

Status Update and Interim Results from the Asymptomatic Carotid Surgery Trial-2 (ACST-2)

ACST-2 Collaborative Group *

WHAT THIS PAPER ADDS

The need for a large-scale randomized trial comparing CEA versus CAS: A Cochrane meta-analysis of CEA versus CAS trials (mainly in symptomatic patients) states “There is a strong case to continue recruitment in current randomized trials comparing carotid stenting with endarterectomy”. Multicentre large clinical trials are particularly needed in asymptomatic patients and the European Stroke Initiative suggests stenting be considered only within randomized trials. The UK National Institute for Clinical Excellence (NICE) recently (April, 2011) also recommended stenting for asymptomatic carotid stenosis be carried out within the ACST-2 trial.

Objectives: ACST-2 is currently the largest trial ever conducted to compare carotid artery stenting (CAS) with carotid endarterectomy (CEA) in patients with severe asymptomatic carotid stenosis requiring revascularization.

Methods: Patients are entered into ACST-2 when revascularization is felt to be clearly indicated, when CEA and CAS are both possible, but where there is substantial uncertainty as to which is most appropriate. Trial surgeons and interventionalists are expected to use their usual techniques and CE-approved devices. We report baseline characteristics and blinded combined interim results for 30-day mortality and major morbidity for 986 patients in the ongoing trial up to September 2012.

Results: A total of 986 patients (687 men, 299 women), mean age 68.7 years (SD \pm 8.1) were randomized equally to CEA or CAS. Most (96%) had ipsilateral stenosis of 70–99% (median 80%) with contralateral stenoses of 50–99% in 30% and contralateral occlusion in 8%. Patients were on appropriate medical treatment. For 691 patients undergoing intervention with at least 1-month follow-up and Rankin scoring at 6 months for any stroke, the overall serious cardiovascular event rate of periprocedural (within 30 days) disabling stroke, fatal myocardial infarction, and death at 30 days was 1.0%.

Conclusions: Early ACST-2 results suggest contemporary carotid intervention for asymptomatic stenosis has a low risk of serious morbidity and mortality, on par with other recent trials. The trial continues to recruit, to monitor periprocedural events and all types of stroke, aiming to randomize up to 5,000 patients to determine any differential outcomes between interventions.

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INTRODUCTION

ACST-1 (1993–2003) was a trial of carotid endarterectomy (CEA) versus no immediate procedure and demonstrated the effectiveness of CEA over deferred surgery in stroke prevention.^{1,2} Asymptomatic surgery has a generally low procedural hazard and, in the more recent Carotid Revascularization Endarterectomy vs. Stent Trial (CREST),³ the 30-day stroke and death rate for asymptomatic patients was 1.4% (CEA) and 2.5% (CAS), comparing favourably with ACST-1, where the hazard for surgery alone was 3%.

Improved medical treatment, especially with statins, newer surgical and interventional techniques, and the generalized use of cerebral protection devices together with greater experience and refinement of patient selection may influence outcomes in carotid intervention.

With the current availability of carotid artery stenting (CAS), if a patient is determined to need an intervention for asymptomatic carotid stenosis, there may be continued substantial uncertainty whether to opt for CEA or CAS based on the limited data currently available. ACST-2 seeks to

* Corresponding author. A. Halliday, Nuffield Department of Surgery, John Radcliffe Hospital, University of Oxford.

E-mail address: alison.halliday@nds.ox.ac.uk

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randomize 5,000 such individuals between CEA and CAS to compare both the immediate hazards of the two procedures when done by experienced doctors and the subsequent stroke rates over the next 5–10 years. In an effort to assure completion of such a large and important trial, the workload per patient in this trial has been minimized, so that the study can be integrated easily into routine healthcare.⁴

MATERIALS AND METHODS

Trial treatments

Patients are randomized in a 1:1 fashion, and all are to be followed up for at least 5 years (mainly by mail) and analysed on an intention-to-treat basis. The eligibility is based on physician uncertainty as to the specific treatment after the decision to treat has been made, and it is intended to ensure large-scale recruitment of an appropriately heterogeneous and representative group. This increases the medical value of the study, perhaps making it possible to determine whether the net effects of CEA/CAS are influenced by certain patient characteristics recorded at entry.

The primary objectives of the trial are to compare on an intention-to-treat basis 1) periprocedural risks (myocardial infarction [MI], stroke and death within the first month after the allocated CEA or CAS is attempted by an experienced practitioner), and 2) long-term (up to 5 or more years) prevention of stroke, particularly disabling or fatal stroke, in subsequent years.

Secondary objectives include data analysis in order to assess whether some types of patients can be identified in which one or other procedure is clearly preferable. As part of a health economic evaluation, procedural costs and stroke-related healthcare costs and quality of life will be assessed.

Patient entry into ACST-2

Each centre must have a collaborating neurologist (or stroke physician), vascular surgeon, and stenting interventionalist. They are jointly responsible for patient recruitment, treatment, and follow-up. The stenting interventionalist can be a radiologist, cardiologist, surgeon, or physician with specialist training in carotid stenting. A “centre” can be organized between colleagues in neighbouring hospitals, making a so-called “hub-and-spoke” arrangement.

Vascular surgeons who may perform CEA in the trial should already have had a reasonable amount of successful experience with the procedure. Likewise, interventionalists who may perform CAS in the trial should already have had a reasonable amount of experience with up-to-date techniques of stenting.

The experience of surgeons and interventionalists is vetted through the study management committees.

