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<b>Corresponding Author:</b>	Alison Halliday, MS FRCS University of Oxford Oxford, UNITED KINGDOM
<b>First Author:</b>	Alison Halliday, MS FRCS
<b>Order of Authors:</b>	Alison Halliday, MS FRCS
	Richard Bulbulia, PhD, FRCS
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## Editorial on the ongoing ACST-2 Trial for the *European Journal of Vascular and Endovascular Surgery*.

Alison Halliday<sup>1</sup>, Richard Bulbulia<sup>2</sup>

<sup>1</sup>Nuffield Department of Surgery, University of Oxford

<sup>2</sup>Nuffield Department of Population Health, University of Oxford

### 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 (<sup>1,2</sup>), 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. 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 5-year follow up, the prevailing annual stroke risk was halved by carotid surgery in each trial (<sup>3-5</sup>). Longer follow up in the largest trial, ACST, showed that this early gain at 5 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 stroke risk, so combining both treatments was particularly successful, with successful surgery reducing subsequent annual stroke rates to under 1%. The overall absolute stroke risk reduction of 6-7% applied to men and to women and to those who were diabetic (<sup>6</sup>).

Trials of a newer, less invasive, carotid stenting procedure, began in the 1990's. Four trials, EVA 3S, SPACE, ICSS and CREST randomised symptomatic patients, thought suitable for both procedures, between surgery and stenting (<sup>7-10</sup>). 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 (<sup>11</sup>).

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 2000's 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 5 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<sup>(12)</sup>.

The ACST-2 trial began in 2008 and has now included over 3200 of 3600 planned patients. Recruitment will be complete in early 2020 and 5-year results should be available by 2021. ACST-2 <sup>(13)</sup> follows Guidelines set out in NICE <sup>(14)</sup> and ESVS <sup>(15)</sup>. 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 5 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. We record the number of days a patient remains in hospital and, 4-6 weeks after intervention, details of the intervention, medications and any major events (generally stroke, myocardial infarction and death) are collected using our simple one-page follow up ([https://acst-2.org/Investigator\\_Section/Study\\_Documentation.html](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](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 our 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 (29%) and mean cholesterol at trial entry is 4.6mmol/L (3.5-5.8). ESVS Guidelines <sup>(15)</sup> 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, treatment continues 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 two-thirds of patients are on 'modern' statins (ie, atorvastatin or rosuvastatin) and over three quarters of our participants are on moderate (ie, simvastatin 40mg, atorvastatin 20mg or rosuvastatin 10mg) or intensive (ie, atorvastatin 40/80mg, rosuvastatin 20-80mg, 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 2020's.

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