Extracranial Carotid Disease Revascularization

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Extracranial carotid artery stenosis is a factor in ≈20% to 30% of all strokes.\textsuperscript{1,2} Revascularization strategies using surgical carotid endarterectomy (CEA) or carotid artery stenting (CAS) offer the possibility of stroke prevention by restoring flow and mitigating the risk for future plaque-associated embolization. Numerous studies have assessed whether these procedures reduce the risk for stroke and improve overall clinical outcome, but many issues and questions remain. The available clinical outcome data have highlighted the differential risk and benefit among symptomatic versus asymptomatic patients, the impact of older age and sex, and the surgical risk for CEA related to either anatomic or medical factors. Likewise, the important issues of operator training and experience and refinement of technique for both CEA and CAS affect the interpretation of clinical trial results and the generalization of these results to broader populations of patients and operators. To what extent other cardiovascular outcomes such as myocardial infarction (MI) and cardiac death should be incorporated into the interpretation of specific clinical trials for stroke prevention is also an important consideration. Finally, the lack of data for comparing contemporary medical therapy with revascularization for reduction of stroke and overall cardiovascular outcomes is a serious shortfall. This review assesses the results of historical and more recent clinical trials of the comparative effectiveness of carotid revascularization in the context of these clinical issues.

Pathogenesis of Stroke Resulting From Extracranial Carotid Artery Stenosis: Role of Medical Therapy

Comparisons between MI and stroke secondary to extracranial carotid artery stenosis are often drawn. Although symptomatic carotid plaques share similarities with vulnerable coronary plaques such as thinned fibrous caps, ulceration, and large necrotic lipid cores,\textsuperscript{3} acute coronary events are related mainly to plaque rupture with secondary thrombosis and may occur frequently in association with only mild or moderate coronary stenosis.\textsuperscript{4} The resultant complete or partial occlusion of the coronary artery leads to downstream infarction resulting from insufficient blood flow or embolic occlusion of the microcirculation. Owing to differences in the cerebral circulation, the complications of carotid stenosis are more often the result of embolic occlusion of intracerebral vessels. The probability of embolic occlusion correlates with the severity of the extracranial stenosis and may also be due to in situ thrombosis from low flow or platelet adherence to plaque constituents.\textsuperscript{5–7}

These subtle differences might be expected to affect the relative benefits of specific medical therapy compared with revascularization strategies. Aspirin therapy lowers the risk for recurrent acute coronary events and is useful for primary and secondary stroke prevention, but it was inferior to CEA when combined with older medical regimens in historical clinical trials.\textsuperscript{5,9} Contemporary intensive blood pressure control and statin therapy may have added benefit in stroke prevention\textsuperscript{10,11} but have not been compared with carotid revascularization in randomized trials.

Comparative Studies of Carotid Revascularization

Comparative data for carotid revascularization are available from older studies of CEA versus medical therapy and more recent studies of CEA versus CAS. The historical randomized clinical trials showed a benefit of CEA over medical therapy for the reduction of stroke and helped to establish CEA as a standard of care for extracranial carotid stenosis\textsuperscript{8,9,12–15} (Table 1). Interpretation of the clinical trial data, however, raises a number of issues concerning the generalizability of the outcomes to current practice, and it is helpful to view the trial results in light of these areas of concern.

Symptomatic Status

Symptomatic status is often defined in clinical trials as a stroke or transient ischemic attack ipsilateral to the carotid stenosis within 180 days before randomization. Among symptomatic patients, CEA provides a significant benefit over older medical therapy for the reduction of ipsilateral stroke during 5 years of follow-up.\textsuperscript{8,12,13} The benefit is large enough that overall death or stroke is also lower for CEA during this interval. The severity of stenosis appears to modify this effect, with an absolute risk reduction in death or stroke for CEA of ≈4%/y for diameter stenosis of 70% to 99% and only ≈1%/y for diameter stenosis of 50% to 69%.