Suitable patients are those with carotid artery stenosis detectable by duplex ultrasound, with no ipsilateral carotid territory symptoms (or none for at least 6 months) and no previous ipsilateral carotid procedure, who are thought

likely to benefit from procedural treatment with CEA or CAS. Patients should already have been started on any appropriate medical treatment (e.g. statin, aspirin, diabetes management, and blood pressure-lowering medication), and should have recovered from any necessary coronary procedures (e.g. coronary artery bypass graft). All patients for the trial should be eligible for both CEA and CAS without excessive risk, have an expected lifespan of at least 5 years, and willing to be followed-up in person (at 1 month) and by annual letter (for at least 5 years). Some type of cross-sectional imaging (e.g. magnetic resonance angiography or computed tomography angiography) must already have been done which has shown that CEA and CAS would both be anatomically practicable.

The doctor and the patient should both, after a full discussion about the hazards and benefits of both interventions, be substantially uncertain about whether to treat with CEA or CAS. Patients should not be included where there is a small likelihood of worthwhile benefit (e.g. very low risk of stroke because stenosis is not severe, or major comorbidity or life-threatening disease, such as advanced cancer, which would be expected to limit lifespan), or where the patient is unsuitable for one or other procedure (e.g. stenosis at carotid siphon that is inaccessible for CEA, or complex vasculature below the stenosis that would hinder CAS, or if the patient is unfit for major surgery). Once these considerations have been completed, the Randomization (ESM Fig. 1) and Consent forms are completed and the patient can be randomized into ACST-2.

The CEA or CAS should then be done as soon as possible (ideally within the first month after randomisation) by a collaborator whose track record for that procedure has been approved. It is the responsibility of this collaborator to use techniques and equipment that are appropriate for routine clinical practice (e.g. in Europe, CE-marked stents). Cerebral protection devices are optional (i.e. at the collaborator’s discretion), but encouraged.

Before discharge, collaborators are advised to schedule a Duplex ultrasound and a 1-month clinical follow-up visit and schedule assessment by a neurologist/stroke physician (within 1 month of the procedure) of whether or not the patient had a periprocedural stroke or MI.

All other care remains the responsibility of the patient’s doctor, and not the trial. Patients do not need to undergo any other tests or examinations beyond those provided as part of their routine care. The 1-month post-procedural form (ESM Fig. 2) has then to be completed and sent to the ACST office.

Longer-term follow-up

Annual follow-up for at least 5 years (to monitor any strokes) will usually be by the ACST office writing to the patient. After the 1-month post-procedural form, no further follow-up by the doctor is required (unless fuller details of a self-reported stroke need to be provided). Patients will be contacted annually for at least 5 years by a letter originating

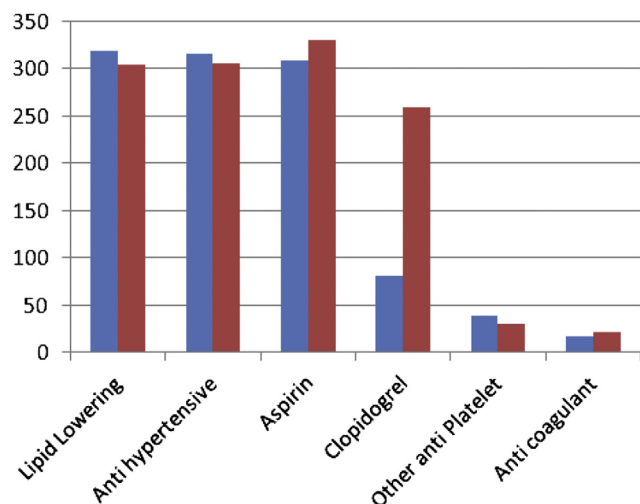


Figure 1. Current therapy at 1-month follow-up. Blue = carotid endarterectomy; red = carotid artery stenting.

from the international ACST office asking if they remain well, and enclosing a brief questionnaire. Both will be in the patient's own language, with a prepaid envelope for return to an ACST office.

Data Monitoring Committee

During the study, interim analyses of major events are being supplied at least annually to an independent Data Monitoring Committee (DMC).

The DMC will advise the Trial Steering Committee (TSC) if there is an unacceptably high morbidity associated with CEA or CAS (either overall, or in particular centres, or in the centres with more limited prior experience), or if there is clear evidence that, for all patients or some particular types of patient, there is proof beyond reasonable doubt that one or the other procedure is preferable. Until then, the TSC and collaborators will otherwise remain unaware of interim unblinded results.

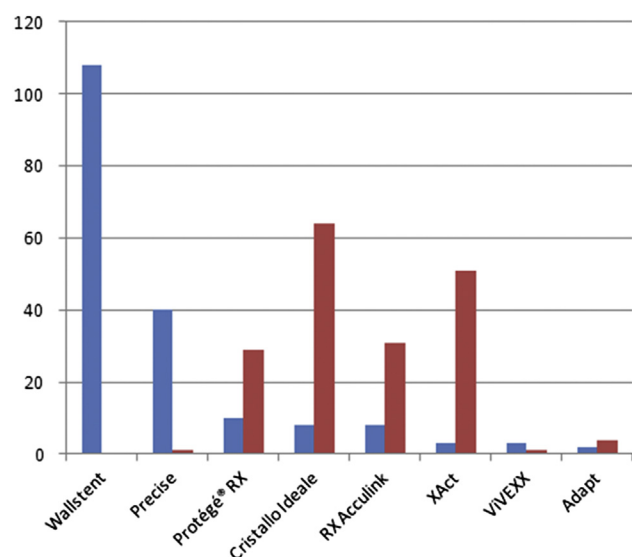


Figure 2. Stents used. Blue = straight stents used; red = tapered stents used.

Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least three standard deviations in an interim analysis of a major endpoint may be needed to justify halting or modifying such a study prematurely.

Major periprocedural events

Strokes (within the first post-procedural month or during long-term postal follow-up). Stroke severity is classified by outcome using the modified Rankin disability scale after 6 months have elapsed since the event:

- 0 No symptoms at all from the stroke.
- 1 No significant disability, despite any symptoms from the stroke: able to carry out usual activities.
- 2 Slight disability because of the stroke: unable to carry out all previous activities but able to look after their own affairs without assistance.
- 3 Moderate disability from the stroke: requiring some help, but able to walk without assistance.
- 4 Moderately severe disability from the stroke: unable to walk without assistance and unable to attend to their own bodily needs without assistance.
- 5 Severe disability from it: bedridden, incontinent, and requiring constant nursing care and attention.
- 6 Died directly or indirectly from the stroke.

Peri- or post-procedural myocardial infarction (within the first month)

It is necessary to report MI only if this occurs during the peri- or post-procedural (1 month) period. Routine post-procedure ECG and enzyme determination are not required. If more than one MI occurs in this month, each should be reported. A definite diagnosis of MI can be made only if at least two of the following criteria are fulfilled:

- 1 Symptoms consistent with MI.
- 2 Positive enzyme or biomarker (e.g. troponin-T) changes consistent with MI.
- 3 ECG changes consistent with MI.

Death

If the patient dies within 1 month of the trial procedure (CEA/CAS), the cause and circumstances are to be described on the 1-month post-procedural form. Otherwise, follow-up is by mail from the ACST office, with later deaths reported by patients' relatives via annual questionnaires.

Statistical analysis

The main trial outcomes will be MI, stroke, or death 1 month after the allocated procedure (CEA or CAS), and long-term (up to 5 or more years) stroke rates. With 5,000 randomized patients, a decrease of about 60% in the periprocedural myocardial infarction rate with stenting versus surgery (e.g. 2% CEA vs. 0.8% CAS) and an increase of about 60% in the 5-year stroke rate (e.g. 3% CEA vs. 5%

CAS) could both be detected at $p < .001$ with 80% probability (i.e. with 80% statistical power), or at $2p < .05$ with 95% power. The exact magnitude of any effect is currently not known, hence the need for the trial, but, taking into account existing information from other trials of CAS versus CEA,³ effects of this size might be realistic, meaningful, and worthwhile. Even smaller effects could be of substantial interest, but might require much larger numbers to be studied.

All patients are followed up (unless they choose to withdraw) whether the trial procedure is carried out or not, since the main trial analyses will be on an intention-to-treat basis. By the end of the recruitment period, data will be available to consider the periprocedural outcomes; in addition, it is anticipated that at least 2 years' follow-up on average will also be available. Analyses will then be possible of the early effects of CEA versus CAS on the annual incidence of stroke type and severity. Continued follow-up will allow more powerful analyses of these longer-term outcomes. In this paper, the early outcomes are blinded, and the DMC does not consider that there is any reason to stop the trial. These results represent a "pilot" study defining the types of patients randomized, the varieties of devices and techniques used, and the early risks of intervention. To understand the longer-term stroke risks after both interventions we will need to have a minimum of 5 years' follow-up on several thousand patients.

RESULTS

Baseline characteristics

Between February 2008 and September 2012, ACST-2 collaborators working in 68 centres across 23 countries randomized 986 patients to either CEA (493) or CAS (493). Baseline characteristics for the whole study population are shown in Table 1 (and, due to a minimization algorithm, both randomized groups are well matched for all measured baseline variables and, due to the size of this study, should be balanced for unmeasured variables as well). Males predominated (70%) and the median age of the current study population is 71 years. Around one-third of participants had a past history of coronary artery disease (37%) or diabetes (30%), but renal impairment (11%) and atrial fibrillation (6%) were less common. Significant hypertension was uncommon (10%) at presentation, and the use of appropriate cardiovascular risk factor reduction medications (antiplatelet agents, 83%; blood pressure lowering agents, 79%; lipid-lowering therapy, 75%) was good at randomization and improved during follow-up (Fig. 1).

The majority of patients treated in ACST-2 had an ipsilateral stenosis $>70\%$ (96%). Most had no significant contralateral carotid disease (63%), but 8% had a contralateral occlusion. Prior (i.e. >6 months old) ipsilateral events were infrequent (7%) as were prior ischaemic lesions on pre-intervention cross-sectional imaging (12%).

Table 1. ACST-2 baseline characteristics.

	Total <i>n</i> = 986 (%)	
Age at entry		
Mean \pm SD (yrs)	68.7 \pm 8.1	
<65	241	(24.4)
65–74	401	(40.7)
≥ 75	344	(34.9)
Sex		
Men	687	(69.7)
Women	299	(30.3)
Pre-randomization SBP (mean)		
<160 mmHg	888	(90.1)
≥ 160 mmHg	98	(9.9)
Plaque echolucency (% soft)		
<25	309	(31.3)
≥ 25	256	(26.0)
Not estimated	421	(42.7)
Risk factors recorded at entry		
Atrial fibrillation	55	(5.6)
Coronary artery disease	364	(36.9)
Diabetes	298	(30.2)
Renal impairment	106	(10.7)
Medication use at randomization		
Antiplatelet	814	(82.6)
Anticoagulant	65	(6.0)
Antihypertension	778	(78.9)
Lipid lowering	736	(74.6)
Stenosis at randomization (%)		
Ipsilateral diameter reduction		
0–49%	0	(0.0)
50–69%	39	(4.0)
70–99%	947	(96.0)
Contralateral diameter reduction		
0–49%	617	(62.6)
50–99%	291	(29.5)
Occlusion	78	(7.9)
Prior ipsilateral events		
Ipsilateral carotid territory symptoms	65	(6.6)
Ipsilateral infarct on CT MRI scan	121	(12.3)

Compliance

Because the trial is ongoing, final compliance is not available, and to date two patients have died before allocated treatment could be performed. For the 691 patients with at least 1-month follow-up (and 6-month Rankin scoring, for any stroke) the crossover rate from allocated to non-allocated treatment at 1-month follow-up was 1.4% (11 patients, 4 allocated to CEA had CAS, 7 allocated CAS underwent CEA).

