

# Multimodality Management of Carotid Artery Stenosis: Reviewing the Class-I Evidence

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Stroke is the third leading cause of mortality in the United States; approximately every three minutes a person will die from a stroke. Extracranial internal carotid artery stenosis (EICAS) accounts for approximately 25% of ischemic strokes, with an incidence as high as 10% in people aged >80 years. Clinically, EICAS can manifest as a transient ischemic attack, although the vast majority of EICAS patients are asymptomatic. Symptomatic EICAS patients are at high risk for ischemic stroke if left untreated, and previous literature has shown that even patients with asymptomatic EICAS require treatment because the natural history of the disease precipitates an overall mortality rate of 4–7%. The three major treatment modalities for EICAS presently are medical management, carotid endarterectomy and carotid angioplasty with stenting. This review examines the class-I evidence (prospective randomized controlled trials) regarding optimal treatment modalities for management of symptomatic and asymptomatic carotid stenosis.

**Key words:** carotid endarterectomy ■ angioplasty ■ stent ■ aspirin

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## INTRODUCTION

Stroke is the third leading cause of mortality in the United States, occurring in approximately 600,000 people annually.<sup>1-2</sup> Accounting for an estimated \$30 billion annually in treatment and lost productivity, approximately every three minutes a person in the United States will die from a stroke.<sup>3-4</sup> Approximately 80% of strokes are ischemic in nature, with the remaining 20% being hemorrhagic.<sup>5</sup>

Extracranial internal carotid artery stenosis (EICAS) accounts for approximately 25% of ischemic strokes.<sup>6</sup> The

incidence of EICAS is approximately 0.5% in the sixth decade and rises to as high as 10% in people aged >80 years.<sup>7-9</sup> The predominant clinical manifestation of EICAS is transient ischemic attack (TIA), although the vast majority of EICAS patients are asymptomatic.<sup>8,9</sup> Patients with symptomatic EICAS are at high risk for ischemic stroke if left untreated. Previous literature has shown that even in patients with asymptomatic EICAS, the natural history of the disease precipitates an annual risk for stroke, stroke mortality and coronary ischemic events of 2%, 0.6% and 7%, respectively, with an overall mortality of 4–7%.<sup>10-13</sup> Consequently, the presence of EICAS necessitates treatment, even in asymptomatic patients.

In this review, the major class-I level studies regarding treatment of symptomatic and asymptomatic carotid stenosis patients will be reviewed and analyzed with regard to impact on patient management in these two patient populations.

## TREATMENT MODALITIES FOR EICAS

The degree of stenosis, determined by angiography or ultrasound, is classically defined as mild (0–29%), moderate (30–69%) or severe ( $\geq 70\%$ ) stenosis at the carotid bifurcation.<sup>14</sup> There are presently three major treatment modalities for EICAS: 1) medical management, 2) carotid endarterectomy, and 3) carotid angioplasty with stenting. A brief description of each modality follows.

### Medical Management

Medical management is by far the most commonly utilized treatment of EICAS, traditionally involving low-dose aspirin (81–325 mg) taken orally on a daily basis.<sup>15,16</sup> It is the only modality considered an essential aspect of management for any patient with EICAS, and is utilized either alone or in conjunction with more invasive treatment modalities. For the majority of studies, medical management with low-dose aspirin is referred to as best medical treatment.

### Carotid Endarterectomy

Carotid endarterectomy is a surgical procedure performed usually by either a neurosurgeon or a general

vascular surgeon. The details of the procedure have been described extensively in previous literature.<sup>17</sup> Briefly, the patient is positioned supine on the operating room table with the head extended and turned away from the side of operation. Neck extension is facilitated using several folded pillowcases between the patient's shoulder blades, and the degree of rotation of the head is determined by the relationship of the external carotid artery and internal carotid artery on preoperative angiography.

Following appropriate anesthesia and intraoperative monitoring, a linear skin incision is made at the level of the carotid bifurcation (preoperatively determined by angiography) along the anterior portion of the sternomastoid muscles. The skin and subcutaneous tissues are sharply divided to the level of the platysma, which is always identified and sharply divided as well. Self-retaining retractors are then placed on the medial side and left superficially to prevent retraction injury to the laryngeal nerves. Dissection proceeds in the mid-portion of the wound down the sternomastoid muscle until the jugular vein is identified, which is the key anatomical landmark. Following retraction of the jugular vein with blunt retractors, several small veins are ligated and divided, enabling the underlying carotid artery to be visualized and the common carotid artery, external carotid artery and internal carotid artery to be isolated. Following complete dissection of the internal carotid artery, the hypoglossal nerve can be visualized and retracted using a vessel loop.<sup>17</sup>

After adequate control distal to the plaque has been achieved, the common carotid artery is cross-clamped, allowing for arteriotomy, plaque visualization and subsequent plaque removal.<sup>17</sup> Following removal, a careful search is made to locate and remove remaining fragments within the vessel wall. Arterial repair is then performed with sutures, after which the cross-clamps are removed and the suture lines are inspected for leaks. The common carotid artery, internal carotid artery and external carotid artery are then checked with Dopplers to ensure patency. Subsequently, the retractors are removed, and the wound is closed in layers, ending the operation.<sup>17</sup> Patients are then transferred to the intensive care unit and are often discharged home within 1–3 days following surgery.

