting

Acute complications

- Intimal dissection
- Arterial spasm
- Bradycardia/asystole
- Hypotension
- Vessel rupture/occlusion
- Guide-wire fracture
- Detachment of filter protection device
- Groin hematoma
- Contrast reactions

Delayed complications

- Cerebral embolism
- Restenosis
- Stent collapse
- Cerebral hemorrhage
- Hyperperfusion syndrome

intravascular volume are used by some interventionalists in an attempt to minimize the risk of hemodynamic complications.

Perhaps the most feared complication of carotid revascularization is mobilization of embolic material into the intracranial circulation and resultant stroke. Plaque disruption may occur during predilation, stent deployment, or postdilation of the deployed stent. Transcranial Doppler monitoring during angioplasty has detected particulate matter moving into the intracranial circulation and occurs more frequently during endovascular treatment compared with CEA.[32,33] Further evidence of embolization is documented in retinal vessels after CAS.[34] Asymptomatic and symptomatic ischemic changes have been noted on brain MRI sequences performed in the post-CAS period.[35–37] The long-term significance of asymptomatic DWI changes has yet to be defined; however, concern is raised that microembolic debris may contribute to sequelae, such as cognitive dysfunction.

Recently, distal embolic protection devices have been developed in an attempt to reduce the risk of procedure-related stroke. Filter protection, balloon occlusion, and flow reversal are the methods used most commonly to decrease the embolic load reaching the cerebral vasculature.[38] Filters are umbrella-shaped devices that use small (approximately 150 μm) pores designed to exclude particulate debris while preserving cerebral perfusion during the procedure. Distal balloon occlusion prevents passage of blood and debris. Both device types are delivered to an arterial segment distal to the stenosis and anchored by apposition to the vessel wall during the critical phase of balloon angioplasty and stenting. Afterwards, the device can be retrieved and engulfed by the catheter. Evidence of captured thrombotic material has been demonstrated after filter device retrieval.[39] The flow reversal technique, used less commonly, prevents distal migration of embolic material by reversing flow in the distal ICA through proximal balloon occlusion of the external carotid and common carotid arteries. Use of distal protection has become routine despite lack of RCT data supporting its benefit. Case series of CAS with and without distal protection demonstrate lower rates of neurologic complications in the postprocedural period when distal protective devices are used.[40–42] Proponents of protective devices highlight their ability to capture debris and reduce cerebrovascular complications. The availability of protective devices in recent years has coincided with improved catheter-based technology and operator experience. The degree to which these latter advances have had an impact on procedure-related complication rates is difficult to assess independently of protective device use. Regardless, the use of distal protection in large RCTs comparing CAS with CEA is evidence of their growing acceptance.

CLINICAL TRIALS OF CAROTID ANGIOPLASTY AND STENTING

Initial trials of CAS were hampered by procedural complications. An early study comparing CAS without distal protection and CEA in patients who had severe ICA stenosis (>70%) was terminated early because of an unacceptably high rate of stroke in the endovascular group. After 17 patients had received allocated treatment, the trial was suspended because 5 of 7 patients randomized to the stenting arm developed stroke (3 major and 2 minor), whereas no patient treated with surgery developed stroke.[43] The industry-sponsored WALLSTENT trial randomized 219 symptomatic patients who had carotid stenosis (60%–99%) to either CAS (without distal protection or antiplatelet prophylaxis) or surgical revascularization. The device used was not a dedicated carotid stent, and no lead-in or feasibility phase was built into the trial. The high rates of perioperative stroke or death at 30 days (12.1%) and risk of ipsilateral stroke, procedure-related death, or vascular death at 1 year (12.1%) in the CAS group was significantly higher than the CEA group and led to early trial termination.[44] The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) was a multicenter, international trial that randomized 504 patients to treatment with carotid angioplasty (with or without stent placement) or surgery.[45] All patients were considered suitable candidates for

surgery or endovascular therapy and the majority (90%) had symptoms referable to the treated artery within the 6-month period before randomization. No significant difference in stroke risk or survival was found between the treatment groups at 30 days. Higher rates of restenosis were noted in the arm treated with angioplasty only. Subsequent clinical trials have benefited from improvements in operator experience, guide-wire/stent technology, and the routine use of distal embolic protection devices to minimize procedure-related morbidity.