By 1-month follow up 348 patients had CEA and 343 had CAS. One-month follow-up was pending for a further 67 patients, and 37 patients (4%) had refused or postponed treatment. The mean time from randomization to treatment was 24 days (SD 30.7 days). By 28 days after randomization, 68% had undergone treatment.

Techniques

Similar numbers of CEAs were performed under general anaesthesia (56%) and local/regional anaesthesia (44%),

but the majority of carotid stents were performed under local anaesthetic (94%). Carotid patching was used in 50% of patients undergoing CEA and 29% of CEA patients were shunted. For CAS, eight types of stent were used (46% tapered), and Wallstent (Boston Scientific Corp., Boston, MA, USA) was the most commonly used device (Fig. 2). Cerebral protection devices (CPDs) were used for almost all CAS (Fig. 3), and eight types of CPD were employed (78% filters, 20% proximal systems including flow reversal and flow arrest systems: Fig. 4). The use of dual antiplatelet agents was more common in the CAS group (Fig. 5).

Thirty-day major morbidity and mortality

Amongst all 691 randomized participants with at least 30 days' follow-up, there were two fatal strokes and a further four non-fatal but disabling strokes (Table 2). Additionally, 14 non-disabling strokes occurred during this period, yielding a 30-day stroke rate of 2.9%. There was one fatal MI and three non-fatal MIs within 30 days of the procedure. Overall, there were seven (1.0%) vascular events during this early post-intervention period resulting in death or disabling stroke.

DISCUSSION

The 30-day results of intervention in the first 691 patients in ACST-2 show that CEA and CAS in the trial have a 1.0% immediate risk of disabling stroke and death. Longer-term follow up will be carried out on all patients for at least 5 years, and these findings will be reported in a future publication.

Stroke is a significant cause of major morbidity and premature mortality in the developed world, and strokes caused by carotid artery stenosis are potentially preventable. When faced with a patient with a haemodynamically significant carotid stenosis (e.g. 70–99%) the treating clinician has a range of options. Clearly, if they are certain that the patient should not have any intervention, or that the patient requires surgery or stenting specifically, then randomization to a trial is not appropriate. However, if they

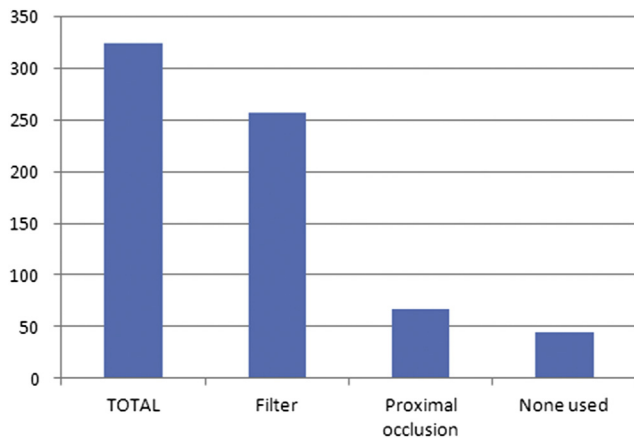


Figure 3. Cerebral protection devices. Blue = number used.

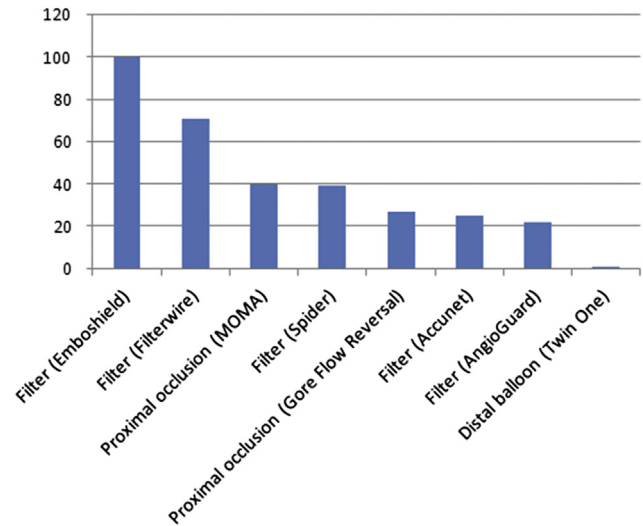


Figure 4. Type of cerebral protection (CP) devices used. Blue = number used.

are uncertain whether any procedure should be performed, enrolment into a randomized trial comparing intervention with a no-procedure control may be appropriate; and if certain that some procedure is required but uncertain as to whether stenting or surgery is best, then they should consider randomizing such patients in ACST-2.

