How Recent Data Have Impacted the Treatment of Internal Carotid Artery Stenosis

Seemant Chaturvedi, MD,*† Ralph L. Sacco, MD*

ABSTRACT

Carotid atherosclerosis accounts for approximately 10% of ischemic stroke cases. Multifaceted medical therapy reduces the risk of stroke in patients with carotid stenosis. Revascularization with endarterectomy or stenting can benefit select patients. In recent years, new information has been obtained regarding optimal selection of revascularization candidates. In addition, new concepts have been formulated regarding the relationship between carotid stenosis and vascular cognitive impairment. Finally, the declining rate of stroke with improved medical therapy has led to the launch of new clinical trials to determine the contemporary risk/benefit ratio of revascularization relative to aggressive medical therapy. (J Am Coll Cardiol 2015;65:1134–43) © 2015 by the American College of Cardiology Foundation.

Carotid atherosclerosis accounts for 7% to 10% of ischemic strokes. Intensive medical therapy and carotid revascularization procedures reduce the risk of stroke. Several developments in the area of carotid stenosis treatment include carotid artery stenting (CAS) and improvements in multimodal medical therapy.

In this update, we shall review current recommendations for management of symptomatic and asymptomatic internal carotid artery (ICA) stenosis. In addition, we shall identify new clinical correlates in “asymptomatic” patients and review the impact of contemporary medical therapy on stroke rates for carotid stenosis patients. Finally, we will discuss current clinical trials regarding ICA stenosis.

PREVALENCE AND PREDICTORS OF CAROTID STENOSIS AND STROKE RISK

In the Framingham Heart Study, the degree of carotid stenosis was predicted by common baseline vascular risk factors such as older age, cigarette smoking, systolic blood pressure, and total cholesterol (1). Patients with asymptomatic ICA stenosis of 60% to 99% have an annual risk of stroke, based on 1990s medical therapy, of 2% to 2.5% per year (2,3). On the other hand, symptomatic carotid stenosis over 70% carries an annual stroke risk of 10% to 15%, based on 1990s medical therapy (4).

The prevalence of severe (≥70%) asymptomatic stenosis in the general population varies according to age and baseline risk factors. In a meta-analysis of 4 individual participant longitudinal studies, the prevalence of severe stenosis ranged from 0% to 3.1% in various age and sex groups (5). Among men, severe stenosis was present in 0.1% (95% confidence interval [CI]: 0% to 0.3%) of subjects <50 years of age and in 3.1% (CI: 1.7% to 5.3%) of those >80 years of age. Among women, the prevalence of severe stenosis was minimal (95% CI: 0% to 0.2%) in subjects <50 years of age and 0.9% (95% CI: 0.3% to 2.4%) in women >80 years of age. The same investigators developed a...
predictive instrument for identifying the presence of severe stenosis. Elements of the score are provided in Table 1.

Although some advocate screening higher-risk patients with coronary artery disease or peripheral arterial disease for ICA stenosis, the evidence to support this practice is limited. The US Preventive Services Task Force reviewed studies pertaining to population screening through 2014 and concluded that routine screening of the general population to detect asymptomatic ICA stenosis is not warranted (6). Among the reasons for this recommendation were the following: 1) concern that low complication rates after carotid endarterectomy (CEA) and CAS could not be replicated in community practice; 2) lack of studies comparing CAS to optimal medical therapy; 3) falling rates of stroke with contemporary medical therapy; and 4) significant generation of “false positives” with duplex ultrasound as the screening tool.

CURRENT EVIDENCE FOR THE TREATMENT OF CAROTID STENOSIS

Contemporary recommendations for patients with symptomatic or asymptomatic ICA stenosis include medical therapy for all patients and revascularization (CEA or CAS) for select patients. With regard to medical therapy, all patients should receive the core elements of vascular disease therapy (7). This includes the following: 1) antiplatelet therapy; 2) aggressive treatment of dyslipidemia; 3) treatment of hypertension to national guideline targets; 4) treatment of diabetes mellitus to national guideline targets; 5) smoking cessation; and 6) lifestyle modification, including dietary modification and exercise.

