Stroke prevention-surgical and interventional approaches to carotid stenosis

Kumar Rajamani, Seemant Chaturvedi
Department of Neurology, Comprehensive Stroke Program, Wayne State University School of Medicine, Detroit

ABSTRACT

Extra cranial carotid artery stenosis is an important cause of stroke, which often needs treatment with carotid revascularization. To prevent stroke recurrence, carotid endarterectomy (CEA) has been well-established for several decades for symptomatic high and moderate grade stenosis. Carotid stenting is a less invasive alternative to CEA and several recent trials have compared the efficacy of the 2 procedures in patients with carotid stenosis. Carotid artery stenting has emerged as a potential mode of therapy for high surgical risk patients with symptomatic high-grade stenosis. This review focuses on the current data available that will enable the clinician to decide optimal treatment strategies for patients with carotid stenosis.

Key words: Carotid endarterectomy, carotid stenosis, carotid stenting

INTRODUCTION

Patients with anterior circulation ischemic stroke or transient ischemic attack (TIA) should be screened for internal carotid artery (ICA) stenosis. Large vessel atherosclerotic disease accounts for about 20% of all ischemic stroke patients of which about half are due to extra cranial carotid artery stenosis. Patients with hemodynamically significant carotid stenosis should be considered for carotid revascularization, either the well-established surgical procedure of carotid endarterectomy (CEA) or carotid stenting.

For patients who have experienced recent carotid territory symptoms, CEA can be very effective in decreasing the long-term stroke risk, if there is moderate to severe stenosis. Many patients without recent carotid territory symptoms (asymptomatic stenosis) also undergo CEA, although, the benefit is less certain for this group of patients. With advances in medical therapy, the benefits of carotid revascularization for asymptomatic carotid stenosis have come under further scrutiny. Some patients with carotid stenosis are not ideal candidates for surgery due to medical comorbidities (e.g., severe heart or lung disease) or surgical-anatomic factors (e.g., previous surgery or radiation to the neck) and are considered as “high-risk for CEA.” In this group of subjects, carotid artery stenting (CAS) is an alternative to CEA for stroke prevention. In this chapter, we shall review the current data pertaining to CEA and CAS for stroke prevention.

CAROTID ENDARTERECTOMY FOR SYMPTOMATIC CAROTID STENOSIS

Before 1990, CEA had been used as a tool for stroke prevention for many decades without much certainty regarding its benefits. After 2 relatively unsuccessful attempts for a definitive answer to the clinical question of CEA’s value,[1,2] two large-scale randomized studies – the North American Symptomatic Carotid Endarterectomy Trial (NASCET),[3] and the European Carotid Surgery Trial (ECST)[4] – were launched in the 1980s. A third randomized study, the Veterans Affairs Co-operative Study,[5] was stopped early for ethical reasons after the NASCET and the ECST reported a clear benefit in the surgically treated patients.

High-grade symptomatic ICA stenosis

The NASCET and the ECST were pivotal studies that evaluated CEA in comparison with best, prevalent medical therapy for prevention of ischemic stroke in patients with symptomatic carotid stenosis. Patients with ICA stenosis determined by angiography, and previous TIA, non-disabling ischemic stroke in the
ipsilateral hemisphere or retinal ischemic symptoms were included in both randomized control trials. Both studies published an interim report in 1991 and a final report in 1998,[6] and both reported a significant benefit with CEA in patients with high-grade stenosis (i.e., 70-99% occlusion). Pooled analysis combining the 2 studies and data from the Veterans Affairs trial (VA309) found CEA was associated with an absolute risk reduction (ARR) of 16% at 5 years.[7] A meta-analysis of these studies reported a relative risk of 0.67 for the combined end point of nonfatal stroke, nonfatal myocardial infarction (MI) and death (95% CI 0.54-0.83).[8] The NASCET and the ECST findings emphasized the efficacy and durability of stroke prevention achieved with CEA in patients with high-grade stenosis, even after more than 8 years of follow-up.

Moderate-grade and low-grade ICA stenosis

The NASCET study reported comparatively less-impressive results for CEA versus medical therapy in patients with moderate carotid stenosis (30-69%) than in patients with high-grade stenosis.[6] Among patients with less than 50% stenosis, the risk of stroke after 5-years’ follow-up did not differ significantly between the surgical-treatment arm and the medical arm (14.9% vs. 18.7%). In patients with stenosis in the range 50-69% (high-moderate stenosis), however, the 5-year risk of ipsilateral stroke was 15.7% in the surgical group compared with 22.2% in the medical group (ARR 6.5%). Notably, in this group, CEA did not confer a benefit to women, patients with diabetes nor those with previous TIA. Women with 50-69% stenosis were found to have a low-risk of stroke on medical therapy, and consequently benefited from surgery only, if they met criteria for additional risk-factors such as age greater than 70 years, severe hypertension, history of myocardial infarction, or a hemispheric (as opposed to a retinal) event.[9] Women also had higher perioperative mortality than men. The influence of gender on benefit with CEA is discussed in more detail later in this article.

