HEALTH TECHNOLOGY ASSESSMENT

VOLUME 20 ISSUE 20 MARCH 2016
ISSN 1366-5278

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NHS
National Institute for Health Research

DOI 10.3310/hta20200

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Declared competing interests of authors: none

Published March 2016
DOI: 10.3310/hta20200

This report should be referenced as follows:

Featherstone RL, Dobson J, Ederle J, Doig D, Bonati LH, Morris S, *et al*. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): a randomised controlled trial with cost-effectiveness analysis. *Health Technol Assess* 2016;**20**(20).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (SciSearch®) and *Current Contents*®/Clinical Medicine.

Health Technology Assessment

HTA EME

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 5.027

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: nihredit@southampton.ac.uk

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This report

This issue of *Health Technology Assessment* contains a project originally commissioned by the MRC but managed by the Efficacy and Mechanism Evaluation Programme. The EME programme was created as part of the National Institute for Health Research (NIHR) and the Medical Research Council (MRC) coordinated strategy for clinical trials. The EME programme is funded by the MRC and NIHR, with contributions from the CSO in Scotland and NISCHR in Wales and the HSC R&D, Public Health Agency in Northern Ireland. It is managed by the NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC) based at the University of Southampton.

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Abstract

Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): a randomised controlled trial with cost-effectiveness analysis

Roland L Featherstone,[1] Joanna Dobson,[2] Jörg Ederle,[1] David Doig,[1] Leo H Bonati,[1,3] Stephen Morris,[4] Nishma V Patel[4] and Martin M Brown[1]*

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Background: Carotid artery stenting (CAS) is an alternative to carotid endarterectomy (CEA) for the treatment of carotid stenosis, but safety and long-term efficacy were uncertain.

Objective: To compare the risks, benefits and cost-effectiveness of CAS versus CEA for symptomatic carotid stenosis.

Design: International, multicentre, randomised controlled, open, prospective clinical trial.

Setting: Hospitals at 50 centres worldwide.

Participants: Patients older than 40 years of age with symptomatic atheromatous carotid artery stenosis.

Interventions: Patients were randomly allocated stenting or endarterectomy using a computerised service and followed for up to 10 years.

Main outcome measures: The primary outcome measure was the long-term rate of fatal or disabling stroke, analysed by intention to treat (ITT). Disability was assessed using the modified Rankin Scale (mRS). A cost–utility analysis estimating mean costs and quality-adjusted life-years (QALYs) was calculated over a 5-year time horizon.

Results: A total of 1713 patients were randomised but three withdrew consent immediately, leaving 1710 for ITT analysis (853 were assigned to stenting and 857 were assigned to endarterectomy). The incidence of stroke, death or procedural myocardial infarction (MI) within 120 days of treatment was 8.5% in the CAS group versus 5.2% in the CEA group (72 vs. 44 events) [hazard ratio (HR) 1.69, 95% confidence interval (CI) 1.16 to 2.45; $p = 0.006$]. In the analysis restricted to patients who completed stenting, age independently predicted the risk of stroke, death or MI within 30 days of CAS (relative risk increase 1.17% per 5 years of age, 95% CI 1.01% to 1.37%). Use of an open-cell stent conferred higher risk than a closed-cell stent (relative risk 1.92, 95% CI 1.11 to 3.33), but use of a cerebral protection device did not modify the risk.

CAS was associated with a higher risk of stroke in patients with an age-related white-matter changes score of 7 or more (HR 2.98, 95% CI 1.29 to 6.93; $p = 0.011$). After completion of follow-up with a median of 4.2 years, the number of patients with fatal or disabling stroke in the CAS and CEA groups (52 vs. 49), and the cumulative 5-year risk did not differ significantly (6.4% vs. 6.5%) (HR 1.06, 95% CI 0.72 to 1.57; $p = 0.776$). Stroke of any severity was more frequent in the CAS group (15.2% vs. 9.4% in the CEA group) (HR 1.712, 95% CI 1.280 to 2.300; $p < 0.001$). There was no significant difference in long-term rates of severe carotid restenosis or occlusion (10.8% in the CAS group vs. 8.6% in the CEA group) (HR 1.25, 95% CI 0.89 to 1.75; $p = 0.20$). There was no difference in the distribution of mRS scores at 1-year, 5-year or final follow-up. There were no differences in costs or QALYs between the treatments.

