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Optimal Treatment of Carotid Artery Disease

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Extracranial carotid artery disease accounts for approximately 25% of ischemic strokes. Although carotid endarterectomy (CEA) is the established gold standard for carotid revascularization, carotid artery angioplasty and stenting (CAS) is continually developing into a safer and more efficacious method of stroke prevention. Embolic protection, improving stent designs, and ever-increasing surgeon experience are propelling CAS towards equipoise with and possible superiority to CEA. One multicenter randomized trial and several nonrandomized registries have successfully established CAS as an accepted treatment for high-risk patients. Clinicians must strive to perform well-designed clinical trials that will continue to aid understanding and improve application of both endovascular and open techniques for extracranial carotid revascularization. We review the data published to date regarding the indications for and recent developments in the use of CAS. (J Am Coll Cardiol 2008;51:979–85)  
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Carotid artery angioplasty and stenting (CAS) has steadily developed over the preceding decade. Current data regarding CAS and carotid endarterectomy (CEA) suggest that CAS is quickly gaining ground on CEA as a first-line treatment of extracranial carotid stenosis. Clinicians must continue to refine their understanding of the appropriate indications for both CAS and CEA. This is done through rigorous, well-designed research. We review the data supporting the implementation of CAS for extracranial athero-occlusive carotid artery disease.

Background

Indications for and outcomes of CEA have been extensively studied. The support for CEA utilization is generated from 4 well-designed multicenter, randomized clinical trials—NASCET (North American Symptomatic Carotid Endarterectomy Trial) (1,2), ECST (European Carotid Surgery Trial) (3,4), ACAS (Asymptomatic Carotid Atherosclerosis Study) (5), and ACST (Asymptomatic Carotid Surgery Trial) (6). The NASCET (1,2) and ECST (4) trials addressed the use of CEA for symptomatic patients with 70% to 99% carotid stenosis or selected patients with 50% to 69% stenosis. These studies resulted in class IA indications for the use of CEA in symptomatic patients meeting appropriate criteria (7). However, it is important to realize that the general population of patients with carotid stenosis has substantially different demographics than those patients who met the strict eligibility criteria for these studies (8). For instance, NASCET excluded patients ≥80 years old and those with intracranial carotid stenosis more severe than the surgically accessible lesion; liver, kidney, or lung failure; cardiac valve or rhythm disorder; previous ipsilateral CEA; uncontrolled hypertension or diabetes; recent myocardial infarction (MI); or major surgery (1). Such patients were considered to have excessive perioperative morbidity (i.e., high risk). Since NASCET was published, patients considered for carotid revascularization are often divided into low- and high-risk groups, and, in fact, recent CAS trial investigators have used such surgical risk stratification as an integral part of their study design.

The ACAS (5) and the ACST (6) trials addressed the use of CEA for asymptomatic patients. The degree of benefit from CEA for asymptomatic lesions is substantially less, and the indications for revascularization are still debated. The ACAS and ACST trials demonstrated a 5.4% to 5.9% absolute risk reduction over 5 years (5,6). Therefore, periprocedural risks are particularly relevant to the decision analysis for treatment of asymptomatic patients, with a morbidity of >3% minimizing any benefit. Despite this, with the publication of ACAS, nearly 75% of CEAs in the U.S. are performed on asymptomatic patients (9).

In the aforementioned trials, carefully selected low-risk patients were treated by highly experienced surgeons at
Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
CAS = carotid artery stenting
CEA = carotid endarterectomy
DWI = diffusion-weighted imaging
MI = myocardial infarction
TIA = transient ischemic attack

high-volume medical centers. The low complication rates seen in NASCET and ACAS are often not obtained in the general population. Studies have demonstrated perioperative stroke and death to range from 0% (10) to 11.1% (11) for symptomatic patients and 0% (12) to 5.5% (11) for asymptomatic patients. In fact, a study of Medicare mortality data from hospitals participating in NASCET and ACAS demonstrated a 1.4% perioperative mortality (8) compared with 0.6% reported in NASCET (1) and 0.1% reported in ACAS (5). Perhaps equally concerning, CEA-related mortality rates have been demonstrated to be higher (2.5%) for low-volume hospitals (8), although other studies have argued that only small differences exist between mortality rates at high- and low-volume hospitals (13).

