Carotid Artery Stenting: Evidence-based Treatment

Robert D. Ecker, M.D., Elad I. Levy, M.D., and L. Nelson Hopkins, M.D.

INTRODUCTION

On August 31, 2004, the Food and Drug Administration (FDA) announced their approval of the first carotid artery stenting (CAS) system for use in patients with 50% or greater symptomatic and 80% or greater asymptomatic carotid stenosis who were viewed by the treating surgeon as high-risk for carotid endarterectomy (CEA) because of anatomic risks or medical comorbidities.[12,13] On March 17, 2005, the Centers for Medicare and Medicaid Services (CMS) approved coverage for symptomatic patients with 70% or greater stenosis considered at high risk for CEA in the opinion of a surgeon.[7,8] With these two decisions, CAS entered the clinical arena as a legitimate alternative to CEA. Worldwide, most carotid interventions are performed by cardiologists.[26] In the United States, the majority of CEAs are performed by vascular surgeons whose fellowship guidelines now require endovascular training.[9] To be involved in the management of patients with carotid artery disease in the future, neurosurgeons will need to receive training in both open surgical and endovascular approaches.

Currently, there are two FDA-approved carotid stents available, the Acculink (Guidant, Santa Clara, CA) and the Xact (Abbott Vascular, Redwood City, CA) and three FDA-approved distal embolic protection (DEP) devises, the Accunet (Guidant), the EmboShield (Abbott Vascular), and the Spider filter (ev3, Plymouth, MN). Approval of devices manufactured by Cordis (Miami Lakes, FL) and Boston Scientific (Natick, MA) is expected soon. In addition to filter devices used for DEP, there are two other embolic protection strategies, proximal occlusion and flow reversal (*Table 23.1*). Unlike CEA, there are numerous industry stakeholders in CAS. A recent New York Times article commenting on the approval of the Abbott stenting sytem predicted that the CAS market could be $1 billion.[11]

Although CAS is almost certainly going to eclipse CEA in the coming years as the treatment of choice for carotid occlusive disease, CAS and CEA remain complementary techniques in 2005. Patients who fit the strict criteria of the Asymptomatic Carotid Atherosclerosis Study (ACAS)[10] and the North American Symptomatic Endarterectomy Trial (NASCET)[1,23] are likely best served by CEA. High-risk patients with exclusion criteria that would have kept them from inclusion in ACAS and NASCET are best served by CAS. A 60-year-old woman with symptomatic carotid artery disease and no significant medical comorbidities is an excellent CEA candidate. The long-term durability of CEA is known for a patient with likely at least two decades more of life. An 80-year-old patient with a type III aortic arch, an occluded external carotid artery, and lesion tortuosity is also better served by CEA, given the complicated access for CAS. However, a patient with significant coronary artery disease who is treated for carotid artery stenosis after coronary artery bypass grafting is served better by CAS, as is a patient with tandem carotid stenotic lesions with the second lesion at the cranial base.

The ideal study design for CAS, as delineated by the Carotid Revascularization versus Stent Trial (CREST) investigators[15] would 1) be multicenter, prospective, and randomized; 2) clearly define signs and symptoms of neurological events; 3) standardize the training of operators to negate the affect of learning curves; 4) provide for long-term enrollment and follow-up to demonstrate statistical equivalency; and 5) assuming a 5% major adverse event (MAE) rate with CEA and less than 2% difference between CEA and CAS, would need to enroll 3000 patients. Until the completion of CREST, this study does not exist. CAS technology and techniques are evolving and improving, making a direct comparison with CEA difficult. This review will address the current best clinical data regarding the safety, efficacy, and durability of CAS, including the high-risk registries, the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial, the Carotid Revascularization using Endarterectomy or Stenting Systems (CaRESS) trial, CREST, the Asymptomatic Carotid Stenosis Stenting versus Endarterectomy Trial (ACT I), the University at Buffalo experience, the European experience, and a brief comment on cognitive outcomes after CEA and how this may apply to CAS.

