

ICSS

International Carotid Stenting Study

Protocol

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Protocol Summary

Background: Clinical trials have shown that carotid surgery prevents stroke but also has significant morbidity. Stenting has become an established alternative treatment for coronary and peripheral vascular disease and has the advantage of avoiding general anaesthesia and neck incision. In July 1997, randomisation was completed in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS). The results did not show a difference in the major risks or benefits of carotid angioplasty and surgery, but the trial did show that both methods still carry a significant risk of causing a stroke. Techniques of carotid angioplasty have improved and stenting is increasingly used. The International Carotid Stenting Study (ICSS or CAVATAS 2) is a follow-on study to CAVATAS designed as an international, multicentre, randomised trial, which will evaluate stenting of carotid artery stenosis in patients with cerebrovascular disease.

Centre requirements: A neurologist or physician with an interest in stroke; a surgeon with expertise in carotid endarterectomy and an interventionalist with expertise in carotid angiography and the techniques of angioplasty and stenting.

Inclusion criteria: Symptomatic atheromatous carotid stenosis, > 50% by NASCET criteria, suitable for stenting and surgical endarterectomy.

Treatments: Patients will be randomised in equal proportions to be treated by carotid endarterectomy or stenting. New design of stents, filters and protection devices will be incorporated into the study to allow tracking of new technology if approved by the Steering Committee. Surgery can be performed with local or general anaesthesia.

Sample size: N = 1500 patients from fully enrolled centres. Sample size calculations show that the 95% confidence intervals will be ± 3.0 percentage points for the outcome measure of 30 day stroke, myocardial infarction and death rate and ± 3.3 percentage points for the outcome measure of death or disabling stroke during follow-up.

Primary outcome measure: Long term survival free of disabling stroke.

Secondary outcome measures: Any stroke, myocardial infarction or death within 30 days of treatment, treatment-related cranial nerve palsy or haematoma. Stenosis (>70%) and occlusion on ultrasound follow-up. Transient ischaemic attack. Stroke during follow-up. Further treatment procedure. Quality of life and economic measures.

International Carotid Stenting Study Protocol

Background

Stroke is the major cause of acquired adult physical disability and is responsible for 12% of all deaths in the UK. Reducing the burden of stroke is one of the priorities of the recent government white paper, *Saving Lives: Our Healthier Nation*. In Europe alone, there are approximately one million new cases of stroke a year. Atherosclerotic stenosis of the carotid artery is an important cause of stroke, which may be heralded by a transient ischaemic attack (TIA) or minor stroke, which recovers without serious disability. The risk of recurrent stroke in recently symptomatic patients with severe carotid stenosis is as high as 28% over two years. The European Carotid Surgery Trial (ECST) and the North American Symptomatic Carotid Endarterectomy Trial (NASCET) have demonstrated convincingly that this risk is reduced significantly by carotid endarterectomy.^{1,2} Carotid surgery has therefore become a standard treatment for these patients. However, the trials showed a significant risk of stroke or death resulting from surgery of between 6 and 8%. Surgery also caused significant morbidity from myocardial infarction during the general anaesthetic used in most centres and minor morbidity, including cranial nerve palsy and wound haematoma from the incision. An increasing number of surgeons are performing carotid endarterectomy under local anaesthesia in the belief that it reduces the risks, although there is currently little evidence to support this practice, until the data from the General Anaesthesia versus Local Anaesthesia for Carotid Endarterectomy (GALA) trial are reported.

Stenting is a new method of treating carotid stenosis, which has evolved from the technique of percutaneous transluminal angioplasty (PTA). Stenting avoids some of the hazards of surgery and has become an established treatment for peripheral and coronary artery stenosis. Stenting is less invasive than carotid endarterectomy and has advantages in terms of patient comfort, because the procedure avoids an incision in the neck, and is usually conducted under local anaesthesia. Hospital stay need only be for 24 hours after treatment if uncomplicated. When given the choice, stenting is preferred by many patients. On the other hand, stenting does not remove atheromatous plaque, has not been shown to prevent stroke and may have an unacceptable incidence of restenosis. We therefore propose a multicentre randomised trial to compare carotid stenting with carotid surgery.

Previous work in the field

Percutaneous transluminal angioplasty: A number of groups have published series of patients with carotid stenosis treated by PTA. The cumulative total of patients in these series is over 1000, with a reported major complication rate of less than 5% at the time of the procedure.³ These data suggested that carotid PTA has a similar risk to carotid surgery, but the results could not be taken as definitive because none of the data were from randomised trials. We therefore started a randomised trial, known as the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) in 1992. We completed randomisation in July 1997.

Results of CAVATAS: 560 patients were entered, from 24 centres in the UK, Australia, Canada, Finland, Germany, Italy, Spain, Switzerland, and the USA. Patients with carotid stenosis suitable for surgery were randomised between PTA (n=251) and carotid surgery (n=253). Patients with carotid stenosis unsuitable for surgery (n=40) and patients with vertebral artery stenosis (n=16) were separately randomised between PTA and medical care alone. The number of patients in these last 2 groups was too small to form any firm conclusions. The analysis has therefore been restricted to the 504 patients with carotid stenosis randomised between PTA and surgery.⁴ Baseline variables were well matched. Almost all patients had severe stenosis (mean 86%). The 30-day outcome events were almost identical in the two groups with a rate of death or any stroke lasting more than 7 days of 10.0% after angioplasty and 9.9% after surgery, giving a hazard ratio of 1.01 (95%CI:0.56,1.81) (NS). Analysis of the other risks of treatment has confirmed that PTA was safer than surgery in terms of minor morbidity. Cranial or peripheral nerve palsy was reported in 9% of surgical patients, but not in any PTA patients (p<0.0001). Haematoma requiring operation or prolonging hospital stay was reported in 7% of surgical patients compared with 1% of PTA patients (p<0.0015). PTA also appeared safer than surgery with regard to perioperative myocardial infarction, which occurred in 0.8% of surgical patients, but not in any PTA patients. Survival analysis from randomisation showed no difference in outcome events of ipsilateral stroke and any disabling stroke or death during follow up for up to 3 years with very few events in either arm after the treatment period, suggesting that both treatments were equally effective at preventing stroke. However, 19% of PTA patients had stenosis of >70% or occlusion by ultrasound criteria at 12 months after randomisation compared to 5% of surgical patients (p<0.0001). Restenosis was not associated with new symptoms, but long-term follow up is limited

Causes and timing of stroke in CAVATAS: The cause of stroke within 30 days of first treatment in CAVATAS was cerebral infarction in 22 patients in the PTA group and 20 patients in the surgery group. Primary cerebral haemorrhage caused the other three strokes in the PTA group and 2 strokes in the surgery group. All but one stroke was ipsilateral to the randomised artery. Surprisingly, a significant proportion of these treatment-related strokes were delayed after the day of treatment. Eight (36%) of the strokes in PTA patients occurred between the second and 21st day after treatment. Delayed stroke was also found in 6 (27%) of the surgical group between the third and 10th day after operation. Delayed stroke may account for the relatively high rate of 30-day morbidity in CAVATAS at 10% compared to 7.5% in ECST and 5.8% in NASCET.

Carotid stenting: Stents suitable for carotid use have only become available recently. The CAVATAS Steering Committee decided to allow the use of stents at the discretion of the interventionist. Stents were used in 55 patients randomised to PTA, usually as a secondary procedure i.e. after initial balloon dilation. The indication for using a stent in these cases was usually an inadequate angiographic result and in some cases stents were deployed because of stroke at the time of full balloon inflation, as a ‘bail-out’ procedure. Only one stroke occurred at the time of stent deployment (1.8%), although there were a small number of delayed strokes after stenting.