In the ACST-1 trial (1993–2003), overall procedural (CEA) morbidity and mortality was 3%, and disabling stroke and death occurred in 1.7% patients.^{1,2} Prior to intervention, as in ACST-2, most patients (~95%) were on antithrombotic (antiplatelet or anticoagulant) treatment and many were on blood pressure and lipid-lowering medicines. In the 5–10 years since ACST-1 completed recruitment, more patients with known severe asymptomatic stenosis are now on these treatments and the number of diabetic patients recruited in ACST-2 has risen to 30%, reflecting the greater prevalence of diabetes in older populations. High blood pressure treatment is started when systolic pressure regularly exceeds 140 mmHg and higher doses of statins are generally prescribed.

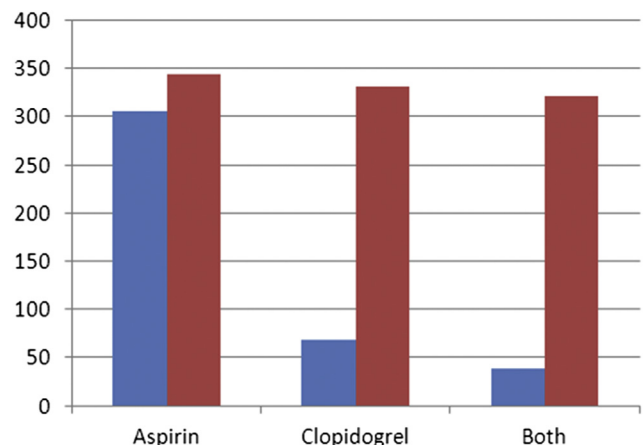


Figure 5. Antiplatelet drug use (during procedure). Blue = carotid endarterectomy (CEA); red = carotid artery stenting (CAS).

Table 2. Major events within 30 days for 691 patients. Unrefuted stroke within 30 days, by severity of worst such stroke

Fatal	2
Disabling	4
Non-disabling (excludes TIA)	14
Total	20
Unrefuted MI within 30 days, by outcome	
Fatal	1
Non-fatal	3
Total	4
Vascular event within 30 days that (eventually) caused death, or disabling stroke within 30 days	7 (1.0%)
Any unrefuted stroke, MI or related death within 30 days	24 (3.5%)
Death in 30 d probably unrelated to stroke, MI or procedure	2

MI = myocardial infarction; TIA = transient ischaemic attack.

The baseline findings in ACST-2 are otherwise similar to ACST-1 but we have now included the presence of known renal dysfunction (~10%). As recruitment increases and follow-up accumulates, we should be able to determine whether diabetes and renal dysfunction have an adverse effect on long-term survival when compared with that seen in ACST-1.

The only completed trial comparing these treatments in asymptomatic patients is CREST. About half those recruited (1,182/2,502) had no prior symptoms and this trial used one stent device and one CPD, both manufactured by Abbott Medical (Abbott Park, IL, USA). To date (4-year follow-up), overall treatment outcomes following CAS in CREST are similar to CEA with an excess of procedure-related non-disabling strokes following CAS and of MI after CEA.³ Detection of MI in CREST included some non-clinical events (with troponin rises alone) which differs from the ACST-2 protocol. In the long-term, however, both trials as well as SPACE-2 should be able to compare quality of life and causes of death and disability following CEA and CAS. ACST-2 intends to compare a wide range of stents and CPDs, thereby reflecting normal (mostly European) practice. However, the ACST-2 trial does not compare intervention with medical treatment alone. This is being carried out in the SPACE-2 and ECST-2 studies which are ongoing.^{5,6} In the longer term, collaboration between all these studies may help determine which patients benefit more from intervention.

We have shown that intervention in asymptomatic carotid stenosis can be achieved with low risks of major complications, and the 1.0% rate of major periprocedural morbidity/early mortality compares favourably with earlier randomized trials and non-randomized registry data. However, because of the low rates of complications, a very large randomized trial with several thousand patients directly comparing early and long-term risks is needed to reliably demonstrate any difference between these interventions. The streamlined design of ACST-2, in which only essential data are collected, enables the trial to fit in well with

routine clinical care and should facilitate recruitment in a wide variety of countries across Europe and further afield.

Debate will continue about which (if any) patients with an asymptomatic carotid artery stenosis will benefit from carotid intervention to prevent a serious stroke. While the overall risk of stroke can be reduced substantially by antiplatelet therapy, blood pressure-lowering agents, and lipid-lowering therapy,⁷ in patients with established severe carotid stenosis, there are no prospective data that medical therapy is effective in reducing stroke risk compared with revascularization. Moreover, we have previously shown that both for patients on statins and those not, allocation to carotid endarterectomy halved their risk of stroke post procedure. So, whilst we recognize that aggressive risk factor reduction medications can (subject to good compliance) substantially reduce global cardiovascular risk (including that of stroke), such risks cannot be completely abolished by long-term medication alone. Therefore, successful carotid intervention should be considered as a useful adjunct to good medical therapy, particularly in patients who could reasonably be expected to survive for around 10 years.

In conclusion, worldwide during this decade, around 1 million asymptomatic patients will have a carotid procedure, thereby preventing over 60,000 strokes. Presently, whether such patients are treated with surgery or stenting is largely decided by the experience, preference, and prejudice of the treating clinician, with marked geographical variation. The minimally invasive nature of carotid stenting is appealing to the general public, and the popularity of this approach could well increase with time. The 30-day results of intervention in the first 691 patients in ACST-2 show that CEA and CAS in the trial have an immediate risk of 1.0% of causing disabling stroke and death, and the independent Data Monitoring Committee report of March 2012 encourages further recruitment in ACST-2, a view shared by the UK National Institute for Health and Clinical Excellence (NICE).⁸

We encourage colleagues to join ACST-2 and, by randomizing several thousand patients, provide uniquely reliable evidence to help guide the treatment of asymptomatic patients undergoing carotid intervention. The protocol for gaining approval and for the trial can be accessed on www.acst.org.uk.

