

# Carotid revascularization: risks and benefits

Marlene O'Brien  
Ankur Chandra

Department of Surgery, Division  
of Vascular Surgery, University of  
Rochester School of Medicine and  
Dentistry, Rochester, NY, USA

**Abstract:** Despite a decline during the recent decades in stroke-related death, the incidence of stroke has remained unchanged or slightly increased, and extracranial carotid artery stenosis is implicated in 20%–30% of all strokes. Medical therapy and risk factor modification are first-line therapies for all patients with carotid occlusive disease. Evidence for the treatment of patients with symptomatic carotid stenosis greater than 70% with either carotid artery stenting (CAS) or carotid endarterectomy (CEA) is compelling, and several trials have demonstrated a benefit to carotid revascularization in the symptomatic patient population. Asymptomatic carotid stenosis is more controversial, with the largest trials only demonstrating a 1% per year risk stroke reduction with CEA. Although there are sufficient data to advocate for aggressive medical therapy as the primary mode of treatment for asymptomatic carotid stenosis, there are also data to suggest that certain patient populations will benefit from a stroke risk reduction with carotid revascularization. In the United States, consensus and practice guidelines dictate that CEA is reasonable in patients with high-grade asymptomatic stenosis, a reasonable life expectancy, and perioperative risk of less than 3%. Regarding CAS versus CEA, the best-available evidence demonstrates no difference between the two procedures in early perioperative stroke, myocardial infarction, or death, and no difference in 4-year ipsilateral stroke risk. However, because of the higher perioperative risks of stroke in patients undergoing CAS, particularly in symptomatic, female, or elderly patients, it is difficult to recommend CAS over CEA except in populations with prohibitive cardiac risk, previous carotid surgery, or prior neck radiation. Current treatment paradigms are based on identifying the magnitude of perioperative risk in patient subsets and on using predictive factors to stratify patients with high-risk asymptomatic stenosis.

**Keywords:** carotid stenosis, carotid endarterectomy, carotid stent

## Background

Each year, approximately 795,000 people suffer a stroke. About 600,000 of these are first attacks, and 195,000 are recurrent attacks.<sup>1</sup> Although the incidence of stroke in the United States has decreased steadily since the 1960s, stroke still continues to be the fourth leading cause of mortality and a major source of chronic disability.<sup>2</sup> Several studies have demonstrated that extracranial carotid artery stenosis is a factor in 20%–30% of all strokes.<sup>3–5</sup> Because carotid atherosclerosis can develop insidiously over time without symptoms, for some patients, the first manifestation of carotid disease is a significant stroke. Asymptomatic carotid stenosis affects approximately 7% of women and more than 12% of men older than 70 years.<sup>6</sup> Clinically significant stenosis, at which point the risk for stroke is increased, is defined as stenosis greater than 50%–60%.<sup>7</sup> Adults with asymptomatic carotid stenosis are at increased risk, from

Correspondence: Ankur Chandra  
University of Rochester School of  
Medicine and Dentistry, 601 Elmwood  
Avenue, Rochester, NY 14642, USA  
Tel +1 585 273 2596  
Fax +1 585 424 1008  
Email [ankur\\_chandra@urmc.rochester.edu](mailto:ankur_chandra@urmc.rochester.edu)

2%–5% per year, for ipsilateral carotid territory ischemic stroke without medical therapy.<sup>8,9</sup> The North American Symptomatic Carotid Endarterectomy (NASCET) trial found that adults with symptomatic carotid stenosis have a 2-year risk for ipsilateral stroke of 26%, even with medical management.<sup>10</sup> Patients with carotid disease, either symptomatic or asymptomatic, represent a population for which there exists several treatment modalities. Identifying patients with existing carotid stenosis and offering either medical or surgical intervention, or both, in a manner that safely slows the progression to or prevents a stroke has been an active area of study since at least 1954, when DeBakey and colleagues performed the first carotid endarterectomy (CEA).

Although the last several decades have seen an increase in heart disease and cancer-related deaths, the incidence of stroke-related death has declined since the 1960s,<sup>1</sup> a phenomenon partially attributable to both improved medical and surgical management of carotid disease. However, despite a decline in stroke-related death, the incidence of stroke has remained unchanged or slightly increased,<sup>11</sup> implying that although the number of strokes per year has not changed, the proportion of them that result in death has decreased. Interestingly, the use of CEA as a means of reducing stroke risk has increased steadily since the 1960s, suggesting a relationship between a decline in fatal strokes and the increase in CEAs performed.<sup>2</sup>

The primary objective of this review is to discuss historical and contemporary data regarding carotid intervention for symptomatic and asymptomatic carotid artery occlusive disease in an effort to summarize the risks and benefits of treatment modalities for the management of patients with this disease.

## Natural history

Risk stratification of carotid stenosis based on the natural history of the disease is still an area of active research and controversy, given that the surgical interventions (CEA and carotid stent [CAS]) are both risk-reducing, and not curative, measures. As previously mentioned, early studies conducted before the initiation of medical therapy aimed at blood pressure and cholesterol control demonstrated that asymptomatic carotid disease carried an ipsilateral stroke rate of 2%–5% per year.<sup>8,9</sup> The Asymptomatic Carotid Atherosclerosis Surgery (ACAS) study, published in 1995<sup>12</sup> projected that the risk for ipsilateral stroke over 5 years with medical therapy alone was 11.0%. The Asymptomatic Carotid Surgery Trial 1 (ACST-1), published in 2004, found that in patients with carotid stenosis higher than 60%, the incidence of stroke or