With regards to patients with moderate stenosis, the ECST findings varied considerably from the NASCET study findings. Patients in the 30-49% and 50-69% stenosis groups, both categorized as moderate-grade stenosis, did not receive major benefit with surgery. This difference in outcome between the 2 major trials is partially related to the different methods each trial used to estimate the degree of stenosis on carotid angiography. Careful review has shown that the method employed in the ECST tended to overestimate the degree of stenosis compared with the NASCET method.[10] Hence many of the patients with moderate-stenosis according to the NASCET criteria were classified as having high-grade stenosis in the ECST – many patients with 50-69% stenosis included in the moderate-grade stenosis group in the ECST would have been classified as having less than 50% stenosis in the NASCET. Clinically, significant differences in the outcomes of the 2 trials, especially, among this group of patients, were seen as a consequence of this difference in methodology. Rothwell et al.[11] reanalyzed the angiograms of patients studied in the ECST according to the method of stenosis measurement used in the NASCET and they demonstrated remarkable consistency in the results of both the severe and moderate stenosis groups in both trials [Table 1]. In the 30-49% stenosis group, surgery was associated with an ARR for stroke or death of 1.3% compared with medical treatment (P=0.6), and in the low-grade stenosis group (<30% stenosis), surgical treatment was actually harmful, increasing the risk of stroke and death (ARR – 3.6%; P=0.007). Accurate measurement of carotid stenosis is therefore critical in clinical decision-making. In their final report, the ECST authors recognize this fact by recommending that the NASCET method of measuring carotid stenosis be adopted as the standard.[11]

In the combined analysis of the symptomatic trials by Rothwell et al., data were included on 6092 patients with 35,000 patient years of follow-up. As mentioned above, the 5 year ARR was 16.0% for patients with 70-99% stenosis (number needed to treat (NNT) of 6.3). For subjects with 50-69% stenosis, the ARR was 4.6% (NNT 22).

Timing of surgery

The issue of proper timing of CEA following TIA or stroke has been much debated. Some are concerned that carotid surgery after a major cerebral infarction could result in adverse outcomes caused by cerebral hemorrhage.[12,13] In the NASCET trial, however, post-operative intracranial hemorrhage occurred in only 0.2% of patients and was nonfatal in each case.[14] Altered auto regulation and hyper perfusion in the ischemic vascular bed distal to the endarterectomy are probably responsible for these intracranial hemorrhages. Others have suggested that the use of antithrombotic agents in

<table>
<thead>
<tr>
<th>Table 1: Risk of ipsilateral stroke at 5 years after carotid endarterectomy compared with best medical therapy in NASCET and ECST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stenosis (%)</td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>70-99</td>
</tr>
<tr>
<td>50-69</td>
</tr>
<tr>
<td>&lt;50</td>
</tr>
</tbody>
</table>

ARR – Absolute risk reduction; ECST – European carotid surgery trial; NASCET – North American symptomatic carotid endarterectomy trial; NS – Nonsignificant
the perioperative and post-operative periods could be the cause of these types of hemorrhages.\[15\]

In the past, concerns about post-operative hemorrhage often led to a delay in surgery for a few months after the initial ischemic event. A delay in surgery, however, exposes the patient to an excess risk of recurrent stroke in the interim period. Lovett et al. have shown that the risk of stroke recurrence within the 1st month is high, especially, in large-vessel disease.\[16\] Another study estimated, the risk of subsequent stroke after TIA to be approximately 10.5% at 3 months, with the majority of recurrent strokes occurring in the 1st week.\[17\] In theory, the risk of recurrence could recede in the months and years after the initial event, possibly as a result of healing or stabilization of the symptomatic plaques, and development of adequate collateral blood vessels.

In the pooled analysis of the symptomatic CEA trials, Rothwell et al. have shown that CEA was not only safe but was most beneficial when performed within 2 weeks of the index event.\[18\] Consequently, current treatment guidelines from the American Academy of Neurology as well as the American Stroke Association/American Heart Association (ASA/AHA) recommend that CEA for patients with non-disabling strokes should be performed without delay and preferably within 2 weeks of the primary stroke.\[19,20\]

Overall, the ASA/AHA guidelines state that CEA is recommended by a surgeon with a stroke/death rate of <6% for patients with severe (70-99%) stenosis and a stroke or TIA in the territory of the stenosed vessel within the preceding 6 months (class I, level A recommendation). For patients with recent symptoms and 50-69% stenosis, CEA is recommended depending on factors such as age, gender, severity of symptoms, and medical co-morbidities (class I, level A). For patients with <50% stenosis, there is no evidence that CEA is useful.\[22\]