The need for a trial of carotid stenting: It would be inappropriate to use the results of CAVATAS to propose the widespread introduction of PTA for the treatment of carotid stenosis as an alternative to surgery, because the 95% confidence interval surrounding the 10% risk of any stroke within 30 days of treatment in the surgical and angioplasty groups is $\pm 5\%$. Nevertheless, the results support the need for further randomised studies. The interventional technique used to treat carotid stenosis has evolved over the 7 years since we started CAVATAS, from the use of simple inflatable balloon catheters at the beginning of the trial to the increasing use of stenting towards the end of the trial. Initially stents were used only as a secondary procedure after full balloon inflation for inadequate results or complications of treatment. The desire to prevent these complications and superior early results in stented patients has led to the increasing use of the technique of primary stenting in which the intention is to deploy a stent in every patient before dilation (but after pre-dilatation to allow the atraumatic passage of the stent)

of the artery⁵. Primary stenting is now accepted as best practice⁵ and has become the radiological technique of choice for carotid stenosis, replacing balloon angioplasty.

Advantages of carotid stenting: The majority of major strokes after carotid PTA are the result of dissection of the carotid artery at the time of balloon inflation with subsequent thrombosis. It is believed that stenting is safer than simple balloon angioplasty because embolisation, dissection and closure of the carotid artery are less likely to occur.^{6,7} The subgroup analysis of stented patients in CAVATAS is consistent with this suggestion. The adverse consequences of dissection are minimised, because the stent maintains laminar flow across the stenosis and seals the site of dissection, preventing a free intimal flap. In addition, the stent mesh limits the size of any thrombus or atheromatous debris that may be dislodged from the plaque at the time of dilation of the artery. Superior dilation achieved by stenting compared with balloon angioplasty may also reduce the rate of stroke in the early post-treatment period. In the coronary circulation, stenting has been shown to produce superior outcomes compared with balloon angioplasty.^{8,9} Individual case series suggest that carotid stenting has a similar rate of procedural stroke to that of carotid surgery,^{6,7} while a recent registry reported a total of 2,048 patients from 24 centres undergoing carotid stenting with a complication rate of stroke and death within 30 days of treatment of 5.8%.¹⁰

Disadvantages of carotid stenting: Although acceptable safety at the time of stenting has been suggested by the case series and registry data, stenting has not been subjected to a randomised trial in comparison to conventional surgical treatment and has not been demonstrated to prevent stroke, which is the aim of treatment. Stenting does not remove atheromatous plaque and stents may stimulate neo-intimal hyperplasia. In the long term it is likely that the rate of restenosis will be greater after stenting than after carotid surgery, which could well result in an unacceptable rate of long-term stroke recurrence. There is an important need to establish the efficacy of carotid stenting in comparison to surgery before the technique is widely introduced without adequate trial based evidence.

Antiplatelet therapy: In cardiological practice, ischaemic complications during coronary stenting have been shown to be significantly reduced by using a combination of two antiplatelet agents, ticlopidine and aspirin. In one coronary trial, stent thrombosis was reduced from 3.6% in patients

assigned aspirin alone down to 0.5% in patients assigned aspirin and ticlopidine.¹¹ A recently completed trial has shown that similar results with less risk of side effects can be achieved during coronary stenting by using the combination of clopidogrel with aspirin.¹² It is likely that this combination would also reduce the risks of stroke during carotid stenting. A pilot study is currently being carried out at one of the centres to establish the safety of the combination of clopidogrel and aspirin given before and for 30 days after carotid stenting. It is likely that this will become standard therapy. Most surgeons currently believe that combination antiplatelet therapy during surgery is hazardous because of excess bleeding.

Economic and quality of life considerations: Quality of life and general health status were assessed in CAVATAS using the SF36 and EuroQol EQ-5D questionnaires. These showed a similar quality of life for patients randomised to either treatment. Operating and radiology suite costs were similar in a sample of patients at two UK centres, but surgery was associated with a longer hospital stay and greater use of ITU beds. Surgery was therefore considerably more expensive than angioplasty (mean difference £946).¹³ However, the mean cost of an angioplasty increased from £1086 to £1864 if a stent was used. The use of stents in every case is therefore likely to increase the costs of stenting close to that of surgery, but this might be counterbalanced by performing carotid stenting as a day case procedure. Surgical length of stay is also declining. Follow up costs might be very different if restenosis is more frequent in one arm. Economic analysis will therefore be an important component of ICSS.

Aims of ICSS

To compare the risks, benefits and cost effectiveness of a treatment policy of referral for carotid stenting compared with referral for carotid surgery.

Trial design

ICSS is an international, multicentre, randomised, controlled, open, prospective clinical trial comparing carotid surgery with carotid stenting.

Participating centre requirements

Each centre must have a neurologist or physician with an interest in stroke who will see patients prior to randomisation and for follow up. Carotid endarterectomy must be carried out by

designated surgeons with expertise in the operation. Carotid stenting will be carried out by designated consultant interventionists with expertise in carotid angiography and the techniques of angioplasty and stenting. Good collaboration between the neurologists, surgeons and interventionists is essential and centres should have regular neurovascular meetings. Attendance at training sessions in carotid stenting provided by credentialing centres will be required for all interventionists prior to participation. Participating centres will be required to submit *curriculum vitae* for all participating clinicians and an audit of recent carotid surgery and PTA/stenting results. An accreditation committee will decide if they have appropriate experience and expertise to join the study. As a guide, surgeons and interventionists will be expected to show a stroke and death rate within 30 days of treatment, consistent with the centres in ECST who had an average rate of 7.0% with a 95% confidence interval of 5.8 to 8.3%.¹ Surgeons will be expected to have performed a minimum of 50 carotid operations with a minimum annual rate of at least 10 cases per year. Interventionists will similarly be expected to have performed a minimum of 50 stenting procedures, of which at least 10 should be in the carotid territory. Centres where there is little or no experience of carotid stenting may join ICSS for a probationary period in order to gain the minimum experience of ten carotid stenting procedures required to join the trial fully. The results in patients randomised during the probationary period will be analysed separately.

All centres will have to provide proof of Ethical Committee Approval for the study before commencing randomisation.

Probationary centres

Probationary centres will be required to fulfil all the other requirements for entry, but will not have to provide audited data on ten carotid stenting procedures initially. Probationary centres will randomise patients within the ICSS protocol between surgery and stenting. Individual interventionists who are not able to satisfy the credentialing requirements will be identified as probationary investigators. Stenting procedures carried out during the probationary period must be proctored by an experienced carotid interventionist, until the proctor is satisfied that the interventionist(s) at the centre can satisfactorily carry out procedures unproctored. Probationary interventionists will become fully enrolled in ICSS when both the proctor is satisfied that the interventionist can perform procedures unsupervised and the interventionist has 10 or more successfully completed cases in the trial, with an acceptable complication rate. When an

investigator has done sufficient successful procedures, the trial office will get comments from the relevant proctor, and then have any decision to promote the investigator or centre signed off by the chair of steering committee.

Proctoring

Proctors for probationary centres will be approved by the accreditation committee in consultation with the probationary centre via the central ICSS office. Probationary centres may suggest an appropriate proctor, but he or she will require prior approval from the accreditation committee, based on review of the proctor's experience of carotid stenting. It is the responsibility of the probationary interventionist to make contact with an approved ICSS proctor and to ensure a convenient date is organised for the stenting procedure at which the proctor can be present. Copies of the relevant radiology should be available for the proctor for review prior to starting the stenting procedure. This should be done prior to randomisation if there was any doubt about the suitability of the patient for stenting. In the event of a centre requiring proctoring for surgery the same procedure will apply.