## Carotid Angioplasty with Stenting

Carotid angioplasty with stenting is an endovascular procedure, usually performed by neurosurgeons, radiologists, vascular surgeons or neurologists who have been certified in interventional neuroradiology (usually through fellowship training). As with carotid endarterectomy, the details of carotid angioplasty have been extensively described in previous literature.<sup>18</sup> In general, the patient is positioned supine on the interventional suite table and is placed under conscious sedation via local anesthesia of the femoral artery region. Pedal pulses are examined and documented for later ref-

erence, after which a sheath is inserted into the common femoral artery and a baseline activated clotting time is obtained. Subsequently, preliminary diagnostic angiography of both carotid arteries, including the intracranial circulation, is performed, and selective catheterization of the common carotid artery is performed, often with small-diameter catheters along with soft-tipped guide wires. Standard angiographic projections (anteroposterior, lateral, ipsilateral anterior oblique) demonstrating the carotid bifurcation are then performed, after which images are obtained to assess the adequacy of the intracranial collateral circulation.

An intravenous loading dose of heparin is then initiated, after which an exchange guide wire is placed in the ipsilateral external carotid artery, and the guiding catheter is advanced over this into the distal common carotid artery using a coaxial system.<sup>18</sup> The guiding catheter is then connected to a continuous pressurized saline and heparin flush, after which the internal carotid artery is traversed with a microcatheter to reduce the risk of embolism and is advanced to the petrocavernous segment of the internal carotid artery. Subsequently, balloon angioplasty is used to predilate the lesion.

A single, 30-second balloon inflation is performed, prior to which intravenous atropine is administered to prevent reflex bradycardia or asystole. After this, a road map is obtained, and the stent-delivery catheter is then advanced over the immobilized guide wire. The stent is carefully advanced across the lesion, and when satisfactorily positioned, it is deployed by immobilizing the delivery catheter and expanding the stent (either self-expanding or balloon expandable). Subsequently, the delivery catheter/balloon can be carefully withdrawn while ensuring the stent remains stationary.<sup>18</sup> Postdeployment angioplasty is performed using a high-pressure, semi-compliant balloon to expand regions of residual stent narrowing, and following stent placement, AP and lateral cerebral angiograms are performed to exclude any embolic branch occlusion and to document new patterns of flow.

Once the APTT has returned to baseline, the femoral sheath is removed. Postoperative hematocrit is obtained, and the patient is monitored in the ICU for 12–24 hours. Administration of clopidogrel 75 mg/day and aspirin 325 mg/day is continued indefinitely. Follow-up ultrasound exam of the neck is subsequently performed at six months to document continued patency, since restenosis usually occurs within the first six months of treatment.<sup>18</sup>

## Levels of Evidence

Research studies provide an objective method of evaluating the efficacy of medical and surgical therapies. The degree to which a study influences management is related to the level of evidence that it provides. There are generally five classes of evidence within which research studies fall, which are listed in Table 1. Of these classes,

class-I evidence (derived from a prospective randomized controlled trial) is the most powerful in assessing the virtue of a particular treatment modality. This review examines the existing class-I evidence for management of symptomatic and asymptomatic carotid stenosis.

## Treatment of Symptomatic Carotid Artery Stenosis

For patients with symptomatic carotid artery stenosis, a number of clinical studies at the class-I level have been completed examining the optimal treatment modalities for this patient population.

## Best Medical Therapy versus Carotid Endarterectomy

Only two class-I studies have been completed comparing medical management versus carotid endarterectomy: the North American Symptomatic Carotid Endarterectomy Trial (NASCET), and the European Carotid Surgery Trial (ECST).<sup>14,19-21</sup> A third trial, the Veterans Affairs Cooperative Studies Program 309 Trial, was also started but was stopped midway following the results of NASCET and ECST.<sup>22</sup>

The NASCET trial involved 50 centers throughout the United States and Canada.<sup>14,19</sup> Patients meeting the definition of symptomatic carotid stenosis in this study had to exhibit carotid distribution TIA or nondisabling stroke in the 4–6 months prior to trial entry. All patients had to have a minimum five-year life expectancy in order to be included. Criteria for permanent exclusion included: 1) an intracranial lesion more severe than the surgically accessible carotid lesion, or 2) cerebral infarction depriving all useful functions in the affected territory. Patients were excluded on a temporary basis if they exhibited one of the following: 1) uncontrolled hypertension, diabetes or unstable angina; 2) myocardial infarction within the previous six months; or 3) signs of progressive neurological dysfunction. For the purposes of

NASCET, best medical therapy was defined as a daily oral dose of low-dose aspirin. Patients deemed eligible were randomized to aspirin alone or aspirin + carotid endarterectomy.

