Carotid Stenting for Asymptomatic Carotid Stenosis

Trial It

Colin P. Derdeyn, MD

Angioplasty and stenting should not be performed for patients with asymptomatic atherosclerotic carotid bifurcation stenosis, except in the context of randomized clinical trials. Surgical carotid endarterectomy (CEA) has been proven effective over medical therapy in select asymptomatic patient populations. The benefit in these patients is small and easily overcome by procedural complication rates over 3%, owing to the relatively low risk for stroke on medical therapy. Until a randomized controlled clinical trial demonstrates reasonable equivalence of carotid angioplasty and stenting (CAS) to CEA for stroke risk reduction in asymptomatic low-surgical risk patients, there is no rationale for its use in this setting. Furthermore, there is no evidence that revascularization by either CEA or CAS is superior to medical therapy for patients that are not good surgical candidates owing to medical comorbidities or anatomic factors. Randomized trials in this high surgical risk patient population must include a medical treatment arm. In this article, we will review the existing data for CAS in patients with asymptomatic atherosclerotic carotid artery stenosis. (Stroke. 2007;38[part 2]:715-720.)

Key Words: angioplasty & stenting  ■ carotid endarterectomy  ■ carotid stenosis  ■ outcomes  ■ randomized controlled trials

A symptomatic stenosis of the extracranial carotid artery is common in North American adults. Population-based studies have found >50% stenosis of at least 1 carotid artery by Doppler ultrasound in 7% of men and 5% of women over the age of 65 years.1 Twenty percent to 30% of patients with prior myocardial infarction or symptomatic peripheral vascular disease have >60% asymptomatic carotid stenosis.2-4

Atherosclerotic carotid stenosis can lead to ischemic stroke. Approximately 10% of patients presenting with stroke have underlying carotid stenosis.5-8 The primary mechanism of stroke in patients with carotid artery stenosis is embolism of atherosclerotic debris or thrombotic material from the plaque into the distal cerebral vasculature.9 Hemodynamic factors are correlated with increased stroke risk in patients with both symptomatic and asymptomatic stenoses.10,11

The surgical removal of this plaque is known as carotid endarterectomy (CEA). This procedure can reduce the risk of future stroke in selected patients, likely as a result of addressing both embolic and hemodynamic mechanisms. The benefit of CEA has been conclusively proven to reduce the risk of future stroke in symptomatic patients12-14 and in selected patients with asymptomatic stenosis.15,16 These clinical trials were generally limited to patients at perceived low risk for periprocedural surgical complications. The risk reduction in asymptomatic patients is small; however, there is a 1% annual absolute risk reduction. In addition, as will be discussed below, this benefit is limited to relatively healthy men.17 The procedure is probably of no benefit in women (Goldstein and Rothwell).

Angioplasty and stenting is a commonly used procedure for the treatment of atherosclerotic stenosis in several arterial territories throughout the body. It is very effective at reducing the degree of arterial narrowing. The procedure involves the crushing of atherosclerotic plaque material against the vessel wall with a high-pressure balloon and the subsequent placement of a metal mesh tube (stent) to hold this material back, prevent elastic recoil, and cover any dissection caused by the angioplasty procedure. This procedure also offers the potential to address embolic and hemodynamic mechanisms of ischemic stroke.

The use of this procedure for carotid bifurcation disease has been increasing, despite very little evidence supporting its value. Advocates of carotid angioplasty and stenting (CAS) cite the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial, a randomized trial of CAS versus CEA in patients at high risk for surgery, as evidence of safety and efficacy for the procedure. The limitations of this study are reviewed in detail in this article. A major issue was the absence of a medical control group. Thirty-day and 1-year outcomes in either group in SAPPHIRE greatly exceeded the natural history risk observed in the medical treatment arms of the large randomized CEA trials. Conclusions regarding the safety and efficacy of CAS cannot be drawn from SAPPHIRE study, nor from many single arm registry studies published to date.
Given the strong evidence of benefit with CEA, CAS has been generally limited to patients with perceived high risk for complications from open surgery.18 Commonly cited factors associated with higher surgical risk have included anatomic factors such as surgically inaccessible lesions, prior endarterectomy or neck irradiation, and medical comorbidities, including severe congestive heart failure, recent unstable angina, recent acute myocardial infarction or unrevascularized >2 coronary vessel coronary artery disease.19 Many of these factors were exclusion criteria for the large surgical endarterectomy trials.15,16