Limitations: Patients and investigators were not blinded to treatment allocation. Interventionists' experience of stenting was less than that of surgeons with endarterectomy. Data on costs of managing strokes were not collected.

Conclusions: The functional outcome after stenting is similar to endarterectomy, but stenting is associated with a small increase in the risk of non-disabling stroke. The choice between stenting and endarterectomy should take into account the procedural risks related to individual patient characteristics. Future studies should include measurement of cognitive function, assessment of carotid plaque morphology and identification of clinical characteristics that determine benefit from revascularisation.

Trial registration: Current Controlled Trials ISRCTN25337470.

Funding: This project was funded by the National Institute for Health Research Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 20, No. 20. See the NIHR Journal Library website for further project information. Further funding was provided by the Medical Research Council, Stroke Association, Sanofi-Synthélabo and the European Union.

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List of abbreviations

ARWMC	age-related white-matter changes
CAS	carotid artery stenting
CAVATAS	Carotid and Vertebral Artery Transluminal Angioplasty Study
CEA	carotid endarterectomy
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CREST	Carotid Revascularisation Endarterectomy versus Stenting Trial
CT	computerised tomography
DBP	diastolic blood pressure
DUS	duplex ultrasound
DWI	diffusion weighted imaging
EQ-5D-3L™	European Quality of Life-5 Dimensions – 3 level response
EVA-3S	Endarterectomy versus Stenting in Patients with Symptomatic Severe Carotid Stenosis trial
HR	hazard ratio
ICSS	International Carotid Stenting Study
ICU	intensive care unit
ITT	intention to treat
MI	myocardial infarction
MRI	magnetic resonance imaging
mRS	modified Rankin Scale
NASCET	North American Symptomatic Carotid Endarterectomy Trial
NICE	National Institute for Health and Care Excellence
NMB	net monetary benefit
OR	odds ratio
OXVASC	Oxford Vascular
PSS	personal social services
QALY	quality-adjusted life-year
RR	risk ratio
SD	standard deviation
SPACE	Stent-Protected Angioplasty versus Carotid Endarterectomy
TIA	transient ischaemic attack

Plain English summary

Narrowing of one of the carotid arteries in the neck by deposits of fat in the artery wall is a major cause of stroke. The International Carotid Stenting Study (ICSS) compared two treatments to prevent stroke resulting from this narrowing. The first was surgical treatment (endarterectomy), which removes the fatty deposits altogether via an incision in the neck. The second was the newer treatment of carotid stenting, in which a wire mesh tube (a stent) is inserted inside the narrowed artery after being threaded up to the neck through the arteries in the leg via a puncture in the groin. The trial included 1713 patients who had recently had a stroke or transient ischaemic attack ('mini stroke') caused by carotid narrowing, at 50 centres in the UK, mainland Europe, Canada, Australia and New Zealand. Half the patients were randomly assigned to stenting and half to surgery. ICSS showed that stenting avoids complications of surgical incision in the neck, but caused more minor strokes at the time of the treatment than surgery. The combination of procedural stroke or death was more frequent in the stenting group. During long-term follow-up (median 4.2 years), the proportion of patients with fatal or disabling stroke was essentially the same for both stenting and endarterectomy. Any stroke during follow-up was more frequent in the stenting group. There were no differences in the costs of the two treatments. Therefore, endarterectomy remains the treatment of choice for patients at higher risk with stenting, but stenting is an appropriate treatment choice for patients if the risk of periprocedural stroke is low.

Scientific summary

Background

Atherosclerotic stenosis of the carotid artery is a major cause of stroke. Carotid endarterectomy (CEA) has been shown in previous trials to significantly reduce the risk of stroke in patients with symptomatic atherosclerotic carotid stenosis. However, carotid artery stenting (CAS) is considered to be less invasive than CEA and has advantages in terms of patient comfort because the procedure avoids an incision in the neck and is conducted under local anaesthesia. At the time of the inception of the International Carotid Stenting Study (ICSS), stenting was being widely adopted for the treatment of carotid stenosis on the basis of case series in the absence of randomised trial evidence. ICSS was initiated to provide such evidence.

Objectives

The primary objective of ICSS was to compare the long-term rate of fatal or disabling stroke in patients randomly allocated a treatment policy of referral for carotid stenting compared with referral for carotid surgery.

Secondary analyses examined:

- short-term and long-term differences in mortality and morbidity related to treatment
- the short-term risk of cerebral ischaemia assessed by magnetic resonance imaging (MRI) after treatment
- predictors of the perioperative risks of treatment
- the rate of restenosis during follow-up
- differences in functional outcome during follow-up
- the cost-effectiveness of carotid stenting compared with surgery.

