

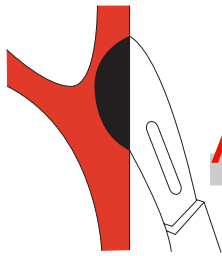


ACST Trial Protocol

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ACST Trial Protocol

Introduction

The current incidence of stroke in Europe and the USA is about 200 per 100,000 population per annum^{1,2}. Eighty percent of strokes are ischaemic and 20% are due to haemorrhage. Approximately half the patients with ischaemic stroke have carotid artery stenosis³ and about one third (~10% all stroke victims) have had no warning symptoms such as transient ischaemic attacks⁴.

European Carotid Surgery Trial (ECST)⁵ and North American Symptomatic Carotid Endarterectomy Trial (NASCET)⁶ have effectively shown that carotid endarterectomy (CEA) can prevent strokes in **symptomatic** patients. The benefit of operation is, at present, confirmed in those with at least 70% stenosis; for 50-69%, the results are somewhat equivocal⁷. In asymptomatic patients the Veterans Administration Study⁸ and the Asymptomatic Carotid Atherosclerosis Study (ACAS)⁹ suggested that surgery may reduce the overall risk of TIA and stroke. There is as yet no convincing evidence in **asymptomatic** patients that moderate or severe stroke (or death) can be prevented by CEA. The aim of this trial is to determine whether CEA and appropriate best medical treatment (BMT) can improve stroke free survival time when compared with BMT alone.

Background

Asymptomatic carotid stenosis (ACS) can be accurately and non-invasively detected by ultrasound^{10,11}. It is often found in patients with contralateral symptomatic stenosis or vascular disease elsewhere, but routine ultrasound screening is also justified in certain population groups. Stenosis of more than 50% is present in ~25% hypertensive patients¹², and in ~12% of those with peripheral vascular disease. Other groups worth screening include those over 60 years who are known to have ischaemic heart disease, aneurysms or hyperlipidaemia, and are smokers^{13,14,15}.

ACS may be an important causative factor in unheralded stroke. Two factors, accurately detectable by ultrasound, are particularly important; severity of stenosis and composition of the stenotic plaque. Approximately three quarters of strokes which do occur in natural history studies of ACS are ipsilateral to the side with severe stenosis, implicating the carotid stenosis as the cause of stroke¹⁶. Bilateral stenosis may carry even greater risk, especially if the patient has an incomplete circle of Willis. There is evidence of higher risk in patients with contralateral occlusion, reduced collateral circulation (measured by transcranial Doppler) and progressively occlusive carotid disease¹⁷.

The type of plaque causing stenosis appears to have important prognostic significance. Ultrasonically echolucent material is, when examined histologically, soft and friable and echogenic plaque is firm and collagenous¹⁸. Several studies have demonstrated that patients with predominantly 'soft' plaques are more likely to have suffered previous TIAs or strokes^{19,20,21,22}. Prospectively, by following patients using serial ultrasound, Langsfield and Bock found that both type and degree of stenosis were positively associated with subsequent development of symptoms^{23,24}.

Although stroke risk is thought to be greatest with stenosis >80%, Satiani showed that patients with >50% stenosis had a 7% risk of stroke after 2 years²⁵ and Moore found that after 5 years one third of hypertensive patients with similar stenoses had had a stroke²⁶. Johnson reported that "even patients with <75% narrowing are at increased risk if the plaque was heterogeneous or soft" and, after 3 years, 20% of patients in this study had either had a TIA or stroke²⁷. Clearly an effective preventative therapy was needed.



Medical treatment of ACS

Treatment of modifiable medical risk factors is appropriate in all patients. Meta-analysis of hypertension trials showed that reduction of systolic blood pressure by 5-6 mmHg was associated with 35-40% fewer strokes and 20-25% fewer myocardial infarctions²⁸. Recommended 'safe' blood pressure limits have been repeatedly lowered²⁹. Regular aspirin usage has been found to reduce deaths from myocardial infarction and non-fatal strokes in symptomatic patients³⁰.

Lipid-lowering therapy may, by reducing total and LDL cholesterol and fibrinogen, effect plaque regressions³¹. It has certainly been shown to reduce the incidence of symptomatic coronary heart disease. Control of diabetes is important as, although strokes may still occur, prevention of hyperglycaemia may attenuate stroke severity³². Smoking directly effects the incidence of carotid stenosis and although there is no evidence yet to suggest that stopping smoking will slow, stop or reverse ACS, it should be strongly discouraged³³. Heavy alcohol consumption has been associated with hypertension and haemorrhagic stroke and should be reduced³⁴. Myocardial infarction is commoner than stroke in patients with ACS and discovery of carotid stenosis is a golden opportunity to uncover and treat heart disease³⁵. Patients with ACS may be non-invasively investigated by ECG and exercise testing, or by modified studies such as ECG chest wall mapping or dipyridamole-thallium exercise scanning³⁶. In some cases, coronary angiography and subsequent angioplasty or by-pass surgery may be necessary. The asymptomatic carotid artery does not usually have to be operated upon when coronary artery by-pass is undertaken³⁷.