The results of NASCET revealed the following for patients with 70–99% stenosis: a two-year ipsilateral stroke risk of 24.5% in the medical group versus only 8.6% in the surgical group. This yielded an absolute risk reduction of carotid endarterectomy of 15.9%, which was statistically significant ( $P < 0.001$ ). Furthermore, the number needed to treat was six, meaning that for every six patients treated with carotid endarterectomy + aspirin instead of aspirin alone, one ipsilateral stroke was prevented at two years following surgery. The findings at five years were remarkably similar: the ipsilateral stroke risk at five years in the medical group was 28% versus 13% in the surgical group, with a number needed to treat of six. The 30-day surgical ipsilateral stroke/death rate was 5.8% at both two and five years.

For patients with 50–69% stenosis, the two-year ipsilateral stroke risk in the medical group was 14.6% versus only 9.3% in the surgical group, for an absolute risk reduction of 5.3% ( $p < 0.05$ ) and a number needed to treat of 19. The five-year ipsilateral stroke risk was similar: 22.2% in the medical group, 15.7% in the surgical group, a statistically significant absolute risk reduction of surgery ( $p < 0.05$ ) and a number needed to treat of 15. The 30-day surgical ipsilateral stroke/death rate was 5.8% at both two and five years.

For patients with 0–49% stenosis, the results were less convincing: the two-year ipsilateral stroke risk was 11.7% in the medical group and 10.2% in the surgical group, a difference that was not significant. This insignificance was also found for the five-year ipsilateral stroke risk, which was 18.7% in the medical group and 14.9% in the surgical group. The 30-day surgical ipsilateral stroke/death rate was 6.5% at both two and five years for these patients.

**Table 1. Levels of evidence classifying the impact of research studies**

Level of Evidence	Design of Research Study	Examples
Class I	Randomized, controlled trial	Prospective study involving predetermined eligibility criteria and outcome measures in which receipt of the treatment under evaluation is randomized.
Class II Class III	Nonrandomized controlled trials Observational studies with controls	Similar to class I but without randomization <ul style="list-style-type: none"> <li>• Retrospective interrupted time studies with controls</li> <li>• Case-control studies with controls</li> <li>• Cohort studies with controls</li> </ul>
Class IV	Observational studies without controls	Similar to class III but without controls; also includes: <ul style="list-style-type: none"> <li>• Case series</li> <li>• Case reports</li> </ul>
Class V	Expert opinion	Invited commentary

The ECST involved 97 centers in 15 European countries, with several similarities to NASCET, including definition of symptomatic carotid stenosis, inclusion criteria, exclusion criteria, definition of best medical therapy and group randomization.<sup>20,21</sup> A main methodologic difference between the two trials relates to the manner by which carotid stenosis was defined. In the NASCET trial, stenosis was defined as: (site of maximal narrowing) / (distal internal carotid artery diameter where vessel walls became parallel and beyond any degree of poststenotic dilatation), whereas in the ECST trial, the definition of stenosis was (site of maximal narrowing) / (estimated diameter of the normal carotid bulb).<sup>14,16,19-21</sup> Therefore, the percentage of stenosis is lower using the NASCET rather than the ECST method—a 16% NASCET stenosis = 30% ECST stenosis, while a 50% NASCET = 70% ECST stenosis, and a 70% NASCET = 82% ECST stenosis.<sup>16,23</sup>

The ECST results revealed that for 70–99% stenosis (ECST criteria), the three-year stroke/death risk in the medical group was 22% versus only 12% in the surgical group. This yielded an absolute risk reduction for carotid endarterectomy of 10%, which was statistically significant ( $p < 0.001$ ). The 30-day surgical ipsilateral stroke/death rate for patients with this degree of stenosis was 7.5%; however, for moderate and mild stenoses (using ECST criteria), the results at four and three years for stroke/death risk found surgery to be harmful versus best medical therapy alone.

These results are likely due to the overestimation of stenosis by the ECST, meaning that, for example, patients deemed with 30% stenosis on ECST would by NASCT criteria have only 16% stenosis, making them far less likely to benefit from surgery over aspirin alone. Consistent with this hypothesis is that subsequent studies reanalyzing the ECST angiograms using NASCET criteria found the results of both studies to be remarkably similar.<sup>24,25</sup>

The concordant results of NASCET and ECST established aspirin + carotid endarterectomy as the gold standard treatment modality for patients with symptomatic carotid stenosis of  $\geq 70\%$  and established aspirin alone as the gold standard for patients with symptomatic carotid stenosis of  $< 50\%$ . In patients with 50–69% symptomatic stenosis, subgroup analyses have determined any of the following characteristics to enhance the benefit of carotid endarterectomy + aspirin over aspirin alone: 1) male sex, 2) hemispheric rather than retinal TIA presentation, 3) higher degree of stenosis, 4) plaque ulceration, 5) presence of white-smatter changes (leukoaraiosis) on head CT, 6) absence of collateral pathways to the distal internal carotid artery, 7) intracranial atherosclerosis (“tandem” lesions), 8) contralateral carotid occlusion, and 9) intraluminal thrombus.<sup>19,23,25-33</sup>

### Carotid Endarterectomy versus Carotid Angioplasty with Stenting

The findings from NASCET and ECST have established carotid endarterectomy as the gold standard for invasive management of symptomatic carotid stenosis patients beyond best medical therapy. Therefore, for carotid angioplasty with stenting to become a legitimate competitor with carotid endarterectomy, class-I data are required to demonstrate the noninferiority of stenting to carotid endarterectomy for this patient population.

