

EDITORIAL

Stenting or Surgery for Carotid Stenosis? The Largest Trial in the World Nears Completion

After symptoms from carotid stenosis, carotid surgery to prevent stroke is supported by more evidence than any other vascular surgical procedure. The ECST and NASCET randomised trials,^{1,2} reported their main findings over 25 years ago, but remain the basis for treating patients today, despite better medical care producing some improvements in stroke risk.

Primary prevention of stroke, using prophylactic carotid surgery to treat ‘asymptomatic’ stenosis, was a natural research question following successful symptomatic trials, as many patients have strokes without warning symptoms. Over a 25 year period (1983–2008) three trials studied this question: the Veteran’s Administration (VA), Asymptomatic Carotid Atherosclerosis Study (ACAS), and the Asymptomatic Carotid Surgery Trial (ACST). Over a five year follow up, the prevailing annual stroke risk was halved by carotid surgery in each trial.^{3–5} Longer follow up in the largest trial, ACST, showed that this early gain at five years, with an absolute reduction in stroke risk of 6–7%, was maintained to 10 years. Since many patients survive over 10 years after surgery, this finding is especially important, ensuring their risk of stroke remains low. Use of statins in ACST patients also halved the stroke risk, so combining both treatments was particularly successful, with successful surgery reducing subsequent annual stroke rates to <1%. The overall absolute stroke risk reduction of 6–7% applied to men and to women and to those who were diabetic.⁶

Trials of a newer, less invasive, carotid stenting procedure began in the 1990s. Four trials, EVA 3S, SPACE, ICSS, and CREST randomised symptomatic patients, suitable for both procedures, between surgery and stenting.^{7–10} Conflicting results emerged: in EVA 3S, the smallest trial, surgery was safer; in SPACE, no treatment differences were observed; and in CREST and ICSS, surgery was safer. The femoral approach to stenting, navigating the aortic arch and crossing a recently symptomatic, unstable carotid stenosis, was thought to account for the increased risk of peri-procedural stroke. After the peri-procedural period, surgery and stenting were equally effective in preventing stroke up to 10 years.¹¹

Treating asymptomatic disease is considered less hazardous than symptomatic stenosis, and surgery and stenting are common practice in some countries. Safer stenting technology now includes different filters, balloon catheters

to reverse internal carotid flow, direct cervical access to the carotid artery, and open mesh, hybrid, or membrane covered stents, all aimed at reducing distal embolism from the atherosclerotic stenosis during and just after the stenting procedure.

More trials in the 2000s are comparing carotid surgery with stenting, concentrating on patients with asymptomatic stenosis, where procedural risks seemed acceptably low, but where meaningful long term differences in treatments, should they exist, might not be seen for some 5–10 years. ACT-1 enrolled patients up to 2013, and, like the asymptomatic group enrolled in the earlier CREST trial, their five year results did not define any clear differences in outcome between procedures, but wide confidence intervals did not rule out clinically meaningful differences that may have been present.¹²

The ACST-2 trial began in 2008 and has now included over 3300 of 3600 planned patients. Recruitment will be complete by early 2020 and five year results should be available by 2021. ACST-2¹³ follows guidelines set out by NICE¹⁴ and ESVS.¹⁵ Centres can join the trial if operators provide satisfactory, independently adjudicated evidence of competence in the procedures, if their patients are suitable for both surgery and stenting and fit for follow up for at least five years. For patients and doctors, there must be no clear reason why one procedure is to be preferred over the other, and this principle has ensured that treatment cross-overs in ACST-2 remain low at 4%.

In the ACT-1 and CREST trials, patients underwent stenting procedures with specific devices. In contrast, ACST-2 permits use of any CE marked stents and cerebral protection device and, currently, 44% stents used are closed cell, 33% open cell, 14% are hybrid, and 9% are newer membrane covered devices. Cerebral protection device use is recommended, but optional, and filters have been used for 68% stenting procedures, reverse flow balloon devices employed in 17%, and no devices were used in 15% of procedures — most of these were carried out by neuro-interventionists.

Surgeons in ACST-2 use their normal techniques — patch, shunt, local or general anaesthesia, eversion or standard — for surgery. The number of days a patient remains in hospital is recorded and, four to six weeks after intervention, details of the intervention, medications and any major events (generally stroke, myocardial infarction, and death) are collected using the simple one page follow up (https://acst-2.org/Investigator_Section/Study_Documentation.html). The EQ-5D Health Outcome instrument is used to determine

patient quality of life for patients from six of the top recruiting countries (Italy, UK, Germany, Sweden, Serbia, and Belgium) (https://euroqol.org/wp-content/uploads/2016/10/Sample_UK_English_EQ-5D-3L_Paper_Self_complete_v1.0_ID_23963.pdf). Costs for both procedures are calculated by the Health Economics group in Oxford.

What do we know so far? At entry, mean patient age is 69 years and 30% are women. Diabetes is common (30%) and mean cholesterol at trial entry is 4.6 mmol/L (range 3.5–5.8 mmol/L). ESVS Guidelines¹⁵ are closely followed for use of antithrombotic agents (96%), blood pressure lowering (89%), and lipid lowering treatments (85%). One month after completing the trial procedures, these medical treatments continue in 98%, 86%, and 88% patients respectively. Yearly monitoring of medical treatments is carried out directly with the patients, who describe all their relevant medications, with doses and frequency for each drug. Currently most of patients are on very effective ‘modern’ statins (i.e., atorvastatin or rosuvastatin) and over three quarters of the participants are on moderate (i.e., simvastatin 40 mg, atorvastatin 20 mg, or rosuvastatin 10 mg) or intensive (i.e., atorvastatin 40/80 mg, rosuvastatin 20–80 mg, or PCSK-9 inhibitors) lipid lowering therapy.

The Data Monitoring Committee (DMC) meets yearly and has commended collaborators on their recruitment and excellent follow up. The DMC also informs collaborators of the blinded procedural major event rate (fatal and disabling stroke) as a marker of procedural competence within the trial. For some years this has been 1.0% (in the first ACST trial, completed 15 years ago, this was 1.7%).

ACST-2 is the largest trial in the world comparing stenting and surgery and the main trial report in 2021 will help guide clinicians’ and patients’ choices for stroke prevention in the 2020s.

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