The benefit of CEA compared with medical therapy in the reduction of ipsilateral stroke is also significant among asymptomatic patients.\textsuperscript{9,14,15} The absolute risk reduction,
however, is lower than for symptomatic patients and in general does not translate into a benefit in overall mortality or stroke when the competing risks of cardiac mortality and the impact of contralateral and other stroke types are considered. The effect of stenosis severity is also unclear. The Asymptomatic Carotid Atherosclerosis Study (ACAS) enrolled patients with diameter stenosis of 60% to 99% and found no difference in the relative risk reduction in ipsilateral stroke based on stenosis severity. Although the numbers in each subgroup were small, the risk for stroke and the absolute risk reduction with CEA were actually higher for diameter stenosis of 60% to 69% (6.3% versus 11.4%) than more severe stenosis (2.1% versus 4.9%).9 In contrast, subgroup analysis from the larger Asymptomatic Carotid Surgery Trial (ACST) showed that the benefit of CEA was limited to stenosis severity >70%.15 Whether less severe stenosis in asymptomatic patients may pose higher or lower risk for future embolic stroke or perioperative complications is important because guideline recommendations are stratified by stenosis severity (Table 2).

**Effect of Age and Sex**

Most trials of CEA versus medical therapy excluded patients >80 years of age, so the perioperative risk and long-term risk versus benefit in these patients are unknown. In ACST, the benefit in asymptomatic patients was limited to those <75 years of age.

Female sex modifies the effect of CEA. Among symptomatic patients in the North American Symptomatic Carotid Endarterectomy Trial (NASCET), women had lower risk for stroke with medical therapy and did not have a significant benefit with CEA compared with medical therapy (14% versus 15%).8 For asymptomatic patients in ACAS, women had higher risk for surgical complications (3.6% versus 1.7%) and no benefit for CEA compared with medical therapy for estimated stroke reduction at 5 years (7.3% versus 8.7%).9 Similarly, in ACST, the absolute risk reduction for nonoperative stroke was lower for women than men (4.1% versus 8.2%).15

**Surgical Risk**

Selection criteria for the CEA versus medical therapy trials included patients who were good candidates for CEA from a technical perspective and excluded patients at high risk for cardiac complications. In addition, the operators were experienced and were able to accomplish revascularization with a relatively low risk of perioperative stroke or death. Each of these factors has important implications for the interpretation of the trial findings and generalizing of the results to a broader population of patients and surgeons. For symptomatic patients, it has been estimated that the risk for perioperative stroke or death should not exceed 6% for a benefit similar to that seen in the clinical trials to be expected.16 For asymptomatic patients, this risk should be <3%.9 For more technically complex surgical patients or less experienced surgeons, these thresholds may be exceeded and the anticipated benefit of CEA may not be realized.

The inclusion of only patients with low to moderate preoperative cardiac risk also affects the interpretation of results. It is likely that inclusion of higher-risk patients would not only increase the risk for perioperative mortality but also reduce the benefit in all-cause mortality or stroke owing to competing mortality risk over time. The importance of perioperative MI as an important safety event was also not recognized in the historical trials and likely has implications for assessing the relative benefit of CEA versus medical therapy, as has been shown in other vascular surgery studies and contemporary studies of CEA versus CAS.17,18 The potential effect modification of cardiac risk is expected to be greatest among the large group of asymptomatic patients in whom the relative benefit for CEA and margin for perioperative risk are already lower. Indeed, even among the lower-risk patients in ACAS and the Veteran Affairs Cooperative Study Group trial, there was no benefit for CEA at 5 years in all-cause mortality and all stroke, mostly as a result of the ongoing risk for cardiac death.9,14 Another single-center randomized clinical trial among asymptomatic patients was stopped early because of an excess of MI in the CEA group.19

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**Table 1. Carotid Endarterectomy Versus Medical Therapy Major Clinical Trials: 5-Year Results**

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>n</th>
<th>Symptom Status</th>
<th>Operative Death or Stroke, %</th>
<th>Ipsilateral Stroke, CEA vs Medical (ARR, P)</th>
<th>Death or Stroke, CEA vs Medical (ARR, P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NASCET</td>
<td>2885</td>
<td>Symptomatic</td>
<td>6.7</td>
<td>9.0 vs 26.0* (17.0, P&lt;0.001)</td>
<td>15.8 vs 32.3* (16.5, P&lt;0.001)</td>
</tr>
<tr>
<td>ECST†</td>
<td>3018</td>
<td>Symptomatic</td>
<td>7.5</td>
<td>(18.7, P&lt;0.0001)*</td>
<td>(21.2, P&lt;0.0001)*</td>
</tr>
<tr>
<td>ACAS§</td>
<td>1662</td>
<td>Asymptomatic</td>
<td>2.3</td>
<td>5.1 vs 11.0 (5.9, P=0.004)</td>
<td>25.6 vs 31.9 (6.3, P=0.08)</td>
</tr>
<tr>
<td>ACST</td>
<td>3120</td>
<td>Asymptomatic</td>
<td>2.8</td>
<td>Total not reported</td>
<td>6.4 vs 11.8 (5.4, P&lt;0.0001)</td>
</tr>
<tr>
<td>VA Cooperative</td>
<td>444</td>
<td>Asymptomatic</td>
<td>3.8</td>
<td>4.7 vs 9.4 (4.7, P=0.06)</td>
<td>41.2 vs 44.2 (3.0, P&lt;0.05)</td>
</tr>
</tbody>
</table>