Treatment decisions are also dependent on patient-specific factors. The presence of comorbidities has significant impact on outcome after CEA. Perioperative stroke and death rates for common comorbidities include congestive heart failure, 8.6% (14,15); age over 75 years, 7.5% (14,15); post-endarterectomy restenosis, 10.8% (16); ipsilateral carotid siphon stenosis, 13.9% (14); intraluminal thrombus, 10.7% to 17.9% (14,17); contralateral carotid occlusion, 14.3% (18); and CEA combined with coronary artery bypass grafting, 16.4% to 26.2% (19,20). It is important to note that in the presence of such comorbidities the natural history of carotid disease itself is more grim. The investigators of the ACSRS “natural history” study followed up 1,115 patients with asymptomatic internal carotid artery stenosis treated with medical therapy alone (21) and identified significant differences in patient subgroups with respect to stroke and death risk. The highest risk group (82% to 99% stenosis by NASCET criteria [1], history of concomitant transient ischemic attack [TIA], and serum creatinine level >0.085 mmol/l) had a 4.3% annual ipsilateral stroke rate compared with 0.7% in the lowest risk group (21,22).

It should also be noted that since the aforementioned major randomized CEA trials were begun, best medical therapy has improved. In NASCET, the primary medical intervention was 1,300 mg of aspirin per day (1). This dose of aspirin is no longer used because lower doses are proven equally efficacious with fewer side effects (23–25). Other antiplatelet drugs, such as clopidogrel and ticlopidine, are also now available (26,27); and the aspirin-dipyridamole combination was shown to be more efficacious than aspirin alone (28). Methods for blood pressure control were not specified in NASCET, whereas it is now known that blood pressures below 120 to 130/70 mm Hg are optimum for cardiovascular risk reduction in patients with medical co-morbidities (7,29,30) and that for primary stroke prevention a 10-mm Hg reduction in systolic blood pressure produces a 31% relative risk reduction for stroke (31). For secondary stroke prevention, angiotensin-converting enzyme (ACE) inhibitors (29,32) and the combination of a thiazide diuretic with an ACE inhibitor (32) have now been proven effective. Additionally, in the past decade, statins have assumed a prominent role in cerebrovascular and cardiovascular risk modification (33–37). In a study of patients receiving medical treatment for severe carotid artery disease, statin use was associated with significantly lower rates of stroke, MI, or death (38). It is likely that medical therapy improvement for carotid atherosclerotic disease and related comorbidities should prompt periodic re-evaluation and risk-benefit analysis fine-tuning for medical therapy versus surgical intervention.

With the great deal of complexity regarding risk assessment in this complex patient population, current standards are limited to minimizing overall surgical risk in order to maximize the likely benefit from surgery. Currently, the guidelines of the American Heart Association (7) and the Canadian Neurosurgical Society (39) establish an upper limit of 6% for perioperative risk in symptomatic patients (7) and a 3% upper limit in asymptomatic patients, assuming a life expectancy of >5 years (20).

Published Data Regarding CAS

The first randomized trial comparing endovascular and surgical treatments for carotid stenosis patients, CAVATAS (CArotid and Vertebral Artery Transluminal Angioplasty Study) (40), which was published in 2001, included 504 patients enrolled between 1992 and 1997 and was designed to compare balloon angioplasty alone versus CEA. Stents, when they became available, were incorporated as well but only accounted for 26% of cases. Twenty-four centers in Europe, Australia, and Canada participated, and like previous CEA trials, high-risk surgical patients were excluded from enrollment—including those with recent MI, poorly controlled hypertension or diabetes mellitus, renal disease, respiratory failure, inaccessible carotid stenosis, or severe cervical spondylosis. The CAVATAS trial demonstrated no statistically significant difference between endovascular and surgical treatment in the rate of disabling stroke or death within 30 days (6.4% CAS vs. 5.9% CEA) and no significant difference in the 3-year ipsilateral stroke rate. These early encouraging results generated a great deal of interest in CAS, and further studies were undertaken.