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PROTOCOL APPROVAL

This protocol, originally prepared by the ACST Office and CTSU, has been extensively reviewed and approved (MREC approval no. 05Q0201/66).

ACST-2 WRITING COMMITTEE

ACST-2 Team

Alison Halliday, University of Oxford, UK.
Richard Bulbulia, University of Oxford, UK.
William Gray, Columbia University, USA.
Ally Naughten, University of Oxford, UK.
Anne den Hartog, University of Oxford, UK.
Antonella Delmestri, University of Oxford, UK.
Carol Wallis, University of Oxford, UK.
Stephanie le Conte, University of Oxford, UK.
Sumaira Macdonald, Freeman Hospital, UK.

Interventionalists. Djordje Radak, Dedinje Cardiovascular Unit, Belgrade, Serbia.

Franco Nessi, Department of Surgery, Umberto I- ASO Mauriziano, Turin, Italy.

Giovanni Torsello, Department of Surgery, St Franziskus-Hospital Münster GmbH, Germany.

Jeroen Hendriks, Department of Thoracic and Vascular Surgery, Antwerp University Hospital, Edegem (Antwerp), Belgium.

Katarina Bjorses, Vascular Center, Skane University Hospital Malmö, Sweden.

Lazar Davidovic, Clinic for Vascular Surgery, Serbian Clinical Centre, Belgrade, Serbia.

Nicola Tusini, Department of Surgery, Santa Maria Hospital, Reggio Emilia, Italy.

Peter Gillgren, Department of Surgery, Södersjukhuset, Sweden.

Renato Casana, Department of Surgery, Istituto Auxologico Italiano, Milan, Italy.

Valerio Tolva, Department of Surgery, Istituto Auxologico Italiano, Milan, Italy; Department of Clinical Medicine and Prevention, University of Milano-Bicocca.

Yvonne Bausback, Angiologist, Park Hospital, Leipzig, Germany.

Physicians. Ali Mehrzad, Physician, Bishop Auckland, UK (Newcastle Hub & Spoke).

Anders Gottsäter, Physician, Vascular Center, Skane University Hospital Malmö, Sweden.

Bernard Esi, Physician, Bishop Auckland, UK (Newcastle Hub & Spoke).

ACST-2 COLLABORATORS

Belgium (52 patients): Antwerp (P Cras, J.M.H. Hendriks, P Lauwers, M Hertoghs, P Van Schil); Bonheiden (L De Jaegher, P Peeters, J Verbist); Brugge (D Dendooven, J De Letter, G Vanhooren); Brussels (P Astarci, I Capron, C Choghari, F Hammer, V Lacroix, A Peeters, R Verhelst); Dendermonde (M Bosiers, K De Meester, K Deloose, E Van Buggenhout, E Vinck); Ghent (M Geenens, D Hemelsoet,

I Van Herzele, F Vermassen); Liège (G De Koster, Q Desiron, A Maertens de Noordhout, D Malmendier, M Massoz, G Saad); Mouscron (S Cirelli, P Dormal, P Lerut, E Thues). *Canada* (5 patients): Calgary (S Coutts, A Demchuk, M Hill, M Hudon, G Klein, M McClelland, W Morrish, G Samis, G Sutherland, T Watson, J Wong). *China* (4 patients): Peking (Bao Liu, Chang-Wei Liu). *Czech Republic* (23 patients): Ceske Budejovice (L Barankova, V Chlouba, J Fiedler, V Priban, L Sterba); Brno (L Kalabova, Z Kriz, P Krupa, M Privara, M Reif, L Souckova, R Staffa, R Vlachovsky, B Vojtisek); Ostrava Poruba (T Hrbac, M Kuliha, V Prochazka, M Roubec, D Skoloudik). *Egypt* (2 patients): Cairo (F Abd Allah, MH Eldessoki, H Heshmat Kassem, H Soliman Gharieb). *France* (42 patients): Nimes (JM Cardon, A Le Gallou Wittenberg); Paris (E Allaire, JP Becquemin, F Cochenec, P Desgranges, H Housseini, H Kobeiter, J Marzelle); Marseille (P Bergeron, R Padovani, JC Trastour). *Germany* (51 patients): Singen (B Biermaier, HM Gissler, C Klotzsch, T Pfeiffer, R Schneider, L Soehl, M Wennrih); Leipzig (Y Bausback, S Botsios, D Branzan, S Braunlich, H Holzer, J Lenzer, C Reichenbecher, C Piorkowski, J Schuster, D Scheinert, A Schmidt, M Ulrich, M Werner); Oldenburg (A Coster, A Engelhardt, CM Ratusinski); Munster (B Berekoven, K Freker, V Gordon, G Torsello). *Greece* (22 patients): Athens (I Bellenis, A Polydorou, V Polydorou, A Tavernarakis); IASO Athens (N Ioannou, M Terzoudi); Larissa (E Chatzinikou, A Giannoukas, G Hadji-georgiou, S Koutsias, S Ralli, N Rousas). *Hungary* (20 patients): Budapest (B Nemes, Z Járányi, A Szabo, D Varga); Szeged (P Barzo, M Bodosi, E Fako, B Fulop, A Kuncz, E Nagy, T Nemeth, S Pazdernyik, K Skoba, E Voros). *Ireland* (1 patient): Dublin (SN Haider, J Harbison, P Madhavan, D Moore). *Israel* (9 patients): Haifa (R Beyar, A Hoffman, T Karram, A Kerner, E Nikolsky, S Nitecki). *Italy* (211 patients): Avenllino (G Amatucci, P Vittorio); Bari (Prof. Frederico, D Marinazzo, G Regina), Catania (A Giaquinta, F Patti, M Veroux, P Veroux); Milan (L Adobbati, G Bertoni, P Bianchi, R Casana, L Cireni, L Martello, V Tolva); Modena (L Arcuri, F Casoni, G Coppi, R Moratto, J Veronesi); Palermo (G Bajardi, G Savettieri); Pavia (R Corbetta, A Odero, P Quaretti, Z Thyron); Perugia (P Cao, V Caso, P DeRango, L Farchioni, G Parlani); Reggio Emilia (G Malferrari, F Strozzi, N Tusini, E Vecchiati); Rome (A Biello, L Capoccia, D Menna, A Rita Rizzo, E Sbarigia, F Speciale, D Toni); San Donato (M Giovanni, G Meola, G Nano, MT Occhiuto, S Stegher, D Tealdi); San Paolo (F Accrocca, C Ambrogio, R Barbazza, G Marcucci); Sienna (A Cappelli, G De Donato, G Palasciano, D Pieragalli, C Setacci, F Settaci); Turin (C Labate, E Ferrero, M Ferri, F Nessi, A Viazzo); Varese (P Castelli, ML Delodovici, M Ferrario, G Piffaretti, G Tomei). *Japan*: Sendai (E Furui, T Inoue, R Kondo, Y Matsumoto, H Shimizu); *Kazakhstan* (2 patients): Almaty (B Aidashova, N Kospanov, R Lyssenko, D Mussagaliev). *Netherlands* (27 patients): Utrecht (GJ De Borst, AG Den Hartog, R Lo, F Moll, R Toorop, HB Van Der Worp, EJ Vonken). *Norway* (8 patients): Oslo (S Bakke, K Krohg-Sorensen, M Skjelland). *Poland* (26 patients): Warsaw (P Andziak, S Drelichowski, M Dratwicki, R Gil, W Iwanowski, K Koncewicz, M Nowicki, J Pniewski, J Rzezak, P Seweryniak); Medical University Warsaw (P Bialek, Z Biejat, W Czepel, A