It is beyond the scope of this review to discuss each of these in detail, but certain observations are worthwhile. For antiplatelet therapy, aspirin is typically used (81 to 325 mg/day) for asymptomatic patients, although there is no level A evidence that aspirin reduces stroke in the setting of asymptomatic carotid stenosis (ACS). There are no data comparing alternative antiplatelet regimens (e.g., clopidogrel or aspirin plus extended-release dipyridamole) to aspirin for patients with ACS. For symptomatic patients, either aspirin, clopidogrel, or aspirin plus extended-release dipyridamole are recommended (8). Ongoing trials are evaluating the 90-day use of clopidogrel plus aspirin compared with aspirin alone for patients with acute transient ischemic attack (TIA) and minor stroke (POINT [Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke] trial), as well as ticagrelor compared with aspirin (SOCRATES [Acute Stroke or Transient Ischemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes] trial), of whom a small subgroup could have symptomatic carotid stenosis. Currently, long-term treatment with aspirin and clopidogrel is not recommended in stroke prevention guidelines (8).

The role of lipid lowering with statins in patients with carotid stenosis has been established from several sources. In the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial, atorvastatin 80 mg/day was compared with placebo in patients with a prior stroke or TIA (9). In a subgroup analysis of patients with carotid stenosis, 1,007 patients had a mean stenosis of 51% (10). In the patients given atorvastatin, low-density lipoprotein (LDL) was lowered from 132 mg/dl at baseline to an average of 70 mg/dl during trial follow-up. In the patients given placebo, LDL decreased from 133 to 130 mg/dl. The atorvastatin-treated patients had a 33% reduction in any stroke, a 43% reduction in coronary events, and a 56% reduction in later carotid revascularization procedures. In ACST (Asymptomatic Carotid Surgery Trial), there was increasing use of lipid-lowering treatment during the course of the trial (3). For patients not undergoing lipid-lowering therapy and treated in the medical arm of the study, the 10-year risk of stroke was 24.9%, much greater than the 14.5% observed among patients who were treated with lipid-lowering therapy. As a result of these observations (and other studies), treatment with high-potency statins is an important element of the management of patients with carotid stenosis (8,11).

As pertains to carotid revascularization, current recommendations were revised on the basis of data from CREST (Carotid Revascularization Endarterectomy vs. Stenting Trial) (12). In CREST, 2,502 patients with either symptomatic stenosis or ACS were randomly assigned to either CEA or CAS. Patients were

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 yrs)</td>
<td>2.2 (1.7-2.8)</td>
</tr>
<tr>
<td>Male</td>
<td>2.5 (1.7-3.6)</td>
</tr>
<tr>
<td>History of vascular disease</td>
<td>2.5 (1.7-3.5)</td>
</tr>
<tr>
<td>Systolic blood pressure (per 10 mm Hg)</td>
<td>1.3 (1.2-1.5)</td>
</tr>
<tr>
<td>Cholesterol/HDL ratio (per point)</td>
<td>1.2 (1.1-1.4)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.6 (1.0-2.5)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>3.0 (2.1-4.4)</td>
</tr>
</tbody>
</table>

Odds ratios greater than 1.0 indicate a greater risk of the presence of severe carotid stenosis. *Data are from de Weerd et al. (5). HDL = high-density lipoprotein.
enrolled with either >70% stenosis by duplex ultrasound or >50% stenosis by angiography for symptomatic patients and >60% stenosis for ACS. The primary endpoint was stroke, death, or myocardial infarction (MI) within 30 days, plus ipsilateral stroke beyond 30 days. For the primary endpoint, there was no difference between CEA and CAS (6.8% vs. 7.2% at 4 years; \( p = 0.51 \)). Patients assigned to CEA had a significantly lower risk of periprocedural strokes (2.3% vs. 4.1%; \( p = 0.01 \)) and a higher rate of periprocedural MI (2.3% vs. 1.1%; \( p = 0.03 \)). There was no significant variation in the treatment results for men compared with women and for asymptomatic compared with symptomatic carotid stenosis (Table 2). There was also no difference in the risk of major stroke during the 4-year study period (11% for CAS vs. 8% for CEA; \( p = 0.52 \)).