The Wallstent trial (41,42), the first multicenter randomized trial designed from inception to evaluate CEA and CAS equivalence, enrolled a total of 219 symptomatic patients with 60% to 99% stenosis. Thirty-day stroke or death rates were 12.1% with CAS and 4.5% with CEA (p = 0.049). Additionally, 12.1% of CAS patients suffered ipsilateral stroke, procedure-related death, or vascular death at 1 year versus 3.6% of CEA patients (p = 0.022), and, as a result, the trial was halted by the Data Safety and Moni-
toring Committee after an interim analysis demonstrated worse outcomes for the CAS group. Critical to interpreting these results is the fact that the Wallstent trial did not employ the use of distal protection devices. A significant portion of major CAS neurological complications are due to atheromatous material embolization (43–46). Devices that capture embolic debris released during CAS have significantly improved procedural safety (43,46–50).

One of the first trials to utilize embolic protection was CaRESS (Carotid Revascularization Using Endarterectomy or Stenting Systems) (51,52), a multicenter, nonrandomized, prospective study comparing CAS with embolic protection (n = 143) and CEA (n = 254) in symptomatic (32%) and asymptomatic (68%) patients with low- and high-surgical risk. An important feature of CaRESS was that the treatment procedure was chosen by the treating physician and the patient, not randomized. Although this study design likely introduced selection bias, the CaRESS trial represents a generalized perspective on carotid revascularization and more closely represents its ‘real world’ application. Baseline group demographics were similar, except patients with previous carotid intervention more often received CAS. No statistically significant difference between 30-day and 1-year death or stroke rates existed between CAS and CEA (2.1% vs. 3.6% and 10.0% vs. 13.6%, respectively), nor did significant differences exist for restenosis, residual stenosis, repeat angiography, and need for carotid revascularization. Overall morbidity and mortality approached NASCET (1,2) and ACAS (5) standards and represented the lowest rates among the major CAS trials to date. The low stroke and death rates may be attributable to the ability of the treating physician to consider patient-specific factors and successfully assign each patient to the safest therapy.

Carotid artery stenting was well established as a treatment option for high-risk patients by SAPPHIRE (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy) (53), a randomized, multicenter trial to determine CAS noninferiority to CEA in high-risk patients. Eligible patients (n = 344) had symptomatic stenosis of at least 50% or asymptomatic stenosis of at least 80%. The 30-day MI, stroke, or death rate was 4.8% for CAS and 9.8% for CEA (p = 0.09). Much of this difference was secondary to MIs in the CEA group, and although not reported in SAPPHIRE, the 30-day rate of stroke and death was ~4.8% for CAS patients and ~5.6% for CEA patients. At 1 year, 12.2% of CAS patients had suffered stroke, MI, or death versus 20.1% of CEA patients (noninferiority analysis: p = 0.004; superiority analysis: intention-to-treat p = 0.053, as-treated p = 0.048). Myocardial infarction and major ipsilateral stroke rates were significantly better after CAS versus CEA (2.5% vs. 8.1%, p = 0.03; 0% vs. 3.5%, p = 0.02; respectively).

As SAPPHIRE had shown such clear noninferiority in high-risk patients, the SPACE (Stent-supported Percutaneous Angioplasty of the Carotid artery versus Endarterec-
and death (9.6%) is substantially higher than in other randomized trials. Therefore, it is hard to accept such an elevated complication rate as representative of the practice of CAS in general. It is more likely that EVA-3S emphasizes the importance of embolic protection as well as rigorous training and credentialing for CAS physicians. The implied importance in EVA-3S of embolic protection has been further supported by numerous radiologic studies examining the frequency of (mostly small, asymptomatic) ischemic (DWI [diffusion-weighted imaging]) lesions on post-operative magnetic resonance imaging. These studies have demonstrated the following: a reduction in the frequency of DWI lesions with distal embolic protection (49% vs. 67%) (48) and fewer DWI lesions after CEA than CAS (11.6% vs. 42.6%, no significant clinical difference) with current embolic protection devices (56), and a low frequency of DWI lesions with more recent embolic protection devices, such as the NeuroProtection System (W.L. Gore & Associates, Flagstaff, Arizona) (57), at a rate not significantly different than that incurred by diagnostic cerebral angiography alone (18.2% vs. 11.5%) (58).

