



Asymptomatic Carotid Surgery Trial-2 (ACST-2): Rationale for a Randomised Clinical Trial Comparing Carotid Endarterectomy with Carotid Artery Stenting in Patients with Asymptomatic Carotid Artery Stenosis

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Abstract Objectives: To compare carotid endarterectomy with carotid artery stenting in the prevention of stroke in patients with asymptomatic carotid stenosis.

Design: A large, simple, pragmatic international trial of at least 5000 patients with asymptomatic carotid stenosis in whom intervention is thought to be needed but where there is substantial uncertainty about the appropriate choice of treatment. The trial is designed to fit in easily with normal clinical practice.

Materials & Methods: A short (~2 min) telephone call is made to randomise patients to either carotid endarterectomy (CEA) or stenting (CAS). Follow-up by the collaborator will be at one month after the procedure (simple 1-page form) and by the ACST office for 5-years post-procedure. Data will be analysed on an intention-to-treat basis; main outcomes will be 30-day myocardial infarction, stroke and death, and 5-year stroke rates. In addition, appropriate subgroup analyses will be undertaken, and health economic evaluation will consider procedural and stroke-related healthcare costs and quality of life.

Conclusion: Collaborators who routinely undertake CEA and CAS are encouraged to participate in ACST-2. This trial, now funded and open for randomisation, will provide important evidence comparing the immediate and long-term safety and efficacy of carotid endarterectomy and stenting in patients with asymptomatic carotid stenosis.

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Patients with significant carotid artery stenosis (60–99%) are 3 times more likely to suffer disabling or fatal ischaemic stroke when compared with the general population.¹ Approximately 100,000 people in the UK and at least one million people in Europe have severe carotid stenosis.^{2,3} Trials in symptomatic patients support use of CEA to prevent stroke, but there is currently no robust evidence that allows us to predict which asymptomatic lesions will cause a stroke; therefore, for some patients with tight asymptomatic carotid artery stenosis intervention may be indicated.^{4,5}

Carotid stenosis may be treated surgically by open removal of plaque through carotid endarterectomy (CEA) or by endovascular means, using carotid stenting (CAS); these procedures may actually cause stroke if thrombosis occurs in the endarterectomised vessel or if emboli are dislodged from the carotid plaque and block the distal cerebral circulation. The long-term outcome balancing peri-operative risk and stroke prevention benefit for both procedures needs careful examination and good medical treatment is essential to minimise stroke risk from other factors.^{6,7,8}

The use of prophylactic carotid endarterectomy in patients with asymptomatic carotid stenosis has caused considerable controversy. The prevalence of carotid stenosis >50% is 5–10% in the older population, and their annual stroke risk in screening studies has been estimated as 1–3%. However, even with this lower risk, because most strokes arise in patients without previous symptoms, the potential benefit of intervention in the form of CEA in asymptomatic patients may be important. A number of randomised trials have been conducted recently comparing stroke rates in asymptomatic patients. The first Asymptomatic Carotid Surgery Trial (ACST-1⁹) and the Asymptomatic Carotid Atherosclerosis Study (ACAS¹⁰) enrolled almost 5000 patients with carotid stenosis and no stroke or stroke-like symptoms in the preceding 6 months. In ACST-1, which reported 5-year results in 2004, 3120 patients were randomised between immediate CEA and medical therapy, and delayed CEA (waiting until operation more clearly needed, for example, if symptoms occurred) and medical therapy. Results showed that even though immediate CEA involved a small (~3%) but definite peri-procedural risk of stroke or death, there was a significant (~3% versus ~12%, $p < 0.001$) reduction in the subsequent stroke rate over the next 5-years and a net gain (~6% versus ~12%) in the overall 5-year risk of stroke or peri-procedural death.⁹ In 1995, for a smaller group, ACAS had shown similar results and CEA reduced the overall 5-year risk of ipsilateral stroke and death from 11% to 5.1% ($p = 0.004$).¹⁰ These results provided robust and contemporary evidence that CEA prevents stroke in patients with asymptomatic carotid stenosis.

Recent data arising from the SPARCL trial indicates that the increased use of statins does reduce stroke risk in patients with asymptomatic carotid disease (although their degree of stenosis was undefined).¹¹ From ACST we know that CEA in patients up to 75 years also significantly reduces stroke risk. When intervention for these asymptomatic patients is indicated. CEA is a well proven procedure but less invasive endovascular stenting is now an attractive alternative.

Endovascular treatment for carotid stenosis is commonly performed under local anaesthetic using remote percutaneous arterial access. Compared to CEA, CAS can be used to reach surgically inaccessible lesions, avoids a surgical wound, reduces the risk of cranial nerve injury, is usually done with shorter hospital stay and might reduce the risk of peri-procedural myocardial infarction or stroke. However, there are complications associated with stenting: injury to the access vessels from introduction of wires and catheters may result in vessel dissection; crossing of the atherosclerotic lesion to place the stent may cause distal embolisation and stroke, even though fine umbrella-like cerebral protection devices have been developed to provide protection. Radiological contrast can precipitate allergic reactions and is nephrotoxic, particularly in patients with previously compromised renal function. CAS is already in wide use: for example, approximately 7000 carotid stents per year are inserted in Germany and worldwide most stents are used in patients with asymptomatic carotid disease. There remains, however, substantial uncertainty concerning the immediate hazards and long-term reliability of CAS, with recent studies highlighting a possible increased incidence of 30-day adverse events in octogenarians and in those with unfavourable plaque morphology.¹²