To this end, two recently completed trials providing class-I evidence have addressed the issue of stenting versus surgery for symptomatic carotid stenosis patients: the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial, and the Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial.<sup>34,35</sup>

The SPACE trial was a randomized noninferiority trial involving 35 institutions throughout Germany, Austria and Switzerland.<sup>34</sup> Each institution was required to compile a multidisciplinary team including an inter-

**Table 2. Summary of the class-I evidence regarding optimal management of symptomatic and asymptomatic carotid stenosis**

Patient Population	Class-I Evidence	Recommendations
Symptomatic Carotid Stenosis	NASCET trial (1991) ECST trial (1991) SPACE trial (2006) EVA-3S trial (2006)	1. Carotid endarterectomy (CEA) + aspirin (ASA) for stenosis $\geq 70\%$ is better than ASA alone 2. ASA alone for stenosis $< 50\%$ is better than ASA + CEA 3. Individualized medical judgment for 50-69% stenosis 4. Carotid angioplasty with stenting + ASA is inferior to CEA + ASA with regard to stroke and death rates at 30 days postprocedure
Asymptomatic Carotid Stenosis	ACAS trial (1995) ACST trial (2004) SAPPHIRE trial (2004)	1. CEA + ASA is better than ASA alone for $\geq 60\%$ stenosis at two and five years of follow-up 2. Carotid angioplasty with stenting + ASA is not inferior to CEA + ASA in patients with $\geq 80\%$ stenosis with regard to incidence of stroke, death or myocardial infarction at 1 year postprocedure

ventionalist, a surgeon and a stroke neurologist. Patient entry criteria involved: 1) hemispheric or retinal TIA within the previous 180 days, and 2) carotid stenosis on ultrasound of  $\geq 50\%$  by NASCET standards. The primary endpoints of this study were ipsilateral stroke or death of any cause between randomization and 30 days following treatment, consistent with NASCET and previous class-I trials.<sup>14,34</sup> Patients deemed by the multidisciplinary team as candidates for either stenting or surgery were randomized towards one or the other; all patients received aspirin preprocedure.

Endpoint comparison between the randomized groups revealed a 6.8% risk in the stenting and a 6.3% risk in the surgery group, a difference not significant ( $p=0.09$ ) to prove noninferiority of stenting versus carotid endarterectomy at 30 days postprocedure. The overall incidence of ipsilateral stroke within 30 days of intervention was 6.5% for the stenting group and only 5.1% for the carotid endarterectomy group. Although this difference was not significant, the trend towards better outcomes in the surgery group in this analysis gave support to the inferiority of stenting versus carotid endarterectomy in this patient population. In the final analysis, the SPACE trial failed to prove the noninferiority of stenting versus carotid endarterectomy as measured by stroke/death rates at 30 days postprocedure in symptomatic carotid stenosis patients.

The EVA-3S trial was a similar randomized noninferiority trial, involving 30 institutions throughout France.<sup>35</sup> Entry criteria included hemispheric/retinal TIA or nondisabling stroke within the previous 120 days, and evidence of  $\geq 60\%$  NASCET criteria carotid stenosis on angiography or ultrasound/magnetic resonance angiography. Similar randomization criteria to the SPACE trial by a multidisciplinary team from each institution was performed, with the same primary endpoints of the SPACE and NASCET trials.

The results of EVA-3S were dramatic, as the trial was stopped short (after 527 patients) of the intended 872 patients to be enrolled for reasons of safety and futility. Endpoint comparison between groups at 30 days revealed a risk of 9.6% in the stenting group and only 3.9% in the surgery group. The absolute risk *increase* of stenting was 5.7%, and for every 17 cases treated with stenting rather than surgery, one additional stroke or death occurred at 30 days post-procedure.<sup>35</sup> These results were sufficient to prove that the difference between stenting and surgery was not significant to prove the noninferiority of stenting versus carotid endarterectomy at 30 days post-procedure ( $p=0.09$ ). The overall incidence of disabling stroke within 30 days of intervention in the stenting group was 3.4% but only 1.5% in the carotid endarterectomy group. As in the SPACE trial, although this difference was not significant, the trend towards better outcomes in the surgery group lended support to the inferiority of stenting versus carotid endarterectomy.<sup>34,35</sup>

Furthermore, the EVA-3S trial revealed that a sig-

nificantly greater proportion of strokes occurred on the same day of the procedure in the stenting group than in the surgery group ( $p=0.05$ ). Therefore, the EVA-3S trial concluded that in patients with symptomatic carotid stenosis of  $\geq 60\%$ , carotid stenting was inferior to carotid endarterectomy with respect to the incidence of stroke and death at 30 days postprocedure. These results, in concordance with the SPACE trial, support the superiority of carotid endarterectomy over carotid angioplasty with stenting in patients with symptomatic carotid stenosis (Table 2).