Carotid registries (CABERNET [Carotid Artery Revascularization using the Boston Scientific FilterWire EX/EZ and the EndoTex NexStent], ARChER [ACCULINK for Revascularization of Carotids in High-Risk patients], CREATE [Carotid Revascularization with ev3 Arterial Technology Evolution], CAPTURE [Carotid Acculink/Accunet Post Approval Trial to Uncover Unanticipated or Rare Events], BEACH [Boston Scientific EPI: A Carotid Stenting Trial for High-Risk Surgical Patients], CASES-PMS [Carotid Artery Stenting with Emboli protection Surveillance—Post Marketing Study], and ALKK [Arbeitsgemeinschaft Leitende Kardiologische Krankenhausarzte]) are nonrandomized outcome records for symptomatic and asymptomatic high-risk CAS patients. Although registries do not provide direct comparison data, they do help establish true adverse event rates in high-risk CAS patients and are a crucial component in improving our understanding concerning the risks of CAS. The collaborators of CABERNET (n = 462 patients) found a 3.9% 30-day rate of stroke or death (59), whereas the investigators of ARChER (n = 581 patients) found a 30-day stroke or death rate of 6.9% as well as a 1-year composite outcome (30-day rate of MI, stroke, or death plus the 1-year rate of ipsilateral stroke) of 9.6% (60). The CREATE registry (n = 419 patients) demonstrated a 6.2% 30-day rate of MI, stroke, and death (61). The CAPTURE registry (n = 3,500) determined that post-CAS incidence of stroke, MI, and death was 6.3% for patients treated with the Acculink/Accunet CAS system (Abbott Vascular, Santa Clara, California), as well as a rate of major stroke or death of 2.9% (62,63). The BEACH investigators (n = 747 patients) found a 30-day MI, stroke, or death rate of 5.8% (64). These results were similar to those in the CASES-PMS registry (5.0%), which examined the use of distal protection by endovascular carotid surgeons who either had previous experience with the device (Angioguard XP, Cordis Endovascular, Miami Lakes, Florida) or who underwent formal training (n = 1,493) (65). Under these rigorous conditions, the 30-day major adverse event rate did not vary significantly between symptomatic and asymptomatic patients and among physicians with high- and low-volume or differing level of experience with the specific distal protection device. The German ALKK registry (n = 1,888 patients), which included patients with standard risk, demonstrated an in-hospital death and stroke rate of 3.8% (66). Interestingly, when this risk was stratified by time, the investigators saw improvement from 6.3% in 1996 to 1.9% in 2004 (p = 0.021). Continued effort to maintain rigorous registries like the above are critical to our eventual understanding of appropriate patient selection and procedural risks.

Current Trials

The 2 major ongoing, randomized trials of CAS versus CEA are CREST (Carotid Revascularization Endarterectomy versus Stent Trial) and ICSS (International Carotid Stenting Study). The CREST trial is an ongoing, National Institutes of Health-funded, multicenter randomized trial seeking to enroll 2,500 patients with >50% symptomatic carotid stenosis or >70% asymptomatic stenosis for randomization to CEA or CAS. Primary end points include death, stroke, or MI at 30 days, and ipsilateral stroke within 60 days. The CREST trial maintains a rigorous credentialing phase for CAS providers (67), requiring up to 20 monitored procedures. During its lead-in phase, CREST demonstrated a 4.6% 30-day stroke and death rate, with MI, stroke, and death rates of 5.7% for symptomatic patients and 3.5% for asymptomatic patients. Similar stroke and death rates were observed for both men and women (68), as well as those treated with or without embolic protection (69). However, patients ≥80 years (70,71) experienced a 30-day stroke and death rate of 12.1%, significantly higher than for patients age 60 to 69 years (1.3%) and 70 to 79 years (5.3%) (p = 0.0006) (70).