It is critical to note that these factors are associated with a higher risk for complications from CEA, not a higher risk for stroke on medical therapy. The natural history for patients with asymptomatic carotid stenosis and risk factors for a poor surgical outcome is unknown. At present, there is no proven high-risk subgroup that may have a larger magnitude of benefit with CEA. Some preliminary data suggest that asymptomatic patients with hemodynamic impairment or silent emboli by transcranial Doppler are at higher risk for stroke than those without these findings.9,11,20

The application of CAS to asymptomatic patients can be divided into 2 distinct categories: those that are good candidates for CEA and those that are not. In the former group, CAS must be proven equivalent to CEA. In the latter, CAS or CEA must be proven superior to medical therapy. At present, there is no such proof for either application. As a consequence, CAS must be limited to randomized clinical trials designed to provide this proof of efficacy. Some trials are either underway or are being organized. These include the Carotid Revascularization: Endarterectomy versus Stent Trial (CREST) and Carotid Angioplasty and Stenting versus Endarterectomy in Asymptomatic Subjects with Significant Extracranial Carotid Occlusive Disease Trial (ACT I).

**Current Regulatory Issues**

Several stents and protection devices have been approved by the Food and Drug Administration (FDA) for use in high surgical risk patients based largely on nonrandomized registry data. The FDA did not stipulate the symptomatic status of the patient for approval. Payment through the Center of Medical Services (CMS) has been approved for asymptomatic patients with ≥80% stenosis only in the context of clinical trials, including industry-sponsored investigational device exemption (IDE) registries (http://www.cms.hhs.gov/ContractorLearningResources/downloads/JA3811.pdf).

**Good Surgical Candidates**

**Natural History and Outcome With Surgery**

CEA has been proven effective for the reduction of the risk of ischemic stroke in a select population of patients (Table 1). Two large, randomized studies of CEA versus best medical therapy have been completed: the Asymptomatic Carotid Atherosclerosis Study (ACAS)15 and more recently the Asymptomatic Carotid Stenosis Trial (ACST).16 The results were remarkably similar. The risk for ipsilateral ischemic stroke was ≈2% per year with medical therapy and was reduced to ≈1% by CEA.

Analysis of the natural history risk of stroke from asymptomatic contralateral stenosis in the European Carotid Surgery Trial, a trial of CEA for symptomatic carotid stenosis, yielded a similar annual risk of 2%.21 The number-needed-to-treat in ACAS and ACST was 17 and 18, respectively: over 17 patients with asymptomatic carotid stenosis would need to undergo CEA to prevent 1 stroke or death over a 5-year period. It should be noted that this degree of risk reduction is similar to smoking cessation or modest control of hypertension.22–24

The risk of perioperative stroke or death was <3% in both trials. Owing to this perioperative risk and the relatively low risk for stroke with medical therapy, the benefit of CEA becomes significant only after several years after surgery. The crossover of the Kaplan-Meier cumulative hazard curves occurred between 1 and 2 years after surgery. The differences in outcome between the 2 groups became significant only after 5 years of follow-up. For these reasons, CEA should not be performed in centers with surgical complication rates >3% or in patients with less than a 5-year life-expectancy.25