**WHICH PATIENTS BENEFIT MOST FROM CAROTID ENDARTERECTOMY?**

The multi-center CEA trials have led to several subgroup analyses of various clinical and radiologic features and their relationship to benefit from surgery. Clinicians should recognize that even when performed by vetted surgeons, CEA is not a benign procedure. In randomized trials of symptomatic patients, the perioperative risk of stroke or death was approximately 7%.\[17\] In fact, if this benchmark of safety cannot be achieved, the benefit of CEA provided to patients by way of stroke prevention is diminished. Hence, identifying the patients most at risk for recurrent events is vitally important, to ensure they receive maximum benefit. Many of the subgroup analyses should be viewed as exploratory because of potential group imbalances and limited statistical power. However, information from the pooled studies is more credible.

**Role of gender-men versus women**

Besides degree of stenosis and the timing of surgery, age greater than 75 years and male sex were statistically significant predictors of benefit in the pooled analysis of the endarterectomy trials.\[18\] It was observed that women on medical therapy had fewer recurrent events but had higher perioperative risk, resulting in a worse surgical risk/benefit ratio compared to men. In a meta-analysis of all published studies between 1980 and 2004, women had a significantly higher risk of perioperative stroke and death than men (odds ratio 1.31; P<0.001).\[21\] The cause for this imbalance is unclear but the smaller size of the carotid arteries in women, relative to men, is a possible explanation. Similar raised risks were described in another report combining data from the NASCET and the Aspirin and Carotid Endarterectomy (ACE) study.\[9\] The benefit from CEA was similar in women and men with high-grade ICA stenosis (5-year ARR 15.1% vs. 17%, respectively), however, women did indeed have higher risk of perioperative stroke and death than men. Although, men benefited from CEA in the moderate-stenosis group, there was no clear benefit in women with the same disease severity.

**Age**

Due to the aging of the population, clinicians will increasingly encounter patients age 80 years and above with carotid stenosis. The NASCET initially excluded patients aged 80 years and older, and although the ECST studied patients of any age, it is not clear how many patients of this age group were actually included. In a review of more than 2500 CEA procedures performed in octogenarians, the combined perioperative stroke and death rate was 3.45%, which is within acceptable limits.\[22\] In another pooled analysis of trials of CEA for symptomatic stenosis in-patients aged >75 years, benefit was higher compared to younger patients.\[21\] Administrative database studies have shown an increased perioperative mortality with increasing age and therefore, careful patient evaluation is mandatory when CEA is contemplated in octogenarians.\[23\] If an elderly symptomatic CEA candidate is medically fit, CEA should not be withheld. As benefit accrues over 1-2 years after surgery, these patients should ideally have life expectancy that exceeds this period.

**Symptoms at presentation: Retinal versus hemispheric stroke**

Risk of stroke recurrence can be stratified on the basis...
of symptoms at presentation. For example, transient visual symptoms resulting from carotid stenosis are more likely to be benign than serious. In the NASCET, the risk of recurrent stroke among medically treated patients presenting with transient monocular blindness was significantly lower than that in those presenting with hemispheric TIA's (10% vs. 20% over 3 years). The risk of subsequent ischemic events was raised in individuals with transient monocular blindness treated medically, if they had co-existing risk-factors including age greater than 75 years, symptomatic peripheral vascular disease, and 80-94% stenosis of the ICA without adequate collateral circulation. Consequently, among patients with transient monocular blindness, CEA was beneficial only when ICA stenosis (>50%) was associated with these additional stroke risk-factors.

**Contralateral ICA occlusion**

Another factor that requires significant consideration when treating a patient with symptomatic carotid stenosis is contralateral ICA occlusion. Although, some authors believe this condition does not impact prognosis after CEA, others have reported that it is associated with raised perioperative risk. Gasecki et al. described 43 patients in the NASCET database with contralateral ICA occlusion. They found the risk of perioperative stroke to be significantly higher in these patients than in those who had significant contralateral stenosis but were not occluded (14% vs. 5%). The long-term outcome at 2 years, however, was better in the surgery group than in the medical group (22% vs. 69% risk of ipsilateral stroke). The authors concluded that there is significant benefit from CEA performed for symptomatic high-grade stenosis, even in the presence of contralateral ICA occlusion.