A single-center RCT comparing the safety and efficacy of CAS without distal protection to CEA was performed at a community hospital in Kentucky, with results published in 2001.[46] One hundred and four patients who had symptomatic carotid stenosis (>70%) in the preceding 3 months were randomized to surgery (n = 51) or stenting (n = 53) of the carotid artery. One death secondary to myocardial infarction (MI) occurred in the surgical group and one TIA occurred in the stent group. No patient experienced a stroke in the follow-up period. The investigators conclude that CAS was equivalent to CEA in correcting carotid occlusive disease without increased risk of stroke or death.

The strict inclusion criteria, use of high-volume centers, and low perioperative morbidity (<3% for asymptomatic patients[15] and <6% for symptomatic patients)[14] in the CEA trials demonstrating the efficacy of surgery has raised concerns about the ability to replicate these results in a more heterogenous stroke-prone population. Patients who have coexisting conditions, such as those listed in **Box 2**, generally were not included in the surgical trials. These conditions increase the risk of perioperative complications that may offset the benefit of surgical intervention. Endovascular techniques may be better suited for stroke prevention in this ''high-risk'' population. The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial attempted to define the role of CAS and CEA in a group of high-risk patients.[47] Patients were eligible for randomization to either surgery or CAS with distal protection if they had at least one coexisting condition believed potentially to increase the risk posed by endarterectomy and if a study surgeon and interventionalist agreed patients could undergo either procedure safely. If differential risk was believed to favor one procedure over the other, subjects were entered into a nonrandomized surgical or stent registry. Eligible patients had symptomatic carotid stenosis of at least 50% or asymptomatic carotid stenosis of at least 80% as assessed by color duplex ultrasonography. The majority of randomized patients were asymptomatic (238 of 334 patients). Enrollment was terminated early because of slowing of patient recruitment after the creation of nonrandomized stent registries. A composite of death, stroke, or MI at 30 days and ipsilateral stroke or death within 1 year were used as primary endpoints. Analysis of 334 patients who underwent randomization found that CAS was not statistically superior to CEA ($P = .053$), but the investigators conclude that carotid stenting with emboli protection was not inferior to CEA in this high-risk population ($P = .004$). Notably, 413 enrolled patients were not randomized and the majority (n = 406) were entered into the stent registry because they were believed poor surgical candidates. The lack of a medical arm for comparison and the inclusion of MI as part of the composite 30-day outcome measure are major critiques of this study. MI, which generally was not included as an endpoint in the early surgical trials, was more frequent in the surgical group and had a heavy impact on the observed differences between CEA and CAS. Additionally, more than 20% of patients in each group had recurrent stenosis greater than or equal to 50% at 12 months. Subsequently, Food and Drug Administration approval has been obtained for the ACCULINK (stent and delivery catheter) and ACCUNET (embolic protection device) systems marketed by Guidant Corporation (St. Paul, Minnesota). In 2005, Medicare reimbursement was approved for carotid stenting in high-risk patients who have symptomatic stenosis greater than or equal to 70% but not for patients who are asymptomatic.

A Cochrane systematic review of available randomized trials comparing endovascular treatment

Box 2
High-risk coexisting conditions

Medical

- Recent MI
- Unstable angina
- Congestive heart failure
- Inevitable cardiac surgery
- Chronic obstructive lung disease
- Advanced age (>80)

Anatomic

- Prior ipsilateral CEA
- Prior neck irradiation
- Contralateral ICA occlusion
- High cervical stenosis
- Tandem lesions
- Cervical immobility
- Tracheostomy
- Contralateral laryngeal palsy

with surgery for carotid stenosis found no significant difference in the odds of death or any stroke at 30 days or in the odds of any stroke or death at 1 year.[48] Cranial neuropathy was significantly less common in the endovascular group (odds ratio 0.13). Five studies met the inclusion criteria for review; two trials were completed, two were stopped early, and one had completed 1-year follow-up at the time of the review. A combined total of 1269 patients who were predominantly symptomatic were treated in the five trials. The wide confidence intervals generated by the small number of heterogenous studies prevented the investigators from excluding a possible difference favoring one treatment modality over the other.