Patients >70 years of age fared better with CEA, whereas patients younger than 70 years of age tended to fare better with CAS (\( p = 0.02 \) for interaction) (13,14). A similar finding was noted in a pre-planned meta-analysis of 3 European studies (15). The event rate for any stroke or death in the patients treated with CEA was 5.7% in subjects younger than 70 years and 5.9% in subjects \( \geq 70 \) years of age. On the other hand, in the CAS group, any stroke or death occurred in 5.8% of subjects younger than 70 years and 12% of subjects \( \geq 70 \) years.

Other trials (EVA-3S [Endarterectomy Versus Angioplasty in Patients With Severe Symptomatic Carotid Stenosis], SPACE [Stent-Protected Angioplasty Versus Carotid Endarterectomy], ICSS [International Carotid Stenting Study]) studied symptomatic patients only and compared CEA with CAS (16–18). Age was the main modifier of the treatment effect, as mentioned above. The EVA-3S investigators recently published long-term follow-up data with regard to outcomes after CEA or CAS (19). At 5 years, for the endpoint of any procedural stroke or death plus ipsilateral stroke beyond the procedural period, the CAS group had an 11.0% event rate compared with 6.3% with CEA (hazard ratio [HR]: 1.85; 95% CI: 1.0 to 3.4; \( p = 0.04 \)). At 10 years, the CAS event rate compared with the CEA group was 11.5% versus 7.6% (HR: 1.70; 95% CI: 0.95 to 3.06; \( p = 0.07 \)). There were no differences in ipsilateral stroke risks in the 2 treatment groups beyond the procedural period. Thus, CEA had a small advantage during long-term follow-up.

On the basis of these data, multidisciplinary panels have provided the recommendations given in the following sections (8,11,20).

**Symptomatic Stenosis.**

1. For patients with a TIA or stroke within the past 6 months and ipsilateral severe stenosis (70% to 99%), CEA is recommended if the perioperative stroke/death rate is estimated to be <6% (Class I, Level of Evidence: A).
2. When the degree of stenosis is <50%, CEA and CAS are not recommended (Class III, Level of Evidence: A).
3. When revascularization is indicated, it is reasonable to perform surgery within 2 weeks rather than delay surgery (Class IIa, Level of Evidence: B).
4. CAS is indicated as an alternative to CEA if the anticipated perioperative stroke/death rate is <6% (Class IIa, Level of Evidence: B).
5. It is reasonable to consider patient age in choosing between CEA and CAS (Class IIa, Level of Evidence: B).

**Asymptomatic Patients.**

1. Selection of asymptomatic patients for revascularization should be based on comorbid conditions and patient life expectancy (Class I, Level of Evidence: C).
2. Highly selected patients may benefit from CEA if the perioperative stroke/death rate is <3% (Class IIa, Level of Evidence: A).
3. CAS might be considered in highly selected patients if the perioperative stroke/death rate is <3% (Class IIb, Level of Evidence: B). The advantage of CAS over medical therapy is not well established.
4. The usefulness of CAS is not well established for patients at high risk for CEA (Class IIb, Level of Evidence: C).

**Selection of Revascularization Method**

CEA is a well-established procedure with several decades of experience in the community. The complications of CEA are well described, including complications pertaining to the brain, systemic complications, and local hazards. The primary neurological complications in the brain are ischemic and hemorrhagic stroke. Symptomatic patients have a higher stroke risk than asymptomatic subjects (21). With regard to systemic complications, the most serious is MI. As mentioned above, in CREST, the periprocedural MI
rate was 2.3% (22). MI was defined as the presence of biomarker elevation with either chest pain or ECG evidence of ischemia. Mortality over 4 years was higher for patients with MI than for those without biomarker elevation (HR: 3.40; p < 0.001). Prior cardiovascular or coronary artery bypass grafting was the major predictor of development of a periprocedural MI (HR: 2.22; p = 0.02). Finally, with regard to local complications, cranial nerve palsies, wound hematomas, and operative site infection are the major concerns. In CREST, cranial nerve palsies were less frequent with CAS than with CEA (0.3% vs. 4.7%; HR: 0.07) (12).