**Carotid plaque ulceration**

The pathophysiologic mechanisms of plaque ulceration and the potential for thrombosis and distal embolization have been studied extensively. After inspection of more than 1,000 post-operative specimens following CEA, Park et al. concluded that plaque ulceration is associated with symptomatic rather than asymptomatic plaques. Fisher et al. confirmed this finding after careful study of samples collected from the NASCET study and Asymptomatic Carotid Atherosclerosis Study (ACAS), but also showed that ulcerated plaques developed in the contralateral carotid artery as often as they developed in the ipsilateral symptomatic artery. In the NASCET study, although, patients were not randomized prospectively on the basis of plaque ulceration, a post-hoc analysis revealed that presence of angiographically determined ulceration significantly increased the risk of stroke in medically treated patients with severe stenosis by up to 3 times. These patients, however, are candidates for CEA because of the degree of stenosis alone. Moreover, detection of carotid plaque ulceration by carotid duplex and angiography is currently unsatisfactory. In a study comparing surgical specimens with angiographic data in 500 patients from NASCET, angiography had a 45.9% sensitivity and 74% specificity with a positive predictive value of 71% for diagnosing plaque ulceration. Future improvements in imaging technologies may allow more accurate identification of plaque ulceration, which could result in more efficient stroke prevention by CEA.

**Carotid “near occlusion”**

When using catheter angiography to assess severe carotid stenosis, the flow in the distal ICA beyond the stenosis is occasionally reduced and seems “collapsed.” These patients are classified as having “near occlusion.” The diagnosis of near occlusion is made by the delayed appearance of contrast in the ipsilateral intracranial ICA compared with the external carotid artery and a smaller diameter of the ICA compared with the external carotid artery. The contrast is diluted because of the collateral circulation. Morgenstern et al. identified 7.6% of the NASCET population as having carotid near occlusion, and observed that the risk of stroke recurrence in this group was significantly less than that in the 90-94% stenosis group (11% vs. 35%). The ARR of stroke in the CEA-treated group with near occlusion was 7.9% compared with the medically treated group. Using combined NASCET and ECST datasets, Fox and co-workers identified subsets of patients with near occlusion; the risk of stroke in the medically treated arm in this group was 15.1% compared with 10.9% in the surgical arm (ARR of 4.2%). The reason for the low-risk of stroke in this group is unclear but could be because of good collateral circulation from the opposite side or the ipsilateral external carotid artery. As acknowledged by the authors, however, the sample size and event rates were too small to make definitive conclusions. CEA can be considered in these patients, although, the benefit is muted.

**CAROTID ENDARTERECTOMY FOR ASYMPTOMATIC CAROTID STENOSIS**

The role of CEA in asymptomatic individuals is much less certain and still much debated. The ACAS and the Asymptomatic Carotid Surgery Trial (ACST) are large studies that have investigated this issue.

In the ACAS, patients were enrolled to receive either best medical treatment or medical therapy + endarterectomy, if they had stenosis greater than 60% but were...
otherwise healthy.\textsuperscript{[35]} The study was stopped early after 2.7 years of average follow-up. In the surgical arm the recurrent combined event rate for ipsilateral stroke, any perioperative stroke and death at 5 years was projected to be 5.1%, compared with 11% in the medical arms—a relative risk-reduction of 55% and an ARR of 5.9%. The marginal benefit with surgery could be a result of the exceptionally low perioperative risk of 1.5% achieved in the trial. Whether this low perioperative stroke rate can be uniformly achieved in “real life” situations is doubtful. For example, in a study of over 1800 asymptomatic CEA cases from Ontario, the perioperative stroke and death rate was 4.7%.\textsuperscript{[37]}

Although, it is frequently reported that the ASCT findings were similar to those of the ACAS, there were important differences in the 2 study designs. In the ACAS, the primary analysis compared strokes occurring in the territory of the operated carotid artery, while the ACST included strokes in any vascular territory. In addition, conventional angiography was not mandated for either group in ACST. After 5-years’ follow-up, the risk of recurrent stroke for the surgical and medical group in ACST was 6.4% and 11.8% respectively.\textsuperscript{[35,6]} This difference was more or less evident even after 10 years- 13.4% versus 17.9% with net benefit of 4.5%.\textsuperscript{[38]} The risk of perioperative stroke or death was 2.8%. Importantly, this study showed a significant reduction of fatal or disabling strokes in the surgical arm (3.5% vs. 6.1% in medically treated group, ARR 2.6%; \textit{P}<0.004). Approximately, half of all ipsilateral recurrent strokes that occurred were classified as fatal or disabling. The ACAS showed a trend towards reduction in fatal and disabling strokes with surgery but did not reach statistical significance (ARR 2.7%; \textit{P}=0.26). There was no clear benefit of CEA in subjects age 75 years and over in ACST.