ONGOING TRIALS OF CAROTID ANGIOPLASTY AND STENTING AND CAROTID ENDARTERECTOMY

Several trials designed to assess the safety and efficacy of CAS are ongoing and continue to enroll patients. The National Institutes of Health–funded Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) is a prospective, multicenter, RCT currently in the enrollment phase. Initially designed to compare CAS and CEA in patients who had symptomatic disease and carotid stenosis ($\geq$50% by angiography or $\geq$70% by duplex ultrasound),[49] the eligibility was expanded to include patients who have asymptomatic carotid stenosis ($\geq$60% by angiography or $\geq$70% by duplex ultrasound) after results of the ACST were published. Concurrent medical therapy includes use of aspirin and clopidrogrel in those randomized to CAS and aspirin alone in those randomized to CEA. Target enrollment is 2500 patients (1500 symptomatic and 1000 asymptomatic) during 4 years with blinded outcome assessment at 30 days (death, stroke, or MI) and 60 days (ipsilateral stroke). The sample size provides 90% power to detect a greater than 1.2% per year difference in primary endpoints.

The CREST study protocol includes a credentialing phase with supervised training of vascular surgeons, neurosurgeons, interventionalists, neurologists, and cardiologists experienced in basic catheter and guide-wire techniques. No significant difference in the 30-day stroke and death rate was observed between surgical specialists (5.3%) and other credentialed specialists (4.4%) during the lead-in phase.[50] Interim results from the lead-in phase show a significantly higher periprocedural stroke and death rate in older patients undergoing CAS.[51] Of 99 patients ages 80 or older, 12 (12.1%) experienced stroke or death in the 30-day postprocedural period. The higher complication rates observed with advancing age persisted despite adjustment for factors, such as symptomatic status, gender, degree of carotid stenosis, or presence of distal arterial tortuosity. Despite positive single-center experience with CAS in older patients,[52] these results raise concerns about endovascular treatment in elderly patients. Initial patient recruitment into CREST was slow, but redoubled efforts, including expanding the number of participating clinical centers and encouraging providing physicians to enroll patients into the study, has helped maintain steady recruitment.[53] Currently, more than 1050 patients are randomized at more than 100 participating clinical sites in the United States and Canada.

As a follow-up to CAVATAS, the International Carotid Stenting Study (ICSS) is a multicenter RCT comparing the risks and benefits of CAS with distal protection to CEA.[54] The protocol has been designed to replicate routine clinical practice as closely as possible in hopes of generating results useful in determining the role of CAS in the treatment of carotid occlusive disease. Centers in Canada, Europe, and Australia are recruiting actively, and enrollment nears 600 patients. The French Endarterectomy versus Angioplasy in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial is designed to compare CEA with CAS with or without distal protection.[55] Planned primary outcome measures occur at 30 days (death or recurrent stroke) and 2 to 4 years. Enrollment in the uprotected CAS arm was halted by the safety committee, because the 30-day stroke risk was found 3.9 times higher than that of CAS with distal protection.[56] Recruitment continues for patients who have had retinal or cerebral ischemic symptoms within the preceding 4 months and enrollment approaches 500 patients. The most advanced European trial in terms of recruitment is the Stent-supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy Trial (SPACE).[57] The German Ministry of Science has sponsored this trial to compare CAS with CEA in patients who have had severe ICA stenosis and referable symptoms in the preceding 6 months. SPACE has a goal recruitment of 1900 patients and nears completion. Investigators from the European trials have agreed to perform a joint data analysis after completion and publication of the three studies.[58] **Table 2** summarizes the ongoing trials of CAS and CEA.