## Asymptomatic Carotid Stenosis

The debate regarding optimal management of carotid stenosis in asymptomatic patients remains as intense as for symptomatic patients, with more at stake due to the fact that the vast majority of carotid stenosis patients are asymptomatic.<sup>8,9</sup> To address this debate, a number of studies providing class-I evidence have been performed.

## Best Medical Therapy versus Carotid Endarterectomy

Three class-I studies comparing medical management with carotid endarterectomy are the most respected with regard to evaluation of treatment modalities: the Veterans Affairs Study, the Asymptomatic Carotid Atherosclerosis Study (ACAS), and the Asymptomatic Carotid Surgery Trial (ACST).<sup>36-38</sup> Of note, two other class-I studies have attempted to address this literature but have been generally discarded. The first of these, the Mayo Asymptomatic Carotid Endarterectomy Trial (MACE), was prematurely stopped after only 71 patients, due to the high myocardial infarction rate (22%) in the surgical group.<sup>39</sup> This rate was likely due to the trial policy of withholding aspirin from patients receiving surgery.<sup>16,39</sup> The second was the Carotid Artery Stenosis with Asymptomatic Narrowing: Operation versus Aspirin (CASANOVA) trial.<sup>40</sup> The study design and conduct of this trial were suboptimal for two major reasons. The first was the high rate of crossovers: 17% of the surgical patients never received carotid endarterectomy, and 20% of the medical patients received either unilateral or bilateral carotid endarterectomy. The second was that there were many criteria for which medical patients could receive surgery. This confused the overall interpretation of the data, because it deprived the study of the high-risk patients previously examined in carotid stenosis class-I studies.<sup>16,40</sup>

The first major class-I study for asymptomatic carotid stenosis was the Veterans Affairs study, which enrolled 444 men with angiographically proven 50–99% asymptomatic stenosis.<sup>36</sup> Patients were randomized as in previous trials (aspirin versus aspirin + carotid endarterectomy). Although the results revealed fewer neurological events for the surgical versus medical groups at four-year follow-up (8% vs. 20%;  $p<0.001$ ), these events included TIA, which is considered inappropri-

ate by most clinicians because TIA by definition does not result in any lasting clinical deficit. Examination of the results excluding TIA and focusing on the primary endpoints used in previous class-I studies revealed that although the rate in the medical group was 9.4% versus 4.7% in the surgical group at four years, these results were not significant.<sup>23,36</sup>

Subsequently, the ACAS study involved 1,662 asymptomatic patients with 60–99% stenosis, with inclusion, exclusion and randomization criteria similar to that of previous class-I studies.<sup>37</sup> In the surgical group, stenosis was defined angiographically, while in the medical group ultrasound was the primary diagnostic modality. Patients were randomized to aspirin alone versus aspirin + carotid endarterectomy. The results were dramatic, as the trial was stopped by the Data and Safety Monitoring Board after <3 years, due to the projected Kaplan-Meier estimate of five-year 5.9% absolute risk reduction favoring surgery, with a number needed to treat of 17.<sup>37</sup> The five-year projected rate of ipsilateral stroke in the medical group was 11%, more than twice the 5.1% rate in the surgical group, and statistically significant ( $P=0.004$ ) with a relative risk reduction of 53%. The five-year projected rate of major ipsilateral stroke in the medical group was 6% compared with 3.4% in the surgical group; however, this difference was not statistically significant ( $P=0.12$ ).

Of note was the 30-day perioperative stroke/death rate of 2.3%; this became a major contention of criticism of the ACAS trial, due to the skepticism that this low rate may not be matched by routine clinical practice.<sup>41</sup> In fact, ACAS rejected 40% of initial applicant surgeons and subsequently barred some surgeons who had adverse operative outcomes during the trial.<sup>42</sup> A retrospective meta-analysis comparing the operative risks of ACAS with those of 46 surgical case series publishing operative risks for asymptomatic carotid stenosis from the time period of ACAS to five years after ACAS publication revealed that the surgical mortality in ACAS was eight times lower than the comparative literature (0.14% vs. 1.11%;  $p=0.01$ ), with a risk of stroke/death in ACAS being three times lower (1.5% vs. 4.3%) among comparable studies in which a neurologist graded the outcome ( $p<0.001$ ).<sup>43</sup>

The third and most recent study was the ACST trial, in which 3,120 patients were enrolled. Eligibility criteria included: minimum 60% stenosis on ultrasound and no symptoms within the previous six months.<sup>38</sup> Patients were randomized to immediate surgery versus indefinite deferral of surgery (1,560 patients to each group). The results were quite significant; the net five-year risk of stroke in the deferred group was 11.8%, compared with only 6.4% in the immediate surgery group ( $P<0.0001$ ). Subdividing with regard to fatal/disabling stroke also yielded significant results, as the immediate surgery group had risk of 3.5% compared with 6.1%

in the delayed surgery group ( $P=0.004$ ). The net five-year risk of nonperioperative carotid territory ischemic stroke was 2.7% in the immediate surgery group versus 9.5% in the deferred group, for an absolute risk reduction of 6.8% ( $P<0.0001$ ). Definitive benefit of surgery was seen in patients <75 years of age but was uncertain in patients  $\geq 75$  years old.<sup>38</sup>