A meta-analysis of data from 5,223 patients from 3 major trials of CEA for asymptomatic carotid stenosis was performed by Chambers and Donnan.\textsuperscript{[19]} Surgery conferred a significant benefit in terms of the composite primary outcome (any perioperative or subsequent stroke, and all-cause perioperative mortality; relative risk 0.69, 95% CI 0.57-0.83). The overall risk of perioperative stroke or death was 2.9%. Subgroup analysis revealed men received more benefit from surgery than did women, and younger patients’ benefited more than older patients. Unlike the symptomatic stenosis trials, stenosis severity did not correlate with benefit from surgery. Despite these findings, some have argued against the routine use and widespread enthusiasm for CEA in asymptomatic patients. Barnett et al. highlight that the absolute annual risk-reduction of stroke in this asymptomatic group is about 1% with a NNT of 83 to prevent one stroke in 2 years.\textsuperscript{[43]} Moreover, it has been estimated that approximately half the strokes in asymptomatic individuals are not related to the stenosed carotid artery but are rather lacunar strokes or caused by cardioembolic events.\textsuperscript{[41]}

As discussed above, the benefit of surgery in patients with carotid stenosis is highly dependent on perioperative stroke risk. A low perioperative stroke risk is especially critical for asymptomatic patients in whom the marginal benefit can be lost, if the risk is not within recommended limits. Practicing clinicians must, therefore, be aware of the local and institutional complication rates, in order to advise patients. In a study of 12 academic centers and 1,160 procedures, Goldstein et al. reported a perioperative risk of stroke or death of 2.8%.\textsuperscript{[42]} Notably, the rate was higher in symptomatic than in asymptomatic individuals. Post-operative stroke and death was also significantly raised in women, older individuals (>75 years), those with associated congestive heart failure, and those undergoing simultaneous CABG surgery. The American Academy of Neurology guidelines thus recommend that CEA for asymptomatic stenosis be considered only for patients’ 40-75-years-old with at least a 5 year life expectancy. In addition, the surgeon’s complication rate should be reliably documented to be less than 3%.\textsuperscript{[19]}

In the last 15 years, the recognition of the role of early and comprehensive medical management of cerebrovascular disease has led to a great but highly underappreciated reduction of stroke risk in this population of patients. There is paucity of data as to the exact annual risk of stroke in patients with asymptomatic carotid stenosis on modern medical therapy. By one estimate, the annual risk of stroke has dropped significantly to \textless1%/year with medical therapy alone, raising serious questions about the benefit of any revascularization procedure.\textsuperscript{[43]} Spence et al.\textsuperscript{[44]} have shown that transcranial Doppler can identify a subgroup of patients with asymptomatic stenosis who have microembolic signals that are at higher risk for stroke than those who do not have these microembolic signals. The risk of stroke in patients with asymptomatic stenosis but without microembolic signals is remarkably low. They further demonstrate that intensive medical therapy of arterial plaques can reduce the number of patients with microembolic signals by 90% and that revascularization procedures should be considered only in the small minority who can be demonstrated to be at high-risk.\textsuperscript{[43]}

Guidelines from the ASA/AHA indicate that patients with asymptomatic stenosis should be screened for other treatable causes of stroke and that intensive treatment of
stroke risk factors should be pursued (class I, level C).\[46\]
In addition, the use of aspirin is recommended in subjects with asymptomatic stenosis. CEA is recommended in only in highly select patients with high-grade stenosis and the surgeon should have a stroke/death rate of <3% (class I, level A). There should be a thorough understanding of the goals of the procedure, the patient’s life expectancy and co-morbidities, and patient preferences.

PERIOPERATIVE DRUG THERAPY
The NASCET investigators initially observed that patients receiving low-dose aspirin (0.325 mg/day) in the perioperative period had higher risk of perioperative stroke and death than those on higher doses (650-1300 mg/day). This observation led to the randomized ACE trial,\[47\] which found that perioperative stroke or vascular death risk in the low-dose aspirin (81-325 mg/day) arm was 6.2% compared with 8.4% in the high-dose arm (650-1300 mg/day), a finding contrary to the previous observation. A more recent systematic review of all trials has attempted to address the question of optimum antiplatelet therapy during CEA for symptomatic and asymptomatic carotid stenosis.\[48\] This study found that perioperative stroke risk among those receiving antiplatelet agents was significantly reduced, however, that the risk of perioperative death was not significantly altered. The findings also indicated that antiplatelet agents could increase the risk of hemorrhage. The widespread belief that antiplatelet agents reduce the risk of native-vessel or graft thrombosis and myocardial infarction after vascular surgery (including CEA), however, means that most clinicians use antiplatelet therapies in the perioperative period for patients undergoing CEA.

Evidence that statins\[49\] and\[50\] beta blockers\[50\] reduce morbidity and mortality when used during vascular surgery is mounting. McGirt et al. reported that use of statins, compared with absence of statin treatment, during CEA significantly reduced the risk of perioperative stroke (1.2% vs. 4.5%; P<0.01) and death (0.3% vs. 2.1%; P<0.01).\[51\] These observations are intriguing but more definitive studies are needed before broad recommendations for routine use of these medications can be advocated in the perioperative period.