It is the responsibility of the probationary interventionist and the proctor in discussion to ensure the lesion is appropriate for treatment (e.g. sufficiently severe), that the patient has received appropriate premedication (e.g. a combination of clopidogrel and aspirin) and that the lesion is suitable for stenting. They should agree the type, range and sizes of equipment required and the probationary interventionist should ensure that this equipment is available to complete the procedure. If any of these conditions are not met, the procedure should be abandoned and if appropriate rescheduled for another occasion.

Catheter or arch angiography is not required in ICSS prior to randomisation if the centre does not routinely perform angiography prior to treatment. However, the centre interventionist, the proctor and the patient should be aware that if preliminary angiography at the time of planned stenting shows a lesion which is not suitable for stenting, the procedure should be abandoned and the patient referred for surgery, or continued medical management. This type of cross over is envisaged in the trial design.

Where a centre has an adequately qualified surgeon and interventionist they may supervise

surgeons and interventionists at the same centre whose experience would not initially qualify them for the trial until they have gained sufficient experience. These new investigators must enrol with the central ICSS office (see participating centre requirements).

Inclusion criteria

- Symptomatic, extracranial, internal or bifurcation, atheromatous carotid artery stenosis that is suitable for both stenting and surgery and is deemed by the randomising clinician to require treatment.
- The severity of the stenosis of the randomised artery should be at least 50% (as measured by NASCET method or non-invasive equivalent).
- Symptoms must have occurred in the 12 months before randomisation. It is recommended that the time between symptoms and randomisation should be less than 6 months, but patients with symptoms occurring between 6 and 12 months may be included if the randomising physician considers treatment indicated.
- The patient must be clinically stable following their most recent symptoms attributable to the stenotic vessel.
- Patients must be willing to have either treatment, be able to provide informed consent, and be willing to participate in follow up.
- Patients must be able to undergo their allocated treatment as soon as possible after randomisation.
- Any age greater than 40 may be included. There is no upper age limit.
- Patients should only be randomised if the investigator is uncertain which of the two treatments is best for that patient at that time.

Exclusion criteria

- Patients refusing either treatment.
- Patients unable or unwilling to give informed consent.
- Patients unwilling or unable to participate in follow up for whatever reason.
- Patients who have had a major stroke with no useful recovery of function within the territory of the treatable artery.
- Patients with a stenosis that is known to be unsuitable for stenting prior to randomisation because of one or more of:

- Tortuous anatomy proximal or distal to the stenosis
- Presence of visible thrombus
- Proximal common carotid artery stenotic disease
- Pseudoocclusion ('string sign').
- Patients not suitable for surgery due to anatomical factors e.g. high stenosis, rigid neck.
- Patients in whom it is planned to carry out coronary artery bypass grafting or other major surgery within 1 month of carotid stenting or endarterectomy.
- Carotid stenosis caused by non-atherosclerotic disease e.g. dissection, fibromuscular disease or neck radiotherapy.
- Previous carotid endarterectomy or stenting in the randomised artery.
- Patients in whom common carotid artery surgery is planned.
- Patients medically not fit for surgery.
- Patients who have a life expectancy of less than two years due to a pre-existing condition, e.g. cancer.

Non-randomised patients

An anonymised log will be kept of patients undergoing treatment for carotid stenosis by the trial investigators but not randomised at the participating centres. Patients undergoing stenting but not randomised should also be included on a suitable registry, such as EUROCAST.

Consent

Written witnessed, informed consent will be obtained from all patients and a copy must be retained by the randomising centre. All patients will be provided with a written explanation of the study.

Randomisation

Randomisation will be by a telephone call or fax to a computerised service provided by the Oxford Clinical Trials Service Unit. Randomisation will be stratified by centre with minimisation of the main risk factors and balanced between the arms. Patients who need treatment of both carotid arteries will only be randomised for the carotid artery to be treated first. Patients can only be randomised once.

Investigations before randomisation

The following investigations are required: Routine haematology (FBC, platelets), blood biochemistry (renal function, blood sugar, cholesterol), chest x-ray, ECG, brain CT or MRI scans. The brain scan is required to exclude other pathology, to identify existing infarcts and to provide a baseline reference against which any subsequent infarction or haemorrhage can be assessed. Copies of the CT or MRI scans should be sent to the ICSS office

Carotid imaging

Mandatory investigation is required for entry into the study to confirm the presence and severity of the ipsilateral stenosis and to assess contralateral carotid disease. The following are acceptable:

1. Arch arteriogram showing both carotid bifurcations,
2. Selective catheter carotid angiography showing the randomised carotid artery with non-invasive investigation of the contralateral carotid bifurcation.
3. Bilateral magnetic resonance carotid angiograms together with a concordant ultrasound scan.
4. Bilateral spiral CT angiograms together with a concordant ultrasound scan.
5. Bilateral duplex and Doppler ultrasound scan, only if this is standard practice to treat on the basis of ultrasound alone in individual centres and the centre has been able to provide proof of the reliability of their ultrasonographic imaging through clinical audit.

The following data from the pre-randomisation imaging will be sent to the Central Office for review:

- 1) A copy of the written reports of the studies.
- 2) A film copy of the view of the vessel to be treated showing the stenosis at its most severe.
- 3) A film copy of the view of the contralateral vessel showing any stenosis at its most severe.
- 4) Velocity data from the ultrasound examination.

Patients who are randomised to stenting after ultrasound or other non-invasive investigation, in which subsequent angiography, prior to stenting, reveals one or more exclusion criteria should be treated by surgery, if appropriate, or medical care only if surgery is not appropriate (e.g. because the stenosis is less than 50%). These patients will continue follow up in the trial and will be

analysed on an intention to treat basis. A similar approach should be taken to patients randomised to surgery in whom contraindications to surgery emerge after randomisation.

Ultrasound

Ultrasound study of the carotid artery to be treated will be performed at or before randomisation, at one month after treatment and then annually after randomisation in all patients. The following information is required for each study: Peak systolic velocity of internal carotid artery (PSV ICA), end diastolic velocity of internal carotid artery (EDV ICA), peak systolic velocity of common carotid artery (PSV CCA). The accuracy of individual ultrasound laboratories will be audited by comparing the pretreatment ultrasound examination against catheter angiography films, which will be available in patients randomised after angiography and in all the patients treated by stenting.

Baseline data

Baseline data collected at randomisation will include demographic data; existing medical risk factors; neurological symptoms including an assessment of disability using the Modified Rankin Scale (see Appendix I); current antiplatelet therapy and blood pressure. Films and/or reports of pre-randomisation imaging as detailed above and in all cases the results of Doppler ultrasound as detailed below are required to allow assessment of any subsequent stenosis.

Baseline assessment

Patients will be seen by the study neurologist or physician interested in stroke prior to randomisation to confirm suitability for the study.