CEA indicates carotid endarterectomy; ARR, absolute risk reduction; NASCET, North American Symptomatic Carotid Endarterectomy Trial; ECST, European Carotid Surgery Trial; ACAS, Asymptomatic Carotid Atherosclerosis Study; ACST, Asymptomatic Carotid Surgery Trial; and VA, Veteran Affairs.

*Results for cohort with 70% to 99% diameter stenosis.
†Results for cohort with 50% to 69% diameter stenosis.
‡Results for ECST based on reanalysis with NASCET criteria. ARR but not event rates per group reported for the 5-year follow-up. Ipsilateral stroke also includes any perioperative stroke or death.
§ACAS was stopped early because of benefit for CEA after 2.7-year median follow-up; 5-year rates were estimated. Ipsilateral stroke includes perioperative stroke or death.
∥Control group were those who deferred CEA (4%/y underwent CEA). Deaths include only perioperative events.
### Table 2. Summary of Recommendations for Carotid Endarterectomy and Carotid Artery Stenting by Medical Society Guideline Writing Groups

<table>
<thead>
<tr>
<th>Guideline Group</th>
<th>CAS Is An Alternative to CEA</th>
<th>CEA May Be Preferred</th>
<th>CAS May Be Preferred</th>
<th>Revascularization Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNSAIP/SCAI/SIR/SNIS/SVM/SVS</strong></td>
<td>Symptomatic patients at low or average surgical risk with 70%–99% stenosis and anticipated rate of perioperative stroke or death &lt;6% (<em>Class I; LOE B</em>)</td>
<td>Asymptomatic patients with 70%–99% stenosis if risk of perioperative death, stroke, or MI is low (<em>Class IIa; LOE A</em>)</td>
<td>Patients with indication for revascularization and unfavorable anatomy for CEA (<em>Class IIa; LOE B</em>)</td>
<td>CAS might be considered in asymptomatic patients with 70%–99% stenosis, but benefit compared with medical therapy alone is not well established (<em>Class IIb; LOE B</em>)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>In symptomatic or asymptomatic patients at high risk owing to medical comorbidities, the benefit of CEA or CAS compared with medical therapy alone is not well established (<em>Class IIb; LOE B</em>)</td>
</tr>
<tr>
<td><strong>European Society of Cardiology</strong></td>
<td>Symptomatic patients at high surgical risk (<em>Class IIa; LOE B</em>)</td>
<td>Symptomatic patients with 70%–99% stenosis for the prevention of recurrent stroke (<em>Class I; LOE A</em>)</td>
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<tr>
<td></td>
<td>Symptomatic patients at low or average surgical risk treated at high-volume centers with documented risk of perioperative stroke or death &lt;6% (<em>Class IIa; LOE B</em>)</td>
<td>Symptomatic patients with 50%–69% stenosis for the prevention of recurrent stroke (<em>Class IIa; LOE A</em>)</td>
<td>Asymptomatic patients with &gt;60% stenosis and life expectancy &gt;5 y treated at high-volume centers with documented risk of perioperative stroke or death &lt;3% (<em>Class IIb; LOE B</em>)</td>
<td></td>
</tr>
<tr>
<td><strong>Society for Vascular Surgery (updated)</strong></td>
<td>Asymptomatic patients with 70% to 99% stenosis only by operators and institutions who have documented risk of perioperative stroke or death &lt;3% (<em>Grade 2; LOE B</em>)</td>
<td>Symptomatic patients with &gt;50% stenosis (<em>Grade 1; LOE B</em>)</td>
<td>Symptomatic patients with &gt;50% stenosis and tracheal stoma, prior ipsilateral surgery or external beam radiotherapy, prior cranial nerve injury, and lesions that extend proximal to the clavicle or distal to the C2 vertebral body (<em>Grade 2; LOE B</em>)</td>
<td>Asymptomatic patients at high risk for CEA should be considered for primary medical management (<em>Grade 1; LOE B</em>)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Asymptomatic patients with &gt;60% stenosis provided life expectancy &gt;3 y and perioperative risk of death or stroke can be &lt;3% (<em>Grade 1; LOE A</em>)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Patients &gt;70 y of age with long (15 mm) lesions, preocclusive stenosis, or lipid-rich plaques and no prior ipsilateral surgery or neck radiation (<em>Grade 1; LOE A</em>)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Symptomatic patients with &gt;50% stenosis and severe uncorrectable coronary artery disease, congestive heart failure, or chronic obstructive pulmonary disease (<em>Grade 2; LOE C</em>)</td>
<td></td>
</tr>
</tbody>
</table>