CAS is a more recent revascularization procedure, the use of which has increased rapidly in community practice (23). For CAS, in addition to the hazards of advanced age described above, the complication rate may be greater with unfavorable aortic arch or carotid bifurcation anatomic features. A tortuous aorta with heavy calcification or the presence of a large burden of atherosclerotic plaques can lead to a greater rate of periprocedural atheroembolic stroke (9). The observation that approximately one-fifth of CAS-related strokes are not in the territory of the treated vessel supports the theory of embolization from the aorta to multiple vascular territories (24). At the bifurcation, angulation of the internal carotid artery, heavy calcification, and long lesion length have been associated with an increased rate of periprocedural stroke (9). Another procedure-specific hazard of CAS is periprocedural bradycardia or hypotension. In some instances, bradycardia or hypotension can be prolonged and lead to intensive care unit admission and increased periprocedural morbidity (25). Hypotension can also follow CEA in up to 12% to 27% of patients (26,27). For the symptomatic patient, Table 3 provides factors that may influence the choice of revascularization technique.

**DEFINING THE ASYMPTOMATIC PATIENT**

Because the asymptomatic patient does not present with overt stroke or TIA, how are these patients identified? Typically, asymptomatic patients are brought to clinical attention after identification of carotid bruits or while being investigated for neurological symptoms in other vascular territories (contralateral carotid or vertebrobasilar). Some patients may have a screening carotid ultrasound performed because of either coronary artery disease or peripheral vascular disease, although this practice is controversial.

Traditionally, an asymptomatic carotid stenosis has been defined as one in which there has not been a stroke or TIA in the territory of the stenotic vessel for the past 6 months. Moreover, there has been concern expressed that considering stroke or TIA alone as the only relevant downstream effect of the carotid narrowing may be too restrictive (28). Specifically, should we consider “silent brain infarcts” in the territory of the stenosed carotid artery a clinical manifestation of carotid disease? Also, what about cognitive dysfunction with or without silent strokes?

With regard to silent strokes, an older study using computed tomography scans found that 19% of patients with asymptomatic stenosis had at least 1 ischemic lesion, with 68% being ipsilateral to the carotid stenosis (29). A more recent systematic review identified 11 studies that evaluated computed tomography lesions with ACS. The median frequency of silent infarcts was 22%, with a 13% rate of nonlacunar cortical and subcortical infarcts (30). In patients with this pattern of nonlacunar infarcts, there was an increased rate of stroke during an average of 3.4 years of follow-up (odds ratio: 4.6; 95% CI: 3.0 to 7.2; p < 0.0001).

Balestrini et al. (31) studied 210 subjects with ≥70% asymptomatic stenosis and 109 subjects without carotid narrowing. A mini-mental status examination (MMSE) was performed at baseline and at 36 months. Cerebral vasomotor reactivity was assessed by use of the breath-holding technique, with abnormal reactivity being defined as a ratio of <0.69. During the follow-up period, of 60 subjects with MMSE worsening of ≥3 points, 52 had carotid stenosis and 45 had an impaired breath-holding index (p < 0.001). These investigators also investigated patients with early Alzheimer disease. Patients who progressed to an MMSE score of <21 (indicative of moderate dementia) were more likely to have carotid stenosis than those without progressive cognitive decline (32). These findings suggest a potential synergistic role between Alzheimer neuropathology and carotid stenosis.

Some limitations of these studies deserve mention. First, there was no documentation of neuroimaging findings in these studies. It is possible that the patients with cognitive impairment were those with

<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>Factors in Choice of Carotid Revascularization Methods</th>
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<tbody>
<tr>
<td>Recently symptomatic patient (&lt;2 weeks)</td>
<td>Favors CEA</td>
</tr>
<tr>
<td>Age &gt;75 yrs</td>
<td>Favors CEA</td>
</tr>
<tr>
<td>Tortuous or heavily calcified aorta</td>
<td>Favors CEA</td>
</tr>
<tr>
<td>Long lesion, heavily calcified lesion</td>
<td>Favors CEA</td>
</tr>
<tr>
<td>Contralateral carotid occlusion</td>
<td>Favors CAS</td>
</tr>
<tr>
<td>Recurrent carotid stenosis</td>
<td>Favors CAS</td>
</tr>
<tr>
<td>Presence of significant cardiac disease</td>
<td>Favors CAS</td>
</tr>
<tr>
<td>Presence of significant lung disease</td>
<td>Favors CAS</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 2.
silent strokes and that silent strokes were the major culprit rather than simply carotid stenosis. Also, the extent of cerebral small-vessel disease can be linked to cognitive dysfunction. Small-vessel disease, especially that which causes diffuse periventricular ischemic changes on brain imaging, is more likely to be related to hypertension control than to carotid stenosis. Other factors that may be related to the development of cognitive impairment are apolipoprotein E isomorph status, brain microbleeds, obstructive sleep apnea (33), and midlife vascular risk factor control (34). For these reasons, a link between ACS and cognitive dysfunction is not firmly established and therefore has not impacted recommendations on carotid revascularization (11).