Stenting protocol

Stenting will be carried out as soon as possible after randomisation using percutaneous transluminal interventional techniques from the femoral, brachial or common carotid artery by a designated interventional consultant using an appropriate stent. A cerebral protection system should be used whenever the operator thinks one can be safely deployed. Stents and other devices used in the trial must be CE marked and approved by the Steering Committee. Pre-medication will be discretionary. The combination of aspirin and clopidogrel is recommended as

the antiplatelet regime of choice to cover the period of stenting and for a minimum of 4 weeks afterwards. Intra procedural heparin is mandatory at a dose determined by the operator, post procedural heparin may be given according to clinical requirements. Patients should be monitored for changes in their neurological status and heart rate throughout the procedure. If femoral or brachial access is being used a long sheath introducer or a guiding catheter is placed in the common carotid artery allowing pre-dilation and stent placement under direct arteriographic imaging. Atropine, or a similar agent, must be administered prior to stent deployment to counteract any effects on the carotid artery baroreceptors, which could lead to severe bradycardia and / or asystole. Virtually all patients will require pre-dilatation of the stenosis by balloon angioplasty prior to stent deployment. This will minimise the embolic load caused by passage of the endoluminal stent through the stenosis. The size of the pre-dilatation balloon will be determined by the size of the delivery system being used. Further balloon dilation of the stent will usually be required to ensure apposition of the stent against the arterial wall. Angiographic images showing the stenosis at its most severe prior to stenting and the same view and any other view that demonstrates the maximum residual stenosis after stenting must be sent to the Central Office. Details of the procedure, including all peri-procedural complications, drug therapy and devices used in the procedure, must be reported and the stenting and cerebral protection technical data sheet returned to the trial Central Office.

Endarterectomy protocol

Endarterectomy is to be done as soon as possible after randomisation by a designated consultant surgeon who has been approved by the Credentials Committee. It is to be carried out using whichever procedures are standard at the individual centre, including the use of local or general anaesthesia, shunts or patches as required by the operating surgeon. Standard or eversion endarterectomy may be performed.

Reporting of suspected problems with surgical or stenting techniques at individual centres

If the local investigator, or other member of the team, at a trial centre has concern about the outcome of their trial procedures, they should inform the ICSS trial office, which will organise a blinded assessment of the relevant outcome events. This will be submitted by the central office to the chairman of the data monitoring committee who may recommend further action, such as suspending randomisation at the centre. Similarly, the database manager at the trial office will

monitor outcome events and if there are two consecutive deaths or three consecutive major events at a single centre within 30 days of treatment in the same arm of the study, then assessment of the events will be triggered. A cumulative major event or death rate of more than 10% over 20 cases would also trigger careful assessment of the relevant outcome events.

Medical treatment

All patients will receive best medical care including antiplatelet therapy or anticoagulation (when appropriate) and control of medical risk factors such as hypertension, smoking and hyperlipidaemia before treatment and throughout the period of follow up.

Prevention of thrombosis

Therapy to prevent thrombosis during or soon after surgery or stenting will be prescribed according to standard practice in each centre. This may include heparin, dextran, aspirin, dipyridamole, ticlopidine, clopidogrel, or a combination of aspirin and another antiplatelet agent. Glycoprotein IIb/IIIa antiplatelet receptor antagonists will not be used routinely.

Follow up

Patients will be followed up by a neurologist or a physician interested in stroke at the participating centres at 30 days after treatment, 6 months after randomisation and then annually after randomisation. All post-procedural complications occurring within thirty days after the procedure will be reported to the central office at the 30 day follow up. At each visit, levels of stroke related disability will be assessed using the modified Rankin Scale (see Appendix 1) and any relevant outcome events will be notified to the Central Office. A Doppler ultrasound will be used to measure carotid arterial diameter to assess patency at one month after treatment and then annually after randomisation. In addition, ultrasound re-examination and CT or MRI scan should be performed in-patients who have any transient ischaemic events and / or stroke during follow up. The duration of follow up will be a minimum of 5 years (or until termination of the trial if earlier). At the 5 year follow up, patients will be asked if they are willing to continue follow up, in which case annual follow up will continue up to a maximum of 10 years from randomisation.

Sample size calculations and recruitment

The planned sample size is 1500 from fully enrolled centres. We do not anticipate any large difference in the principal outcome between surgery and stenting. We propose to estimate this difference and present a confidence interval for difference in 30-day death, stroke or myocardial infarction and for three-year survival free of disabling stroke or death. For 1500 patients, the 95% confidence interval will be the observed difference \pm 3.0 percentage points for the outcome measure of 30 day stroke, myocardial infarction and death rate and \pm 3.3 percentage points for the outcome measure of death or disabling stroke over three years follow up. However, the trial will have the power to detect major differences in the risks of the two procedures, for example if stenting proves to be much riskier than surgery or associated with more symptomatic restenosis. The difference detectable with power 80% are 4.7 for 30 day outcome and 5.1 percentage points for survival free of disabling stroke. Similar differences are detectable for secondary outcomes. We expect to achieve this recruitment within 6 years.

Principal research questions to be addressed

Primary analysis

- What is the difference in the long-term rate of fatal or disabling stroke in any territory of patients with severe symptomatic stenosis after randomisation to a policy of carotid stenting compared to surgery?

Secondary analysis

- What are the differences in mortality and morbidity within 30 days of carotid stenting compared to surgery?
- What is the rate of symptomatic and asymptomatic restenosis after carotid stenting compared to surgery?
- What are the differences in the rate of ipsilateral stroke during follow-up after carotid stenting compared to surgery?
- What is the cost-effectiveness of carotid stenting compared to surgery?
- What are the risk factors for stroke within 30 days and during long term follow up (including those related to age, gender, symptoms, imaging, centre and technique)?

Outcome events

(see Appendix 1)

- Any stroke or death.
- Transient ischaemic attack.
- Myocardial infarction within 30 days of treatment.
- Cranial nerve palsy within 30 days of treatment.
- Haematoma caused by treatment requiring surgery, transfusion or prolonging hospital stay.
- Stenosis greater than 70% or occlusion during follow up.
- Further treatment of the randomised artery by interventional radiology techniques or surgery after the initial attempt.
- Quality of life, health status and Health Service costs (see paragraph below).

Outcome event reporting

Outcome events will be documented in detail by the investigating centre, censored after receipt at the central office to remove clues as to the treatment received, and then adjudicated by an independent neurologist. Patients suffering stroke should have a CT or MRI brain scan as soon as possible after the event. A film copy of this, together with a film copy of the pre-randomisation scan (if done) should be submitted together with a report of the event. The event report should include copies of discharge summaries; death certificates and post mortem results if relevant. Deaths of UK patients will be tracked by flagging patients against the UK Registry of Births and Deaths. Disability after stroke and cranial nerve palsy will be assessed 30 days and six months after treatment or onset, using the Modified Rankin scale (see Appendix I). Duration of symptoms will be recorded and outcome events will be classified as disabling if the Rankin score is 3 or more at six months.

Learning curve

Carotid stenting is a new procedure, while the techniques of carotid surgery are well established. It is likely that there will be a learning curve for carotid stenting and the results may improve with experience during the trial. However, we believe it is better that carotid stenting should be performed as part of a randomised clinical trial at this stage of its development, because this will ensure careful assessment and follow up of all patients treated in the trial and supervision from

the Data Monitoring and Ethics Committee ensures that continuing treatment with the new technique remains ethical. The influence of the early part of the learning curve for carotid stenting will be limited by careful training of individual interventionists. The total experience of carotid PTA and stenting of individual interventionists will be recorded prior to entry into the trial. This will allow the average duration of the learning curve to be analysed, taking into account the current experience of the individual interventionists. This information may have implications for interpretation of the results of the trial and for the future training and supervision of the procedure. Similarly, there may be improvements in individual surgical or anaesthetic techniques during the trial.

Effect of changes in technology during the course of the study

The field of carotid stenting is an area of fast changing technology. The protocol does not at present specify the type or manufacturer of the stents or protection devices to be used, but devices to be used in the trial will be CE marked and approved by the Steering Committee who will expect a peer reviewed report of device safety. More than one device may be recommended to allow the interventionist to tailor the choice of stent to the individual stenosis and to use new designs of stent or protection devices if appropriate. The protocol will not specify the technique to be used during carotid surgery. Decisions about the use of shunts or specific suture materials will be left to the individual surgeon. Local or general anaesthesia will be allowed in both arms. Technical details of surgical and stenting technique, including the manufacturer and type of stent used, the use of local or general anaesthesia, and the use of antithrombotic agents, will be recorded. The analysis will include a subgroup comparison of different techniques in both arms and the data will be presented to the DMC meetings to ensure that no one technique is significantly inferior to another. Randomisation will use a computer programme to minimise variation between centres and over time, so that equal numbers of patients will be entered into the stenting and surgery arms before and after any change in practice.