death at 5 years with medical management was 11.8%, which is similar to ACAS.<sup>13</sup> Many of these patients were identified on the basis of a carotid bruit, a selection bias that includes patients without significant occlusive disease and omits patients without an audible bruit but underlying stenosis. In NASCET, an ipsilateral carotid bruit only had a sensitivity of 63% and specificity of 61% for 70%–99% stenosis.<sup>10</sup> With improvements in duplex ultrasound, computed tomography angiography (CTA), and magnetic resonance angiography (MRA) in identifying patients with high-risk lesions, it has been possible not only to identify asymptomatic patients with carotid disease but also to risk-stratify them on the basis of the degree of stenosis. Meta-analysis of incidence rate data from prospective single-group cohorts of medical therapy alone for asymptomatic carotid stenosis showed that the incidence rate of ipsilateral stroke was 1.68% per year and 1.13% in studies conducted in the past decade.<sup>14,15</sup> Recent data show that rates of stroke associated with asymptomatic internal carotid artery (ICA) disease are only 0.5%–1.0% per year in patients with a carotid stenosis of more than 50%.<sup>14,16,17</sup>

Although the risk for ipsilateral stroke with asymptomatic carotid stenosis is declining with improvements in medical therapy, there is still an increased risk for stroke in patients who develop more than 60% carotid stenosis. It is still up for debate whether a patient with an asymptomatic stenosis of 80%–99% is at a higher risk of developing a stroke than an asymptomatic patient with 60%–79% stenosis based on natural history of the disease. In 1998, Olin et al<sup>18</sup> followed the natural history of moderate carotid stenosis (60%–79%) in 465 patients to determine the degree to which these asymptomatic patients progressed. The estimated cumulative rate of progression to 80%–99% stenosis at 1 year was 5%, 11% at 2 years, and 20% at 3 years. Ipsilateral neurologic events occurred more frequently in those who progressed (12.5%) than in those who did not progress (3.1%). A similar study by Rockman et al<sup>19</sup> found that strokes occurred more frequently in those arteries that progressed than in those that remained in the 50%–79% category (10.4% versus 2.1%). Patients were more likely to remain asymptomatic if the artery did not progress compared with if progression occurred (92.7% versus 62.5%). Most recently, Conrad et al demonstrated that the incidence of stroke in 794 patients monitored for progression of moderate carotid stenosis (50%–69%) over the course of 5 years was 11.3%.<sup>20</sup>

For patients who do experience symptoms ipsilateral to carotid stenosis, there are strong data to predict an increased annual risk for stroke. NASCET<sup>21</sup> found that symptomatic patients with carotid stenosis 70%–99% had a 26% risk for

stroke over the course of 2 years, a number that could be brought down to 9.0% with CEA. The European Carotid Surgery Trial (ECST),<sup>22</sup> also inclusive of symptomatic patients, found that risk for major ischemic stroke ipsilateral to the unoperated symptomatic carotid artery increased with the severity of stenosis. ECST estimated frequency of a major stroke or death at 3 years as 26.5% for patients treated with nonoperative management.

In short, atherosclerotic carotid stenosis is a progressive disease that carries an increased annual risk for stroke, despite medical therapy. Patients with increasing stenosis likely have increased risk of developing neurological symptoms, and the stratification of these patients into low-, moderate-, and high-risk groups is an active area of research, with the goal of treatment therapy being maximum stroke risk reduction with minimum iatrogenic risk.

## Pathology

The majority of carotid occlusive disease occurs at the carotid bifurcation. Because the area of the carotid bulb is wider than points proximal or distal, this change in caliber, along with the flow divider at the carotid bifurcation, creates a pattern of turbulent flow and areas of variable shear stress along the walls of the carotid vessels.<sup>23,24</sup> Experiments performed by Zarins et al in the 1980s demonstrated that the carotid plaque is consistently found along the outer wall of the ICA, opposite the flow divider, which corresponds to an area of low shear stress<sup>25</sup> and is often at the level of the C4 vertebrae. Similar to atherosclerotic plaques that form in other vessels, the carotid plaque begins as fibrointimal thickening and progresses to become symptomatic in a variety of ways.<sup>26–28</sup> Studies relating pathologic findings with symptoms have demonstrated that intraplaque hemorrhage, thrombus formation, and ulceration are consistent with a vulnerable plaque that may cause symptoms.<sup>29–31</sup> Most plaque ruptures occur at the midpoint of the plaque, rather than at the edges or shoulders.<sup>27</sup> Embolic potential and symptomatic status have been correlated with hypoechoic and homogeneous patterns on duplex ultrasonography.<sup>29,32,33</sup>

## Presentation and imaging

Patients presenting with symptoms of carotid disease will typically have focal neurological dysfunction in the form of numbness, paresthesias, slurred speech, weakness, or monocular blindness (amaurosis fugax). If these symptoms resolve within 24 hours without any permanent neurological deficit, the incident is termed a transient ischemic attack (TIA). Symptoms lasting for longer than 24 hours represent

a completed stroke and can be classified according to the National Institutes of Health Stroke Scale. Patients who have multiple episodes of focal neurological deficit punctuated by failure to return to baseline are classified as having crescendo TIAs. Those patients whose symptoms progress and worsen over the course of hours to days are classified clinically as having a stroke-in-evolution.<sup>34,35</sup> Patients with any of the symptoms described here should undergo bilateral carotid duplex ultrasound to determine whether carotid stenosis is a contributing factor to their symptoms. These symptomatic patients, however, represent a minority of patients who present with carotid disease. The majority of patients are asymptomatic.