CEA is probably of no benefit for women. The ACST trial reported a benefit with women, but their subgroup analysis was performed as a comparison of outcome in the medical group versus the outcome in the surgical group after the 30-day perioperative period. Perioperative complications were not included in their subgroup analyses. Rothwell and Goldstein extracted the perioperative complication rates for women from data posted on the Lancet website that accompanied the ACST publication.17 They performed a post hoc pooled analysis of the data from ACAS and ACST and found no evidence for benefit in women.17 The physiological basis for this observation is unknown. There were nonsignificant trends for a lower risk of stroke on medical therapy and higher perioperative complication rates in women.17

No significant relationship was found between increasing degrees of stenosis and natural history risk, as is present in patients with symptomatic stenosis.13 Pooled data from the ACAS and ACST studies do not support the hypothesis that patients with >80% stenosis, a common threshold for intervention, are at any greater risk for ipsilateral stroke with medical therapy than those with 60% to 80% stenosis (Table 2). This threshold is largely based on a single-center study of 696 asymptomatic patients that reported a 1.3%
annual risk of stroke for patients with <75% stenosis by Doppler US and a 3.3% annual risk for those with >75% stenosis.26

One possible explanation for the lack of correlation between the degree of stenosis and the risk for stroke on medical therapy may be the relative low frequency of hemodynamic impairment in the asymptomatic population. Patients with asymptomatic stenosis are much less likely to have evidence of hemodynamic impairment, as compared with those with symptomatic stenosis.27 Most patients with asymptomatic stenosis, regardless of degree, have normal hemodynamic status. In fact, asymptomatic patients with complete occlusion of the carotid artery rarely have evidence of hemodynamic impairment.28 The lack of correlation between the degree of stenosis and stroke risk in asymptomatic patients may be related to the low rate of hemodynamic impairment in this population.

Patients over the age of 80 were also excluded from ACAS. Some studies have suggested an increased risk of poor outcome after CEA in this population.29,30

### Outcome With CAS in Low Surgical Risk Patients

There is no data to support the preferential use of CAS over CEA in asymptomatic patients that are good surgical candidates. The few completed randomized studies have been limited to either symptomatic patients31,32 or asymptomatic patients at high risk for surgical complications.19 Most CAS data for asymptomatic patients comes from nonrandomized registries, generally industry-sponsored IDE studies (Table 3). These studies are generally designed to gain approval, not to prove efficacy. The applicability of these data to this population is limited. Many of these studies have been presented at national meetings in abstract form but not published and subjected to peer review. The primary end points for most studies are the 30-day incidence of stroke, death and myocardial infarction. Some studies have also included ipsilateral stroke up to 1 year of follow-up but not beyond. Many have lacked independent adjudication of stroke end points. Most studies have included both symptomatic and asymptomatic patients, with no separate reporting of outcome by symptomatic status. Finally, many of the asymptomatic patients would have been excluded from the CEA trials for high surgical risk. Periprocedural stroke and death rates in these registries are consistently over the 3% bar set in the large CEA trials (Table 3). This complication rate would obviate any benefit with CAS for asymptomatic patients, based on the rates observed in the ACAS and ACST surgical trials. One large National Institutes of Health (NIH)-supported study with independent neurological assessment of outcome in 519 asymptomatic patients with ≥70% stenosis found a 3.7% rate for periprocedural stroke and death.32 The long-term stroke risk reduction remains undetermined, however.

### High Surgical Risk Patients

It is critical to note that this category indicates a high risk for a poor outcome with CEA, not a high risk of stroke with medical therapy (Table 4). The stroke risk with medical therapy for these patients is unknown. Some of the factors that are commonly cited as a high risk for surgery are in fact associated with a low risk of stroke with medical therapy.