Furthermore, for net five-year risk of stroke, ACST found no significant difference between patients with 60–79% stenosis versus patients with 80–99% stenosis, and found no difference between patients who had never been symptomatic versus those symptomatic >6 months previously. A significant difference between ACST and the other two class-I asymptomatic carotid stenosis studies is that the primary endpoint included all strokes (i.e. contralateral, vertebrobasilar), not just ipsilateral strokes.<sup>16,38</sup>

## Carotid Endarterectomy versus Carotid Angioplasty with Stenting

The findings from these studies, particularly the ACST, established carotid endarterectomy as efficacious in asymptomatic carotid stenosis of  $\geq 60\%$ . Thus far, only one class-I study has attempted to compare carotid angioplasty and stenting with carotid endarterectomy for patients with asymptomatic carotid stenosis: the Stent and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial.<sup>44</sup> However, even in this trial, only 71% of the patients were asymptomatic, so there is yet to be a completed study with class-I evidence involving purely asymptomatic patients examining stenting versus surgery.<sup>44</sup>

The SAPPHIRE study was a randomized noninferiority trial involving 29 institutions throughout the United States, and a multidisciplinary team at each institution (comprised of a stroke neurologist, a physician trained in carotid endarterectomy and a physician trained in carotid stenting) deemed 334 high-risk patients as ideal candidates for either stenting or surgery. If any member of the team felt that a patient was not a good candidate for stenting or surgery, that patient was not included in the trial.<sup>44</sup> Coexisting conditions in this trial defining patients as high-risk included: significant cardiac or pulmonary disease, lateral laryngeal nerve palsy, previous radical neck surgery or radiation therapy, contralateral carotid artery occlusion, recurrent stenosis after previous carotid endarterectomy, and age  $>80$ .<sup>44</sup> Patients had to have either symptomatic stenosis of 50% or asymptomatic stenosis of 80% on ultrasound. Two-hundred-thirty-eight (71%) of the 334 patients were asymptomatic.

Patients were then randomized to stenting or surgery, with both groups receiving low-dose aspirin starting 72 hours prior to the procedure and continuing indefinitely. Of note, the primary endpoint of this study included the cumulative incidence of stroke, death or myocardial infarction within 30 days, or ipsilateral stroke between

31 days and one year—the same endpoints as NASCET and previous class-I trials with the exception of the inclusion of myocardial infarction.

Primary endpoint comparison at one year postintervention revealed the risk in the stenting group to be 12.2% compared with 20.1% in the surgery group. This difference was significant ( $P=0.05$ ) to prove noninferiority of stenting versus carotid endarterectomy at one year posttreatment. The overall incidence of stroke within one year of treatment was 6.2% in the stenting group and 7.9% in the surgery group, a difference that was not significant ( $P=0.60$ ). Similarly, the incidence of ipsilateral stroke at one year was 4.3% in the stenting group and 5.3% in the surgery group, a difference that was also not significant ( $P=0.09$  for major stroke;  $P=0.34$  for minor stroke). However, the trend towards stenting leading to reduced stroke incidence compared with surgery lent support to the noninferiority of stenting versus carotid endarterectomy at one year of follow-up.<sup>44</sup>

The criticisms of the SAPHIRE trial include its small sample size (334 patients) compared with previous class-I data in this patient population ( $\geq 1,000$  patients), and the relatively short follow-up (one year) compared with previous studies comparing medical management with carotid endarterectomy (2–5 years in NASCET, ECAS, ACST, etc.). However, the biggest criticism relates to the inclusion of myocardial infarction in the primary endpoint, since this was not previously used in class-I carotid stenosis studies. Without this variable, the endpoint comparison between the stenting and surgery groups would have not been significant (5.5% vs. 8.4%;  $P=0.36$  rather than 0.05) to prove noninferiority of stenting versus carotid endarterectomy.<sup>44,45</sup> The inclusion of myocardial infarction was likely due to practical considerations, as otherwise the study would not have been powered to adequately detect differences in stroke or death between the stenting and surgery groups.<sup>45,46</sup>

## Future Directions

Since the NASCET trial, medical management of carotid stenosis has considerably improved, due to the introduction of statins and newer antiplatelet agents.<sup>41</sup> Two recent retrospective case series have demonstrated the value of such improved regimens for improving outcomes following carotid endarterectomy: one demonstrating the role of preoperative statin use in decreasing the number of carotid endarterectomy patients initially presenting with stroke/TIA, and the second demonstrating operative-day glucose levels  $>200$  as independently predictive of stroke/TIA, myocardial infarction and death following carotid endarterectomy.<sup>47,48</sup> Therefore, future class-I studies will be necessary to determine the role of these newer medical agents in the management of both symptomatic and asymptomatic carotid stenosis.