Health service research issues

If the trial confirms the hypothesis that carotid stenting and surgery are equivalent in terms of the major risks of stroke and death, then the choice between the two procedures will be determined primarily by differences between the two procedures in other outcomes e.g. the disadvantage of a scar or cranial nerve palsy, or the effects of surgery on health related quality of life. If these

differences are minor, the choice between the procedures will be made primarily on economic grounds. The effects of cranial nerve palsy may be detected by a minor increase in the disability score, but it is not easy to assess the effect of these outcomes during follow up on clinical examination alone. Quality of life and health status will therefore be assessed using the EuroQol (EQ5D) questionnaire¹⁴ to compare patients' feeling of well-being, health and quality of life before and after stenting or surgery at one month, six months and annual follow up. The results will be analysed blind to treatment arm. The first questionnaire will be completed at the time of randomisation and subsequent questionnaires at each follow-up visit. The investigator performing randomisation or follow-up should ensure the patient completes the EQ5D at the same time. The English language version of the EQ5D has been modified to record the date on which it is completed and the patients trial number. Those centres using versions in other languages should also record the date and trial number on each completed form. If patients are too disabled to complete the questionnaires themselves, the patient's carer may complete them. The EQ5D should be returned to the central office with the other trial forms.

Information on hospital resource use during the treatment and follow up, including the type and manufacturer of the devices employed in carotid stenting procedures, will be collected to measure treatment costs and estimate the costs of stroke and any consequences of restenosis (e.g. retreatment) during follow up. Unit costs will be obtained from a sample of representative centres. The costs of stroke caused by treatment are a major component of the total cost of treatment, and therefore have a major influence on cost effectiveness. As the additional length of stay in hospital resulting from stroke largely drives these costs, the prospective collection of length of stay data will be designed to capture the stroke-related data in addition to direct operative stay. The economic evaluation will address cost-effectiveness and cost-utility (cost per QALY). The latter will be estimated from patients' responses to the EuroQol (EQ-5D) questionnaires using the York MVH tariff. Uncertainty regarding specific parameters within the analysis will be subjected to a sensitivity analysis, and uncertainty around the point estimate of the cost utility ratio will be represented using cost-effectiveness acceptability curves. To inform the economic analyses, the preferences of potential patients and clinicians between carotid endarterectomy and carotid stenting given various differences in outcomes will be explored using the technique of conjoint analysis (discrete choice experiments). A sample of members of the general population (matched to the ICSS patients) and clinicians will be asked to complete a

questionnaire after completion of randomisation, informed by the preliminary safety results. Preliminary work, structuring and piloting the conjoint analyses, will be undertaken earlier.

Stenosis after treatment

Patency of the carotid artery will be monitored by Doppler ultrasound at a minimum of 30 days after treatment and then annually after randomisation. Restenosis should only be treated by further angioplasty or surgery if the patient has relevant new symptoms. Restenosis is usually the result of smooth muscle hypertrophy or neo-intimal hyperplasia, rather than recurrence of atherosclerosis and hence may not cause embolic stroke. Asymptomatic restenosis will not be an indication to retreat the lesion because the risk of disabling symptoms after restenosis is not known.

Crossovers

Crossovers before any attempt to treat the randomised artery by the allocated treatment will be avoided unless clinically essential, because the trial data will be analysed by intention to treat. Patients who are randomised to stenting after ultrasound or other non-invasive investigation, in whom subsequent angiography prior to stenting, reveals one or more exclusion criteria should be treated by surgery, if appropriate, or medical care only if surgery is not appropriate (e.g. because the stenosis is less than 50%). These patients will continue follow up in the trial and will be analysed on an intention to treat basis. A similar approach should be taken to patients randomised to surgery in whom contraindications to surgery emerge after randomisation. Patient refusal of the treatment to which they are randomised can be minimised by careful consent. Patients requiring re-treatment because of further symptoms should be re-treated with whichever treatment is most appropriate. This is also the case if the non-randomised carotid artery requires treatment. Patients in whom an attempt at stenting fails may proceed to early surgery if appropriate and vice versa.

Data analysis

The data will be analysed by intention to treat using standard statistical tests by the trial statistician. The analyses will compare the treatment groups with respect to the length of time before treatment failure (i.e. occurrence of an outcome event) by means of the Mantel-Haenszel chi-squared test and Kaplan-Meier survival curves. Secondary analysis will compare the

proportions of outcome events within 30 days of treatment. All analyses will be adjusted for centre and predetermined risk factors. Subgroup analyses will examine risk factors for outcome events and will examine the influence of different devices, surgical techniques and experience within the trial. Results at probationary centres will be analysed separately. The results of any interim data analysis will remain confidential to the trial statistician and Data Monitoring Committee until after completion or early discontinuation of the trial. Investigators and the Steering Committee will remain blind until such point.

Publication

Publication of the results of ICSS will be prepared by the Central Office and circulated to participating centres for comment prior to submission of the manuscript for publication on behalf of all the ICSS collaborators.

Ethical Committee approval

Multicentre Research Ethics Committee approval will be sought in the UK. In addition, individual centres are expected to obtain local ethical committee approval for the study.

Data Monitoring Committee

The safety aspects of the trial will be overseen by a Data Monitoring Committee consisting of an independent neurologist, medical statistician surgeon and interventionist. The progress of the study will be assessed at regular intervals determined by the Data Monitoring Committee. During the period of intake to the study, interim analyses of mortality and of any other information that is available on major endpoints (including serious adverse events believed to be due to treatment) will be supplied, in strict confidence, to the chairman of the Data Monitoring Committee, along with any other analyses that the Committee may request. In the light of these analyses, the Data Monitoring Committee will advise the chairman of the Steering Committee if, in their view, the randomised comparisons in ICSS have provided **both** (i) "proof beyond reasonable doubt" that for all, or for some, specific types of patients, one particular treatment is clearly indicated or clearly contraindicated in terms of a net difference in outcome, **and** (ii) evidence that might reasonably be expected to influence materially patient management. Appropriate criteria of proof beyond reasonable doubt 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 prematurely. This criterion has the practical advantage that the number of interim analyses is of little importance.

Steering Committee

Steering Committee Committee, consisting of individuals participating in and independent of the trial with experience in stroke medicine, neurology, vascular surgery, vascular radiology, interventional neuroradiology, health economics, clinical trials and statistics, will oversee the management of the trial.

Trial organisation

The study will be organised on behalf of the collaborators by the central office, located at the UCL Institute of Neurology in London. The office will be responsible for protocol design, data collection and management, and analysis of the results in consultation with the Steering and Data Monitoring Committees, but will consult with the collaborators at an annual meeting and at other times as necessary. Communication with investigators will also take place via a regular newsletter and the trial website.

Payments to centres

While funding is available, the Lead Institution (UCL Institute of Neurology, London) will pay the participating centres a one-off payment of £100 for each patient randomised patient for whom correctly filled-out randomisation, technical data and one month follow-up forms have been received. Participating centres must invoice to the Lead Institution within 6-months of receipt of this revised protocol and thereafter 6 monthly in arrears. The Lead Centre may vary or terminate such payments in the future in accordance with budgetary needs and will inform the participating centre of such changes as they occur.