CEA indicates carotid endarterectomy; CAS, carotid artery stenting; ASA, American Stroke Association; ACCF, American College of Cardiology Foundation; AHA, American Heart Association; AANN, American Association of Neuroscience Nurses; AANS, American Association of Neurological Surgeons; ACR, American College of Radiology; ASNR, American Society of Neuroradiology; CNS, Congress of Neurological Surgeons; SAIP, Society of Atherosclerosis Imaging and Prevention; SCAI, Society for Cardiovascular Angiography and Interventions; SIR, Society of Interventional Radiology; SNIS, Society of NeuroInterventional Surgery; SVM, Society for Vascular Medicine; SVS, Society for Vascular Surgery; and LOE, Level of Evidence.
Comparative Studies of CEA and CAS

The availability of CAS has sparked debate on whether CAS and CEA are equally effective revascularization options for the prevention of stroke and whether CAS may be preferred in some patients who are at higher risk for surgery. Despite the limitations of the historical CEA versus medical therapy trials, comparative studies of CAS have accepted CEA as the standard of care and control therapy. These studies have provided insight into the comparative effectiveness of CAS versus CEA among patients at higher surgical risk and have highlighted the importance of cardiac risk on overall outcomes, but many questions remain from individual studies of patients with standard surgical risk.

CEA Versus CAS in Patients With Increased Risk for Surgery

The Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial randomized 334 patients with carotid stenosis >50% and symptoms or >80% without symptoms who were deemed to be at increased risk for CEA because of medical comorbidity or anatomic factors to undergo CAS with an emboli protection device or CEA.20 The trial was stopped early because of slow enrollment. The primary end point of 30-day death, stroke, MI, ipsilateral stroke, or death from 31 days to 1 year was noninferior for CAS (12.2% versus 20.1%; \(P = 0.053, P = 0.004\) for noninferiority). The numeric difference in favor of CAS was driven by fewer perioperative MI and late deaths, whereas the frequencies of ipsilateral stroke (4.3% versus 5.3%) and any stroke (6.2% versus 7.9%) were similar for CAS versus CEA. The interaction between treatment assignment and symptom status was not significant. By 3 years, the primary end-point composite estimate remained similar whereas the frequencies of ipsilateral stroke (4.3% versus 6.3%) and any stroke (6.2% versus 7.9%) were similar for CAS versus CEA. The Stent-Supported Percutaneous Angioplasty of the Carotid Artery Versus Endarterectomy (SPACE) trial randomized 1200 of a planned 1900 patients before stopping as a result of low conditional power and funding concerns.27 As in EVA-3S, there were substantial differences in operator experience between CEA and CAS. Physicians who had performed as few as 10 CAS procedures could treat patients in the study under the supervision of a tutor.30 Embolic protection devices were used in only 27% of patients. Despite these limitations, the observed 30-day primary end point of ipsilateral stroke or death was similar for CAS and CEA (6.8% versus 6.3%). Unfortunately, these results were interpreted as a failure to meet the prespecified noninferiority margin of 2.5% (risk difference, 0.5%; 90% confidence interval, −1.9–2.9), but in fact, the study had insufficient statistical power to assess noninferiority owing to early termination. It should be noted that among the subgroup (n=255) >75 years of age, there was a larger observed difference in the primary end point for CAS versus CEA (11.0% versus 7.5%).