HIGH-RISK REGISTRIES

Before the introduction of embolic protection techniques, the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS)[6] and the Endarterectomy ver-

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TABLE 23.1. Embolic protection strategies

	Sponsor/Company	Target Vessel Size
Filter		
Accunet	Guidant	3.25–7.0 mm
Angioguard	Cordis	3.5–7.5 mm
Embolic Protection Inc. (EPI)	Boston Scientific	3.5–5.5 mm
Filterwire EX, EZ		
EmboShield	Abbott	3.5–6 mm
ev3	Spider	3.0–7.0 mm
Interceptor	Medtronic	4.25–6.25 mm
NeuroShield	Mednova	2.8–6 mm
Balloon occlusion		
Percusurge Guardwire	Medtronic	3.5–5.5 mm
TriActiv System	Kensey Nash	3.0–5 mm
Flow reversal		
Parodi Anti-Embolic System	W.L. Gore & Associates	3.5–5.5 mm

sus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S)[21] were performed, which demonstrated unprotected CAS as inferior to CEA with respect to morbidity and mortality and durability. In fact, the first randomized trial comparing CAS and CEA was halted because of the high complication rates.[22] The high-risk registries marked a stepping-off point for the age of DEP in CAS. A list of these industry-sponsored CAS registries for patients considered high-risk candidates for CEA is provided in *Table 23.2*. High-risk criteria for most of these registries included the standard ACAS and NASCET exclusion criteria. Patients with symptomatic disease and more than 50% stenosis and those with more than 80% asymptomatic stenosis were entered in all registries except Carotid Artery Revascularization Using the Boston Scientific FilterWire EX/EZ and the Endo-Tex NexStent (CABERNET)[19] and Carotid Revascularization with ev3 Arterial Technology Evolution (CREATE).[24] CABERNET dropped the asymptomatic threshold to a stenosis severity of 60%, and CREATE allowed 70%.

The major difference in these registries is the use of different stents and DEP devices. The overall 30-day morbidity and mortality ranged from 3.9% in CABERNET[19] (Boston Scientific: EPI filterwire, NexStent) to 8.3% in ACCULINK for Revascularization of Carotids in High-Risk Patients (ARCHeR)[14] (Guidant: Acculink, Accunet) (*Table 23.2*). The 1-year follow-up data has been presented for CABERNET, Boston Scientific EPI: A Carotid Stenting Trial for High-Risk Surgical Patients (BEACH), and ARCHeR 1 and ARCHeR 2, with CABERNET at a morbidity and mortality rate of 4.5% and ARCHeR 2 at 10.2%.[14,18,19] At 30 days and 1 year, CABERNET has had a lower morbidity and mortality rate than the other trials, which is attributable at least in part to patient selection. Operators who treated patients felt to be anatomically at high-risk for CAS were removed from the study if they persisted in treating this population (LN Hopkins, personal communication, October 2005). It should be remembered that reported morbidity and mortality rates in CAS trials include myocardial infarction (MI), which was not part of the NASCET and ACAS reporting. Although the composite morbidity and mortality in the

TABLE 23.2. High-risk registries[a]

Trial	Stent	DEP device	Sample size	Composite 30-day MAE	Status
ARCHeR	Acculink	Accunet	581 (phases I–III)	8.3%	Closed
BEACH	Wallstent Rx	Filterwire EX	480 (400)	5.4%	Closed
CABERNET	NexStent	EPI Filterwire EX/EZ	443	3.9%	Closed
CREATE	Protége	Spider	400	N/A	Closed
MAVErIC	Medtronic AVE self-expanding stent system	Guardwire	99 (I)	MAV I–5.1%	Closed
		Plus	399 (II)	MAV II–5.3%	Closed
		(Interceptor Plus in Phase III)	N/A (III)	N/A	Ongoing
PASCAL	Medtronic AVE	Any approved device	115	8%	N/A
SECURITY	Xact	Neuroshield, now EmboShield	320	7.2%	N/A
SHELTER	Wallstent Rx	Guardwire Plus	400	N/A	N/A

[a]MAE, major adverse event rate (death/stroke/MI); N/A, not available; MAVErIC, Evaluation of the Medtronic AVE Self-Expanding Carotid Stent System with Distal Protection In the Treatment of Carotid Stenosis; PASCAL, Performance And Safety of the Medtronic AVE Self-Expandable Stent in Treatment of Carotid Artery Lesions; SECURITY, Study to Evaluate the Neuroshield Bare Wire Cerebral Protection System and X-Act Stent in Patients at High Risk for Carotid Endarterectomy; SHELTER, Stenting of High risk patients Extracranial Lesions Trial with Emboli Removal.

high-risk registries exceed the standards set by NASCET and ACAS at 6% for symptomatic patients and 3% for asymptomatic patients, the expected composite rate for historical controls in this high-risk population exceeds 14%. The high-risk registries, although not controlled randomized studies, have shown that a morbidity/mortality rate better than that achieved in historical standards could be achieved in select high-risk patients.