## CONCLUSION

For patients with symptomatic carotid artery stenosis, class-I data support aspirin + carotid endarterectomy as the gold standard of care at both two and five years postoperatively for patients with  $\geq 70\%$  stenosis, and aspirin alone for patients with  $<50\%$  stenosis. Carotid angioplasty with stenting is associated with significantly more morbidity and mortality than carotid endarterectomy for symptomatic carotid artery stenosis patients at 30 days postintervention. For patients with asymptomatic carotid artery stenosis, class-I data support aspirin + carotid endarterectomy for patients with  $\geq 60\%$  stenosis as efficacious at five years postsoperatively, yet for asymptomatic patients with  $\geq 80\%$  stenosis, carotid angioplasty with stenting is not inferior to carotid endarterectomy at one year postintervention. Improvements both in medical therapy and carotid stenting technologies will require future studies to provide class-I evidence for determining the optimal treatment modalities for symptomatic and asymptomatic carotid artery stenosis patients.

## REFERENCES

1. Minino AM, Heron MP, Smith BL. Deaths: Preliminary Data for 2004. National vital statistics reports; vol 54 no 19. Hyattsville, MD: National Center for Health Statistics; 2006.
2. Bonita R, Beaglehole R. Stroke: populations, cohorts, and clinical trials. In: Whisnant JP, eds. Stroke mortality. Oxford, UK: Butterworth-Heinemann; 1993;59-79.
3. American Heart Association. 1999 heart and stroke statistical update Dallas, TX: American Heart Association, 1998;13-15.
4. Matchar D, Duncan P. Cost of stroke. *Stroke Clin Updates*. 1994; 3:9-12.
5. Ingall TJ. Preventing ischemic stroke: current approaches to primary and secondary prevention. *Postgrad Med* 2000;107(6):34-50.
6. Dyken M. Stroke risk factors. In: Norris JW, Hachinski VC, eds. Prevention of stroke. New York, NY: Springer-Verlag; 1991;83-102.
7. Ricci S, Flamini FO, Celani MG, et al. Prevalence of internal carotid artery stenosis in subjects older than 49 years: a population study. *Cerebrovasc Dis*. 1991;1:16-19.
8. Prati P, Vanuzzo D, Casaroli M, et al. Prevalence and determinants of carotid atherosclerosis in a general population. *Stroke*. 1992;23:1705-1711.
9. O'Leary DH, Polak JF, Kronmal RA, et al, for the CHS Collaborative Research Group. Distribution and correlates of sonographically detected carotid artery disease in the Cardiovascular Health Study. *Stroke*. 1992; 23:1752-1760.
10. Meissner I, Wievers DO, Whisnant JP, et al. The natural history of asymptomatic carotid artery occlusive lesions. *JAMA*. 1987;258:2704-2707.
11. Bogousslavsky J, Despland PA, Regli F. Asymptomatic tight stenosis of the internal carotid artery: long-term prognosis. *Neurology*. 1986;36:861-863.
12. Hennerici M, Hulsbomer HB, Heffer, et al. Natural history of asymptomatic extracranial arterial disease: results of a long-term prospective study. *Brain*. 1987;110(Pt 3):777-791.
13. Inzitari D, Eliasziw M, Gates P, et al. The causes and risk of stroke in patients with asymptomatic internal-carotid-artery stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med*. 2000;342:1693-1700.
14. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Eng J Med*. 1991;325:445-453.
15. Taylor DW, Barnett HJ, Haynes RB, et al. Low-dose and high-dose acetylsalicylic acid for patients undergoing carotid endarterectomy: a randomised controlled trial. ASA and Carotid Endarterectomy (ACE) Trial Collaborators. *Lancet*. 1999;353(9171):2179-2184.