Czlonkowska, A Dowzenko, J Jedzrejewska, A Kobayashi, J Leszezyuski, A Malek, J Polanski, R Proczka, M Skorski, M Szostek). *Serbia* (70 patients): Belgrade, Dedinje Cardiovascular Unit (N Aleksic, S Babic, J Kolar, D Radak, D Sagic, S Tanaskovic); Belgrade, Serbian Clinical Centre (M Colic, L Davidovic, D Jovanovic, I Koncar); *Slovak Republic* (6 patients): Ruzomberok (D Bartko, P Beno, F Rusnak, K Zelenak). *Slovenia* (16 patients): Izola (M Gasparini, A Grad, I Kompara, Z Milosevic); Maribor (V Flis, J Matela, K Miksic, F Milotic, B Mrdja, B Stirn, E Tetickovic). *Spain* (25 patients): Barcelona (A Chamorro, V Obach, V Rimbau, S Roman); Guadalajara (E Blanco, AY Izquierdo, M Guerra). *Sweden* (115 patients): Helsingborg (E Campbell, H Lindgren, J Nyberg, G Plate, H Parsson, P Qvarfordt); Malmo (S Acosta, K Bjorses, K Brandt, N Dias, A Gottsater, J Holst, T Kristmundsson, T Kuhme, T Kolbel, B Lindblad, M Lindh, M Malina, T Ohrlander, T Resch, V Rönnle, B Sonesson, M Warvsten, Z Zdanowski); Stockholm (B Bengt, M Delle, J Formgren, P Gillgren, L Jarl, TB Kall, P Konrad, N Nyman, C Skioldebrand, J Steuer, R Takolander). *Switzerland* (9 patients): Basel (FJ Ahlhelm, L Bonati, S S Engelter, T Eugster, H Gensicke, P Lyrer, L Mariani, P Stierli, C Stippich, T Wolff); *United Kingdom* (206 patients): Bishop Auckland (A Mehrzad, E Brown, B Esisi); Cambridge (N Butler, DJ Day, P Hayes, N Higgins, E Jumilla, P Martin, J Mitchell, K Varty); Carlisle (A Birt, P Davies, J George, A Graham, L Jonker, T Joseph, N Kelsall, C Potts, T Wilson); Durham (P Davey, R Hayman, G. Tervitt); Hull (A Abdul-Hamiq, J Bryce, I Chetter, D Ettles, R Lakshminarayan, K Mitchelsonm, C Rhymes, G Robinson, P Scott, A Vickers); Kent (H Baht, I Balogun, I Burger, L Cowie, G Gunathilagan, D Hargroves, R Insall, S Jones, H Rudenko, J Senaratne, G Thomas, A Thomson); Liverpool (P Enevoldson, H Nahser, I O'Brian, F Torella D Watling, R White); London (A Clifton, C Eley, N Khanom, J O'Reilly, A Pereira, C Bicknell, N Cheshire, R Gibbs, M Hamady, A James, M Jenkins, A Lacey, M Mireskandari, T Sachs, J Wolfe); Luton (D Hardy, F Justin, L Phiri, L Sekaran, S Sethuraman, L Tate); Manchester (J Akyea-Mensah, A Chrisopoulou, JV Smyth); Middlesbrough (I Nichol, A Parry, G Young); Newcastle (M Clarke, M Davis, A Dixit, A Dyker, G Ford, R Jackson, S Kappadath, D Lambert, T Lees, S Louw, S Macdonald, N Parr, G Stansby, L Wales, V Wealleans, L Wilson, M Wyatt, P Dorman, A Hughes, D Jones, A D Mendelow, H Rodgers); Nottingham (S MacSweeney, N McConachie, A Southam, W Sunman); Oxford (D Briley, C Darby, A Handa, L Hands, W Kuker, K Michael, J Perkins, U Schulz, D, Smith, R Teal); Preston (M Donnelly, S D'Souza, A Asehosem Egun, B Gregory, C Kelly, S Punekar, S Raj, D Seriki, G Thomson); Sheffield (J Beard, T Cleveland, J Humphreys, A Jenkins, C King, R Lonsdale, R Nair, S Nawaz, F Okhuoya, D Turner, G Venables); Southend (J Brown, R Durairajan, P Guylar, P Harman, M Jakeways, C Khuoge, A Kundu, T Loganathan, D Sinha, V Thompson, S Tysoe); Sunderland (Dr Barer, A Brown, S Crawford, P Dunlop, Dr Majmudar, D Mitchell, Dr O'Brien, Dr O'Connell, Dr Scott, S Vetrivel); Wythenshawe (R Ashleigh, S Butterfield, G Gamble, J Ghosh, C McCollum, M Welch, S Welsh); *United States of America* (1 patient): Toledo (V Kazan, M Nazzal, V Ramsey-Williams).