SAPPHIRE

In October of 2004, in the awkward language of the FDA, the investigators of the SAPPHIRE trial concluded, "Among patients with severe carotid-artery stenosis and coexisting conditions, carotid stenting with the use of an emboli-protection device is not inferior to carotid endarterectomy."[28] In combination with the ARCHeR trial data, the results of the SAPPHIRE trial led to the approval of CAS by the FDA. SAPPHIRE was a randomized trial that compared CAS with DEP and CEA in a high-risk patient population with symptomatic stenosis of at least 50% and asymptomatic stenosis of at least 80%. The CAS package was the Angioguard or Angioguard XP and the Smart or Precise stent (Cordis). During the study period, 747 patients were enrolled, and 344 underwent randomization. Primary end points included a composite of death, stroke, and MI within 30 days and death or ipsilateral stroke at 31 days and 1 year.

At 1 year, 12.2% of patients undergoing CAS had reached the primary end point versus 20.1% of the CEA group (P value for superiority, 0.053; P value for lack of inferiority, 0.004). Revascularization occurred in 4.3% of the CEA group versus 0.6% of the CAS group ($P = 0.04$). Looking at secondary end points at 1 year, CAS was superior to CEA with respect to MI (2.5% CAS versus 8.1% CEA; $P = 0.03$) and major ipsilateral stroke (0% CAS versus 3.5% CEA; $P = 0.02$). The 3-year follow-up data for SAPPHIRE has been presented.[27] At 3 years, the overall MAE rate (30.3% CEA, 25.5% CAS; $P = 0.20$) and incidence of death (24.2% CEA, 20.0% CAS; $P = 0.280$), ipsilateral stroke (7.1% CEA versus 6.7%; $P = 0.945$), and target lesion revascularization (7.1% CEA versus 3.0% CAS; $P = 0.084$) all favor CAS over CEA, but not to statistical significance. In addition, the SAPPHIRE investigators have calculated the absolute percentage of stroke (all strokes to 30 days and major ipsilateral strokes from 31 to 1080 days) in three categories: all randomized patients (3.6% CEA versus 3.5% CAS), randomized symptomatic patients (3.2% CEA versus 5.0% CAS), and randomized asymptomatic patients (3.8% CEA versus 2.9% CAS). The new data suggest the continued "lack of inferiority" of CAS over CEA in this high-risk population. With respect to stroke morbidity, this data suggest that asymptomatic patients are slightly better served by CAS and symptomatic patients by CEA.

Criticisms of and rebuttals for the SAPPHIRE trial abound. 1) Fewer than 30% of the patients were symptomatic. Nationally, approximately one-third of patients receiving treatment for carotid artery disease are symptomatic; so the SAPPHIRE trial was representative of the patient population treated in the United States today. 2) Of the 400 patients who were not randomized, only 7 underwent CEA. This suggests a bias toward stenting, but this is a high-risk population in which CEA is known to carry a composite morbidity and mortality exceeding 6%. 3) On the basis of NASCET and ACAS, the population of patients treated did not benefit. It must be remembered that this is a non-NASCET, non-ACAS population, which makes this kind of extrapolation unreliable. 4) The lead author invented the filter device used. Although this is certainly true and such conflicts of interest in modern medicine are not rare, the data for SAPPHIRE was warehoused and analyzed by independent reviewers. At 3 years, the bottom line is that in the high-risk patients studied and with the end points chosen, CAS was not inferior to CEA in MI, stroke, and target lesion revascularization. Because of patient preference alone, clinical equipoise between CAS and CEA equals superiority of CAS. The results of the SAPPHIRE trial provide some of the best available evidence to support equipoise.

CaRESS

CaRESS is a multicenter, nonrandomized, prospective study comparing CAS with DEP and CEA.[4,5] Importantly, the choice of CEA versus CAS was left up to the treating physician. In this way, the CaRESS study likely represents a more "real-world" perspective on carotid intervention. Symptomatic patients with greater than 50% stenosis and asymptomatic patients with greater than 75% stenosis were considered for treatment. The primary end point was all-cause mortality at 30 days and 1 year. Secondary end points included composite 30-day all-cause mortality or stroke, residual stenosis, restenosis, repeat angiography, and carotid (target lesion) revascularization at 30 days and 1 year, and quality of life changes at 1 year.