THE RISKS ASSOCIATED WITH CAROTID ENDARTERECTOMY
The risks of surgery should be carefully discussed with patients before CEA. Risks include perioperative ischemic stroke, hemorrhagic stroke, cranial nerve injury, myocardial infarction, congestive heart failure, and neck hematoma with consequent airway compromise. Perioperative ischemic stroke occurs as a result of thrombotic occlusion of the operative site, distal thromboembolisim of debris from the operative site, cross clamping of the ICA, or a combination of these factors. Ischemic stroke usually occurs within the first 12-24 h after surgery but can also occur later in recovery. If a patient wakes up from anesthesia with a deficit or develops one soon thereafter, emergent exploration of the operative site for thrombosis and consequent occlusion or other correctable operative defects is usually undertaken. Cerebral angiography can be performed with a view to identifying occluded vessels. The benefit of reoperation, however, cannot be predicted. Of the ten patients, who underwent reoperation in the NASCET, none demonstrated any benefit.\[14\] Furthermore, Findlay and Marchak reported that 13 of 24 patients had post-operative strokes following CEA and underwent emergency reoperation,\[52\] yet only 4 of these patients were reported to show any benefit.

Hemorrhagic stroke is, fortunately, rare. Only 0.2% of the NASCET cohort was reported to have this type of stroke. In a retrospective review of patients undergoing CEA, Piepras et al. found this complication occurred in 0.6% patients, mainly in those with hypertension.\[13\]

Severe carotid stenosis with limited collateral flow could result in post-operative hyper perfusion syndrome. In addition to increased blood-flow, which is associated with this syndrome, use of anticoagulation or occurrence of a perioperative ischemic event with subsequent hemorrhagic transformation might also be important. The prognosis is often grave and early recognition during surgery – by noting increase in the cerebral blood flow is important. Wound complications such as infections and hematoma occurred in 9.3% of patients in the NASCET. Wound hematoma is a particular concern because in the NASCET it was associated with raised perioperative stroke risk (14.5% vs. 5.9% in patients without hematoma).\[14\] Large hematomas can also result in airway compromise, requiring immediate evacuation. Smaller hematomas can be managed expectantly and more conservatively. Cranial nerve injuries include those to the hypoglossal nerve, vagus nerve, or branches of the facial nerve and occur in 8.6% of patients but are commonly transient and mild.

Overall, the risk of complications with CEA is raised in symptomatic patients, those with contralateral ICA occlusion, those with hemispheric rather than retinal ischemic events, in patients aged 75 years or more, in women, and in those undergoing reoperation.\[42,53,54\] Severe systemic illnesses such as congestive heart
failure, severe respiratory insufficiency, uncontrolled hypertension, and angina are contraindications to CEA.

CAROTID ARTERY STENTING

In the past 10-15 years, CAS has attracted increased attention as a less invasive alternative to CEA. The CAS procedure has continued to evolve over the years in terms of operator experience as well as technological advances; however, the indications for performing this procedure are still being debated.

CAS in “high-risk” patients

Previously discussed trials of CEA such as NASCET and ACAS excluded patients who were at high-risk for perioperative mortality and morbidity and these patients had substantially worse outcomes than that reported in the trials.[23,55] Patients at “high-risk” for CEA have been treated with CAS as part of either industry-supported registries or randomized trials. Commonly used criteria for “high-risk” CEA candidates are delineated in Table 2.

One randomized study, the Study of Angioplasty with Protection in Patients at High-Risk for Endarterectomy (SAPPHIRE) [56] included both symptomatic and asymptomatic patients (close to 70% asymptomatic) with ICA stenosis who were judged to be high-risk for CEA. Patients were randomly assigned to CEA or CAS. In the study population as a whole, the investigators concluded that CAS with distal emboli protection was not inferior to CEA in high-risk patients. The 30 day risk of stroke, death or myocardial infarction was 4.4% in the CAS group compared to 9.8% in the CEA group. At 1 year follow-up, the combined rate of stroke, death and myocardial infarction was 6.34% for the CAS group compared to 12.4% in the CEA group. The 30 day risk of stroke, death or myocardial infarction was significantly less often in the CAS group compared to the CEA group (0.6% vs. 4.3%). Most of the difference in the SAPPHIRE endpoint rates was due to the lower risk of non Q wave MI events in the CAS cohort.

