# The Second European Carotid Surgery Trial

The new ECST-2 is a randomized clinical trial that will compare medical therapy alone with CEA or CAS for patients with asymptomatic and symptomatic carotid artery stenosis using a new measure called the Carotid Artery Risk Score.

**BY ROLAND L. FEATHERSTONE, PHD, AND MARTIN M. BROWN, MA, MD, FRCP**

The original trials comparing carotid endarterectomy (CEA) to medical treatment alone (NASCET and ECST) in patients with symptomatic stenosis showed an overall benefit of CEA in preventing stroke during long-term follow-up. The data from ECST were used by Rothwell et al to develop a model that predicted the risks of stroke in medical treatment using the patients' clinical characteristics. This was used to examine whether patients benefited from CEA in the trial.[1,2] The model was validated using data from NASCET and showed that only patients at a higher predicted risk of stroke during follow-up were likely to benefit from CEA. The largest trial of CEA for asymptomatic carotid stenosis (ACST) also showed a benefit of CEA compared to medical treatment alone, but the benefit was much less than in the trials of symptomatic stenosis.[3,4]

Since the original trials of CEA ended, medical treatment for secondary stroke prevention has changed considerably (eg, widespread use of statins and lower blood pressure [BP] targets). Statins were not available in ECST or NASCET and were used by only 17% of patients in the first 4 years of ACST.[3] Several studies have shown that statins lower stroke risk by approximately one-third and halve the numbers requiring CEA.[5-7] No previous trial incorporated targets for BP or cholesterol levels, which can be expected to further reduce recurrent stroke rates in patients with carotid stenosis treated without CEA. Thus, it is likely that a considerable proportion of patients in whom CEA is currently recommended will not benefit from surgery because the risks of perioperative stroke may equal or exceed the risks of recurrent stroke on medical treatment. To identify patients in whom the risk of stroke on medication alone is such that they may not need additional revascularization, we have adapted the model of Rothwell et al and developed a new measure of stroke risk based on clinical characteristics, which we have called the Carotid Artery Risk (CAR) score. This predicts the 5-year risk of stroke in patients with carotid stenosis who are treated with optimized modern medical therapy.

Carotid artery stenting (CAS) may be a suitable alternative to CEA in selected patients. A meta-analysis of three trials comparing CEA with CAS found evidence that in the short-term, the relative harm of stenting compared with endarterectomy decreases with younger age; in patients younger than 70 years, the 120-day stroke or death risk after either CEA or CAS was virtually identical.[8] ECST-2 will therefore include patients in whom it is planned that carotid revascularization would be performed by stenting, so long as the randomizing clinician, supported by a multidisciplinary team, considers CAS to be preferable to CEA in the individual patient. Centers will be asked to prespecify

whether CEA or CAS is planned should the patient be allocated revascularization.

## HYPOTHESIS

Our main hypothesis is that patients who have clinical characteristics that predict a 5-year risk of future stroke of < 15% when treated with modern optimized medical treatment (OMT) alone will not benefit from early revascularization by surgery or stenting in addition to OMT because any reduction in future stroke rates after revascularization will be balanced by an excess of procedural stroke and death.

## TRIAL DESIGN

To test our hypothesis, we have designed and initiated the Second European Carotid Surgery Trial (ECST-2). This 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. OMT in both arms will consist of: (1) optimal antiplatelet (or anticoagulant) therapy, (2) treatment to lower cholesterol adjusted to maintain a target total cholesterol < 4 mmol/L and a low-density lipoprotein < 2 mmol/L, and (3) treatment to lower blood pressure adjusted to maintain a target BP of 135/85 mm Hg or less. Patients will also undergo risk factor modification (eg, advice on smoking and optimization of glycemic control).

### Inclusion Criteria

Patients with asymptomatic and symptomatic atherosclerotic stenosis of at least 50% in severity will be screened using a web-based tool, and those with a CAR score of < 15% (indicating a low or intermediate 5-year risk of stroke) will be eligible for inclusion in ECST-2.

### Exclusion Criteria

Patients will be excluded if they have a CAR score indicating high risk, they refuse either treatment, are unable to consent, or are unsuitable for revascularization due to anatomy, ill health, or disabling stroke.

### Follow-Up

Consenting patients will be followed regularly to assess compliance with OMT and record outcome events for up to 5 to 10 years after randomization. Patients will have brain magnetic resonance imaging (MRI) at randomization and then during follow-up at 1 month and 2 and 5 years after randomization. This will allow a blinded analysis of outcome, independent of any reports of clinical outcomes by the patient or investigator.

### Pilot/Safety Study

An interim analysis will be performed after recruitment and follow-up of 320 patients to assess the safety of the treatment policies and to inform the design and sample size calculations for the full trial, using MRI to determine rates of cerebral infarction and hemorrhage.