Surgery for ACS

Because carotid endarterectomy can be performed with low perioperative morbidity and mortality, surgeons may be tempted to operate. In a collective review of over 2300 endarterectomies for ACS, Colburn found that the perioperative stroke rate and 30-day mortality was 1.5% and 0.8% respectively³⁸. Comparisons of outcome with and without surgery may suggest that surgery is beneficial; Moneta in 1987 reported that 19% of patients with >80% stenosis had strokes or died within 2 years, in contrast to 5.8% of the surgically treated group³⁹. Bias occurs within non-randomised trials however, and even 'natural history' studies do not include patients who have been pre-selected for surgery, potentially altering results.

Clinical Trials of ACS

The ideal means of investigating the importance of ACS should be a clinical trial. The North American and European symptomatic carotid surgery trials (**ECST** and **NASCET**) have successfully demonstrated the value of endarterectomy for symptomatic carotid stenosis^{5,6}. But, to date, four trials of surgery for ACS have been inconclusive.

The **Mayo Clinic trial (MACE)** compared aspirin with surgery and was terminated after only 71 patients had been entered because an excess of patients in the surgical group had myocardial infarctions⁴⁰.

CASANOVA, a German trial, took ten years, reporting in 1991⁴¹. Four hundred and ten patients in 10 centres were entered. All were given aspirin and were completely asymptomatic. Patients with >90% stenosis were excluded, and several different treatment options such as unilateral or bilateral endarterectomy, and unilateral endarterectomy or medical treatment were permitted. Operative intervention occurred frequently during medical patients' follow up (e.g. if bilateral stenoses exceeded 50%). The trial end points were stroke and death. The trial was stopped when only 122 patients, who had unilateral surgery, were available for comparison with 111 who had medical treatment. At this point only 9.8% of the unilateral surgical group and 12.6% of the medical group had reached an endpoint ($p=0.321$). The trial organisers concluded that "at least 2000 randomised patients are needed to detect 25-33% reduction of stroke risk.. (and this information).. will not be available from one single study but will require meta-analysis of all available trials".



The **Veterans' Administration trial (#167)** ran from 1983-91⁷. Only men were eligible and 444 out of a target of 500 were recruited. Patients with previous ipsilateral cerebral infarction (clinical or CT) were excluded and the endpoints were TIA, stroke and death. After TIA, crossover to surgery was permitted. For stroke prevention, results were again inconclusive, but 12.8% of the surgical group had stroke or TIAs compared with 24.8% of the medical group. They concluded that "to detect a reduction of 50% in strokes in the surgical group would require more than 3000 patients – beyond the scope of any contemporary clinical trial" in ACS.

Currently, the largest clinical trial is the **Asymptomatic Carotid Artery Study (ACAS)**⁸ in the US, which recruited 1662 patients. The minimum preoperative stenosis was 60%, with angiography compulsory in the operated group⁴². The trial, using projected life table analysis to 5 years, showed a reduction in expected ipsilateral stroke rate from 2% per annum to 1% per annum in the surgical group. A subgroup analysis to identify higher risk groups (for example, those with soft plaque or greater than 90% stenosis) was not possible, and the results still leave many questions unanswered.

In ECST and NASCET four CEAs needed to be carried out to prevent one disabling stroke in patients with 70-99% symptomatic stenosis. To date, the ACAS results have not yet been able to show that surgery can reduce the risk of disabling strokes. This study is now terminated and high risk groups have not been identified. Therefore the ACST is the only continuing study to determine the value of operation in effectively preventing stroke in asymptomatic patients.

The ACAS results have not yet been shown to be generalisable; the American Heart Association guidelines⁴³ recommended CEA only if operative mortality and morbidity was <3.0%. Several large studies^{44,45} have shown that operative mortality and morbidity may exceed 4-5%, suggesting that medical therapy may be safer than operation.





The Asymptomatic Carotid Surgery Trial (ACST)

Aim of the trial

This is a multi-centre randomised trial of carotid endarterectomy (CEA) in patients with asymptomatic carotid artery stenosis.

The aim is to determine whether CEA and best medical treatment (BMT) improve stroke-free survival time when compared with best medical treatment alone. The trial will also identify high risk groups in whom the benefits of surgery and of best medical treatment may be greater.