The interim safety results at 120 days from the randomized International Carotid Stenting Study (ICSS) of 1713 symptomatic, standard-surgical-risk patients showed higher rates of any stroke (7.7% versus 4.1%; \(P = 0.002\)) and death, stroke, or procedural MI (8.5% versus 5.2%; \(P = 0.006\)) with similar low rates of death or disabling stroke (4.0% versus 3.2%; \(P = 0.34\)) for CAS versus CEA.28 Important limitations of this study include the optional use of distal embolic protection (used in 72%), failure to obtain cardiac biomarkers routinely, and allowance of supervised investigators during the randomized phase, leading to suspension of 2 sites owing to a high rate of disabling stroke and death in the CAS group.

The Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) is the largest study of CAS and CEA to date.31 There were several important differences between CREST and the 3 above-mentioned studies. First, CAS investigators in CREST underwent a rigorous credentialing process. In addition to demonstration of clinical experience that included at least 15 prior CAS procedures with a low complication rate and optimal technique, all but 73 (exempted because of high volume and low complication rates) of the 224 operators also performed between 5 and 20 cases during a lead-in study under careful monitoring of an interventional management committee.32 Ultimately, only 52% of CAS investigators who applied to participate were selected for the randomized study. Second, an embolic protection device was required in CREST per study protocol and was used in 96% of CAS patients. Finally, the importance of perioperative MI was recognized and included as a component of the primary end point. Among the 2502 randomized patients, there was no surgical operators of at least 25 CEAs in the prior year. In addition, the protocol requirement for embolic protection devices was added after nearly one third of the subjects were enrolled and an interim analysis had shown a significantly higher risk for stroke among patients not receiving protection. Importantly, perioperative MI was not a part of the primary end point and required a stringent definition of prolonged chest pain or new Q waves in addition to biomarker elevation, thus occurring infrequently after CAS and CEA (0.4% versus 0.8%).
difference for CAS versus CEA in the primary end point of death, any stroke, or MI during the periprocedural period or ipsilateral stroke during the 4-year follow-up (7.2% versus 6.8%; \( P = 0.51 \)). Concern has been raised because the components of the primary end-point composite moved in opposite directions, with MI more frequent after CEA (1.1% versus 2.3%; \( P = 0.01 \)) and stroke more frequent after CAS (4.1% versus 2.3%; \( P = 0.01 \)). Although weighted equally in the composite, quality-of-life analyses suggested a greater impact from stroke than MI. Nevertheless, the occurrence of MI, whether defined by protocol as requiring clinical evidence of ischemia (hazard ratio, 3.40; 95% confidence interval, 1.67–6.92) or by biomarker elevation alone (hazard ratio, 3.57; 95% confidence interval, 1.46–8.68), was associated with an increased risk for subsequent mortality.

CREST was designed initially as a study of symptomatic patients, but because of slow enrollment and changes in clinical practice over time, asymptomatic patients were included later and finally represented 47% of the study population. CREST did not demonstrate a statistical interaction between treatment assignment and symptomatic status for the primary end point. There was, however, an observed difference for perioperative death or stroke between symptomatic (6.0% versus 3.2%) and asymptomatic (2.5% versus 1.4%) patients for CAS versus CEA.

CREST demonstrated a significant interaction between treatment assignment and age resulting from an increased risk for stroke associated with CAS at >70 years of age. For patients at standard surgical risk, the available evidence indicates a slightly higher risk of periprocedural stroke for CAS. This increased risk is small for operators with greater clinical experience and with the routine use of embolic protection and must be weighed against the increased risk for short-term cardiac complications with CEA and the long-term impact of these complications on mortality.

Current Controversies and Future Directions

There are several remaining controversies concerning the future roles of CEA and CAS for patients with carotid stenosis. They include treatment selection among the large group of patients with asymptomatic disease and the relative risk for CEA and CAS in other important subgroups depending on age, sex, anatomy, and other treatment-specific risks. Although society guidelines have attempted to address some of these issues, the absence of consensus has also generated controversy (Table 2).

Asymptomatic Carotid Stenosis

More than 87% of the revascularization procedures performed in the US Medicare population are for asymptomatic disease. This likely represents a small proportion of all individuals with asymptomatic carotid stenosis who would be identified if there were routine screening, which is currently considered reasonable only in those patients with carotid bruit (Class IIA) or could possibly be considered in patients with peripheral vascular disease or ≥2 risk factors for atherosclerosis (Class IIB). These patients are at increased risk for ipsilateral stroke and the cardiovascular outcomes of MI and death. To what extent the presence of asymptomatic carotid stenosis represents a marker of systemic atherosclerosis risk compared with a specific increased risk for stroke and whether carotid revascularization adds relative benefit beyond aggressive medical therapy for risk factor management are simply unknown, and a rigorous test of this comparison is a critical next step in determining the best management strategy. The low risk for perioperative stroke with contemporary CEA or CAS as shown in CREST may support the use of either revascularization strategy, although there is insufficient evidence for a valid comparison of CEA and CAS in this subgroup. The Asymptomatic Carotid Trial I (ACT I) is designed to study this question but faces enrollment challenges.

