Among patients with significant carotid artery narrowing but no recent neurologic symptoms (stroke or transient ischemia), the balance of surgical risk and long-term benefits from carotid endarterectomy (CEA) were unclear. Researchers in the United Kingdom claim in the Asymptomatic Carotid Stenosis Trial (ACST), that an artery-widening procedure could halve stroke incidence among high-risk patients.\(^1\)

ACST is a multicenter, randomized trial of carotid endarterectomy in patients with asymptomatic carotid artery stenosis. During the period from 1993 to 2003, 3,120 asymptomatic patients with significant carotid narrowing were randomized equally between immediate CEA—half received CEA by 1 month, 88% by 1 year—and infinite deferral of any CEA—only 4% per year got CEA—and were followed for up to 5 years (mean, 3.4 years). The investigators aimed to determine whether CEA and best medical treatment (BMT) improve stroke-free survival time when compared to BMT alone. ACST is the first trial of its kind to employ a medical treatment arm.

**BACKGROUND**

Asymptomatic carotid stenosis (ACS) may be a cause of stroke. Using ultrasound technology, ACS can be accurately and noninvasively detected, keeping two factors in mind: severity of stenosis and stenotic plaque composition. ACS is commonly found in patients with contralateral symptomatic stenosis or vascular disease elsewhere, whereas other at-risk populations include patients over 60 years of age who have ischemic heart disease, aneurysms, or hyperlipidemia, and who are smokers. Approximately 75% of natural strokes occurring in natural history studies of ACS are ipsilateral to the side with severe stenosis, indicating that carotid stenosis has caused the stroke. Bilateral stenosis may heighten risk, especially if the patient has an incomplete circle of Willis. There is evidence of higher risk in patients with contralateral occlusion, reduced collateral circulation, and progressively occlusive carotid disease.

There are several randomized trials that tested the efficacy of CEA in preventing stroke. These include the ACAS, VA asymptomatic trial, the M AYO carotid trial, and the CASANOVA trial. The VA asymptomatic trial showed benefit of CEA in transient ischemic attack was included. The Mayo trial was halted prematurely due to the high rate of complication in the surgical arm. ACAS was the only one that was able to show benefit in preventing stroke. However, this benefit was limited to male patients and those without diabetes. In addition, the patients assigned to best medical therapy in these trials did not receive modern medical therapy including ACE-I, statins, and clopidogrel, all of which may decrease the risk of stroke in the BMT arm, thus reducing the benefit of CEA. For these reasons, the role of CEA in the treatment of ACS has been controversial.

However, in the US, it is estimated that 60% to 70% of all CEA performed are for ACS.

The ACST trial hopes to shed light to this very important issue, and this article will summarize its findings.

**EVALUATION AND RANDOMIZATION**

All patients with uni- or bilateral carotid stenosis were considered for ACST. Percentage stenosis and plaque composition were determined through ultrasound of both carotid arteries. CT brain and neurological examinations were conducted and risk factors were identified. If coronary bypass or angioplasty were needed, this was done before trial entry. If the carotid artery under consideration was asymptomatic for 6 months or more, and the patient was willing for operation—if randomized into that treatment arm—entrance into the trial was granted. Either BMT or BMT plus CEA were the allocated treatments.

If the patient was randomized to carotid endarterectomy, the procedure was conducted at earliest opportunity. BMT for all patients was conducted during all phases of the trial.
Follow-Up

Follow-up was ideally conducted by the neurologist or stroke physician in collaboration with the surgeon when possible. During the follow-up period, all patients were seen at 4 months after randomization, 12 months, and yearly for 5 years. Points of interest during the follow-up examination included any carotid symptoms such as stroke and death, any current duplex stenosis, increases in plaque echolucency, any clinical myocardial infarct, and current drug therapy and blood pressure. At each visit, an up-to-date duplex Doppler examination of both carotid arteries was conducted. If patients developed neurologic symptoms, excluding stroke, they were immediately assessed by a neurologist. If the patient had a stroke, an assessment and CT scan were immediately conducted by the neurologist.

ELIGIBILITY

Patients eligible for inclusion in this trial were those whose carotid stenosis had not caused symptoms for at least 6 months, who had no history of ipsilateral disabling or severe contralateral stroke, and who had no indications for, or contraindications for, carotid endarterectomy. Patients were asymptomatic if they had residual neurologic signs but no symptoms to specific questioning. The patient was eligible for entry into ACST if the surgeon determined that the lesion was clinically and technically appropriate for operation—i.e., randomized into that treatment arm—if the patient was willing, and if there was substantial uncertainty about whether surgery or BMT was optimal.