Eligibility

Patients whose carotid stenosis has not caused symptoms for at least 6 months, who have no past history of ipsilateral disabling or severe contralateral stroke, and who have no indications for, or contra-indications to carotid endarterectomy, are eligible for ACST. Patients already in ECST cannot be entered into this Trial as a patient can only be randomised once, even though they have two carotid arteries.

The participating neurologist should ensure that they are asymptomatic. If they have residual neurological signs **but have nevertheless no symptoms to specific questioning**, then they are asymptomatic. The presence of residual signs should be recorded by the neurologist and the patient considered eligible for the trial.

It is well known that the commonest cause of death in patients with carotid stenosis is ischaemic heart disease and screening for this, even in patients without symptoms, is strongly encouraged.

Patients are therefore eligible if in the view of the responsible physician or surgeon:

- 1) They have unilateral or bilateral carotid artery stenosis appropriate for surgery. The severity of stenosis is not defined specifically - some will have stenoses >90% and some may have stenosis of ~50% with soft plaque; patients with contralateral occlusion may be randomised. **The patient may be entered into ACST if the surgeon is satisfied that the lesion is clinically and technically appropriate to operate on, if randomised to that option.**
- 2) The patient is fit for, and willing to have surgery if recommended and accessible for follow-up, with no known illness preventing long-term follow-up.
- 3) There is substantial uncertainty about whether the patient is better treated by surgery and appropriate medical treatment or by medical therapy alone.

Reasons for **not entering** patients into the Trial are specified by the responsible surgeon or physician, not by the protocol, but include:

- 1) a small likelihood of worthwhile benefit such as:-
 - (i) low risk of cerebral infarction from a smooth calcified carotid plaque not causing significant stenosis;
 - (ii) some major life-threatening disease other than stroke.
- 2) a high risk of adverse effects of trial treatment such as:
 - (i) recent acute myocardial infarction;
 - (ii) intracerebral neoplasia or aneurysm.
- 3) Restenosis of the artery following previous CEA.
- 4) Patients with a likely cardiac source of emboli.



Consent for Entry into ACST

The degree of consent is left to individual doctors to decide for individual patients in the light of any advice they may receive from their local Ethical Committee. However, written consent *is required* and any consent required should be sought **before** randomisation. At all times the local requirements for operative surgery consent should be met and if necessary, a full description of the operation and perioperative care provided. This should also be taken to include appropriate consent for invasive radiological procedures if they are undertaken in trial patients. The collaborating surgeons and physicians will be responsible for patient care in the normal way and the trial should not alter their normal practice.



Choice of Treatments

Best Medical Treatment (for ALL patients)

Patients' 'best medical treatment' is extremely important. Risk factors for stroke and death (the trial end-points) specifically targeted are smoking, hypertension, diabetes, obesity, hyperlipidaemias, polycythaemia and ischaemic heart disease. These should all be rigorously managed.

As randomisation will be within centres, slight differences in medical management between centres should not influence overall results but all centres will be expected to ensure that all patients receive optimal care. Although treatment is only recorded at trial follow-up, it should be strictly adhered to and the controlling physician should, by appropriately frequent visits, ensure patient compliance.

Smoking should be strongly discouraged and if possible stopped completely.

Hypertension should be controlled within 'safe' limits (a systolic blood pressure consistently >140 mmHg and a diastolic pressure consistently >90 mmHg may be generally considered to confer a higher than normal risk of stroke).

Diabetes should be recognised, treated and controlled.

Ischaemic Heart Disease, whether symptomatic or uncovered by investigation should be appropriately treated. Treatment of coronary artery disease by angioplasty or by-pass surgery is **not** a contra-indication for future entry into ACST (however, in this trial CEA cannot be performed simultaneously with coronary by-pass surgery). Entry into ACST should be as soon as the patient is considered fit for further surgery **after** by-pass or angioplasty has been successfully performed.

Hyperlipidaemia should be treated. Cholesterol level should ideally be <5.0 mmol/l.

Antiplatelet therapy may be considered as 'best medical treatment' unless the patient is already on long-term anticoagulants, e.g. warfarin, or there is a specific contraindication to aspirin or clopidogrel treatment such as allergy or gastrointestinal haemorrhage.

Anti-coagulant drugs may be given as part of treatment for other conditions, e.g., mitral valve replacement or if TIAs continue after surgery despite antiplatelet therapy (mitral valve cases should not be in the trial), or as part of therapy for disease related to carotid stenosis, e.g., femoro-distal by-pass grafting using PTFE.

Surgical Treatment (50% patients)

Carotid endarterectomy should be carried out as soon as routinely possible if the patient is randomised to surgical treatment. The surgeon may wish to undertake preoperative angiography before or after randomisation. This is not mandatory as some surgeons now perform CEA without angiography.