The ICSS study resulted from the favorable results of CAVATAS and is also known as CAVATAS-2 (72). It is a multinational prospective trial randomizing symptomatic patients equally suited for CAS or CEA. Additionally, lessons learned from EVA-3S are being applied. Attendance at a CAS training course is required, as well as mandatory proctoring for centers with limited experience admitted to the trial on a probationary status. Further, embolic protection is recommended whenever the endovascular physician believes a protection device can be safely deployed.

An additional ongoing study is ACT I (Asymptomatic Carotid Stenosis, Stenting versus Endarterectomy Trial), a randomized trial of low-risk patients with asymptomatic 80% to 99% carotid stenosis at multiple centers across North America (73,74). The primary outcomes will be 30-day MI, stroke, and death rates and 5-year stroke-free survival. The TACIT (Transatlantic Asymptomatic Carotid Intervention Trial) will randomize standard- and high-risk patients with asymptomatic carotid stenosis into 1 of 3 treatment arms:
optimal medical therapy only (antiplatelet, antilipidemic, antihypertensive, strict diabetes control, and smoking cessation), optimal medical therapy plus CEA, or optimal medical therapy plus CAS with embolic protection (75,76). Planned enrollment is 2,400 patients with a primary end point of stroke and death occurrence at 3 years. Secondary end points include rates of TIA and MI, economic cost, quality-of-life analysis, neurocognitive function, and carotid restenosis. Continued effort and the eventual completion of these trials will improve our understanding of the relative indications and contraindications of CAS and CEA.

Optimal Treatment Selection

Given the existence of surgical and endovascular therapies for patients with carotid stenosis, optimal treatment selection for each given patient will be the eventual method by which the lowest morbidity rates with the most favorable outcomes are achieved. Fundamental to treatment selection is an understanding of the demographics used to categorize patients as high risk. High-risk demographics are previously defined in large surgical studies, such as NASCET (1) and ACAS (5). These demographic criteria include:

Anatomical: 1) restenosis after CEA; 2) contralateral occlusion; 3) previous neck radiation or surgery; 4) surgically inaccessible lesions (e.g., located above the C-2 level, below the clavicle); 5) neck immobility; 6) tracheostomy; 7) contralateral laryngeal palsy; 8) bilateral severe stenotic lesions requiring treatment; and 9) severe intracranial stenosis.

Medical comorbidities: 1) unstable angina; 2) poor cardiac ejection fraction; 3) congestive heart failure; 4) planned coronary artery bypass operation; 5) obstructive pulmonary disease; and 6) advanced age (>75 or 80 years, depending on the trial).

Given the continually mounting evidence, it appears appropriate to offer CAS over CEA to all patients meeting the above high-risk categorizations, symptomatic or asymptomatic. However, whether patients do or do not strictly meet the above criteria, other characteristics need to be taken into account. For instance, patients with heavily calcified plaques, a complex aortic arch, excessively tortuous vessels, or internal carotid arteries with lumen diameters smaller than 3 mm are likely better served with endarterectomy (77–85). This is because heavily calcified plaques often result in insufficient endovascular revascularization secondary to their being refractory to balloon remodeling; loops and significant vessel tortuosity make stable guide catheter placement as well as filter and stent deployment excessively difficult, and lumen diameters smaller than 3 mm do not safely accommodate most distal protection devices.

Conclusions

Carotid artery stenting is continually developing into a safer and more efficacious therapy for extracranial carotid artery stenosis. The greater weight of the evidence, as confirmed in a Cochrane review (86), suggests no significant difference between CAS and CEA. However, CAS is still a burgeoning technology with many questions still needing to be answered. Future clinical research should address many of these questions. As we move towards the future, the question posed should now be “what is the optimal treatment for carotid artery stenosis in this patient?” not “what is the optimal treatment for carotid artery stenosis?” Endovascular physicians must rigorously apply the lessons learned from previous well-designed trials to avoid treating patients who are at higher risk for complications with CAS. Continued enrollment in rigorously randomized trials such as CREST will provide a great deal of insight into such patient-specific risk factors. The use of CAS and CEA as complementary therapies, while optimizing current medical treatments, will provide the greatest likelihood of minimizing poor patient outcomes.

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