Methods

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

Participants

Patients of either sex over the age of 40 years with symptomatic atherosclerotic stenosis of the carotid artery.

Inclusion criteria

- Symptomatic, extracranial, internal or bifurcation atheromatous carotid artery stenosis suitable for both stenting and surgery, and deemed to require treatment.
- The severity of the stenosis of the randomised artery had to be at least 50% (as measured by the North American Symptomatic Carotid Endarterectomy Trial method or non-invasive equivalent).
- Symptoms must have occurred in the 12 months before randomisation. It was recommended that the time between symptoms and randomisation should be < 6 months, but patients with symptoms between 6 months and 12 months could be included if treatment was indicated.
- The patient had to be clinically stable following their most recent symptoms.
- Patients could only be randomised if the investigator was uncertain which of the two treatments was best for that patient at that time.

Exclusion criteria

- Patients unable or unwilling to give informed consent or participate in follow-up.
- Patients who had previously had a major stroke with no useful recovery of function.
- Patients with a stenosis 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
    - pseudo-occlusion ('string sign').
- Patients not suitable for surgery owing to anatomical factors (e.g. high stenosis).
- Patients in whom it was 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 CEA or stenting in the randomised artery.
- Patients in whom common carotid artery surgery was planned.
- Patients medically not fit for surgery.
- Patients who had a life expectancy of < 2 years owing to a pre-existing condition (e.g. cancer).

Randomisation

Patients were randomly allocated in equal proportions to endarterectomy or stenting. Randomisation was performed by a telephone call or fax to a computerised service provided by the Oxford Clinical Trials Service Unit and was stratified by centre with minimisation of the main risk factors balanced between the arms.

Interventions

Endarterectomy was carried out as soon as possible after randomisation by a consultant surgeon approved by the accreditation committee, using procedures standard at the centre.

Stenting was carried out as soon as possible after randomisation by an approved consultant interventionist using an approved stent. A cerebral protection system was used whenever the operator thought that one could be safely deployed.

Data collected at baseline

Baseline data collected at randomisation included demographic data, medical risk factors, symptoms and an assessment of disability using the modified Rankin Scale (mRS), antiplatelet therapy and blood pressure, films and reports of pre-randomisation brain imaging, and the results of duplex ultrasound (DUS).

Follow-up

Patients were followed up by a neurologist or a stroke physician at 30 days after treatment, 6 months after randomisation and, then, annually. At each visit, levels of stroke-related disability were assessed using the mRS and any outcome events were notified to the Central Trial Office. A DUS of the carotid arteries was performed at each follow-up visit. In addition to the clinical data, patients were asked to complete a European Quality of Life-5 Dimensions-3 level response (EQ-5D-3L™) questionnaire to assess health-related quality of life at baseline and each follow-up. Utility values calculated from the EQ-5D-3L questionnaire responses were used to calculate quality-adjusted life-years (QALYs) for every patient. Patients were followed up to the end of 2011 (a maximum of 10 years after randomisation).

Resource use and costs

For every patient, the cost of the index procedure and the cost of follow-up were calculated using resource-use data collected prospectively. The former included: surgeon and radiologist time; operating theatre time, including nursing staff, drugs, consumables and overheads; anaesthesia; materials and devices, including stents, shunts, patches, cerebral protection devices, catheters, wires and sheaths; and length of hospital stay in the intensive care unit (ICU) and inpatient ward. The latter included additional carotid artery procedures; complications within 30 days of index procedure [fatal and non-fatal myocardial infarction (MI), severe haematoma and disabling cranial nerve palsy]; imaging tests; drug treatment; and non-disabling, disabling and fatal strokes. Length of stay in the ICU was not collected for individual patients, but mean values were collected by centre. From these data we assumed that where patients were admitted to the ICU post-operatively, it was for 1 day.

Results

Between May 2001 and October 2008, 1713 patients from 50 centres in the UK, mainland Europe, Australia, New Zealand and Canada were randomised. Patients were followed up for a median of 4.2 years and a maximum of 10 years after randomisation, amounting to 7355 patient years of follow-up.