CEA may not be scheduled before, or at the same time as planned elective coronary artery by-pass surgery. The carotid endarterectomy technique is that with which the surgeon is familiar. Specific procedures, such as shunting, are undertaken at the surgeon's discretion.

The surgeons collaborating in this trial will already have experience in undertaking CEA in patients who are symptomatic and have clear clinical indications for surgery. The surgeon collaborators should have a track record of their own results which should compare favourably with standards elsewhere in Europe and the USA. Before becoming a collaborator in ACST, each surgeon submits a record of their last 50 endarterectomies, specifying the number done for asymptomatic disease, and the number of disabling strokes or deaths occurring within 30 days of surgery. They should keep on-going records of their results and will be asked on a yearly basis to submit the numbers of CEAs undertaken with



indications for surgery. Specific results will not be requested for operations outside the Trial. However, if an individual surgeon's results in this trial show an unacceptably high morbidity or mortality (as found by the Audit Committee) they may be asked not to enter any further patients. Complete follow-up on those already entered will be necessary and the collaborator would be asked to continue within the Trial on a 'follow-up only' basis.

Following surgery, and before discharge, patients should be assessed by the neurologist to ensure there is no neurological deficit. If one is uncovered, the patient should be investigated for stroke and the major event form completed and returned. Routine postoperative and follow-up treatment usually includes antiplatelet therapy.

No surgery form is required by the ACST office. However, if the patient has a stroke or dies, a major event form must be filled out and returned as soon as possible. All details which may be relevant (e.g. operative procedure, postoperative course and complications) should be recorded within the patient's notes and will then be of help in filling out the major event form. As major events will eventually provide the Trial end points, these details are of vital importance. A telephone call or fax should be sent to the ACST office to indicate that surgical complications have occurred **as soon as the events take place**; details can then be provided on the form.

Telephone Randomisation: Made easy with the Randomisation Notepad

No entry form is needed for ACST and no unusual tests are required. Entry is by means of a direct dial telephone call (or fax) to the randomisation service in Oxford to answer a few questions about the patient. Calls should be made between 0900-1700 UK time. The telephone call is made easier and quicker by use of the randomisation notepad to prepare answers for the questions:

- a) Name and country of surgeon or agreed collaborator in charge.
- b) Patient name, date of birth, sex.
- c) Relative - name and phone number/address
(in UK or the Netherlands give GP's name and postcode).
- d) Current therapy and blood pressure.
- e) Carotid artery history, evidence of infarct on brain scan, presence of echolucent plaque and estimate (%) of carotid stenosis.
- f) Intention (if surgery drawn) to operate on left or right artery.

At the end of the telephone call after the pre-randomisation details have been provided, and written patient consent has been confirmed, the randomisation service allocates the patient's treatment: either best medical treatment and surgery, or best medical treatment alone. All patients are then **irrevocably** in the trial whether treatment is carried out or not since the trial analysis will be on 'intent to treat'. Surgery should therefore be carried out as soon as possible on a planned elective basis, and any surgical complications reported as soon as they occur.

Follow-up and the development of symptoms or major events

In contrast to ECST, the surgeon is usually the physician who screens for, detects and initially assesses the majority of patients with asymptomatic carotid stenosis. This may not be the case in all European countries or in all practices.

Follow-up is best done by the neurologist (or stroke physician) in collaboration with the surgeon wherever possible. During trial follow-up all patients should be seen at 4 months




after randomisation, 12 months, and yearly thereafter. An up-to-date duplex Doppler examination of both carotid arteries should be carried out at each follow-up visit, if possible. The follow-up is simple, requiring answers for the questions:

- a) Name of surgeon or agreed collaborator, and date.
- b) If randomised to surgery; date and side.
- c) Any clinical myocardial infarct.
- d) Any other carotid surgery since last follow up; and date, and side.
- e) Any carotid symptoms either side; stroke, death, and date.
- f) Current duplex stenosis, (where practicable), any definite increase in plaque echolucency.
- g) Current drug therapy and blood pressure.

If patients develop neurological symptoms (not stroke) they must be seen and assessed promptly by the neurologist. If the patient has a stroke, assessment by the collaborating neurologist (including CT scan) should be carried out promptly and a major event form completed and returned to the ACST office. Appropriate clinical action should be taken which may include patients on medical treatment alone going on to have CEA. This **does not** exclude them from the trial and follow-up should continue on the same basis for all patients. **All patients remain within in the trial until the trial is completed.**

Duplex Reporting

At randomisation and follow-up the estimated stenosis and plaque composition is entered. If possible the following simple duplex data should be separately recorded (by the collaborator or the vascular laboratory staff) and sent to the ACST office .