Information on the 3 year outcome of patients in SAPPHIRE has been reported, although, follow-up was incomplete (78% of patients had 3 year data).[57] For the outcome of periprocedure (within 30 days) stroke, MI, or death, or ipsilateral stroke between days 31 and 1080 days, there was not a significant difference in the outcome in the CEA and CAS groups. 74% of the CAS subjects and 70% of the CEA patients were free of this endpoint at 3 years. The relatively high 3 year death rate in both groups, averaging 22%, is concerning and raises questions about the value and necessity of either procedure in a high surgical risk cohort. A recent study found significant heterogeneity in the treatment of “high surgical risk” patients, with a substantial proportion still receiving CEA.[58]

There have been numerous single center case series and registry publications reporting results of CAS. In industry sponsored registries, the 30 day combined risk of stroke, death and MI has varied from 3.8% to 8.6%.[59]

Predominantly based on the above, the FDA has approved the usage of stenting systems (Abbott Vascular Acculink/Accunet and the Abbott Xact/Embolishield CAS systems) for limited applications in treatment of carotid artery disease. The Center for Medicare and Medicaid Services currently reimburses treatment with the approved devices for symptomatic high-risk patients with >70% stenosis only. Symptomatic patients with 50-69% stenosis and asymptomatic patients with >80% stenosis will be reimbursed only, if treated under the setting of an approved clinical trial or registry.

The ASA/AHA guidelines state that in patients with symptomatic stenosis of >70% in whom the stenosis is difficult to access surgically or with significant medical co-morbidities, CAS is not inferior to CEA and can be considered (class IIb, level B). CAS practitioners should have a periprocedural stroke/death rate of <4-6% (class IIa, level B).[20]

CAS in “traditional-risk” patients

Several recent randomized controlled trials of CAS compared to CEA in traditional risk patients have been published. The Stent – Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy trial (SPACE)[60] analyzed 1183 symptomatic patients who were randomized to either CAS or CEA. The 30 day risk of ipsilateral stroke or death was 6.84% for the CAS group compared to 6.34% and the study could not prove non-inferiority of the stenting procedure. At 2 years the risk of the primary outcome in this study (ipsilateral stroke over 2 years or any perioperative stroke or death) was similar in both groups. The study found an excess risk of

<table>
<thead>
<tr>
<th>Table 2: Commonly cited criteria determining “high-risk” for carotid endarterectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical</strong></td>
</tr>
<tr>
<td>Left ventricular EF &lt;30%</td>
</tr>
<tr>
<td>Age ≥80 years</td>
</tr>
<tr>
<td>Recent MI (&lt;30 days)</td>
</tr>
<tr>
<td>Class III/IV angina or CHF</td>
</tr>
<tr>
<td>Severe COPD</td>
</tr>
<tr>
<td>Need for CABG in &lt;30 days</td>
</tr>
<tr>
<td>Significant renal failure</td>
</tr>
</tbody>
</table>

EF = Ejection fraction; CHF = Congestive heart failure; COPD = Chronic obstructive pulmonary disease; CABG = Coronary artery bypass grafting; MI = Myocardial infarction
carotid restenosis in the CAS group, although, most were asymptomatic.\textsuperscript{[61]} A similar study, the Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Stenosis,\textsuperscript{[62]} was stopped earlier than planned for futility and safety. The 30 day rate of stroke and death was 3.9% in the CEA group compared to 6.1% in the CAS group. This discrepancy was significant and persisted after 6 months and at 4 years.\textsuperscript{[63]} The authors concluded that widespread use of CAS is not justified in this group of patients. The 4 year analysis of this study showed that the differences in outcomes were largely due to periprocedural outcomes while the risk of subsequent ipsilateral strokes was similarly low in both groups. There was criticism of both these trials because of limited training of the interventionists, multiple device types used (some without embolic protection) often with minimal training, and lack of standardized medical therapy.\textsuperscript{[64]}

The National Institutes of Health-supported Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) recruit patients with symptomatic (>70% stenosis by ultrasound or >50% by angiography) and asymptomatic (70-99%) stenosis. The primary end point (stroke, MI and perioperative death and ipsilateral stroke after an average follow-up of 2.5 years) were similar in the 2 groups (7.2% in the stenting arm vs. 6.8% in the CEA arm). They reported a slightly elevated but significant 30 day risk of perioperative stroke in the stenting arm (4.4% vs. 2.3%) while there were significantly more patients who developed perioperative MI in the CEA arm (1.1% vs. 2.3%). While some have argued that this suggests that the 2 procedures are equivalent, others have pointed out that strokes result in greater impairment in quality of life compared to MI and consequently current stenting procedures could result in more harm. Women had a higher periprocedural complication rate with CAS compared to CEA.\textsuperscript{[65]} Age produced a significant effect on the outcomes-with a cutoff at about 70 years. Patients less than 70 years fared better with CAS and those older fared better with CEA.\textsuperscript{[66]} This is contrary to what one might intuitively expect – i.e., CAS being less invasive procedure would be better suited for older patients. It is likely the more tortuous and atherosclerotic calcified vessels in older patients’ results in more strokes possibly from the introduction of the embolic protection devices.