TRIAL ORGANISATION AND COMMITTEES

Principal Investigators (PIs)

Alison Halliday, Professor of Vascular Surgery, University of Oxford, UK.

Richard Bulbulia, Consultant Vascular Surgeon and Research Fellow, CTSU, Oxford, UK.

Christina Davies, Senior Research Fellow, CTSU, Oxford, UK.

Richard Peto, Professor of Medical Statistics & Epidemiology, CTSU, Oxford, UK.

Jean-Pierre Becquemin, Professor of Vascular Surgery, Hôpital Henri Mondor, Paris, France.

Alastair Gray, Director, Health Economics Research Centre (HERC), Oxford, UK.

Borislava Mihaylova, HERC, Oxford, UK.

Trial Steering Committee (TSC), reporting to (but independent of) the funding bodies

John Potter (chair), Professor of Medicine for the Elderly, University of East Anglia, UK.

Richard Bulbulia (co-PI), Consultant Vascular Surgeon and Research Fellow, Clinical Trial Service Unit, Oxford, UK.

Christina Davies (co-PI), Senior Research Fellow, Clinical Trial Service Unit, Oxford UK.

Marcus Flather, Professor of Medicine and Clinical Trials at the University of East Anglia, UK.

Alison Halliday (PI), Professor of Vascular Surgery, University of Oxford, UK.

Sumaira Macdonald, Consultant Radiologist, Freeman Hospital, Newcastle, UK.

William Gray, Director, Endovascular Services, Columbia University, USA.

Averil Mansfield, Chair BMA Scientific Committee, UK.

Richard Peto (co-PI), Professor of Medical Statistics and Epidemiology, University of Oxford, UK.

Barbara Farrell, Observer, Trial Director of the CORONIS and INIS Trials, National Perinatal Epidemiology Unit (NPEU).

Kazem Rahimi, Deputy Director of the George Centre for Healthcare Innovation and Consultant Cardiologist, Oxford, UK.

David Simpson, Lay Patient Representative, Oxford, UK.

Dafydd Thomas, National Hospital for Neurology & Neurosurgery, London, UK.

Co-opted Member: Hans-Henning Eckstein, SPACE-2 PI, Professor of Vascular Surgery, Klinikum an der Rechts den Isar, Munich, Germany.

Technical Management Committee (reviewing Track Records of prospective collaborators)

Michael Gough (chair), Consultant Vascular Surgeon, Leeds, UK.

Marc Bosiers, Head of Surgery, Hôpital A.Z St. Blasius, Dendermonde, Belgium.

Piergiorgio Cao, Professor, San Camillo Hospital, Rome, Italy.

Sumaira Macdonald (TSC; interventional radiologist).

Endpoint Review Committee (classifying the nature and severity of any strokes and MI)

Peter Rothwell (chair), Professor of Clinical Neurology, University of Oxford, UK.

Matthew Giles, Consultant in Care of the Elderly, Oxford, UK.

Kazem Rahimi, Consultant Cardiologist, Oxford, UK.

Peter Leopold, Consultant Vascular Surgeon, Frimley Park Hospital, Surrey, UK.

Anna Belli, Consultant Radiologist, SGUL, London, UK.

Economic Evaluation Committee

Alastair Gray (chair), Heath Economics Research Unit (HERC), Oxford, UK (co-PI).

Borislava Mihaylova (co-PI), HERC, Oxford, UK.

Frank Vermassen, Department of Vascular Surgery, Ghent University Hospital, Belgium.

Independent Data Monitoring Committee (DMC)

Peter Sandercock (chair), Professor of Neurology, University of Edinburgh, UK.

Richard Gray, Professor of Medical Statistics, University of Oxford, UK.

Cliff Shearman, Professor of Vascular Surgery, University of Southampton, UK.

Andrew Molyneux, Consultant Neuroradiologist, Frenchay Hospital, Bristol, UK.

Project Management Group

All PIs and other individuals named above, except DMC members.

Project staff from the ACST Office

Elizabeth Hayter, (2007-11), Ally Naughten (2010-12), Steffi le Conte, Carol Wallis and the Oxford CTSU (Mike Lay, Andrew Munday, Alan Young, Antonella Delmestri).

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