Short-term outcomes

In the intention-to-treat (ITT) analysis, the risk of stroke, death or procedural MI between randomisation and 120 days was significantly higher in patients in the stenting group than in patients in the endarterectomy group (8.5% vs. 5.1%), representing an estimated 120-day absolute risk difference of 3.3% [95% confidence interval (CI) 0.9% to 5.7%] with a hazard ratio (HR) in favour of surgery of 1.69 (95% CI 1.16 to 2.45, log-rank $p = 0.006$). There was no significant difference in the rate of disabling stroke or death between groups (4.0% in the stenting group vs. 3.2% in the endarterectomy group). The observed treatment effect was largely driven by the higher number of non-disabling strokes in the stenting group. Cranial nerve palsies were almost completely avoided by stenting [risk ratio (RR) 0.02, 95% CI 0.00 to 0.16; $p < 0.0001$). There were also fewer haematomas in the stenting group than in the endarterectomy group (RR 0.59, 95% CI 0.38 to 0.93; $p = 0.0197$). Stenting was associated with a higher risk of stroke within 30 days of treatment compared with endarterectomy in patients with an age-related white-matter changes (ARWMC) score on baseline brain imaging of 7 or more (HR for any stroke 2.98, 95% CI 1.29 to 6.93; $p = 0.011$; HR for non-disabling stroke 6.34, 95% CI 1.45 to 27.71; $p = 0.014$), but there was no risk difference in patients with an ARWMC score of < 7. In a separate analysis restricted to ICSS patients who were randomised to and completed stenting treatment, age was an independent predictor of the risk of stroke, MI or death within 30 days of CAS (relative risk increase 1.17% per 5 years of age, 95% CI 1.01% to 1.37%), as were a right-sided procedure (RR 0.54, 95% CI 0.32 to 0.91), aspirin and clopidogrel in combination prior to CAS (RR 0.59, 95% CI 0.36 to 0.98), smoking status and the severity of index event. The use of an open-cell stent conferred higher risk than use of a closed-cell stent (RR 1.92, 95% CI 1.11 to 3.33), but the use of a cerebral protection device did not modify the risk. In a separate multivariable analysis restricted to ICSS patients who were randomised to and completed endarterectomy, only diastolic blood pressure at baseline was a significant predictor of the risk of stroke, MI or death within 30 days of CEA. Independent risk factors modifying the risk of cranial nerve palsy after CEA in a multivariate analysis were cardiac failure (RR 2.66, 95% CI 1.11 to 6.40), female sex (RR 1.80, 95% CI 1.02 to 3.20), and the degree of contralateral carotid stenosis and time from randomisation to treatment > 14 days (RR 3.33, 95% CI 1.05 to 10.57). The risk of haematoma after CEA was increased in women, by the prescription of anticoagulant drugs pre procedure and in patients with atrial fibrillation.

Magnetic resonance imaging substudy findings

A total of 231 patients had MRI before and after treatment. Sixty-two (50%) of 124 patients in the stenting group and 18 (17%) of 107 patients in the endarterectomy group had at least one new ischaemic lesion detected on post-treatment MRI performed a median of 1 day after treatment (adjusted odds ratio 5.21, 95% CI 2.78 to 9.79; $p < 0.0001$).

Primary outcome

In the ITT analysis, the primary outcome event, fatal or disabling stroke between randomisation and end of follow-up, occurred in 52 patients in the stenting group, corresponding to a cumulative 5-year risk of 6.4%, and in 49 patients in the endarterectomy group (5-year risk of 6.5%), without any evidence for a difference in time to first occurrence of an event (HR 1.06, 95% CI 0.72 to 1.57; $p = 0.76$).

Other long-term outcomes

In the ITT analysis, any stroke (5-year risks of 15.2% vs. 9.4%) (HR 1.71, 95% CI 1.28 to 2.30; $p = 0.0003$), as well as the combination of any procedural stroke, procedural death or ipsilateral stroke during follow-up (11.8% vs. 7.2%) (HR 1.72, 95% CI 1.24 to 2.39; $p = 0.001$), occurred significantly more often in the stenting group. However, there was no difference in functional outcome between the groups as assessed by the distribution of mRS scores at 1-year follow-up, 5-year follow-up or at the end of follow-up.

A total of 737 (98.0%) patients in the stenting group and 793 (97.8%) in the endarterectomy group were followed up with carotid ultrasound for a median of 4.0 years after treatment. There was no significant difference in long-term rates of severe carotid restenosis (≥ 70%) or occlusion, which occurred in 72 patients in the stenting group (5-year risk of 10.8%) and in 62 patients in the endarterectomy group [5-year risk 8.6% (HR 1.25, 95% CI 0.89 to 1.75; $p = 0.20$)].