ASYMPTOMATIC CAROTID SURGERY TRIAL Carotid Duplex Follow-up Form

Patient name:
Surname Forename

Date of examination (day/month/year):

Left	Right
PSV (CCA)= <input style="width: 40px;" type="text"/> cm/s	PSV (CCA)= <input style="width: 40px;" type="text"/> cm/s
EDV (CCA)= <input style="width: 40px;" type="text"/> cm/s	EDV (CCA)= <input style="width: 40px;" type="text"/> cm/s
PSV (CCA)= <input style="width: 40px;" type="text"/> cm/s	PSV (CCA)= <input style="width: 40px;" type="text"/> cm/s
EDV (CCA)= <input style="width: 40px;" type="text"/> cm/s	EDV (CCA)= <input style="width: 40px;" type="text"/> cm/s
Doppler angle = <input style="width: 40px;" type="text"/> °	Doppler angle = <input style="width: 40px;" type="text"/> °
% stenosis = <input style="width: 40px;" type="text"/> %	% stenosis = <input style="width: 40px;" type="text"/> %
Is >25% of the plaque soft (echolucent)? Yes <input type="checkbox"/> No <input type="checkbox"/> Don't know <input type="checkbox"/>	Is >25% of the plaque soft (echolucent)? Yes <input type="checkbox"/> No <input type="checkbox"/> Don't know <input type="checkbox"/>
Blood pressure = <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <small style="display: flex; justify-content: space-around; width: 100%;">Systolic Diastolic</small>	ACST Office Use Only

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Major events and stroke classification

Strokes and deaths should be **immediately** reported as they are major events. The audit committee classifies them when adequate information, including modified Rankin scoring for strokes has been received. Copies of the clinically relevant data such as ECG, CT/MR scans and post-mortem reports may be requested. (The cost of sending copies of relevant CT/MR scans will be supported, at present up to £20 sterling.)

If a patient dies, the major event form should be completed and returned. There is only one double sided form to return, covering follow up and major events.





Analysis

Main and Subsidiary Analyses

The main comparisons will be of:

1. Stroke and death rates in the BMT plus surgery group versus medical treatment alone in the first 4 months after randomisation and at yearly intervals to 5 years.
2. Duplex results in the medical treatment plus surgery group versus those having medical treatment alone at the same intervals as in 1.

Subsidiary analyses in an effort to identify high and low risk groups will include:

The effect of risk factors such as the presence or absence of silent cerebral infarcts on clinical outcome.

Other exploratory analyses will be performed to examine the data available thoroughly.

Interim Analyses - The Data Monitoring Committee

During the study, interim analyses of major events will be supplied to the Data Monitoring Committee. They will advise the Steering Committee whether there is an unacceptably high morbidity associated with surgery. During follow-up further interim analyses will be carried out.

The Data Monitoring Committee will advise the Steering Committee if there is:

1. proof beyond reasonable doubt* that for all or some types of patient one particular treatment is contraindicated in terms of net difference in mortality or morbidity; and
2. evidence that might reasonably be expected to influence materially patient management by clinicians who are already aware of the results of other main trials.

* *This cannot be specified precisely but a difference of at least 3 standard deviations in an interim analysis of a major endpoint may be needed to justify halting or modifying the study.*

Should this happen and one treatment is clearly indicated or contra-indicated in terms of net difference in mortality or stroke the trial would thereby influence patient management and would either be stopped or modified to seek extra data. The Trial Committee and collaborators will otherwise remain ignorant of interim results.

The overall survival and major stroke free survival curves for both treatment groups will be analysed. These may cross because of greater hazards initially in the surgical group during the perioperative period. Similar life table analyses will be used to compare the survival in unoperated groups with soft (echolucent) Gray Weale Type 1&2, and echodense (Gray Weale Type 3&4) carotid plaques of differing stenoses. As no minimum stenosis has been specified, the range of stenoses entered and the proportion of plaque types cannot be predicted until recruitment is well under way.

Validation of the Doppler technique will not be formally tested in each collaborating centre. It has been the practice of a number of centres to perform CEA without angiography for some years. Centres who screen with Doppler **and** perform angiograms may be requested by the Data Monitoring Committee to provide angiography films on a randomly selected sample of patients, to ensure that the relationship between Doppler stenosis and angiography has a positive predictive value of around 90%. Simple Duplex data is requested from the laboratories (see page 11).



All patients undergoing CEA at each centre should be logged locally and a reason for not putting them in the trial should be recorded, e.g. patient in ECST, or symptomatic with a >70% stenosis. A yearly request for local CEA logs will be sent to each centre.