### Specific Factors Associated With Increased Risk From CEA

The presence of contralateral carotid occlusion in patients with asymptomatic carotid stenosis is associated with a lower risk of stroke with medical therapy than patients with asymptomatic stenosis and a patent contralateral carotid.33 There was no evidence of benefit of CEA in this population, not because of increased surgical risks but rather lower rates of stroke with medical therapy. The assumption that this patient

### TABLE 2. Relationship Between Degree of Stenosis and Risk of Stroke With Medical Therapy (Pooled From ACAS and ACST)

<table>
<thead>
<tr>
<th>Stenosis</th>
<th>No. with stroke/total No.</th>
<th>Note: degree of stenosis in ACAS was ascertained by catheter angiography in a subset of patients (522) and by ultrasound in ACST.</th>
</tr>
</thead>
<tbody>
<tr>
<td>60%–69%</td>
<td>60/774 (7.8%)</td>
<td>70%–79% 40/541 (7.4%)</td>
</tr>
<tr>
<td>80% or more</td>
<td>28/550 (5.1%)</td>
<td>29,30 Some studies have suggested an increased risk of poor outcome after CEA in this population.</td>
</tr>
</tbody>
</table>

### TABLE 3. Outcome From Selected Completed CAS Registries With Available Data

<table>
<thead>
<tr>
<th>Registry</th>
<th>N</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acculink for Revascularization of Carotids in High-Risk Patients (ARCHeR)</td>
<td>581</td>
<td>30 days stroke/D/MI 8.3% 1 y stroke/D 9.6%</td>
</tr>
<tr>
<td>Boston Scientific EPI: A Carotid Stenting Trial for High Risk Surgical Patients (BEECH)</td>
<td>558 ASx</td>
<td>30 days stroke/D/MI 5.0%</td>
</tr>
<tr>
<td>Carotid Artery Revascularization using Boston Scientific EPI Filterwire EX/EZ and the EndoTex NexStent (CABERNET)</td>
<td>454</td>
<td>30 days stroke/D/MI 3.8%</td>
</tr>
<tr>
<td>Carotid Acculink/Accunet Post Approval Trial to Uncover Rare Events (CAPTURE)</td>
<td>1603</td>
<td>30 days stroke/D/MI 5.1%</td>
</tr>
<tr>
<td>Carotid Revascularization: Endarterectomy vs Stent Trial (CREST)</td>
<td>749</td>
<td>30 days stroke/D 4.4%</td>
</tr>
<tr>
<td>Evaluation of the Medtronic AVE Self-expanding Carotid Stent System with Distal Protection in the Treatment of Carotid Stenosis (MAVeRIC II)</td>
<td>399</td>
<td>30 days stroke/D/MI 5.3%</td>
</tr>
<tr>
<td>Registry Study to Evaluate the NeuroShield Bare Wire Cerebral Protection System and X-Act Stent in Patients at High Risk for Carotid Endarterectomy (SECuRITY)</td>
<td>398</td>
<td>30 days stroke/D/MI 8.5%</td>
</tr>
</tbody>
</table>

*Unpublished; D indicates death; MI, myocardial infarction; d, days; y, years.
population may benefit from CAS owing to a lower perioperative complication rate is not valid.

Patients with severe coronary artery disease requiring coronary artery bypass graft surgery represent a large group with a high risk for perioperative complications from CEA, most frequently myocardial infarction. The prevalence of asymptomatic carotid stenosis in this population ranges from 17% to 30%. The risk of stroke during CABG is increased in patients with asymptomatic carotid stenosis. Simultaneous CABG and CEA is associated with a relatively high complication rate. Whether preoperative CEA or CAS lowers the perioperative risk of stroke remains unknown. Nonrandomized case series and small randomized studies comparing simultaneous to staged procedures have shown similar aggregate rates of stroke, death, and myocardial infarction. The need for a randomized clinical trial in this patient population has been recognized by other investigators.

**Outcome With CAS in High-Surgical Risk Patients**

There is no evidence that asymptomatic patients over the age of 80 are better treated with CAS than with medical therapy. Hobson et al reported the 30-day stroke and death rates for the 745 patients enrolled in the lead-in, on-randomized phase of the Carotid Revascularization Endarterectomy Trial. A significant relationship with age was found, with increasing risk with advancing age. Patients <70 years of age had <2% 30-day stroke and death rates. The rate was 5.1% for patients age 70 to 79 and 12.1% for those 80 and above. These rates were not significantly different after adjustment for symptomatic status. It is unlikely that the natural history risk in these patients will justify intervention.