Benefit of Revascularization in Women and Older Patients

In addition to lesser benefit in women for CEA compared with medical therapy, in CREST, a possible further increase in perioperative events for CAS versus CEA was observed.

Both SPACE and CREST demonstrated a higher risk for stroke among older patients for CAS versus CEA. This is an important question because a study of general practice from the National Inpatient Sample reported that nearly 60% of revascularization procedures are performed in patients >70 years of age. The higher risk of stroke for CAS among older patients may highlight more general concerns of case selection based on anatomic considerations and operator experience. Indeed, 2 large series from high-volume centers with experienced operators have reported low rates of periprocedural stroke for CAS among patients >80 years of age with careful case selection and attention to anatomic considerations of increased tortuosity and calcification.

Representing these subgroups adequately in future studies and addressing the relative risks and benefits of medical therapy versus revascularization and CEA versus CAS become even more important as the population ages and women represent an increasing proportion of patients with new stroke.

Improving Safety of Carotid Revascularization

Both CEA and CAS are associated with lower risk for perioperative stroke in the hands of selected, experienced operators. In the case of CEA, contemporary results for experienced operators and standard-risk patients show low rates of perioperative stroke or death in symptomatic and asymptomatic patients and across subgroups. The anatomic factors associated with increased risk for perioperative stroke after CEA are well defined (Table 3), and it is generally accepted that CAS is preferred in most of these settings (Table 2). Furthermore, the risk for MI and cardiac complications reduces the benefit of CEA in both high- and standard-risk patients. The limitations of CAS are related to an increased risk for periprocedural stroke, and although individual risk factors are less well defined, several factors are clear. Increased tortuosity and calcification of the aortic arch and supraaortic vessels, the presence of thrombus, and lesion length >15 mm increase the risk for embolic complications, and operator experience and use of emboli protection mitigate the increased risk. In all cases, but especially...
Table 3. Conditions Associated With High Risk for Carotid Endarterectomy

<table>
<thead>
<tr>
<th>Anatomic (1 Factor From Below)</th>
<th>Comorbid Clinical Conditions (1 Factor From Below)</th>
<th>Comorbid Clinical Conditions (≥2 Factors From Below)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contralateral carotid occlusion*</td>
<td>Age &gt;80 y</td>
<td>Age ≥75 y</td>
</tr>
<tr>
<td>Previous CEA with recurrent stenosis*</td>
<td>Recent myocardial infarction*</td>
<td>≥2 Proximal or major diseased coronary arteries with ≥70% stenosis that have not been or cannot be revascularized</td>
</tr>
<tr>
<td>Prior radiation treatment to the neck* or radical neck surgery</td>
<td>Congestive heart failure class III/IV*</td>
<td>Planned peripheral vascular surgery or other major surgeries after carotid stenting</td>
</tr>
<tr>
<td>Surgically inaccessible lesion (eg, lesions above the level of C2 or below the clavicle)</td>
<td>Left ventricular ejection fraction ≤30%</td>
<td></td>
</tr>
<tr>
<td>Tracheostoma or tracheostomy</td>
<td>Unstable angina*</td>
<td></td>
</tr>
<tr>
<td>Contralateral laryngeal nerve (cranial nerve IX) palsy or laryngectomy</td>
<td>Dialysis-dependent renal failure</td>
<td></td>
</tr>
<tr>
<td>Tandem lesions ≥70% stenosis</td>
<td>Severe pulmonary disease FEV₁ ≤30% predicted</td>
<td></td>
</tr>
<tr>
<td>At risk for wound infection</td>
<td>Currently on a list for major organ transplantation (ie, heart, lung, liver, kidney) or is being evaluated for such</td>
<td></td>
</tr>
<tr>
<td>Carotid artery dissection</td>
<td>Uncontrolled diabetes mellitus defined as fasting glucose &gt;400 mg/dL and ketones &gt;2+</td>
<td></td>
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<tr>
<td></td>
<td>Spinal immobility: inability to flex neck beyond neutral or kyphotic deformity</td>
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<tr>
<td></td>
<td>Concurrent requirement for aortocoronary bypass or cardiac valve surgery</td>
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</tr>
<tr>
<td></td>
<td>History of liver failure with elevated prothrombin time</td>
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</tbody>
</table>