IMPROVED MEDICAL THERAPY AND RELEVANCE TO CAROTID DISEASE

The landmark carotid stenosis trials that established the value of CEA were initiated over 25 years ago before the widespread use of statins (2,4). In addition, blood pressure control and management of lifestyle and other vascular risk factors in older studies were suboptimal. For example, in NASCET (North American Symptomatic Carotid Endarterectomy Trial), the mean systolic blood pressure 2 years into the study was 147 mm Hg (35). Declining temporal trends in outcome rates for stroke recurrence among secondary prevention trials over the past 50 years have been observed that suggest an overall improvement in blood pressure control, tobacco smoking, and background medical therapies (36,37).

SYMPTOMATIC ICA STENOSIS. Has optimal medical therapy (OMT) reduced the rate of stroke? Merwick et al. (38) analyzed data from 2,770 TIA patients from 11 centers; 387 of these patients had carotid stenosis, defined as ≥50% stenosis. These authors analyzed the rate of stroke with or without statin pre-treatment. In patients with statin pre-treatment, the 7-day risk of stroke (unrelated to revascularization procedures) was 3.8%, compared with 13.2% in patients not taking statins (p = 0.01).

Dual-antiplatelet therapy, as opposed to monotherapy, could also be useful in symptomatic patients with carotid narrowing. In the CHANCE study (Clopidogrel in High-Risk Patients With Acute Non-disabling Cerebrovascular Events), 5,170 patients with minor stroke or TIA within 24 h of symptom onset were assigned to treatment with aspirin (75 mg) monotherapy or dual therapy with aspirin (75 mg for the first 21 days) plus clopidogrel (300 mg loading dose followed by 75 mg/day) (39). At 90 days’ follow-up, the rate of stroke was 8.2% with dual-antiplatelet therapy and 11.7% with aspirin monotherapy (p < 0.001). No increase in hemorrhage was seen with combined antiplatelet therapy. Wong et al. conducted a systematic analysis of 14 studies involving 9,012 patients pertaining to dual- versus single-antiplatelet therapy in patients treated within 3 days of the index event (40). The results demonstrated that dual-antiplatelet therapy reduced the risk of stroke recurrence by 31% (p < 0.001), without a significant increase in hemorrhagic complications. The proportion of patients with extracranial ICA stenosis in CHANCE was not specified. In addition, studies of stroke patients with long-term (18 months or more) dual-antiplatelet therapy (e.g., MATCH [Management of Atherothrombosis With Clopidogrel in High-Risk Patients] and PRoFESS [Prevention Regimen for Effectively Avoiding Second Strokes]) have reported increased rates of life-threatening bleeding events (MATCH, 2.6%; PRoFESS, 1.3%), whereas severe bleeding (according to the GUSTO [Global Utilization of Streptokinase and tPA for Occluded Arteries] definition) occurred in only 0.2% of cases in the dual-antiplatelet therapy arm and 0.2% in the aspirin-only arm in CHANCE (41,42). The significant difference in bleeding rate in CHANCE compared with every other dual-antiplatelet therapy trial confirms the need for study reproduction.

The studies mentioned above included a heterogeneous population with respect to stroke pathogenesis. However, there exist surrogate marker studies to support the value of dual-antiplatelet therapy in patients with symptomatic carotid stenosis. With the use of transcranial Doppler, microemboli detection correlates with the subsequent rate of neurological events such as stroke or TIA. A previous randomized trial of 107 patients found that the use of combined aspirin plus clopidogrel treatment compared with aspirin alone reduced the rate of microembolic signals by 40% (43). In terms of clinical events, there were 4 strokes and 7 TIs in the aspirin-only group compared with 0 strokes and 4 TIs in the dual-antiplatelet therapy group.