Reviewing the demographics of the CaRESS study population, the only statistically significant difference was that more patients who had undergone previous CEA and CAS were included in the CAS cohort. Surprisingly, many high-risk criteria in other studies—including contralateral stenosis, coronary artery disease, and congestive heart failure—were not statistically significantly different between treatment groups. The lack of statistical significance in the primary outcome of this study suggests that the treating physicians were able to triage these high-risk groups successfully.

The results of the CaRESS study showed no statistically significant differences between CAS and CEA for death or stroke at 30 days (2.1% CAS versus 3.6% CEA) or 1 year

(10.0% CAS versus 13.6% CEA). Reviewing the rate of death/stroke/MI at 30 days (2.1% CAS versus 4.4% CEA) and 1 year (10.9% CAS versus 14.3% CEA), there was also no statistically significant difference. Looking at secondary end points, restenosis (6.3% CAS versus 3.6% CEA), residual stenosis (0.9% CAS versus 0.0% CEA), repeat angiography (3.6% CAS versus 2.1% CEA), and carotid revascularization (1.8% CAS versus 1.0% CEA), there was no statistical difference in treatment groups. In summary, in a "real-life" setting, CAS exhibited a trend toward lower morbidity and mortality than CEA but seemed slightly less durable at 30 days and 1 year. Importantly, the morbidity and mortality overall approached the range of the ACAS and NASCET figures, with a significant percentage of high-risk patients.

CREST

As of October 2005, more than 700 patients have been enrolled in CREST. In the lead-in phase, the MAE for symptomatic patients was 5.7% and 3.5% for asymptomatic patients. Asymptomatic patients were not included initially in this randomized study but have been enrolled since January of 2005. The conclusion of enrollment and the global statistical analysis are anxiously awaited.

LOW-RISK TRIAL

The Asymptomatic Carotid Stenosis, Stenting Versus Endarterectomy Trial (ACT I) is currently ongoing and is enrolling low-risk patients with asymptomatic stenosis. The devices used in this trial are the EmboShield DEP and the Xact stent (Abbott Vascular). The randomization is 3:1 for CAS to CEA. Studies like ACT I will likely lead to the broader application of CAS in nearly all carotid interventions if CAS is found either equal to or superior to CEA.

THE UNIVERSITY AT BUFFALO NEUROSURGERY EXPERIENCE

At the University at Buffalo, the same neurosurgeons perform both CEA and CAS. All cases are reviewed by at least three surgeons who perform both procedures; and CAS, CEA, or continued observation is recommended. We hypothesized that patient selection should be idealized in the practice setting where surgeons perform both procedures and, therefore, morbidity and mortality lowered. We then compared the results of 129 CAS procedures in 123 patients with 100 CEA procedures performed in 95 patients. Seventy-eight percent undergoing CAS would have met the trial criteria for high-risk patients. Using the NASCET and ACAS standards and not including MI, the 30-day composite incidence of death and stroke was 2.4% for CAS and 1.1% for CEA. Including MI, these figures increase to 3.3% for CAS and 3.2% for CEA. Confirming the CaRESS data, at the University at Buffalo, we were able to achieve the NASCET and ACAS 30-day composite rates of morbidity and mortality in our patients including in 78% of CAS patients who would not have qualified for enrollment in either of these studies.

THE EUROPEAN EXPERIENCE

The Imaging in Carotid Angioplasty and Risk of Stroke (ICAROS) trial[2] and the European Long-term Carotid Artery Stenting (ELOCAS) registry[3] are both worth reviewing in the smorgasbord of material available on evidence-based carotid stenting. Other than the categories in the Sundt risk classification for CEA (*Table 23.3*),[25] little formal guidelines are available to inform the interventionist on which lesions are higher risk for CAS. The ICAROS investigators looked to establish whether gray-scale median (GSM; a computer-generated score of the echolucency of the plaque on B-mode

TABLE 23.3. Sundt classification of CEA risk[a]

Classification	Definition
Group 1	Neurologically stable patients with no major medical and no angiographically defined risks, with unilateral or bilateral ulcerative-stenotic CA disease
Group 2	Neurologically stable patients with no major medical risks, but with significant angiographically defined risks
Group 3	Neurologically stable patients with major medical risks with or without significant angiographically defined risks
Group 4	Neurologically unstable patients with or without associated major medical or angiographically defined risks
Medical risk factors	Angina pectoris, MI of <6 mo duration, congestive heart failure, severe obesity, chronic obstructive pulmonary disease, age >70 yr
Neurological factors	Progressive neurological deficit, deficit of <24 h duration, frequent daily TIAs, multiple cerebral infarctions with deficits
Angiographic factors	Occlusion of contralateral ICA, ICA siphon stenosis, evidence of a soft thrombus from an ulcerative lesion