*High-risk criteria as identified by Center for Medicare and Medicaid Services (CMS). Other criteria from the ACCULINK for Revascularization of Carotids in High-Risk Patients (ARCHER), Boston Scientific EP! A Carotid Stenting Trial for High-Risk Surgical Patients (BEACH), Carotid Artery Revascularization Using the Boston Scientific FilterWire EX/EZ and the EndoTex NexStent (CABERNET), Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy (SAPPHIRE), or Medtronic AVE Self-expanding Carotid Stent System With Distal Protection in the Treatment of Carotid Stenosis (MAVERIC II) studies, which are acceptable to CMS as high-risk criteria for reimbursement.

With more challenging lesions, operator training and expertise are the most important factors and likely account for most of the difference in stroke rates between studies. This is highlighted by a decline in periprocedural stroke rates for clinical trials over time and is supported in the major guideline recommendations (Table 2). More recently, use of a proximal protection device, or flow reversal, has been associated with reduced cerebral embolization assessed by diffusion-weighted magnetic resonance imaging or transcranial Doppler and low risk of stroke in a 1300-patient nonrandomized study. Furthermore, the success of the credentialing process in CREST suggests that CAS outcomes may be improved by a requirement to meet key criteria in volume and experience, and it seems reasonable that any effort to extend carotid stenting to a wider range of operators must be in conjunction with a similar process for training and credentialing.

Cost-Effectiveness and Case Selection

Lower cost is frequently one of the indications for preferring a less invasive treatment strategy. In general, even though endovascular therapies may be associated with slightly higher procedural costs, this is usually more than balanced by reductions in early complications and reduced length of hospital stay. This does not appear to be the case for carotid revascularization in that costs remain higher for CAS compared with CEA in the periprocedural and follow-up periods. This is likely due to a small difference in the length of the index hospitalization and similar rates of early and late events and suggests that factors other than costs should drive patient and societal choices for treatment approaches. One factor is patient-specific benefit versus risk for adverse outcome. Currently, this can be assessed only with modifiers such as stenosis severity and predicted cardiac risk. Future studies must advance our understanding beyond stenosis severity to an analysis of plaque characterization that may improve risk stratification and treatment selection for specific lesions and patients. The risks for other procedure-related complications such as cranial nerve palsy and wound complications must also be considered from an individual-patient perspective.

Conclusions

Both CEA and CAS offer successful revascularization strategies for stroke prevention in patients with atherosclerotic disease of the internal carotid artery. The greatest benefit for stroke reduction is in patients with recent symptoms of transient ischemic attack or ipsilateral ischemic stroke and severe carotid stenosis (≥70%). Less dramatic benefit exists for asymptomatic patients, for whom other factors such as...
peroperative neurological and cardiac risk, age, and possibly sex must be more carefully considered. Both procedures have a low risk for periprocedural stroke among experienced operators, with a slightly higher risk for CAS in symptomatic patients who have standard surgical risk. Certain anatomic factors and medical comorbidities may favor CAS over CEA owing to increased technical difficulty or inaccessibility for CEA or increased risk for cardiac complications with increased risk for periprocedural MI and associated late mortality. Ongoing research and quality improvement efforts to improve the safety of both CEA and CAS and case selection based on clinical and lesion characteristics will likely result in more appropriate use of revascularization and improved outcomes. For CAS, clinical trial and registry data demonstrate a clinically significant reduction in adverse outcomes over a relatively short time, but it seems clear that expanded use should be restricted to centers and operators with technical expertise, volumes, and outcomes that meet certain benchmarks for success. This is especially true for older patients and others with high-risk anatomy for CAS, in whom careful lesion assessment is critical. It is unknown whether contemporary medical therapy may offer the best treatment strategy in many patients, including those who either are asymptomatic or have high-risk features for both CEA and CAS, and future comparative effectiveness studies must incorporate this comparison.

Disclosures

Dr Cutlip has received research support from Medtronic paid to his institution. Dr Pinto has received research support from Covidien paid to his institution.

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Circulation. 2012;126:2636-2644
doi: 10.1161/CIRCULATIONAHA.112.110411
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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