### Sample Size and Primary Outcome Event

The trial has a sample size of 2,000. The primary outcome measure for the main trial will be any stroke at any time or procedural death attributed to carotid revascularization. The primary analyses will examine the following question: What is the difference in the long-term survival free of any stroke or periprocedural death in patients with atherosclerotic carotid stenosis at low and intermediate risk for stroke after randomization to a policy of carotid revascularization with OMT compared to OMT alone?

## PROGRESS TO DATE

Ethical approval has been obtained, and the trial opened at the lead center, University College London Hospitals, in March 2012. The trial has been registered and has been given ISRCTN 97744893. Seventy centers in the UK, Europe, and Australia have already expressed an interest in joining the trial, but new centers will be welcomed. A trial website has been established at www.ecst2.com.

## RELATIONSHIP TO OTHER TRIALS

ECST-2 differs from the early trials of CEA in its application of a mathematical risk model to identify suitable subgroups of symptomatic patients for inclusion and in its use of targets for blood pressure and cholesterol levels and risk factor moderation in OMT. Currently, the Second Asymptomatic Carotid Surgery Trial (ACST-2) in the UK and ACT-1 in the US are comparing CEA with CAS but do not include a medical arm and only recruit patients with asymptomatic stenosis. ACST-2 and ECST-2 have an agreement stating that their trials are complementary: ACST-2 only recruits patients with asymptomatic stenosis if the clinician is convinced treatment is required, whereas ECST-2 recruits patients with both symptomatic and asymptomatic stenosis when the clinician is uncertain of the benefit of revascularization.

A third trial, the Stent-Protected Angioplasty in Asymptomatic Carotid Artery Stenosis (SPACE-2) study is randomizing patients with asymptomatic stenosis three ways between CAS, CEA, and best medical treatment. Thus, SPACE-2 requires the clinician to believe the patient and the stenosis are equally suit-

able for stenting and CEA, whereas the view of the ECST-2 investigators, based on the results of our recent Cochrane review,[9] is that in the majority of patients, CEA will be safer than CEA, and therefore CEA alone should be the main comparator for medical treatment. SPACE is also currently restricted to Germany, Austria, and Switzerland.

The proposed second Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST-2) will also compare revascularization with medical therapy in patients with carotid artery disease. ECST-2 has been holding discussions with the CREST-2 investigators to harmonize the protocols of the two trials as much as possible, but it is likely that CREST-2 will only include patients with asymptomatic stenosis. ECST-2 is therefore distinct from the other trials in five main ways: (1) it selects patients using a predictor of risk; (2) it will include a different population of patients to the other trials; (3) it asks a question relevant to a larger population of patients than the other trials (ie, both asymptomatic and lower-risk symptomatic stenosis); (4) it will investigate the benefits of "optimized medical treatment" rather than "best medical treatment;" and (5) it will incorporate an MRI-based assessment of outcome. ■

*Roland L. Featherstone, PhD, is Clinical Trials Manager at the UCL Institute of Neurology in London, United Kingdom. He has disclosed that he has no financial interests related to this article.*

*Martin M. Brown, MA, MD, FRCP, is Professor of Stroke Medicine at the UCL Institute of Neurology in London, United Kingdom. He has disclosed that he has no financial interests related to this article. Prof. Brown may be reached at +44 20 3448 4753; office@ecst2.com.*

1. Rothwell PM, Warlow CP; on behalf of the European Carotid Surgery Trialists Collaborative Group. Prediction of benefit from carotid endarterectomy in individual patients: a risk modelling study. Lancet. 1999;353:2105-2110.
2. Rothwell PM, Mehta Z, Howard SC, et al. From subgroups to individuals: general principles and the example of carotid endarterectomy. Lancet. 2005;365:256-265.
3. Halliday A, Mansfield A, Marro J, et al. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. Lancet. 2004;363:1491-1502.
4. Gladstone DJ, Sahlas DJ. Should people with asymptomatic carotid artery stenosis undergo endarterectomy for primary stroke prevention? JAMA. 2004;171:726-727.
5. The Heart Protection Study Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20536 high-risk individuals: a randomised placebo controlled trial. Lancet. 2002;360:7-22.
6. Henrik Sillesen H, Amarenco P, Hennerici MG et al. Atorvastatin reduces the risk of cardiovascular events in patients with carotid atherosclerosis. Stroke. 2008;39:3297-3302.
7. Milionis HJ, Giannopoulos S, Kosmidou M, et al. Statin therapy after first stroke reduces 10-year stroke recurrence and improves survival. Neurology. 2009;72:1816-1822.
8. Bonati LH, Dobson J, Algra A, et al. Short-term outcome after stenting versus endarterectomy for symptomatic carotid stenosis: a preplanned meta-analysis of pooled individual patient data. Lancet. 2010;376:1062-1073.
9. Bonati LH, Lyrer P, Ederle J, et al. Percutaneous transluminal balloon angioplasty and stenting for carotid artery stenosis. Cochrane Database Syst Rev. 2012;12:CD000515.