The SAPPHIRE study was a randomized noninferiority trial comparing CEA to CAS in patients with risk factors for increased rates of surgical complications (Table 4). There was no medical therapy control group. Most of the patients (224 of the 324 randomized patients) were asymptomatic. Asymptomatic patients in this study were required to have ≥80% stenosis. The risk of stroke, death, or myocardial infarction within 30 days of CEA was 10.2%. The 30-day rate for these adverse outcomes after CAS was 5.4%. Reported follow up was obtained out to one year for the occurrence of ipsilateral stroke. Ipsilateral stroke between 30 days and 12 months after the procedure occurred in 10.3% of patients after CEA and 4.5% after CAS. The difference in outcomes in asymptomatic CAS and CEA patients was not statistically significant but reached statistical significance when the data analysis included an additional 100 symptomatic patients.

The aggregate risk at 1 year for periprocedural stroke, myocardial infarction or death and subsequent ipsilateral stroke was 9.9% for CAS patients in SAPPHIRE. These patients were clearly at high risk for surgery, as demonstrated by the outcome observed in the CEA group. However, they may not have been at high risk for stroke on medical therapy. If the risk of stroke on medical therapy in these patients at high risk for surgery is similar to the stroke risk in patients that are good surgical candidates, there would certainly be no benefit with CAS (Figure). Therefore, a randomized trial against medical therapy is necessary.

**Future Research Directions**

**Improvement in Devices**

In addition to randomized trials of CAS versus CEA or medical therapy, there are several other important avenues of research that should be pursued. Advances in stent and protective devices design are necessary. Stent cell design may affect the ability of plaque material to embolize. The incidence of delayed in-stent stenosis is not known and may limit the benefit with CAS. Recent randomized or concurrent nonrandomized cohort studies have shown little significant reduction in the rates of stroke or silent ischemic lesions on diffusion-weighted magnetic resonance images in patients undergoing carotid angioplasty and stenting with and without distal protection devices. It should be noted that the clinical significance of these silent diffusion-weighted imaging lesions is unknown. The efficacy of these devices in capturing embolic debris and the risks of deployment and retrieval may outweigh the benefits in a general population of patients undergoing these procedures.
High Risk (for stroke) Asymptomatic Patients
Advances in patient selection are also necessary. The benefit of CEA is marginal in low surgical risk patients. CAS is unlikely to be superior to CEA in stroke risk reduction, although procedural morbidity and mortality may be lower in certain patient populations. Consequently, specific subgroups of patients with higher risk of stroke on medical therapy need to be identified. Potential approaches include molecular imaging methods to identify atherosclerotic plaque that is likely to be embolic by virtue of morphology or inflammatory constituents,40 transcranial Dopper to identify clinically silent emboli,9,20 and hemodynamic assessment to identify patients with inadequate collateral supply and higher risk of stroke owing to hemodynamic mechanisms.11

Conclusions
Given the proven efficacy of CEA in healthy men with asymptomatic carotid stenosis >60%, the only rational use of CAS in this population is in the setting of randomized trials designed to prove equivalence with CEA. Such trials are underway and should be supported (Table 5). In patients with low surgical risk but no proven benefit from CEA (eg, women, patients with <5 years life-expectancy), there is no role for CAS. It is not reasonable to assume that CAS is safer or more effective than CEA in patients at low risk for surgery. Current randomized trials of equivalency are underway in this population. The use of CAS in patients that are at high risk for surgery should be limited to randomized clinical trials against medical therapy. Nonrandomized registry data will not provide any useful information to help guide therapeutic decisions in this population.

Sources of Funding
This work was supported in part by funding from National Institutes of Health (NIH) grants NS39526, NS35966.

Disclosures
Dr. Derdeyn is a consultant for W.L. Gore and Associates.

References


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Stroke. 2007;38:715-720
doi: 10.1161/01.STR.0000249395.98417.49
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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