Screening asymptomatic patients for carotid stenosis is not part of recommended clinical practice in the United States;<sup>7</sup> however, the 2011 guidelines published by the American Heart Association (AHA)/American Stroke Association (ASA)<sup>36</sup> and Society for Vascular Surgery (SVS)<sup>37</sup> report that it is “reasonable” to perform carotid duplex on asymptomatic patients with a bruit and “may be considered” in patients with symptomatic peripheral arterial disease (PAD) or coronary artery disease (CAD) and in patients who have two or more of the following risk factors: hypertension, hyperlipidemia, tobacco smoking, a family history in a first-degree relative of atherosclerosis manifested before age 60 years, or a family history of ischemic stroke. To date, no prospective randomized controlled trials have been conducted to demonstrate a reasonable number needed to treat to make screening a cost-effective mandate. A recent study by Kakkos et al<sup>38</sup> examined 1,121 patients with asymptomatic carotid stenosis of 50%–99% and assigned them to carotid duplex every 6 months to assess regression, no change, or progression during a mean follow-up of 4 years. In the absence of progression, the 9-year cumulative ipsilateral stroke rate was 12%; it was 9% if the stenosis were unchanged and 16% if there was progression. However, given the low frequency of progression and its relatively low associated stroke rate (only 30% of all strokes occurred in the progression group), the authors concluded that the clinical value of screening for stenosis progression was “limited”. With respect to initial screening recommendations, however, on the basis of the AHA/ASA/SVS guidelines, many primary care physicians and cardiologists recommend routine screening in patients with 2 or more risk factors or known PAD or CAD. As a result, Medicare beneficiaries are increasingly being evaluated with noninvasive imaging studies for this indication.<sup>39</sup>

Carotid duplex ultrasound is the first-line imaging tool for patients with suspected carotid occlusive disease.

Duplex criteria for diagnosis of carotid stenosis were standardized in 1987 by Dr Strandness at the University of Washington.<sup>32</sup> This first set of criteria, known as the University of Washington criteria, stratified carotid stenosis into six categories, using both duplex and B mode evaluation.<sup>32</sup> The percentage of stenosis in the carotid artery could be reliably predicted as 0%, 1%–15%, 16%–49%, 50%–79%, 80%–99%, or complete occlusion based on duplex criteria. According to this scale, patients with duplex peak systolic velocities of more than 125 cm/second in conjunction with end diastolic velocities of more than 140 cm/second were likely to have high-grade (80%–99%) stenosis. These methods had a sensitivity of 99% and a specificity of 84% when compared with angiography.<sup>32</sup> A number of years later, the Society of Radiologists in Ultrasound released a consensus statement<sup>33</sup> using the internal carotid artery-to-common carotid artery peak systolic velocities ratio as a parameter, stating that a ratio greater than 4.0 was representative of more than 70% occlusion. In addition to being highly operator-dependent, other limitations of duplex ultrasound are its inability to accurately determine velocities in the presence of heavily calcified plaque because of artifact created by shadowing and in the setting of contralateral carotid occlusion. Although many surgeons can safely rely on carotid duplex for preoperative imaging, there are certain cases in which more information is necessary before proceeding to surgery, such as with the aforementioned heavy calcifications, unexpectedly low velocities, or atypical presentation.

Digital subtraction angiography (DSA) was, for a number of years, the gold standard for diagnosis of carotid stenosis; however, CTA and MRA have now supplanted DSA as an anatomic imaging modality. First described for carotid artery stenosis in 1994,<sup>40</sup> CTA is now a reasonable tool available for preoperative evaluation in patients for whom ultrasound results are nondiagnostic. Because it allows for multiplanar diameter measurements, CTA diameter can accurately estimate stenosis and yield useful information about surrounding anatomy, as demonstrated by several reports,<sup>40–42</sup> and has been validated with regard to Strandness duplex criteria against DSA-derived diameter measurements used in NASCET.<sup>43</sup>

MRA is another option for preoperative cross-sectional imaging. In a systematic review of published studies on duplex ultrasound and MRA, using DSA as the gold standard, MRA was found to be both sensitive and specific at detecting carotid stenosis and, in fact, was found to be more discriminatory than duplex ultrasound at detecting stenosis between 70% and 99%.<sup>44</sup> MRA without contrast can also be used in

patients with renal insufficiency. Pitfalls of MRA evaluation include overestimation of stenosis (more so with noncontrast examinations) and the inability to discriminate between subtotal and complete arterial occlusion. More problematic is the inability to examine the substantial fraction of patients who have claustrophobia, extreme obesity, or incompatible implanted devices such as pacemakers or defibrillators, many of whom are at high risk.<sup>44</sup>

Recent studies have demonstrated the ability of imaging to discriminate plaque features that are associated with symptomatic presentation and that may be indicative of plaque vulnerability.<sup>45,46</sup> Several studies have compared the accuracy of MRA, CTA, and color Doppler ultrasonography with DSA. Anzidei et al found that CTA is the most accurate technique for evaluating carotid stenosis, although blood-pool-enhanced steady-state MRA has identical accuracy with regard to degree of stenosis and plaque morphology.<sup>47</sup> Most recently, Korn et al demonstrated that dual-energy CTA is superior to contrast-enhanced MRA at detecting the degree of internal carotid stenosis.<sup>48</sup> The Plaque at RISK (PARISK)<sup>49</sup> study, a prospective multicenter cohort study of patients with symptomatic carotid disease, is in progress. This study will include symptomatic patients not scheduled for CEA or CAS, with recent neurological symptoms, who will be imaged by magnetic resonance imaging, multidetector-row CTA, color Doppler ultrasonography, and transcranial Doppler, either alone or in combination, to identify carotid plaque features that may improve identification of a high-risk subgroup of patients with less than 70% carotid artery stenosis. The combined primary endpoint will be ipsilateral recurrent ischemic stroke or TIA or new ipsilateral ischemic brain lesions on follow-up brain magnetic resonance imaging. The results of this study should provide further guidance for clinicians in the risk-stratification of symptomatic patients.