Indemnity

ICSS is an academic trial performed as a collaborative effort for the benefit of patients, and is not performed for, or on behalf of an industry sponsor. The trial compares two existing forms of treatment currently used in many hospitals. The various devices approved for use in the trial are not investigational devices and are required by the protocol to be marketed and already in use in the carotid artery as recognised by the CE mark. Hence, the trial is not an industry sponsored test

of a new treatment with unknown hazards. The trial protocol anticipates that some patients may be harmed inadvertently as a result of treatment in the trial. Indeed, the determination of the rate of these adverse outcome events is a major aim of the trial. However, we believe that the risks of these adverse events will be outweighed by the benefits of treatment in either arm of the trial. The trial protocol does not subject patients to hazards that the patient would not have encountered if they had received the trial treatments outside the context of the trial in routine practice. Hence, the organisers of the trial cannot take responsibility for any harm occurring to patients as a result of partaking in the trial. Individual investigators and hospitals are required to take responsibility for the occurrence of any adverse events in the same way as they would do if the treatments were performed outside the trial.

Website

The trial website contains updated information about the trial together with downloadable copies of the protocol, trial data collection forms, newsletters and contact information. The names of the collaborating centres will be included on the website. The website address is www.cavatas.com and all the pages are accessible to the public, patients and collaborators alike without a password. At present, the data collection forms cannot be completed on line.

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APPENDIX I

Definitions of Outcome Events

- **Transient ischaemic attack (TIA):** An acute disturbance of focal neurological function with symptoms lasting less than 24 hours attributed to cerebrovascular disease.
- **Transient monocular blindness (Amaurosis fugax):** Acute total or partial loss of vision in one eye with recovery within 24 hours attributed to vascular disease. This will be included as a variety of TIA.
- **Stroke:** An acute disturbance of focal neurological function with symptoms lasting more than 24 hours resulting from intracranial vascular disturbance. It must be established whether the cause is infarction or haemorrhage (primary intracranial or subarachnoid). Visual loss resulting from embolic or haemodynamic retinal ischaemia lasting more than 24 hours will be included within the category of stroke.
- **Myocardial Infarction:** Two of the following have to be documented: specific cardiac enzymes more than twice the upper limit of normal, a history of chest discomfort for at least half an hour, or the development of specific abnormalities (e.g. Q waves) on a standard 12 lead electrocardiogram.
- **Cranial Nerve Palsy:** weakness or sensory impairment in the distribution of one of the cranial nerves attributed to treatment.
- **Haematoma:** bleeding attributed to the treatment of carotid narrowing requiring new surgery, transfusion or prolonging hospital stay.
- **Disabling Outcome Events:** disability after stroke and cranial nerve palsy will be assessed using the Modified Rankin scale (defined below). Outcome events will be classified as disabling if the Rankin score is 3 or greater for more than 30 days after onset. The Rankin scale will be recorded at one and six months after treatment and then at annual follow up. Investigators will be asked to estimate the Rankin scale at one and six months after onset of new stroke when they see the patient more than 6 months after onset of stroke.
- **Recovered strokes:** in patients who make a full recovery from stroke or other outcome events, the duration from onset to full recovery will be recorded in days.

- **Modified Rankin Scale**

The following modified Rankin scale will be used to assess residual disability from stroke at randomisation to establish a baseline level of disability and at every follow up visit to assess the severity of any subsequent stroke:

- 0 Asymptomatic.
- 1 Non-disabling symptoms which do not interfere with lifestyle.
- 2 Minor disability - symptoms which lead to some restriction of lifestyle but do not interfere with the patient's capacity to look after themselves.
- 3 Moderate disability – symptoms which significantly interfere with lifestyle or prevent totally independent existence, but able to walk without assistance.
- 4 Moderately severe disability – symptoms which clearly prevent independent existence, unable to walk without assistance, although the patient does not need constant attention day and night.
- 5 Severely disabled – totally dependent requiring constant attention day and night.
- 6 Dead.

APPENDIX II

Trial Steering Committee

<i>Independent Chairman:</i>	Dr. John Bamford, Consultant Neurologist and Stroke Physician.
<i>Chief investigator:</i>	Professor Martin M. Brown, Professor of Stroke Medicine, Institute of Neurology, UCL.
<i>Vascular Surgery:</i>	Professor Andrew Bradbury , Professor of Vascular Surgery, Birmingham University. Mr Jonathan Beard, Consultant Vascular Surgeon, Sheffield Vascular Institute. Miss Alison Halliday, Consultant Vascular Surgeon and Principal Investigator, Asymptomatic Carotid Surgery Trial.
<i>Vascular Radiology:</i>	Professor Peter Gaines, Consultant Vascular Interventionist, Sheffield Vascular Institute.
<i>Cardiology</i>	Dr Iqbal Malik, St Mary's Hospital London
<i>Neuroradiology:</i>	Dr Andy Clifton, Consultant Neurointerventionist, Atkinson Morley's Hospital
<i>Neurology:</i>	Dr Graham Venables, Consultant Neurologist, Royal Hallamshire Hospital, Sheffield.
<i>Radiologist advising: on Ultrasound Studies</i>	Dr Paul Sidhu, Kings College Hospital, London
<i>Epidemiology:</i>	Dr Ale Algra, University of Utrecht, the Netherlands
<i>Health Economics:</i>	Professor AJ McGuire, Professor of Health Economics, London School of Economics
<i>Statistics:</i>	Professor Martin Bland, Professor of Health Statistics, University of York
<i>Representatives of other ongoing trials</i>	Professor Werner Hacke, Principal Investigator of SPACE, University of Hiedelberg, Germany Professor Jean-Louis MAS, Principal Investigator EVA-3S, Hôpital Sainte-Anne, Paris France

External Adjudicators for Outcome Events

Dr José M. Ferro, MD, PhD Serviço de Neurologia Hospital de Santa Maria 1649-035 Lisboa

Dr Dafydd Thomas, St Mary's Hospital London, UK

Trial Data Monitoring Committee

Professor C. Warlow, Chairman, Western General Hospital, Edinburgh, Scotland

Professor Rory Collins, Clinical Trial Service Unit, University of Oxford, England

Interventionist Dr Andrew Molyneux, Consultant Neurointerventionist, Radcliffe Infirmary, Oxford

Surgeon Mr Ross Naylor (Senior Lecturer in Surgery, Leicester University);

Dr H Watt (Statistician, The National Hospital)

Trial Office

The Central Trial Office at the Institute of Neurology is manned by a Trial Manager, Data Manager, Clinical Research Fellow and Research Nurse – Box 6 The National Hospital Queen Square London WC1N 3BG. Tel +44 (0)207 676 2194

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APPENDIX III

Collaboration between ICSS, SPACE and EVA-3S

It has been prospectively agreed that ICSS, the stent-protected percutaneous angioplasty vs carotid endarterectomy study (SPACE) (carried out in Germany), and the endarterectomy versus angioplasty in patients with severe symptomatic carotid stenosis study (EVA-3S) (carried out in France), will combine their results after completion of initial randomisation and follow up, to conduct a combined European meta-analysis of the data. The data will be combined and analysed at the Institute of Neurology in London on behalf of the investigators in all three studies. To facilitate the meta-analysis, it has been agreed that all three trials will collect and use the following outcome events and definitions.

Baseline data collected in all 3 studies at randomisation will include age; gender; existing medical risk factors; current systolic blood pressure; symptoms prior to randomisation (hemisphere or ocular transient ischaemic attack, hemisphere or ocular stroke); severity of ipsilateral stenosis; presence or absence of contralateral occlusion and date of randomisation.