Conclusion

A simple trial has been launched to answer the question '*Does carotid endarterectomy prevent disabling stroke or death in patients with asymptomatic carotid artery stenosis?*'. The normal practice of collaborating surgeons and physicians will be studied, and appropriate best medical treatment will be given to all trial patients. In addition to medical treatment, one half of patients will undergo carotid endarterectomy. Entering patients in ACST is simple and the trial is designed to minimise extra work for busy collaborators.



APPENDIX: Sample forms & Information Sheet

PATIENT INFORMATION SHEET: 1 (UK only)

TAKING PART IN RESEARCH The Asymptomatic Carotid Surgery Trial

You are being invited to take part in a research project. Here is some information to help you decide whether or not to take part. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything you do not understand or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

1. You may or may not receive any direct benefit from taking part in the study. However, information obtained during the study may help us to understand better your condition or illness. It may also help us in selecting treatment for future patients.
2. It is up to you to decide whether to take part or not. If you do decide to take part you will be given an information sheet and consent form. Even if you do decide to take part, you are free to withdraw at any time and without giving a reason. This will not affect the standard of care you will receive. Your doctor will not be upset if you decide not to take part.
3. All the information collected about you during the study will be kept strictly confidential. Any published report of the study will not identify you.
4. Your GP will usually be informed that you are taking part in this study. If this is a problem for you, you should discuss it with your study researcher.
5. Sometimes during the study new information becomes available. Your study doctor will talk to you about this and discuss with you whether you want to continue in the study. If you decide to withdraw, the study doctor will make arrangements for your care to continue. If you decide to continue in the study you may be asked to sign an updated consent form.
6. Since this study may involve surgery, you will be asked to consent to that surgery if and when it is allocated. You should understand that surgery is a necessary part of this study and be happy to have the surgery if it is allocated, before agreeing to take part.
7. If you have private medical insurance you should let the insurers know that you intend to take part in a research project. They will be able to tell you if this will affect your medical insurance.
8. Consumers for Ethics in Research (CERES) publish a leaflet entitled 'Medical Research and You'. This leaflet gives more information about medical research and looks at some questions you may want to ask. You can obtain a copy from:

CERES, PO Box 1365, London N16 0BW



APPENDIX: Sample forms & Information Sheet

PATIENT INFORMATION SHEET: 2 (UK only)

INVITATION TO JOIN A STUDY OF STROKE PREVENTION TREATMENT

The Asymptomatic Carotid Surgery Trial

We'd like to explain to you about the study we're doing and then ask if you are willing to help with it.

Background to the study: Every day in this country, lots of people have a stroke or warning symptoms of a stroke. We are looking at some treatments that might reduce the risk of stroke in patients who have a narrow carotid artery - that is the artery that supplies blood to the part of the brain often affected by stroke. All patients who may have an increased risk of stroke should receive medical treatment and advice to help reduce this risk; this includes treatment of high blood pressure, diabetes, high blood fat levels, heart disease and abnormally high red blood cell counts whenever these are found. We will of course use all the standard treatments for these problems.

An operation called **carotid endarterectomy** may, by successfully removing the narrowing in the artery, reduce the risk of subsequent stroke. However, the risks of this operation include an increased risk of stroke at the time of, and for a few days after the operation. We know from other studies that the risk of operation is justified in patients who have had warning symptoms of stroke (or a minor stroke) provided that their carotid artery is narrowed by more than 70%. We are uncertain whether medical treatment or an operation would be best for your condition. Therefore we cannot definitely recommend or discourage operation on present evidence. The purpose of this study is to determine if carotid endarterectomy reduces the risk of stroke in people who have had no previous warning symptoms.

Why have I been chosen? Your doctor has seen that you have a narrowing of the carotid artery, but you haven't yet had any symptoms related to that artery (or you had symptoms but they occurred more than six months ago).

Who is organising the study? The study is international and is organised from the Department of Cardiological Sciences at St. George's Hospital Medical School, London, UK. It is sponsored by the UK Medical Research Council (MRC).

What will happen to me if I take part? If you decide to take part you will receive all the standard treatments which you would normally receive and you will have the best medical care regardless of which arm of the study you are in. In addition, you would agree to undergo carotid endarterectomy if selected to do so. The selection is carried out at random by computer, and you have a 50% chance of being selected for surgery. The operation would be carried out by your specialist vascular surgeon, in exactly the same manner as he or she routinely does for other patients. Everyone in the study will be followed up at 4 months, 12 months and annually for at least five years by a visit to the surgeon and a repeat Doppler carotid artery scan (which you have already had).

Are there other ways of treating my condition? There are standard medical treatments for this condition, and all patients (whether assigned surgery or not) will receive these in any case. There is also a procedure called carotid angioplasty available.