Ultimately, patients who present with acute focal neurological deficits, transient or prolonged, should undergo carotid duplex to rule out carotid disease as a source of ischemia. Patients who are asymptomatic but who have a bruit or history of PAD, CAD, or familial atherosclerosis, as well as those with two or more environmental risk factors such as hypercholesterolemia, hypertension, or tobacco use, should undergo routine screening for carotid disease. This screening should begin with carotid duplex ultrasound and, if nondiagnostic, should consist of multiplanar CTA, or alternatively, contrast-enhanced MRA. These recommendations are congruent with those outlined in the AHA/ASA/SVS guidelines on extracranial carotid disease.<sup>36,37</sup>



## Medical management

Primary management of both symptomatic and asymptomatic carotid disease is aggressive medical therapy with risk factor modification. Smoking cessation is strongly advised. Smoking increases the relative risk for ischemic stroke by 25%–50%,<sup>50–52</sup> and smoking cessation alone decreases stroke risk substantially during a 5-year period when compared with continuing smokers.<sup>53,54</sup> In the Cardiovascular Health Study, the severity of carotid artery stenosis was greater in current smokers than in former smokers, and there was a significant relationship between the severity of carotid stenosis and pack-years of exposure to tobacco.<sup>55</sup> In addition to smoking cessation, patients with extracranial or vertebral atherosclerosis are recommended to undergo statin therapy to target a target low-density lipoprotein lower than 100 mg/dL.<sup>36</sup> The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial<sup>56</sup> prospectively compared the effect of atorvastatin (80 mg daily) against placebo on the risk for stroke among patients with recent stroke or TIA. Statin therapy reduced the absolute risk for stroke at 5 years by 2.2%, the relative risk for all stroke by 16%, and the relative risk for ischemic stroke by 22%. In 2002, the Heart Protection Study<sup>57</sup> provided evidence that statin therapy can reduce the progression, or perhaps even induce regression, of carotid disease, with a 50% reduction in CEA patients randomized to statin therapy. There is no question that statin therapy is part of an “optimal medical therapy” regimen with regard to contemporary carotid disease.

Antihypertensive treatment is also recommended in patients with asymptomatic extracranial disease to achieve a target blood pressure of less than 140/90 mmHg. The relationship between hypertension and increased stroke is well-established.<sup>58</sup> Most striking, however, is the finding that for each 10 mmHg increase in blood pressure, the risk for stroke increases by 30%–45%.<sup>59</sup> In the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) trial, combined use of an angiotensin-converting enzyme inhibitor and thiazide diuretic reduced the risk for recurrent stroke by 30%, even in nonhypertensive patients. In symptomatic patients with high-grade carotid stenosis, however, it is unclear whether rigid blood pressure control reduces stroke risk, as low blood pressure may exacerbate cerebral ischemia and hypoperfusion.<sup>60</sup>

With regard to antiplatelet therapy, aspirin in doses of 75–325 mg is recommended for patients with carotid atherosclerosis.<sup>36</sup> Similar to CAD and myocardial infarction (MI), the benefit of aspirin has not been proven for prevention of stroke in asymptomatic patients.<sup>61</sup> However, the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid

Stenosis (CARESS) trial demonstrated that in patients with recently symptomatic carotid stenosis, combination therapy with clopidogrel and aspirin was more effective than aspirin alone in reducing asymptomatic embolization.<sup>62</sup> In addition, recent results from the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial also showed a benefit of aspirin plus clopidogrel given for 21 days after TIA.<sup>63</sup> Because of the risk for intracerebral hemorrhage in patients receiving long-term dual-antiplatelet therapy, it is unclear whether there is a benefit to patients receiving dual therapy beyond this short-term time; however, there is good evidence to show that dual antiplatelet therapy should be at least be temporarily started in patients presenting with TIA.

Several papers have argued that medical therapy alone should be the preferred treatment for severe asymptomatic carotid stenosis.<sup>15,16,64</sup> This is not an unreasonable argument, given that the many patients with asymptomatic carotid stenosis face a greater risk for death caused by MI than of stroke<sup>65</sup> and that meta-analysis of incidence rate data shows that medical therapy alone for asymptomatic carotid stenosis incurs an ipsilateral stroke rate of 1.68% per year, particularly in studies conducted in the past decade (1.13% per year).<sup>14</sup> Not to be overlooked, however, is the large body of data in favor of carotid intervention in a select group of patients, an area of research spanning more than 30 years. The 2011 SVS Consensus Guidelines<sup>37</sup> note that “neurologically asymptomatic patients with >60% stenosis should be considered for CEA provided that the patient has a 3–5 year life expectancy and perioperative stroke and death rates can be <3%”, whereas the 2011 American Stroke Consensus Guidelines<sup>36</sup> state that “patients ... who experience nondisabling ischemic stroke or transient cerebral ischemic symptoms ... within 6 months ... should undergo CEA if the diameter of the lumen of the ipsilateral internal carotid artery is reduced more than 70% as documented by noninvasive imaging ... and the anticipated rate of perioperative stroke or mortality is less than 6%”. The guidelines also state that “it is reasonable to perform CEA in asymptomatic patients who have more than 70% stenosis of the internal carotid artery if the risk for perioperative stroke, MI, and death is low”. Understanding the pivotal studies that support these conclusions is necessary to assess the risks and benefits of revascularization for carotid atherosclerotic disease.