Doppler ultrasound will be carried out at the time of randomisation and then annually after randomisation to assess restenosis rates. Peak systolic velocity of common carotid artery (PSV CCA), peak systolic velocity of internal carotid artery (PSV ICA), and end diastolic velocity of internal carotid artery (EDV ICA) will be recorded in m/s to facilitate central analysis.

The following outcome events and date of onset will be recorded in all three trials:

- Any stroke or death.
- Transient ischaemic attack
- Myocardial infarction within 30 days of treatment.
- Cranial nerve palsy within 30 days of treatment.
- Haematoma caused by treatment requiring surgery or transfusion.
- Ipsilateral occlusion or stenosis greater than 70% during follow up.
- Further treatment of the randomised artery by interventional radiology techniques or surgery after the initial attempt.
- Duration of treatment related hospital stay.

The severity of neurological outcome events will be assessed by duration of symptoms and effect on the Modified Rankin Scale, using the definitions in Appendix I of the ICSS protocol (see above).

APPENDIX IV SUBSTUDIES

Substudy 1 Carotid artery 'in-stent' stenosis measurements with duplex ultrasound

Lead Investigators

P.J. Nederkoorn, J. Stam, Y.B. Roos, J.A. Reekers, W. Mali, B. van der Worp, M.M. Brown.

Background

Carotid endarterectomy (CEA) is a well established treatment for secondary prevention of stroke in patients with symptomatic carotid artery stenosis.¹ Carotid angioplasty with stenting (CAS) is relatively new, increasingly used less-invasive treatment, which is being evaluated in randomized trials.^{2,3} One of the variables important in the evaluation of CAS is the degree of possible 'in-stent' restenosis. Traditionally, degree of carotid artery stenosis was measured with conventional digital subtraction angiography (DSA). To date, this is not ethical anymore and the degree of stenosis is measured by one or a combination of non-invasive tests.⁴⁻⁷

In the follow-up of patients with a stent, duplex ultrasound (DUS) is used to monitor the patency of the stent and the occurrence of in-stent restenosis. For routine evaluation of the carotid artery DUS is a well validated diagnostic test and the cut-off criteria for the different degrees of stenosis are clear.^{5,8} The peak systolic velocity is considered the most accurate estimator of the degree of stenosis for DUS.¹⁰ For measurements within stents, however, these criteria are yet unknown. Possibly, blood flow and blood turbulence behave differently in an artificial stent than in a normal, probable more elastic, vessel wall. Therefore, the cut-off criteria for the degrees of an in-stent stenosis might be different. A precise estimate of in-stent restenosis is crucial in the follow-up of patients treated with a stent. Recently, several studies on 'in-stent' stenosis measurements with DUS have been published, but these were relatively small and the prevalence of in-stent restenosis was low.¹¹ Furthermore, because a reference test was only performed when a patient was suspected of having restenosis at DUS, these studies suffer from verification bias, precluding a reliable estimate of the diagnostic accuracy.¹¹

The aim of the proposed study is to validate the use of DUS for in-stent stenosis measurements during follow-up after carotid artery stenting and to determine reliable cut-off criteria for the different degrees of stenosis.

Design and methods

Study population

We will examine a minimum of 150 patients 1 year after treatment with a carotid artery stent, or, if patients are included more than one year ago, at the first (yearly) visit. Eligible centres take part in the International Carotid Stenting Study (ICSS), an international controlled randomized trial comparing primary stenting of carotid artery stenosis in patients with symptomatic disease with endarterectomy. The principal investigator of the ICSS, Professor M.M. Brown, approved the research proposal for this additional diagnostic study. From the ICSS data, baseline characteristics, medical history, and follow-up of cardio-vascular events will be available of all patients. It is important that the two diagnostic tests, DUS (the test under evaluation in this

study), and CTA (the reference test) are done not earlier than 1 year after treatment. With earlier evaluation, the prevalence of the outcome, i.e. in-stent restenosis, would be too low, precluding a valid estimate of the optimal cut-off criteria for DUS for diagnosis of restenosis.

Sample size

We estimate a prevalence of 10 to 20% in-stent restenosis (>50%) after one year based on the literature (in which estimates substantially differ, due to different definitions of restenosis and different follow-up periods). To obtain estimates of sensitivity of approximately 90% with a confidence interval of maximum 10%, and a prevalence of restenosis after one year of 20%, we would require a minimum of 172 patients. The proposed number of 150 patients, however, is estimated based on the minimum number of patients we will be able to include in practice.

Diagnostic testing

All ICSS patients undergo regular DUS examination at the yearly follow-up visit according to the ICSS protocol. In this study we will perform one additional computed tomography angiography (CTA) of the carotid arteries as a reference test; only in the subgroup of patients treated with a stent. The choice for CTA instead of intra-arterial digital subtraction angiography (DSA) is based on ethical considerations. DSA traditionally is considered the gold standard for stenosis measurements in the carotid artery. However, it has a non negligible morbidity and mortality and is not used routinely anymore. CTA is a minimally invasive technique providing good quality imaging for the purpose of this study; (but still more invasive and less cost-effective than DUS).

Stenosis measurements

The DUS and CTA test results will be read by two independent observers blinded for clinical information and the results of the other test, following the Standards for Reporting of Diagnostic Accuracy (STARD) guidelines. From the DUS examinations, all in-stent flow-velocity parameters will be collected. The grade of stenosis on CTA will be measured according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria, on post-processed images. For a detailed state-of-the-art protocol for stenosis measurements on the reference test CTA we refer to reference 12.

Statistics

Receiver operating characteristic (ROC) curves will be constructed for the diagnoses of 70%-99% and 50%-69% stenoses. The associated optimal sensitivities, specificities, and peak-systolic-velocity thresholds will be derived from the ROC curves.

Reporting

A scientific paper will be published under behalf of the principal investigator of ICSS professor M.M. Brown.

Costs

The costs of this study are limited to the CTA and should preferably be paid with local grants or sources. A grant application has been submitted to the 'Dutch Heart Foundation' and participants will be kept informed about possible financing.

Ethics

The study has been approved by the central Dutch ethical committee as an amendment to the ICSS. Applicability to international centres will be investigated as soon as they take part in this sub-study.

Literature

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Substudy 2: Symptomatic and asymptomatic ischaemic and haemorrhagic brain injury following protected and unprotected stenting versus endarterectomy in the International Carotid Stenting Study – the ICSS-MRI sub-study

Lead Investigators:

Leo H Bonati, Lisa Jongen, Stefan Wetzel, Willem Mali, Stefan Engelter, Martin M Brown

Summary

Background and aim

Diffusion weighted imaging (DWI) – a modern magnetic resonance imaging (MRI) technique – may detect ischaemic brain lesions after carotid interventions in patients who do not experience symptoms. Previous studies showed that DWI lesions are found more frequently after endarterectomy than after stenting of carotid stenosis, and more frequently after stenting without the use of cerebral protection devices than after protected stenting. However, methodological shortcomings of those non-randomised studies may account for the observed differences. Moreover, it is not clear how ischaemic lesions on DWI relate to the risk of clinically apparent cerebrovascular events (stroke or TIA) associated with the intervention. About one in ten strokes occurring as a complication of carotid interventions is caused by intracerebral haemorrhage (ICH), but asymptomatic ICH after carotid interventions has never been assessed. We therefore aim to study the frequency and significance of symptomatic and asymptomatic ischaemic and haemorrhagic brain injury in protected and unprotected stenting and endarterectomy in a randomised trial.

Primary objective

- To compare the rate of ischaemic brain injury detectable on MRI after treatment of symptomatic carotid stenosis by stenting or endarterectomy.