A recent systematic review and meta-analysis of ten mainly symptomatic trials of CEA versus CAS concluded that both procedures were equivalent in terms of death and nonfatal myocardial infarction. The pooled data was not sufficient to determine the differential impact on stroke rates, though results suggested a trend towards an increase in stroke risk following CAS.^{13,14}

No large trial has specifically set out to compare CAS and CEA in asymptomatic patients, although four published trials of CEA versus CAS and the lead-in phase of the Carotid Revascularisation Endarterectomy versus Stent Trial (CREST) have included some asymptomatic patients^{15–19} (see Table 1). In randomised trials patient populations were mostly symptomatic and none reported separate subgroup analysis for asymptomatic patients. A pooled subgroup analysis of asymptomatic patients from these trials did not provide meaningful conclusions because of small numbers of patients and wide confidence intervals.¹³ The only trial involving solely asymptomatic patients was small ($N = 85$) and reported no major complications (stroke or death) in either CEA or CAS treated groups.¹⁸ Because of the lack of randomised trial evidence, a 2008 review of guidelines by the European Stroke Initiative recommends that CAS in patients with asymptomatic carotid stenosis should only be undertaken in randomised controlled trials.

Because stroke risk (for CEA and for CAS) is lower for asymptomatic patients, a large international multi-centred trial is required to compare immediate (30-day) procedural risk and long-term stroke risk reduction in patients with asymptomatic carotid stenosis. ACST-2 aims to compare CEA with CAS in asymptomatic patients and provide clinicians with robust evidence as to which (if either) intervention is least hazardous and which can provide best long-term stroke reduction benefit. The trial is designed to fit in easily with everyday clinical practice. The trial protocol is summarised in Appendix I. We invite all clinicians who practice CEA and/or CAS to consider joining ACST-2, by contacting us through our website (www.acst.org.uk),

Table 1 Characteristics of randomised trials of CAS versus CEA which include asymptomatic patients

Author (year)	Trial name	Total Patients, No.	Use of stents, %	Use of cerebral protective devices, %	Mean age of subjects, year	No. asymptomatic patients	Operative risk	Follow-up, months	Degree of stenosis, %
CAVATAS (2001) ¹⁵	CAVATAS	504	26	0	67.0	30 in CAS group, 22 in CEA group	Average	36	Not reported
Brooks (2004) ¹⁸	Kentucky	85	100	0	68.2	85 randomised between CAS and CEA	Not reported	48	>80
Yadav (2004) ¹⁶	SAPPHIRE	334	100	95.6	72.6	117 in CAS group, 119 in CEA group	High	36	>80
Ling (2006) ¹⁷	TESCAS-C	166	100	100	63	Undefined	Not reported	6	>70

CAVATAS, Carotid and Vertebral Artery Transluminal Angioplasty Study; SAPPHIRE, Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy; TESCAS-C, Treatment of Carotid Atherosclerotic Stenosis in China.

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Appendix I Design and Objectives of ACST-2

The ACST-2 trial is a large, international randomised trial comparing CEA versus CAS in patients with asymptomatic carotid stenosis. Patients are suitable if prompt physical intervention is thought to be needed, but where (after suitable angiography has shown both procedures to be possible) there is still substantial uncertainty shared by patient and doctor about whether CEA or CAS is the more appropriate choice. Half will be randomised to CEA and half to CAS. All patients will be followed up for 5 years and analyses will be on an intention-to-treat basis. Basing eligibility on uncertainty should ensure large-scale recruitment of an appropriately heterogeneous group, thereby increasing the applicability of the study, and enabling determination of the effects of patient characteristics or of the devices used.

Each centre will have a collaborating neurologist (or stroke physician), vascular surgeon and stenting interventionalist, responsible for patient recruitment, treatment and follow-up. The stenting interventionalist may be a radiologist, cardiologist, surgeon or physician with specialist training in carotid stenting. A 'centre' may be organised between colleagues in neighbouring hospitals but the neurological assessments will be carried out by a participating neurologist or stroke physician. Each collaborator must send a 'Track Record' of their previous experience with CEA or CAS before starting the trial, countersigned by the local collaborating stroke physician or neurologist. These records will be anonymised and then reviewed by the technical management committee. Doctors must have performed 25 or more of the particular procedure in order to participate in the trial, but their overall experience will be taken into account. In general collaborators should have $\leq 8\%$ stroke and death risk for symptomatic patients and $\leq 4\%$ stroke and death risk for asymptomatic patients, or some appropriate combination of these percentages.

Ethical approval is required for each centre and the ACST office is happy to assist prospective collaborators with the process of obtaining this. Additionally, a 'Memorandum of Intent' must be signed by each centre, and is countersigned by the University of Oxford. Once this is done, ethical approval obtained and Track Records approved centrally, eligible patients can be enrolled.

The trial is designed to maximize recruitment by minimising each collaborator's workload and it can be

integrated easily into routine healthcare. Annual follow-up will then be organised by the ACST office and the randomisation form and 1-month post-procedural form are the only forms that routinely need completion by the doctor.

The primary objectives of the trial are to compare 1) peri-procedural risks (MI, stroke and death within the first month after the allocated CEA or CAS is attempted), and 2) long-term (up to 5 or more years) prevention of stroke, particularly disabling or fatal stroke in the two treatment groups. The secondary aims are health economic evaluation for procedural costs, stroke-related healthcare costs and quality of life assessment. Further subgroup analyses may identify patient groups in which one or other procedure is clearly preferable.

The complete trial protocol may be downloaded from: www.acst.org.uk.

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