APPENDIX: Sample forms & Information Sheet

PATIENT INFORMATION SHEET: (UK only)

Are there any disadvantages in taking part in this study? You should understand the reasons for taking any medicines and the possible symptoms which might occur due to the narrow artery. If you have problems with these, you should discuss this with your doctor.

What are the possible risks of taking part? The risks of surgery will be explained by your doctor as well as the risks after operation.

What are the possible benefits of taking part? We hope that any treatment you receive will reduce the risk of stroke. However, this cannot be guaranteed. The information we get from this study may help us to treat future patients with asymptomatic carotid disease better.

Is my doctor being paid for including me in the study? Neither your doctor or the hospital will receive any payment for including you in this study.

What happens when the study stops? If the study stops and it is found that the surgery is beneficial, then you will be offered the choice of having the surgery (assuming you were not allocated surgery). If the study stops without being able to tell if surgery is beneficial, it will be up to your doctor and yourself to decide if you want surgery. If surgery is found not to be beneficial, then you will also be informed by your doctor.

Are there any restrictions on what I might eat or do? If your cholesterol or blood fats are high, or you have other medical conditions such as diabetes then advice and appropriate treatment will be given. If you have heart disease or high blood pressure your doctor will discuss and initiate suitable treatment with your consent.

What if something goes wrong? If you are harmed by taking part in this study, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you have any cause to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you. The study is being undertaken to seek treatments to prevent stroke. If you should have a stroke you will be looked after by your doctors using the appropriate investigations, treatments, and rehabilitation.

Confidentiality - who will know I am taking part in the study? The information collected as part of the study will be sent to the central trial office, who will hold it strictly confidential. Information on individual patients will not be published as part of the trial results, and your name will never be released. Your General Practitioner will usually be notified that you are participating in the trial.

What will happen to the results of the study? The results of the study will be communicated to the MRC, the Stroke Association, and peer-reviewed journals.

ACST/IL/1/401





APPENDIX: Sample forms & Information Sheet

WRITTEN CONSENT FOR RANDOMISATION



ASYMPTOMATIC CAROTID SURGERY TRIAL Consent Form: (UK only)

Title of Project:

Name of Researcher:

Name and number of independent person:

Please read each statement below and initial each box if you agree

1. I confirm that I have read and understand the information sheets (version ACST/ILA/1/0998 and ACST/ILB/1/098) for the above study.
2. I understand that my participation is voluntary and that I am free to withdraw at any time without my medical care or legal rights being affected.
3. I am willing to allow access to my medical records but understand that strict confidentiality will be maintained. The purpose of this is to check that the study is being carried out correctly.
4. I agree to take part in the Asymptomatic Carotid Surgery Trial.

Name of Participant Date Signature

Name of Person taking consent Date Signature
(if different from researcher)

Researcher Date Signature

3 copies: 1 for participant; 1 for researcher; 1 to be kept with hospital notes

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APPENDIX: Sample forms & Information Sheet

RANDOMISATION FORM



ASYMPTOMATIC CAROTID SURGERY TRIAL RANDOMISATION -Answer ALL questions

Then either:

phone: 0900-1700 UK time, weekdays,
England: (+44) (0)1865-240972

or if unable to phone, you can fax:

England (+44) (0)1865-404849 Reply within 1 working day.
Incomplete forms will be sent back for further details.

N.B. Patients in ECST **must** not be entered

N.B. Return fax number **must** be given if faxed

1. Has the patient already signed their informed consent to enter this study? Yes
2. Collaborator/Centre:
3. Neurologist:
4. Patient's family name:
5. Patient's given name:
6. Patient's date of birth (day/month/year):
7. (UK or Holland only) GP's surname and postcode:
8. (Not UK & Holland) Relative (not husband/wife) name, phone no. (include area code):
Name:
Address:

(N.B. * means tick 1 answer ONLY)