Secondary objectives

- To test for an interaction between the use of cerebral protection devices and ischaemic brain injury associated with stenting.
- To compare the rate of haemorrhagic brain injury detectable on MRI after treatment of symptomatic carotid stenosis by stenting or endarterectomy.
- To evaluate the usefulness of ischaemic and haemorrhagic brain lesions visible on MRI as surrogate markers of the procedural risk of carotid interventions.

Methods

Multi-centre prospective MRI sub-study of the International Carotid Stenting Study (ICSS). Multimodal MRI to detect ischaemic and haemorrhagic brain injury will be performed at 3 time points in patients with symptomatic carotid stenosis randomised to stenting or endarterectomy in ICSS: 1-3 days before, 1-3 days after and again 30+/-3 days after intervention.

Background and aim

Carotid stenting has emerged as a treatment alternative to endarterectomy in patients with symptomatic carotid stenosis. Cerebral protection devices are used in stenting with the aim of reducing the risk of plaque embolisation during the procedure. Recently completed randomised trials comparing the safety of stenting and endarterectomy yielded conflicting results^{1, 2}. Concern that stenting without cerebral protection may be associated with an increased risk of stroke led to the abandonment of unprotected procedures in one trial³ but in another trial, there was no difference in the risk of stenting with and without protection². Although clear evidence that cerebral protection enhances treatment safety is lacking⁴, protection devices are widely used today, significantly contributing to the cost of carotid stenting.

Until clinical trials investigating the benefit of cerebral protection devices can be realised, surrogate markers of brain injury may provide further insights into the risk of protected and unprotected stenting in comparison to endarterectomy. Diffusion weighted imaging (DWI), a modern magnetic resonance imaging (MRI) technique, may show ischaemic lesions after carotid interventions even in patients who do not experience symptoms⁵. In previous studies new ischaemic lesions on DWI were detected more frequently after stenting than after endarterectomy⁶⁻¹². DWI lesions were also more frequent after unprotected stenting than after protected stenting^{13, 14}. However, selection bias and the use of historical controls may be accountable for the observed differences in these non-randomised comparisons. Moreover, it is not clear how ischaemic lesions on DWI relate to the risk of clinically apparent cerebrovascular events (stroke or TIA) associated with the intervention. Larger studies with randomised treatment allocation are needed to gain further insight into the significance of asymptomatic DWI lesions and their potential role as surrogate markers of treatment risk.

About one in ten strokes occurring as a complication of carotid interventions is caused by intracerebral haemorrhage (ICH). A special MRI technique (so called gradient echo imaging) allows the detection of small intracerebral bleedings, but has never been applied to detect ICH after carotid interventions. Asymptomatic ICH may be an expression of subclinical reperfusion damage following carotid revascularisation.

Thus, there is a clear need to study symptomatic and asymptomatic ischaemic and haemorrhagic brain injury in protected and unprotected stenting and endarterectomy in a randomised trial.

Objectives

The primary objective of this sub-study is to compare the risk of ischaemic brain injury assessed on MRI in patients with symptomatic carotid artery stenosis undergoing stenting in comparison to those undergoing endarterectomy.

Secondary objectives are: to assess the effect of protection devices on the risk of ischaemic brain injury associated with stenting; to compare the risk of haemorrhagic brain injury assessed on MRI in stenting compared to endarterectomy; and to gain further insight into the usefulness of ischaemic and haemorrhagic brain lesions on MRI as surrogate markers of the risk of carotid interventions.

Study design

This project is an MRI-based sub-study of a multicentre randomised trial known as the International Carotid Stenting Study¹⁵, which is comparing the risks and benefits of stenting and endarterectomy of symptomatic carotid stenosis using clinical endpoints, e.g. stroke and death.

The ICSS-MRI sub-study allows a randomised comparison of the procedural risk of symptomatic and asymptomatic ischaemic and haemorrhagic brain injury visible on MRI between stenting and endarterectomy. The use of cerebral protection devices in patients undergoing stenting is not subject to randomisation in ICSS. However, the participating centres systematically use either protected or unprotected stenting. The risk of brain injury associated with either stenting technique can therefore be compared to a randomised control group of patients undergoing endarterectomy.

Outcome measures and analyses are defined as follows:

Primary outcome measure:

- **Rate of symptomatic and asymptomatic ischaemic brain injury detectable on MRI after endarterectomy and stenting**

Secondary analyses:

- **Interaction between the use of protection devices and ischaemic brain injury in patients undergoing stenting**
- **Rate of symptomatic and asymptomatic haemorrhagic brain injury detectable on MRI after endarterectomy and stenting**
- **Relation of brain injury on MRI to risk of stroke during procedure and follow-up**

Subject selection

Inclusion criteria

Patients are eligible to participate in the ICSS-MRI sub-study if they are enrolled in the ICSS trial and separately provide written informed consent to undergo three MRI exams. Detailed inclusion and exclusion criteria for ICSS are provided elsewhere¹⁵. In short, patients with recently symptomatic $\geq 50\%$ carotid stenosis who are equally suitable for endarterectomy and stenting are eligible for enrolment in ICSS.

Exclusion criteria

Patients with contraindications to MRI, e.g. pacemakers, metallic implants, and claustrophobia, are excluded from the ICSS-MRI sub-study.

MRI protocol

Patients enrolled in the ICSS-MRI sub-study will undergo three MRI investigations, 1-3 days before, 1-3 days after and 30+/-3 days after the intervention. The following sequences will be performed in all three investigations:

- **Diffusion weighted imaging (DWI)** to detect acute ischaemic brain injury associated with the procedure.
- **Gradient echo T2*-weighted sequences** to detect haemorrhagic brain injury associated with the procedure.
- **T1-weighted, T2-weighted and fluid-attenuated inversion recovery (FLAIR)** sequences will be used to assess whether acute brain lesions detected on DWI after the procedure lead to permanent scarring at 1 month.

Data acquisition

Baseline data (such as age, gender, medical risk factors, degree of carotid stenosis, etc.) will be collected as part of ICSS.

Two researchers will independently score the presence, size and location (vascular territory) of ischaemic and haemorrhagic lesions on the MRI scans. A third researcher will review the scans in case of disagreement. The scans will be reported and scored blind to patient identifiers, treatment, date and time of the scans.

Patients will be clinically examined by a neurologist at the time of MRI examination and will be followed up after treatment as part of ICSS to determine outcome events including transient ischaemic attack, stroke, myocardial infarction and death.

Statistical considerations

Statistical analysis

The rates of ischaemic and haemorrhagic brain lesions will be compared between patients undergoing endarterectomy and stenting using χ^2 and Fisher's exact tests. Significance will be declared at $p < 0.05$.

Sample size calculation

Power calculations are based on the primary outcome measure. The two largest series reported new ischaemic lesions on DWI after carotid endarterectomy in 17% and 34% of patients respectively^{16, 17}. If a rate of new DWI lesions after endarterectomy of 25% is assumed, a total sample size of 200 patients would have a 90% power to detect a twofold increase in the DWI lesion rate associated with carotid stenting. Testing the interaction between the use of cerebral protection devices and the rate of DWI lesions after stenting would have less power. 126 patients have been enrolled in the ICSS-MRI sub-study from its initiation in 2004 until July 2007 in two participating centres (Utrecht and Basel). The projected number of enrolled patients at the end of the ICSS randomisation period in those centres is 170. The target population of 200 could be reached with a contribution of 30 patients enrolled in ICSS centres in the UK.

Withdrawal of consent

Subjects enrolled in the ICSS-MRI sub-study can withdraw their consent at any time during the substudy. This will not affect their enrolment in ICSS or the standard of care they receive.

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APPENDIX V

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