## Carotid endarterectomy in symptomatic patients

The first major randomized trial in patients with symptomatic carotid artery stenosis was NASCET.<sup>10,21,66</sup> It involved

50 medical centers and 659 patients with carotid stenosis 70%–99% randomized to medical or surgical treatment. The trial was scheduled to proceed for 5 years, but because of a statistically significant difference in favor of CEA compared with maximal medical antiplatelet therapy with aspirin, the study was stopped at 2 years. The 2-year risk for ipsilateral stroke was 26% in patients treated with medical management compared with 9% in patients treated with surgery ( $P < 0.0001$ ). Among the patients with severe stenosis who underwent endarterectomy, the 30-day rate of death or disabling ipsilateral stroke was 2.1%; this rate increased to only 6.7% at 8 years. Patients with moderate stenosis of 50%–69%, however, only had a modest benefit from CEA, whereas those with less than 50% stenosis had no benefit.

The ECST,<sup>22,67</sup> another large randomized trial comparing CEA plus medical management with medical management alone, also found a benefit to CEA in symptomatic patients with stenosis more than 80%. ECST randomized more than 3,000 patients in Europe and Australia in 97 centers, with a follow-up of 6 years. Patients were required to have an ischemic cerebral vascular event in a distribution ipsilateral to a carotid stenosis greater than 60% within 6 months of randomization. The 3-year stroke or death risk for the 70%–99% stenosis group was 26.5% for the control group and 14.9% for the surgery group, with an absolute benefit from surgery of 11.6%. There was no overall effect below about 70%–80% stenosis, leading the authors to conclude that the benefit of the treatment was based on a stenosis of 80% or above.

An important distinction between NASCET and ECST was the method used to calculate degree of stenosis. The NASCET study measured the degree of stenosis by taking the luminal diameter at the maximal stenosis and comparing it with the luminal diameter of the portion of the “normal” internal carotid artery distal to the area of stenosis, using the following formula: percentage of stenosis =  $[1 - (\text{minimal diameter}/\text{distal diameter})] \times 100$ .<sup>21</sup> ECST approximated the outer wall diameter at the point of maximum stenosis in the internal carotid artery or carotid bifurcation and then calculated the true luminal diameter at the area of maximal stenosis.<sup>22</sup> The percentage of stenosis was calculated by dividing the minimal luminal diameter by the estimated outer wall diameter. This led to a discrepancy between the two trials, where the NASCET-calculated degree of stenosis was somewhat less than the ECST-calculated degree of stenosis. To convert this difference, a formula was calculated by Rothwell et al<sup>68</sup> in 1994 in which the ECST-measured degree of stenosis was equal to 0.6 times the NASCET-measured degree of stenosis plus 40. Taking this standardization a step

further, Rothwell et al went on to reanalyze the ECST, data using the NASCET method.<sup>67</sup> On the basis of a direct comparison of groups with standardized stenoses, this reanalysis showed that surgery is highly effective in patients with 70%–99% stenosis, and not just 80%–99%, an observation that was confirmed by further meta-analysis of the trials.<sup>69</sup> The 21.2% reduction in 5-year absolute risk for any stroke or surgical death with surgery in the ECST in patients with 70%–99% stenosis without near occlusion was comparable to the 15.0% absolute risk reduction at 2 years originally reported in NASCET.

Although these two major trials demonstrated the benefit of CEA in symptomatic carotid patients, they did not address the issue of time to intervention after onset of symptoms. A meta-analysis of major trials of carotid endarterectomy showed that the benefit from this procedure was greatest when it was performed within 2 weeks after a TIA or stroke.<sup>70</sup> A recent study found that 25% of strokes are preceded by a TIA, and 45% of the TIAs occur the week prior.<sup>71</sup> Interestingly, carotid intervention for patients with a stroke-in-evolution (worsening symptoms over the course of hours to days) is unclear,<sup>72,73</sup> with poor outcomes for patients with stroke-in-evolution, regardless of medical or surgical management.<sup>72</sup>

## Carotid endarterectomy in asymptomatic patients

The most appropriate management of asymptomatic carotid stenosis is less clear than for symptomatic disease (Table 1). The ACAS trial<sup>12</sup> was a multicenter, randomized trial conducted in 39 medical centers in the United States and Canada that enrolled patients between 1987 and 1993. In this trial, 1,662 patients with asymptomatic carotid artery stenosis greater than 60% were randomized to medical therapy or CEA. The results demonstrated a 5-year stroke risk of 11% versus 5.1% for medical therapy versus CEA, suggesting a benefit to CEA for asymptomatic patients; the trial was discontinued after a mean follow-up of 2.7 years. The combined risk for perioperative stroke or death was 1.5%. This study demonstrated clearly a benefit for the surgical treatment of asymptomatic carotid stenosis greater than 60% if the perioperative stroke rate can be kept less than 2.3%. Unfortunately, this benefit was not substantiated in women.

Because ACAS reported a 47% relative reduction in the risk for ipsilateral stroke and perioperative death in patients randomized to surgery, its results led to major increases in rates of endarterectomy for asymptomatic stenosis in some countries, most notably the United States. In contrast, the