The International Carotid Stenting Study (ICSS)\textsuperscript{[67]} was a multi-center study comparing CEA to CAS in symptomatic patients. The interim report was a safety analysis, which showed 8.5% risk of stroke, death, and MI in the CAS group compared to 5.2% in the CEA group. Moreover, an magnetic resonance imaging sub-study\textsuperscript{[68]} of the ICSS revealed presence of 3 times more new ischemic lesions in the stenting group compared to CEA group. The study hence, concluded that CEA should remain the treatment of choice in these patients until the long-term results were available. The ICSS had important differences from the CREST, which could have contributed to the differing outcomes. ICSS included only symptomatic patients and interventionists underwent a less stringent vetting procedure – both of which could result in poorer outcomes in the CAS arm.

A large comprehensive meta-analysis of trials comparing CAS versus CEA has recently been published.\textsuperscript{[69]} It provides good statistical evidence for a 20% relative risk increase of periprocedure stroke or death and ipsilateral stroke with CAS; there is a 15% relative risk reduction in periprocedure MI compared to CEA. A national analysis of CAS outcomes in Medicare patients in the United States showed a high periprocedure mortality of 1.9%.\textsuperscript{[70]} This is significantly higher than in CREST and has given regulatory authorities pause as to whether CAS is “ready for prime time” in standard surgical risk patients. An overview of current CAS recommendations can be found in Table 3.

### CONCLUSIONS

CEA underwent resurgence in the 1990s after the landmark clinical trials demonstrated its benefit in carefully selected patient populations for secondary, and to a lesser extent primary, stroke prevention. This procedure prevents stroke in symptomatic patients with high-grade and moderate-grade ICA stenosis of more than 50%. In asymptomatic patients with high-grade stenosis, the benefit is less and highly sensitive to the periprocedure stroke risk. “High risk” patients such as those with comorbid medical conditions should be considered for CAS if they have high-grade symptomatic stenosis. Those high-risk patients with moderate grade symptomatic or with asymptomatic stenosis >80% may be considered for CAS only in the setting of a clinical trial or registry. It remains unclear, if any revascularization procedure is necessary in asymptomatic patients who are at high surgical risk. Regulatory approval of CAS

<table>
<thead>
<tr>
<th>Table 3: Status of carotid stenting according to patient profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic high-risk patients with 70-99% stenosis can be considered for CAS</td>
</tr>
<tr>
<td>Symptomatic high-risk patients with 50-69% (moderate) stenosis should be offered CAS only in the setting of an approved clinical trial or registry</td>
</tr>
<tr>
<td>Asymptomatic high-risk patients with &gt;80% stenosis should be offered CAS only in the setting of an approved clinical trial or registry</td>
</tr>
<tr>
<td>Role for CAS in conventional risk patients with symptomatic &gt;50% is evolving and should be avoided in patients &gt;70 years with tortuous and calcified arteries</td>
</tr>
</tbody>
</table>

CAS – Carotid artery stenting
for conventional risk patients is still lacking. For all categories of patients, including both symptomatic and asymptomatic, new studies should be undertaken to assess the value of intensive, modern medical therapy.[22] Finally, documentation of the institutional complication rates for both CEA and CAS is critically important.

REFERENCES


43. Abbott AL. Medical (Nonsurgical) intervention alone is now best for prevention of stroke associated with asymptomatic severe carotid stenosis: Results of a systematic review and analysis. Stroke 2009;40:e573-83.


How to cite this article: Rajamani K, Chaturvedi S. Stroke prevention-surgical and interventional approaches to carotid stenosis. Indian J Neurosurg 2013;2:30-40.

Source of Support: Nil, Conflict of Interest: None declared.

Author Help: Online submission of the manuscripts

Articles can be submitted online from http://www.journalonweb.com. For online submission, the articles should be prepared in two files (first page file and article file). Images should be submitted separately.

1) First Page File:
Prepare the title page, covering letter, acknowledgement etc. using a word processor program. All information related to your identity should be included here. Use text/rtf/doc/pdf files. Do not zip the files.

2) Article File:
The main text of the article, beginning with the Abstract to References (including tables) should be in this file. Do not include any information (such as acknowledgement, your names in page headers etc.) in this file. Use text/rtf/doc/pdf files. Do not zip the files. Limit the file size to 1 MB. Do not incorporate images in the file. If file size is large, graphs can be submitted separately as images, without their being incorporated in the article file. This will reduce the size of the file.

3) Images:
Submit good quality color images. Each image should be less than 4096 kb (4 MB) in size. The size of the image can be reduced by decreasing the actual height and width of the images (keep up to about 6 inches and up to about 1800 x 1200 pixels). JPEG is the most suitable file format. The image quality should be good enough to judge the scientific value of the image. For the purpose of printing, always retain a good quality, high resolution image. This high resolution image should be sent to the editorial office at the time of sending a revised article.

4) Legends:
Legends for the figures/images should be included at the end of the article file.