If we look at contemporary OMT, there is suggestive evidence that a multimodality approach is best for reducing stroke in patients with large-artery atherosclerotic events. In the SAMMPRIS trial (Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis), patients were enrolled with TIA or stroke in the past 30 days and 70% to 99% stenosis of a major intracranial vessel, such as the middle cerebral artery or basilar artery (44). All patients received aggressive medical therapy as outlined in Table 4. The primary endpoint occurred in 12% of patients at 1 year, or approximately 50% less
than the projected event rate. This result was superior to the more invasive approach with OMT plus intracranial stenting, which illustrates the potential of aggressive medical therapy.

For patients with extracranial carotid stenosis, the potential of OMT to reduce events in symptomatic patients was illustrated by a recent study from Denmark (45). Patients were referred to a vascular surgery clinic after stroke or TIA for consideration of CEA. After a protocol was established to treat the patients with a multimodal approach (loading-dose aspirin/clopidogrel and then dual therapy with aspirin plus clopidogrel with a statin) until the CEA decision was made, it was noted that the rate of neurological events (including stroke or TIA) while waiting for the CEA decision was much lower in patients who received OMT. Specifically, the neurological recurrence rate was 29% before the use of the OMT “cocktail” and 2.5% after the initiation of the OMT approach (p < 0.00001). All the events in the group that received OMT were TIAs, and there were no documented strokes in this group. Compared with historical figures of a 10% to 20% 90-day stroke rate after the initial TIA in patients with large-vessel atherosclerosis, the low rate seen in the Danish study suggests the value of a multimodal approach for patients with symptomatic carotid stenosis.

**ASYMPTOMATIC ICA STENOSIS.** In patients with ACS, data increasingly support the value of OMT. Spence et al. (46) have published data from their stroke prevention clinic pertaining to patients with ACS. A total of 468 with at least 60% stenosis were enrolled and followed up since January 2000. A comparison was undertaken of patients enrolled between 2000 to 2002 and 2003 to 2007. In the second group, there was intensified medical therapy, which resulted in a drop in systolic blood pressure from 146.6 to 141.4 mm Hg (p = 0.01). Also, LDL cholesterol decreased from a mean of 94 to 50 mg/dl. With the intensified medical therapy, the percentage of patients with microemboli on transcranial Doppler decreased from 12.6% in the earlier group to 3.7% in the later group (p < 0.001). The number of vascular events also decreased dramatically with more aggressive medical therapy. The combined rate of stroke, death, MI, or CEA performed because of symptoms declined from 17.6% before 2003 to 5.6% since 2003 (p < 0.001). **Table 5** compares the stroke rates seen with asymptomatic stenosis in older studies (ACAS [Asymptomatic Carotid Atherosclerosis Study], ACST) and more recent longitudinal studies. The more recent community-based studies are relatively small but suggest that the annual stroke rate with asymptomatic stenosis treated with current medical therapies is now likely to be <1% per year and perhaps even as low as 0.5% per year. A systematic analysis also documented falling rates of stroke in patients with asymptomatic ICA stenosis (47).

Two important demographic subgroups to consider in treatment decisions for ACS are women and the elderly. In a combined analysis of ACAS and ACST, it was found that men with ACS had a 51% relative risk reduction in the rate of stroke, whereas women did not have a reduction in stroke (48). In plaque analysis studies, it has been noted that women have lower macrophage staining in carotid plaques and more smooth muscle, which provides for an overall “more stable” plaque than seen in men (49). Because women were underrepresented in previous carotid stenosis trials, some have called for a future clinical trial dedicated to women with carotid stenosis (35,50).