In the per-protocol analysis of events occurring more than 30 days after completed treatment up to the end of follow-up, there was no significant difference in the rates of ipsilateral stroke in the territory of the treated artery (4.7% vs. 3.4%) (HR 1.29, 95% CI 0.74 to 2.24; $p = 0.36$). However, stroke of any severity occurred more often after stenting (8.9% vs. 5.8%) (HR 1.53, 95% CI 1.02 to 2.31; $p = 0.039$). This difference was largely attributable to stroke occurring in the territory of the contralateral carotid artery or the vertebrobasilar circulation among patients treated with stents, and the majority of these strokes were non-disabling.

Cost–utility analysis

There were no differences in costs or QALYs between the treatments. Mean costs per patient were £7351 (95% CI £6786 to £7915) in the stenting group ($n = 853$) and £6762 (95% CI £6154 to £7369) in the endarterectomy group ($n = 857$). Mean QALYs per patient were 3.247 in the stenting group (95% CI 3.160 to 3.333) and 3.228 in the endarterectomy group (95% CI 3.150 to 3.306). There were no differences in adjusted costs between groups (mean incremental costs for stenting vs. endarterectomy £537, 95% CI –£238 to £1312) or adjusted outcomes (mean QALYs gained –0.010, 95% CI –0.117 to 0.097). The incremental net monetary benefit for stenting compared with endarterectomy was not significantly different from zero at a maximum willingness to pay for a QALY of £20,000 (mean –£723, 95% CI –£3134 to £1670). Sensitivity analyses showed little uncertainty in these findings.

Conclusions

The functional outcome of patients with symptomatic carotid stenosis treated by stenting is similar to endarterectomy. CAS has a higher short-term (periprocedural) risk than CEA in terms of stroke but a lower rate of severe haematoma and it avoids injury to cranial nerves during endarterectomy. The additional short-term risk associated with CAS is largely attributable to non-disabling strokes. More extensive white-matter changes on baseline brain imaging and older age of the patient increase the procedural risks of stenting. The primary analysis of the trial showed that stenting is equivalent to endarterectomy in preventing fatal or disabling stroke up to 10 years after treatment. Severe restenosis or occlusion of the treated carotid artery was rare, with no difference between treatment groups. Stenting also appeared to be as effective as endarterectomy in preventing ipsilateral stroke occurring during follow-up after the

30-day procedural period. Stenting and endarterectomy had similar costs (index procedure costs, follow-up costs and total costs) and outcomes (utility values, QALYs). This was despite the finding in the trial of higher rates of non-disabling strokes in the stenting group. Comprehensive sensitivity analyses showed little uncertainty in this finding. Non-significant differences in utility values and QALYs mirror differences in mRS scores and all-cause mortality found in the trial.

Implications for health care

The data from ICSS show that stenting is a reasonable alternative to endarterectomy, especially if there are features suggesting that the risk of procedural stroke with stenting is likely to be similar or lower than that of endarterectomy (e.g. younger age or less than average severity of white-matter disease). Such patients should be offered stenting after informed consent giving full consideration of the overall periprocedural risks in the relevant groups. In addition to taking into account clinical and imaging features, treatment decisions should take into account patient preferences with reference to the differing nature of the risks with the two procedures. The findings of ICSS mean that there is no reason to prefer either stenting or endarterectomy on economic grounds; other factors should be taken into account when deciding which option to use to treat patients with symptomatic carotid stenosis.

Implications for research

Given the effect of stenting on silent infarction noted in ICSS–MRI substudy, measurement of cognitive function might be an important part of any future study of stenting and/or CEA. Another important area for future studies is identifying the clinical characteristics of patients that determine how likely they are to benefit from revascularisation in the context of optimised medical therapy.

Trial registration

Current Controlled Trials ISRCTN25337470.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research. Further funding was provided by the Medical Research Council, Stroke Association, Sanofi-Synthélabo and European Union.

Chapter 1 Introduction

Background

Stroke is the major cause of acquired adult physical disability and is responsible for 12% of all deaths in the UK. 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 causing serious disability. The risk of recurrent stroke in recently symptomatic patients with severe carotid stenosis is as high as 28% over 2 years. The European Carotid Surgery Trial and the North American Symptomatic Carotid Endarterectomy Trial (NASCET) demonstrated that this risk was reduced significantly by carotid endarterectomy (CEA) compared with best medical treatment alone.[1–3] 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 (MI) during the general anaesthetic used in most centres and minor morbidity, including cranial nerve palsy and wound haematoma, from the incision.