Table I. Evidence for the Treatment of Asymptomatic Carotid Stenosis

	Year and location	Patients, n (follow-up time, years)	Stenosis Inclusion	Excluded medical conditions	Composite primary endpoint	Findings	Perioperative risk of stroke or death within 30 days	Major criticisms
ACAS <sup>12</sup>	1995, United States	1,662 (median 2.7)	≥60% stenosis	TIA or stroke symptoms, lifespan <5 years	Ipsilateral stroke or any perioperative stroke and death	5-year stroke risk of 11% vs 5.1% for medical therapy vs CEA (P=0.004)	1.5%	Medical management not contemporary; surgeon inclusion criteria too stringent
ACST <sup>13</sup>	2004, Europe	3,120 (mean 3.4)	≥60% stenosis	Previous ipsilateral CEA, poor surgical risk, cardiac source of emboli	Perioperative death, stroke or MI, nonperioperative stroke	5-year stroke risks 11.8% vs 6.4% for medical vs CEA (<75 years old; P<0.0001)	3.1%	Medical management not contemporary
SAPPHIRE <sup>20</sup>	2008, North America	237 (=3.0)	≥80% stenosis with one or more criteria for high surgical risk	Ischemic stroke <48 hours, intraluminal thrombus, target vessel occlusion, intracranial aneurysm, bleeding disorder, ostial lesion of common carotid or brachiocephalic	Cumulative incidence of death, stroke, or myocardial infarction during follow-up of 3 years	3-year CAS vs CEA, 24.6% vs. 26.9% (no statistical comparison) for high-risk asymptomatic	CAS 5.4%, CEA 4.6% for high-risk asymptomatic	Biased randomization, industry-sponsored, surgeon/interventionalist skills biased
CREST <sup>21</sup>	2010, United States	1,181 (median 2.5)	≥60% stenosis on angio, ≥70% by ultrasound	Disabling stroke, chronic atrial fibrillation <6 months	Stroke, MI, death 30 days periprocedural or ipsilateral stroke during follow-up	4-year CEA vs CAS, 4.9% vs 5.6% (P=0.56) for asymptomatic	CAS 2.5%, CEA 1.4% for asymptomatic	CAS patients received more intensive antiplatelet therapy, inclusion of asymptomatic patients, age-stratified difference

**Abbreviations:** ACAS, Asymptomatic Carotid Atherosclerosis Surgery; ACST, Asymptomatic Carotid Stenosis Trial; CREST, Carotid Revascularization Endarterectomy Versus Stenting Trial; CEA, carotid endarterectomy; ASA, aspirin; CAS, carotid artery stent; TIA, transient ischemic attack; CTA, computed tomography angiography; MRA, magnetic resonance angiography; MI, myocardial infarction; SAPPHIRE, Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy; vs, versus.

ACAS results had little effect on endarterectomy rates in other countries, such as the United Kingdom, where it was felt that the benefit did not justify the cost. One of the major criticisms of ACAS was that it only accepted surgeons with an excellent safety record, rejecting 40% of initial applicants and subsequently barring from further participation some surgeons who had adverse operative outcomes during the trial.<sup>74</sup> This hampered replication of outcomes similar to ACAS in a number of case series after its publication.<sup>75</sup>

A similar study in Europe, the ACST,<sup>13,76</sup> enrolled patients between 1993 and 2003, randomizing 3,120 patients with more than 60% mainly asymptomatic carotid stenosis (12% had symptoms at least 6 months previously) to immediate CEA plus medical treatment versus medical treatment alone or until the operation became necessary. Surgeons were required to provide evidence of an operative risk of 6% or lower for their last 50 patients having an endarterectomy for asymptomatic stenosis, but none were excluded on the basis of his/her operative risk during the trial. Selection of patients was based on the “uncertainty principle”, with very few exclusion criteria and with stenosis assessed by Doppler ultrasonography. Although the 5-year risk for any stroke or perioperative death in the nonsurgical group was lower in ACST (11.8%) than in ACAS (17.5%), the absolute reductions in 5-year risk with surgery (5.3%) were not substantially different from ACAS (5.1%). The only other major difference was the 30-day perioperative stroke or death: 3.1% compared with 1.5% in ACAS. Unlike trials in symptomatic patients, neither ACST nor ACAS showed increasing benefit from surgery with increasing degree of stenosis within the 60%–99% range. In both studies, the absolute risk reduction for stroke associated with CEA was only 1 percentage point per year; a small but definite reduction in the risk for disabling or fatal stroke with surgery that is likely only applicable to patients with a prolonged life expectancy.

Because these two trials were conducted two decades ago, their data have prompted some authors to conclude that the benefit of CEA over medical therapy was a result of inadequate medical therapy at the time. Spence et al reviewed data on 468 patients with asymptomatic, high-grade carotid stenosis: 199 treated before 2003 and 269 after 2003.<sup>77</sup> The latter group received an intensified medical regimen aimed to achieve a better control of plasma lipids. The primary outcomes were microemboli detected by transcranial Doppler, plaque progression by ultrasound, and cardiovascular event rates. Before 2003, 17.6% had stroke, death, MI, or CEA for symptoms versus 5.6% after 2003 ( $P<0.001$ ). The rate of carotid plaque progression in the first year of follow-up

has declined from 69 to 23 mm<sup>2</sup> ( $P<0.001$ ).<sup>77</sup> Marquardt et al found that the average annual event rates with optimal medical treatment were 0.34% for any ipsilateral ischemic stroke, 0% for disabling ipsilateral stroke, and 1.78% for ipsilateral TIA during a mean follow-up period of 3 years.<sup>17</sup> In this case, “optimal medical therapy” (OMT) was defined as antiplatelet therapy with aspirin or clopidogrel, statin therapy, and antihypertensive therapy for those patients whose blood pressure was higher than 130/80 mmHg. Successful achievement of target values for these factors was never mentioned. In contrast to this, a recent retrospective study on 794 asymptomatic patients with moderate (50%–69%) carotid stenosis concluded that OMT failed to prevent carotid disease progression or development of ipsilateral symptoms in 45% of patients.<sup>20</sup> In this case, OMT was defined as a low-density lipoprotein goal of lower than 100 mg/dL and aspirin. Smoking cessation and blood pressure goals were not included. To address the controversy stemming from best medical therapy versus surgical intervention in patients with carotid stenosis, the ECST-2 is now recruiting patients with asymptomatic or symptomatic carotid stenosis in whom the clinicians are uncertain whether revascularization is required. Patients will be included on the basis of a carotid artery risk score modeled after risk stratification described in ECST-1<sup>78</sup> and randomized to immediate revascularization or initial optimized medical management alone. Of note, the SVS recently released its high-impact clinical research priorities, “defin[ing] the optimal management of asymptomatic carotid stenosis” as its top priority.<sup>79</sup> Data from ECST-2 and other ongoing trials should yield more useful and clinically applicable information relevant to patients being treated with optimal medical therapy.