With regard to the elderly, patients >80 years of age were not enrolled in ACAS. There was no upper age limit in the ACST, and therefore, the ACST has the largest clinical trial cohort of patients >75 years of age. In this group, there was no definite benefit seen with CEA in patients >75 years of age, although the study was not powered to examine this subgroup. Because elderly patients have a reduced life

| **TABLE 4** Elements of Intensive Medical Therapy in SAMMPRIS Study |
|---------------------|---------------------|
| **Treatment**       | **Comments**         |
| Aspirin + clopidogrel| For initial 90 days  |
| Aspirin alone       | Beyond 90 days       |
| Rosuvastatin        | Target LDL <70 mg/dl |
| Systolic BP lowering| Target <140 mm Hg    |
| Systolic BP lowering| Target <130 mm Hg    |
| INTERVENT program   | Lifestyle modification assistance (smoking cessation, exercise, diet) |

**TABLE 5** Annual Risk of Stroke in Patients With Asymptomatic Stenosis

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients in Medical Arm</th>
<th>Stroke Risk Per Year, %</th>
<th>Ref. #</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACAS</td>
<td>834</td>
<td>2.2</td>
<td>(2)</td>
</tr>
<tr>
<td>ACST</td>
<td>1,560</td>
<td>2.4</td>
<td>(3)</td>
</tr>
<tr>
<td>London, Ontario (without ME)</td>
<td>431</td>
<td>1.2</td>
<td>(46)</td>
</tr>
<tr>
<td>Oxford</td>
<td>101</td>
<td>0.34</td>
<td>(54)</td>
</tr>
<tr>
<td>SMART</td>
<td>193</td>
<td>0.5</td>
<td>(55)</td>
</tr>
</tbody>
</table>

ACAS = Asymptomatic Carotid Atherosclerosis Study; ACST = Asymptomatic Carotid Surgery Trial; ME = microemboli; SMART = Second Manifestations of Arterial Disease.
expectancy, it is important to carefully evaluate the 5-year life expectancy in elderly patients being considered for carotid revascularization. Clinical features such as prior cardiac disease, renal impairment, and diabetes mellitus have been associated with reduced 5-year survival (51). A proposed algorithm for management of patients with ICA stenosis is provided in the Central Illustration.

CURRENT AND FUTURE CAROTID STENOSIS TRIALS

Advances in medical therapy and refinement of CEA and CAS techniques have fueled interest in conducting a new generation of carotid stenosis trials. Table 6 provides an overview of current and future trials.

CREST 2 (Carotid Revascularization Endarterectomy Stenting Trial 2) will be conducted in North America (52). CREST 2 will recruit patients with ACS of at least 70% by duplex ultrasound. Patients will be evaluated by local medical teams to determine suitability for CEA or CAS. All patients will receive OMT as used in the SAMMPRIS study, with antiplatelet monotherapy instead of dual-antiplatelet therapy. Depending on patients’ suitability for CEA or CAS, the local team may consider enrolling the patient in 1 of the study’s 2 arms. These will

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**Central Illustration** Carotid Artery Stenosis Treatment Algorithm

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Treatment approach for patients with internal carotid artery stenosis.
compare either OMT alone versus OMT plus CEA or OMT alone versus OMT plus CAS. Each of the parallel trials has a sample size of 1,240, although the investigative plan includes a provision for increasing the sample size if the event rate is substantially lower than expected. It is recommended that local teams evaluate patient characteristics such as age in determining the study arm. For example, patients >75 years of age will likely be more appropriate for the CEA portion of the study because of the higher complication rate with CAS in the elderly. A trial being conducted predominantly in Germany and Austria (SPACE 2) has a similar design, with 2 parallel studies in patients with asymptomatic stenosis (53).

The only current study to include symptomatic patients is the European Carotid Surgery Trial 2 (ECST 2). Symptomatic patients are evaluated with the carotid risk score (http://www.stroke.ox.ac.uk/model/form1.html), and if the estimated stroke risk is <3% per year, then they may be enrolled in the study, which will compare OMT alone versus OMT plus carotid revascularization.

**CONCLUSIONS**

There have been several significant developments in the evaluation and treatment of carotid artery stenosis. Additional insights have been gained regarding which patients should be treated with which revascularization method. The evidence base has advanced to provide comprehensive recommendations for the management of asymptomatic and asymptomatic carotid stenosis patients. The potential relationship between carotid stenosis and cognitive impairment suggests that TIA and stroke are not the only measure of whether or not a carotid stenosis is asymptomatic. Finally, a new generation of clinical trials has been launched to determine whether advances in medical therapy have altered the decisions regarding the selection of revascularization procedures in important patient populations.

**REFERENCES**


**KEY WORDS** atherosclerosis, carotid stenosis, endarterectomy, stenting, stroke prevention, stroke risk