16. Chaturvedi S, Bruno A, Feasby T, et al. Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Carotid endarterectomy—an evidence-based review: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2005;65(6):794-801.
17. Loftus CM, Quest DO. Technical issues in carotid artery surgery 1995. *Neurosurgery*. 1995;36(4):629-647.
18. Phatouros CC, Higashida RT, Malek AM, et al. Carotid artery stent placement for atherosclerotic disease: rationale, technique, and current status. *Radiology*. 2000;217(11):26-41.
19. Barnett HJ, Taylor DW, Eliasziw M, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med*. 1998;339(20):1415-1425.
20. European Carotid Surgery Trialists' Collaborative Group. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. European Carotid Surgery Trialists' Collaborative Group. *Lancet*. 1991;337(8752):1235-1243.
21. European Carotid Surgery Trial. Endarterectomy for moderate symptomatic carotid stenosis: interim results from the MRC European Carotid Surgery Trial. *Lancet*. 1991;337(9015):1591-1593.
22. Mayberg MR, Wilson SE, Yatsu F, et al. Carotid endarterectomy and prevention of cerebral ischemia in symptomatic carotid stenosis. Veterans Affairs Cooperative Studies Program 309 Trialist Group. *JAMA*. 1991;266(23):3289-3294.
23. Findlay JM, Chappell ET. Cerebrovascular surgery. In: Evidence-based neurosurgery: an introduction. Haines SJ, Walters BC, eds. New York, NY: Thieme Medical Publishers; 2006:105-128.
24. Barnett HJ, Warlow CP. Carotid endarterectomy and the measurement of stenosis. *Stroke*. 1993;24(9):1281-1284.
25. Rothwell PM, Eliasziw M, Gutnikov SA, et al. Carotid Endarterectomy Trialists' Collaboration. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet*. 2003;361(9352):107-116.
26. Morgenstern LB, Fox AJ, Sharpe BL, et al. The risks and benefits of carotid endarterectomy in patients with near occlusion of the carotid artery. North American Symptomatic Carotid Endarterectomy Trial (NASCET) Group. *Neurology*. 1997;48(4):911-915.
27. Rothwell PM, Gibson R, Warlow CP. Interrelation between plaque surface morphology and degree of stenosis on carotid angiograms and the risk of ischemic stroke in patients with symptomatic carotid stenosis. On behalf of the European Carotid Surgery Trialists' Collaborative Group. *Stroke*. 2000;31(3):615-621.
28. Eliasziw M, Streifler JY, Fox AJ, et al. Significance of plaque ulceration in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial. *Stroke*. 1994;25(2):304-308.
29. Gasecki AP, Eliasziw M, Ferguson GG, et al. Long-term prognosis and effect of endarterectomy in patients with symptomatic severe carotid stenosis and contralateral carotid stenosis or occlusion: results from NASCET. North American Symptomatic Carotid Endarterectomy Trial (NASCET) Group. *J Neurosurg*. 1995;83(5):778-782.
30. Barnett HJ, Meldrum HE, Eliasziw M, North American Symptomatic Carotid Endarterectomy Trial (NASCET) collaborators. The appropriate use of carotid endarterectomy. *CMAJ*. 2002;166(9):1169-1179.
31. Kappelle LJ, Eliasziw M, Fox AJ, et al. Importance of intracranial atherosclerotic disease in patients with symptomatic stenosis of the internal carotid artery. The North American Symptomatic Carotid Endarterectomy Trial. *Stroke*. 1999;30(2):282-286.
32. Henderson RD, Eliasziw M, Fox AJ, et al. Angiographically defined collateral circulation and risk of stroke in patients with severe carotid artery stenosis. North American Symptomatic Carotid Endarterectomy Trial (NASCET) Group. *Stroke*. 2000;31(1):128-132.
33. Streifler JY, Eliasziw M, Benavente OR, et al. North American Symptomatic Carotid Endarterectomy Trial Group. Prognostic importance of leukoaraiosis in patients with symptomatic internal carotid artery stenosis. *Stroke*. 2002;33(6):1651-1655.
34. SPACE Collaborative Group, Ringleb PA, Allenberg J, Bruckmann H, et al. 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. *Lancet*. 2006;368(9543):1239-1247.
35. Mas JL, Chatellier G, Beyssen B, et al. EVA-3S Investigators. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. *N Engl J Med*. 2006;355(16):1660-1671.
36. Hobson RW, Weiss DG, Fields WS, et al. Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. *N Engl J Med*. 1993;328:221-227.
37. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid stenosis. *JAMA*. 1995;273:1421-1428.
38. MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomized controlled trial. *Lancet*. 2004;363:1491-1502.
39. Mayo Asymptomatic Carotid Endarterectomy Study Group. Effectiveness of carotid endarterectomy for asymptomatic carotid stenosis: design of a clinical trial. *Mayo Clin Proc*. 1992;67:904.
40. Carotid surgery versus medical therapy in asymptomatic carotid stenosis. The CASANOVA Study Group. *Stroke*. 1991;22:1229-1235.
41. Redgrave JN, Rothwell PM. Asymptomatic carotid stenosis: what to do. *Curr Opin Neurol*. 2007;20:58-64.
42. Moore WS, Young B, Baker WH, et al. Surgical results: a justification of the surgeon selection process for the ACAS trial. The ACAS Investigators. *J Vasc Surg*. 1996;23:323-328.
43. Rothwell PM, Goldstein LB. Carotid endarterectomy for asymptomatic carotid stenosis: asymptomatic carotid surgery trial. *Stroke*. 2004;35:2425-2427.
44. Yadav JS, Wholey MH, Kuntz RE, et al. Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy Investigators. Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med*. 2004;351(15):1493-1501.
45. Gottfried ON, Couldwell WT. Review of Yadav JS, Wholey MH, Kuntz RE, et al. *Neurosurg Focus*. 2005;18(1):EJC1.
46. Cambria RP. Stenting for carotid artery stenosis. *N Engl J Med*. 2004;351:1565-1567.
47. Brooke BS, McGirt MJ, Woodworth GF, et al. Preoperative statin and diuretic use influence the presentation of patients undergoing carotid endarterectomy: results of a large single-institution case-control study. *J Vasc Surg*. 2007;45(2):298-303.
48. McGirt MJ, Woodworth GF, Brooke BS, et al. Hyperglycemia independently increases the risk of perioperative stroke, myocardial infarction, and death after carotid endarterectomy. *Neurosurgery*. 2006;58(6):1066-1073. ■