- | | | | | | |
|--|-------------------------------|--|---------------------------------------|---------------------------------|-------------------------------------|
| * 9. Male <input type="checkbox"/> Female <input type="checkbox"/> | YES | NO | | | |
| * 10. Diabetic | <input type="checkbox"/> | <input type="checkbox"/> | | | |
| * 11. Definite coronary artery disease | <input type="checkbox"/> | <input type="checkbox"/> | | | |
| * 12. Needs coronary bypass or angioplasty | <input type="checkbox"/> | <input type="checkbox"/> | | | |
| * 13. Currently taking: antihypertensive therapy | <input type="checkbox"/> | <input type="checkbox"/> | | | |
| * 14. Currently taking: antiplatelet therapy | <input type="checkbox"/> | <input type="checkbox"/> | | | |
| * 15. Currently taking: anticoagulant therapy | <input type="checkbox"/> | <input type="checkbox"/> | | | |
| * 16. Currently taking: lipid lowering therapy | <input type="checkbox"/> | <input type="checkbox"/> | | | |
| 17. Total cholesterol (mmol/l): <input type="text"/> OR mg/100ml: <input type="text"/> | | | | | |
| 18. Present blood pressure (mmHg): | Systolic <input type="text"/> | Diastolic <input type="text"/> | | | |
| 19. Duplex doppler % stenosis | Left <input type="text"/> | Right <input type="text"/> | | | |
| * 20. Is more than 25% of the plaque soft (echolucent)? | Left <input type="checkbox"/> | Right <input type="checkbox"/> | Both <input type="checkbox"/> | None <input type="checkbox"/> | Don't know <input type="checkbox"/> |
| 21. Infarct on CT scan | Left <input type="checkbox"/> | Right <input type="checkbox"/> | Both <input type="checkbox"/> | None <input type="checkbox"/> | Not done <input type="checkbox"/> |
| * 22. Infarct on MRI scan | Left <input type="checkbox"/> | Right <input type="checkbox"/> | Both <input type="checkbox"/> | None <input type="checkbox"/> | Not done <input type="checkbox"/> |
| * 23. Which side are you considering surgery for? | Left <input type="checkbox"/> | Right <input type="checkbox"/> | | | |
| * 24. Any prior symptoms this side more than 6 months ago? | None <input type="checkbox"/> | Amaurosis fugax <input type="checkbox"/> | Cortical TIA <input type="checkbox"/> | Stroke <input type="checkbox"/> | Other <input type="checkbox"/> |
| * 25. Any prior contralateral symptoms? | None <input type="checkbox"/> | Amaurosis fugax <input type="checkbox"/> | Cortical TIA <input type="checkbox"/> | Stroke <input type="checkbox"/> | Other <input type="checkbox"/> |
| * 26. Previous CEA | Left <input type="checkbox"/> | Right <input type="checkbox"/> | Both <input type="checkbox"/> | No <input type="checkbox"/> | |

Information to be obtained from phone call: Date: (day/month/year)

Treatment allocated: Best medical treatment and **surgery**
OR Best medical treatment alone

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APPENDIX: Sample forms & Information Sheet

FOLLOW-UP FORM (OBVERSE)



ASYMPTOMATIC CAROTID SURGERY TRIAL FOLLOW-UP

Patient's family name:

Patient's given name:

Patient's date of birth (day/month/year):

If 1st follow-up after Trial Surgery, give date of operation: (day/month/year)

and side operated on Left Right

Perioperative clinical myocardial infarct <30 days post CEA Yes No

Any other carotid surgery since last follow-up Yes No

If YES, give date of operation (day/month/year)

and side operated on Left Right

Since randomisation/last follow-up

Left carotid territory symptoms Yes No

Right carotid territory symptoms Yes No

Any non-fatal stroke Yes No and date (day/month/year)

Patient died Yes No and date (day/month/year)

N.B. If answer to either is YES, complete major event form also (on reverse of this form)

Duplex results at this follow-up

Maximum % stenosis carotid artery Left Right

Any definite increase in plaque echolucency Left Right Both None Don't know

Current drug therapy

Antihypertensive Yes No

Antiplatelet Yes No

Anticoagulant therapy Yes No

Lipid lowering Yes No

Current blood pressure Systolic Diastolic

Name of collaborator:

Neurologist:

Day (day/month/year):

Please return this form promptly to: ACST Trial Office
Department of Cardiological Sciences
St George's Hospital Medical School
Cranmer Terrace
London SW17 0RE
or Fax (+44) (0)20 8725 3782

(see Reverse for Major Event Reporting)

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APPENDIX: Sample forms & Information Sheet

FOLLOW-UP FORM (REVERSE)



ASYMPTOMATIC CAROTID SURGERY TRIAL MAJOR EVENT

(complete if patient has a stroke or dies)

Patient's family name:

Patient's given name:

Patient's date of birth (day/month/year):

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Surgeon:

Neurologist:

History at randomisation: Give short account of history, particularly notable risk factors, operative history and ECG, CT, angiogram and doppler plaque type results)

Follow-up (short account)

Event

a) Stroke: give date, side, neurological details and CT report of results with date (early to exclude haemorrhage, later if normal at first to show infarct).

b) Death: give date, **all details of cause** and post mortem results (if done)

c) Any postoperative event (<30 days of surgery)

Details from operation notes, general description of operation, plaque appearance, degree of stenosis found, exact time of death or stroke after operation (hours or days: please specify), description of action taken and outcome, with CT results (early to exclude haemorrhage and later if first CT normal) in patients who have stroke.

Please return this form promptly to: ACST Trial Office
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 London SW17 0RE
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