## Carotid stenting

CAS has emerged as an alternative to carotid endarterectomy in patients at high risk for complications from endarterectomy, such as those with contralateral occlusion, severe coronary artery disease, prior neck radiation, or prior carotid endarterectomy. The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE)<sup>80</sup> study enrolled symptomatic patients with carotid stenosis higher than 70% to CAS versus CEA. SAPPHIRE found that stenting (with an embolic protection device) was not inferior to endarterectomy with respect to stroke, MI, or death at 30 days (4.8% versus 9.8%) and the rate of ipsilateral stroke or death between 31 days, 1 year and, 3 years.<sup>80</sup> Sharp criticism<sup>81,82</sup> of SAPPHIRE, however, centers around biased randomization with regard to surgeon/



interventionalist skills, exclusion of more than 400 patients from the trial because of surgeon-deemed “high-risk status”, industry-sponsored interests, lack of experience of surgeons performing CEA, a heterogeneous patient population, and lack of information regarding antiplatelet therapy. These flaws have prevented it from being strong evidence that CAS is equivalent to CEA.

Similar in outcome to SAPHIRE, the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE)<sup>83</sup> trial randomized 1,200 patients with symptomatic carotid stenosis greater than 70% to CAS versus CEA. The trial was terminated early as a result of low conditional power and funding concerns.<sup>84</sup> The 2-year rate of ipsilateral or periprocedural stroke or death did not differ significantly, at 9.5% for CAS versus 8.8% for CEA; however, pooled subgroup analysis has since demonstrated that symptomatic patients older than 70 years had a twofold risk for stroke with CAS compared with CEA. Drawbacks to this study were that physicians who had performed as few as 10 CAS procedures could treat patients in the study under the supervision of a tutor, and embolic protection devices were used in only 27% of patients.

In favor of CEA over CAS, the International Carotid Stenting Study (ICSS)<sup>85</sup> is a randomized trial comparing symptomatic patients with carotid stenosis greater than 50%. The outcome in the published interim analysis was 120-day stroke, death, or procedural MI. According to the interim analysis, CEA had lower rates of stroke, death, or periprocedural MI at 5.4% compared with 8.5% for CAS. Some have claimed the CAS operators in ICSS were inexperienced and less skillful than many currently performing the procedure, thereby making the trial obsolete. Many felt that the CAS procedures described in ICSS did not reflect the current state of the art, arguing that another study using stents and embolic protection devices with higher efficacy was warranted.<sup>86</sup> The Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S),<sup>87</sup> a randomized clinical trial in Europe comparing CAS with CEA in symptomatic patients with stenosis greater than 60%, was stopped early after randomization of 527 patients to CEA or CAS as a result of 30-day safety concerns with CAS. The 30-day rate of disabling stroke and death was 1.5% after CEA and 3.4% after CAS, with a relative risk of 2.2 with CAS.<sup>87</sup> The cumulative probability of periprocedural stroke or death and nonprocedural ipsilateral stroke after 4 years of follow-up was higher with stenting than with endarterectomy (11.1% versus 6.2%),<sup>87</sup> likely associated with variable stent operator experience.<sup>88</sup> Perioperative MI was not included as a primary endpoint. Follow-up to this study demonstrated

that technical and anatomic factors, especially extreme angulation of the carotid artery, had an effect on the risks of carotid angioplasty and stenting.<sup>89</sup> Recent pooled analysis of SPACE, ICSS, and EVA-3S shows that operator experience with stenting in these three studies had a significant effect on 30-day risk for stroke or death, leading its authors to conclude that carotid stenting should be performed only by operators with an annual procedure volume of 6 or more cases per year.<sup>90</sup>

Perhaps the most widely regarded and only level 1 trial on carotid stenting is the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST),<sup>91</sup> a National Institutes of Health-sponsored, randomized, multicenter trial comparing CAS with CEA. The study randomized 2,502 patients undergoing procedures from 2000–2008 and included patients with standard risk with either symptomatic disease and greater than 50% stenosis or asymptomatic disease with greater than 60% stenosis (although these asymptomatic patients were only enrolled from 2005 onward). CREST operators underwent a vigorous credentialing process. Outcomes were MI, stroke, or death within 30 days and ipsilateral stroke during a 4-year follow-up period. Rates of 30-day MI, stroke, or death were not significantly different between CAS (5.2%) and CEA (4.5%), nor were ipsilateral 4-year stroke rates (7.2% for CAS and 6.8% for CEA).<sup>91</sup> These results allowed the authors to conclude that the risk for CAS and CEA “did not differ significantly” in patients with symptomatic and asymptomatic carotid disease. There was also no difference in the rate of restenosis between the groups during the 2-year follow-up (6.0% for CAS and 6.3% for CEA).<sup>92</sup> Subgroup analysis, however, showed that CAS had a higher rate of perioperative stroke (4.1% versus 2.3%), particularly in symptomatic patients,<sup>93</sup> whereas CEA had a higher rate of MI (2.3% versus 1.1%).<sup>91</sup> Women<sup>94</sup> and patients aged 65 years or older<sup>95</sup> also had higher rates of stroke and death with CAS compared with CEA. One of the limitations to CREST is that patients randomized to CAS received more intense antiplatelet therapy than those who underwent CEA,<sup>91</sup> potentially confounding the MI endpoint. In addition, although stroke and MI were considered equivalent endpoints, non-Q wave troponin elevation MI was significantly less disabling than was stroke, an overlooked functional outcome. Regardless of functional outcome, however, both minor MI and minor stroke were associated with decreased life expectancy,<sup>96</sup> which may be one reason these endpoints were grouped. In aggregate, several meta-analyses and case studies on carotid stenosis have been unable to show superiority of CAS to CEA with regard to incidence

of stroke or death for periprocedural outcomes, especially in symptomatic patients.<sup>97–102</sup>