[a]CA, carotid artery; TIA, transient ischemic attack; ICA, internal carotid artery (adapted from Sundt TM, Sandok BA, Whisnant JP: Carotid endarterectomy. Complications and preoperative assessment of risk. **Mayo Clin Proc** 50:301–306, 1975 [25]).

ultrasound imaging) score is predictive of stroke during and after CAS.[2]

The results of the ICAROS study showed that GSM scores of less than 25 (representing echogenic plaque) are associated with higher embolic potential. The investigators created a prospective registry of 418 CAS cases from 11 centers and recorded GSM scores preprocedurally. Eleven (7.1%) of 155 patients with GSM less than or equal to 25 had strokes, versus 4 (1.5%) of 263 patients with GSM greater than 25 (P value of 0.005). Carrying this one step further, the authors validated the use of DEP in patients with GSM greater than 25 ($P = 0.01$) but not in those with GSM at most 25.

The ELOCAS registry is a 5-year follow-up study of more than 2100 patients who have undergone CAS at high-volume centers in Europe.[3] At 1, 3, and 5 years, the stroke/death rates were 4.1%, 10.1%, and 15.5%, respectively. Although not a prospective, randomized, controlled study, the ELOCAS registry provides the best available long-term evidence for the long-term safety of CAS in the age of DEP. More than 85% of the registry patients underwent stenting with DEP. In addition, the ELOCAS registry, CaRESS study, and the University at Buffalo experience all show that outcomes for CAS can be achieved on a par with those for NASCET and ACAS.

COGNITIVE OUTCOMES AND CEA

The available data on cognitive outcomes after CEA is not conclusive but raises important issues for patients with carotid occlusive disease. Perceived cognitive changes after CEA are thought to be related to either embolic phenomena or clamp time. CAS with DEP does not interrupt flow, but embolism can still occur both intraprocedurally and periprocedurally. Heyer et al.[16] reported on 112 patients with at least 70% stenosis who underwent CEA. Formal neuropsychometric studies were performed at 1 and 5 months preoperatively. These investigators found that 80% of patients had a decline in one or more test score, and 60% of patients had one or more improved test score. With subsequent follow up, the percentage of declined scores decreased and the percentage of improved scores increased. In a follow-up study, Heyer et al.[17] reported on neuropsychometric testing in 80 patients undergoing CEA compared with 25 age-matched control patients undergoing lumbar spine surgery. Formal cognitive testing was performed preoperatively and at 1 and 30 days postoperatively. Subtle cognitive deficits persist for several weeks after CEA that were absent in the control group.

More recently, Johnston et al.[20] evaluated 4006 right-handed men and women at least 65 years of age without a history of stroke, transient ischemic attack, or CEA. Carotid stenosis was studied with duplex imaging in each patient. A stenosis severity of 75% qualified patients for inclusion in the high-grade group. Cognitive impairment was defined as a Modified Mini-Mental Status (MMMS) examination score of less than 80. Cognitive decline was defined as an average decrease of more than 1 point annually in the MMMS during up to 5 years of follow-up. All patients were studied with MMMS at the time of admission to the study. Although the study population consisted of a small cohort of 32 patients, high-grade left carotid artery stenosis was associated with both cognitive impairment and cognitive decline. The work of Johnston et al., in combination with the CEA studies conducted by Heyer et al., hints that a cognitive benefit is associated with carotid revascularization. Studies need to be performed comparing the cognitive outcomes of CEA with CAS to determine whether there is any difference between these two revascularization strategies.

CONCLUSIONS

In 2005, CAS and CEA are complementary techniques. In patients deemed high risk for CEA, CAS has become the "gold standard." The results of low-risk trials will show whether CAS is appropriate for minimal-risk patients with carotid stenosis. The CaRESS and ELOCAS studies, in concert with a review of our own experience, have shown that morbidity and mortality for CAS with DEP on a par with NASCET and ACAS can be achieved in cohorts that include a significant portion of high-risk patients, even though the acceptable morbidity and mortality for carotid intervention in these patients is unknown because most would not have been entered into NASCET or ACAS. Technological applications, such as the GSM score, and further development of CAS devices, including proximal protection strategies, will improve outcomes in patients with a high burden of necrotic plaque and thrombus. Cognitive outcomes need to be rigorously studied in patients undergoing CAS and CEA. Cerebrovascular neurosurgeons of the future will need to be dual trained in CAS and CEA.

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