Currently, CAS is used outside of clinical trials for treatment of patients who have circumstances believed to favor an endovascular approach. Technically difficult surgical approaches (ie, high carotid bifurcation), comorbid medical conditions that may increase the risk of surgery with general anesthesia, radiation-induced occlusive disease,

Table 2
Ongoing clinical trials of carotid endarterectomy and carotid angioplasty and stenting

Trial	Country	Sample Size	No. Randomized to Date	Protection Used?
ICSS	International	1500	~750	Yes if possible
CREST	United States	2500	~1050	Yes (ACCUNET only)
SPACE	Germany + Austria	1900	~1500	Optional (5%–10% so far)
EVA-3S	France	1000	~500	Recent protocol amendment

or restenosis after surgery are common scenarios. Additionally, CAS is used in selected cases of fibromuscular dysplasia, Takayasu's arteritis, or after arterial dissection. Based on published results and expanding knowledge of CAS, the ASA has published evidence-based recommendations regarding the use of CAS. CAS is considered not inferior to endarterectomy in the aforementioned clinical situations and may be considered a therapeutic alternative to surgical revascularization when performed by operators who have established periprocedural morbidity and mortality rates of 4% to 6%.[19]

COST-EFFECTIVENESS AND DURABILITY OF CAROTID STENTING

As the results of ongoing clinical trials become available and the efficacy and safety of CAS are defined more clearly, additional factors, such as cost-effectiveness and durability of results, will be scrutinized before measuring the final impact of endovascular treatments on current clinical practice. Data from three studies demonstrate an increased cost of CAS compared with CEA despite shorter postprocedure hospital stays.[59–61] Higher equipment and physician costs were the primary factors influencing these observations. A cost analysis of CAS and CEA in high-risk patients (NASCET ineligible) at a single institution finds no statistically significant cost advantage for either procedure.[62]

In contrast to CEA, the durability of CAS is less well defined. Individual case series report restenosis rates after CAS ranging from 3% to 21%.[63–65] Comparison of restenosis rates after CAS to CEA from individual case series is difficult given the differences in patient populations and variable use of risk factor modification strategies in the postprocedural period. Evaluation of restenosis rates for CAS and CEA in the setting of a RCT likely will yield a more accurate estimate of the frequency of this complication. One-year duplex ultrasonography follow-up of patients enrolled in CAVATAS finds a significantly higher rate of restenosis in the endovascular group (14%) versus the surgical group (4%).[45] Less than one third of patients treated with angioplasty received a stent, however. One-year follow-up of patients enrolled in SAPPHIRE found restenosis greater than 70% by duplex ultrasonography in 1 of 122 (0.8%) patients who had CAS and 4 of 96 (4.2%) patients who have CEA ($P = 0.17$); restenosis of greater than 50% was found in 20% of patients who had CAS compared with 31% in the CEA group ($P = 0.06$).[47] Existing data do not allow clear conclusions to be drawn regarding the durability of CAS compared with CEA, but hopefully the question will be answered in the context of an ongoing or future RCT.[66]

SUMMARY

As operator experience and device technology continue to improve, the theoretic advantages of endovascular approaches to treat carotid occlusive disease may be closer to realization. Currently, data from controlled trials of CAS is minimal, but several multicenter RCTs comparing CAS to CEA are recruiting patients actively and preliminary results show procedural morbidity and mortality rates for CAS that compare favorably to CEA. Community-based experience with CAS continues to grow and further refinements in patient selection based on plaque morphology and other variables offer further hope that endovascular approaches to carotid occlusive disease may benefit selected patients. Given the proved efficacy and durability of CEA for treatment of extracranial carotid stenosis, surgical revascularization remains the recommended standard of care for most patients. CAS will have to be proved equivalent or superior to surgery and as cost-effective to facilitate its widespread acceptance as a treatment alternative for carotid occlusive disease.

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