The myriad of results from carotid stenting trials have made it clear that patient subgroup analysis, operator experience and technique, symptomatic versus asymptomatic status, medical management goals, and the primary endpoints studied all affect interpretation of the results. A recent paper by Jim et al demonstrates no difference in 30-day outcomes on the basis of sex for either CEA or CAS.<sup>103</sup> Further studies are needed to strengthen this argument and validate long-term outcomes. To date, there are several ongoing large trials actively enrolling patients in an effort to improve the body of knowledge on these topics. ECST-2 is a randomized, controlled, open, prospective clinical trial with blinded outcome assessment comparing current carotid revascularization therapies (CEA or CAS) in combination with OMT for atherosclerotic carotid stenosis with OMT alone for symptomatic and asymptomatic patients with a stenosis of at least 50%. Unlike ACST-2, in which asymptomatic patients are deemed in need of treatment, either medical or procedural, ECST-2 is recruiting patients with both symptomatic and asymptomatic stenosis when the clinician is uncertain of the benefit of revascularization. A third trial, the SPACE-2 study, is randomizing patients with asymptomatic stenosis three ways between CAS, CEA, and best medical treatment in Germany, Austria, and Switzerland. The proposed CREST-2 will also compare revascularization with medical therapy in patients with asymptomatic carotid artery disease.

## Conclusion

Despite a decline during the recent decades in stroke-related death, the incidence of stroke has remained unchanged or slightly increased,<sup>11</sup> and extracranial carotid artery stenosis can be implicated in 20%–30% of all strokes.<sup>3–5</sup> Patients with symptoms of TIA or stroke should undergo carotid duplex ultrasound in addition to standard stroke protocol imaging of the head. Although no prospective randomized controlled trials have demonstrated a reasonable number needed to treat to make screening of carotid disease in asymptomatic patients a cost-effective mandate, current practice guidelines in the United States state that it is reasonable to conduct a carotid duplex ultrasound in patients with a bruit, symptoms of TIA, CAD, PAD, or two or more cardiovascular risk factors.<sup>36</sup> CTA and MRA should be reserved for patients in whom duplex results are unequivocal or for preoperative planning.<sup>104–106</sup> Medical therapy and risk factor modification are first-line therapies for all patients with carotid occlusive disease, including smoking cessation, statin therapy, antiplatelet therapy, and antihypertensive therapy.<sup>15,64</sup> Evidence for the treatment

of patients with symptomatic carotid stenosis higher than 70% with either CAS or CEA is compelling, and several trials demonstrate a benefit to carotid revascularization in the symptomatic patient population.<sup>21,22,93</sup> Asymptomatic carotid stenosis is perhaps more controversial, with the largest trials only demonstrating a 1% per year risk stroke reduction with CEA.<sup>12,76</sup> Although there are sufficient data to advocate for aggressive medical therapy as the primary mode of treatment for asymptomatic carotid stenosis (Table 1), there are data to suggest that certain patient populations will benefit from stroke risk reduction with carotid revascularization. In the United States, the ASA, AHA, and SVS have created consensus guidelines<sup>36</sup> stating that CEA is reasonable in patients with high-grade asymptomatic stenosis, a reasonable life expectancy, and perioperative risk of less than 3%.<sup>36,37</sup>

The best-available evidence with regard to CAS versus CEA demonstrates no difference between the two procedures in early perioperative stroke, MI, or death, and no difference in 4-year ipsilateral stroke risk.<sup>91</sup> However, as a result of higher perioperative risks of stroke in patients undergoing CAS, particularly in symptomatic, female, or elderly patients, it is difficult to recommend CAS over CEA except in populations with prohibitive cardiac risk, previous carotid surgery, or prior neck radiation.<sup>80,107</sup> Newer data, demonstrating lower risk in these previously deemed high-risk populations<sup>103</sup> will certainly alter these recommendations as the field evolves.

At this time, there is a great deal of interest surrounding the magnitude of perioperative risk in specific asymptomatic patient subsets and about using predictive factors to stratify patients with high-risk asymptomatic stenosis in an attempt to identify those best suited to surgery. In recent years, several studies have demonstrated low risk for CEA in women,<sup>108</sup> octogenarians,<sup>109</sup> and patients undergoing CEA using local anesthesia.<sup>110</sup> Several papers have also favored the eversion technique of CEA, reporting that it prevents carotid sinus denervation and low baroreflex sensitivity, an independent risk factor for cardiovascular disease.<sup>111–113</sup> Likewise, several studies have identified factors predicting risk stratification for carotid disease, such as contralateral occlusion,<sup>114</sup> chronic kidney disease,<sup>20</sup> homocysteine levels,<sup>115</sup> and plaque quality based on advanced imaging modalities.<sup>45–47,49</sup> Many authors have proposed algorithms for the stratification of patients to parse out those patients who may benefit the most from revascularization.<sup>38,101,116</sup> Until the results of large, well-designed randomized controlled trials are available, these algorithms are the most reasonable models to predict the risks and benefits of carotid revascularization for an individual patient.

## Disclosure

The authors report no conflicts of interest in this work.

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