Reasons for not entering the trial included a small likelihood of worthwhile benefit such as a low risk of cerebral infarction from a smooth calcified carotid plaque not causing significant stenosis, as well as a life-threatening disease other than stroke. A high risk of adverse effects of trial treatment, such as recent acute myocardial infarction and intracerebral neoplasia or aneurysm, were also reasons for noninclusion. Additionally, restenosis of the artery after previous CEA, and patients with a likely cardiac source of emboli, were also reasons patients were unable to participate in the trial.

FINDINGS

The researchers found that the 5-year stroke risks among participants allocated to immediate CEA versus all allocated deferral (but excluding such perioperative events) was 3.8% versus 11%, with a gain of 7.2%. This gain involved ischemic stroke in the carotid area, of which half were disabling or fatal, as were half of the perioperative strokes. Perioperative events, such as death from stroke, disabling stroke, cardiac death, and non-fatal myocardial infarction, were more common in the deferred CEA group compared to the immediate group (4.5% to 2.8%). When these perioperative events and nonperioperative strokes were combined, the 5-year net risks were 6.4% versus 11.8% for all strokes, versus 6.1% for fatal or disabling strokes, and 2.1% versus 4.2% for fatal strokes alone.

On May 13, 2004, Doctors Dafydd Thomas and Alison Halliday reported that immediate CEA is better than deferred CEA for reducing the 5-year stroke risk in patients with ACS, halving the stroke risk from 12% to 6%. “Our trial shows that immediate surgery is the best option for some patients with severe narrowing of the carotid artery,” said Dr. Halliday. Full compliance with allocation to immediate CEA or deferral would likely have produced slightly larger differences in the numbers being operated on and the 5-year results. The 10-year results are not yet available. Dr. Halliday also reported that there was no significant difference in CEA risk between men and women or among different age groups.

CONCLUSION

Overall in ACST, the net 5-year risk of stroke, including perioperative stroke/death, was 6% with immediate CEA and 12% with deferred CEA. The difference (2-tailed P = .00001) was highly significant. The significant benefits for men and
women aged <65 years and aged 65 to 74 years present at 70%, 80%, or 90% stenosis. More information is needed regarding which types of patient gain worthwhile benefit, as well as the generalizability of the findings.

**POINTS OF CONTROVERSY**

Outside investigators, when reviewing ACST data, inferred that when great numbers of patients and outcomes are investigated, a modest benefit of endarterectomy is seen in women and in patients who have a disabling stroke. This subgroup was of interest to the ACST team because ACAS had failed to show benefit in males. This is due to the fact that women have a higher operative risk coupled with a lower risk of stroke without surgery. Additionally, unstable carotid plaque composition differs between the sexes.

Critics have raised questions regarding this compared benefit for endarterectomy in women versus men. One points out that the analysis of treatment effect by sex was based only on the risk of stroke, and excluded operative strokes and deaths. The effect of sex on the operative risk of stroke and death was reported separately, and the overall balance of hazard and benefit was not reported. Other critics point out that there was no significant benefit from CEA for women in ACAS, and, although ACST reports such a benefit, the absolute risk reduction of 4.08% seen in women was only half the 8.21% absolute risk reduction observed in men. Assuming that the projected risk reduction after 5-years follow-up is distributed equally in the time frame, this would correspond to an absolute risk reduction of 0.8% per year. This would require 125 successful endarterectomies to prevent one stroke per year in women.3

**ACST INVESTIGATORS RESPOND**

The ACST writing committee responds that a study like theirs that randomized only 3,000 patients cannot be expected to yield results that are separately significant in each subgroup that the correspondents wish to consider. They state that the judgments proposed by their report about likely risks and benefits for particular future patients should generally be based on the statistically stable overall results of the ACST rather than the less stable subgroup results. This consideration holds true even when a particular subgroup, like women, comprise a third of the entire study. Results show that women have a risk of 3.7% from immediate CEA (95% CI of 2.2-5.9), and benefit by 1.25% per year. The annual benefit is significant (P = .0004), but has a wide 95% CI of .55-1.95.

If, among women, a hazard of 3.7% is followed by a benefit of 1.25% per year, the immediate versus deferred results would match at about 3 years in women as opposed to 1.5 years in men. Although the 6-year net benefit is separately significant for men only, it does not hold true for men and women combined. Certainly, it will take several years for reliable statistics on the net benefit for women versus men and stroke incidence rates to surface.4

A new trial of surgery versus stenting in asymptomatic patients, ACST-2, is planned. For details, contact acst.sgu.ac.uk.