The potential benefit of endovascular treatment (angioplasty with or without stenting) as an alternative to CEA was first highlighted by the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS).[4] This trial showed that endovascular treatment largely avoided the main complications of the endarterectomy incision (namely cranial nerve injury and severe haematoma). However, the rate of stroke or death within 30 days after treatment was high in both groups. Since completion of CAVATAS, stenting has largely replaced angioplasty, and stents and protection devices specifically designed for the carotid artery have been introduced.

At the time of the inception of the International Carotid Stenting Study (ICSS), stenting was a new method of treating carotid stenosis, which had evolved from the technique of percutaneous transluminal angioplasty. Stenting avoids some of the hazards of surgery and has become an established treatment for peripheral and coronary artery stenosis. Stenting is considered less invasive than CEA 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. However, stenting does not remove the atheromatous plaque, has not been shown to prevent stroke and might have an unacceptable incidence of restenosis.

Rationale

It would have been inappropriate to use the results of CAVATAS to propose the widespread introduction of percutaneous transluminal angioplasty for the treatment of carotid stenosis as an alternative to surgery, because the 95% confidence interval (CI) surrounding the 10% risk of any stroke within 30 days of treatment in the surgical and angioplasty groups was ± 5%. Nevertheless, the results supported the need for further randomised studies. The interventional technique used to treat carotid stenosis evolved during 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 for inadequate results or complications of treatment after full balloon inflation. The desire to prevent these complications and superior early results in stented patients led to the increasing use of the technique of primary stenting, in which the intention is to deploy a stent in every patient before dilatation (but after pre dilatation if required to allow the atraumatic passage of the stent) of the artery.[5] Primary stenting is now accepted as best interventional practice[6] and has become the radiological technique of choice for carotid stenosis, replacing balloon angioplasty. ICSS was initiated to provide randomised trial evidence on whether or not carotid artery stenting (CAS) was as effective as CEA in preventing recurrent stroke that is associated with symptomatic carotid artery stenosis.

Potential risks and benefits

Both surgical endarterectomy and stenting carry a risk of causing a stroke at the time of the treatment. Previous trials showed a significant risk of stroke or death at the time of surgery or stenting of between 6 and 10 in every 100 patients. However, patients were randomised to the study because the risk of strokes resulting from surgical or stenting treatment was believed to be less than leaving the carotid artery narrowing untreated. The majority of major strokes after carotid percutaneous transluminal angioplasty 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.[5,6] The subgroup analysis of stented patients in CAVATAS was 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 dilatation of the artery. Superior dilatation 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.[7,8] Individual case series suggested that carotid stenting has a similar rate of procedural stroke to that of carotid surgery.[5,6,9]

Surgery also carries a risk of perioperative MI. Approximately 1 in 10 patients has temporary tongue or facial weakness as a result of cranial nerve palsy. A large blood clot (haematoma) may form at the site of incision, which may require removal. Surgery results in a permanent scar in the neck. Angiography and stenting may also result in bruising or haematoma at the site of injection (usually in the groin) and can cause temporary discomfort or pain in the neck. There is a small risk of allergic reactions to the contrast reagent used during angiography.

Although acceptable safety at the time of stenting had been suggested by the case series and registry data, at the time ICSS was initiated, stenting had not been subjected to a randomised trial in comparison with conventional surgical treatment and had not been demonstrated to prevent stroke, which is the aim of treatment.[10] Stenting does not remove the atheromatous plaque and stents may stimulate neointimal hyperplasia. In the long term, it is possible that the rate of restenosis would be greater after stenting than after carotid surgery, which could well result in an unacceptable rate of long-term stroke recurrence. There was, therefore, an important need to establish the efficacy of carotid stenting in comparison to surgery at a time when the technique was being widely introduced without adequate trial-based evidence for its safety and effectiveness.

Chapter 2 Methods

Objective

The objective of ICSS was to compare the risks, benefits and cost-effectiveness of a treatment policy of referral for carotid stenting compared with referral for carotid surgery.

Design

The ICSS was an international, multicentre, randomised controlled, open, prospective clinical trial comparing carotid surgery with carotid stenting. The trial was approved by the Northwest Multicentre Research Committee in the UK and by local ethics committees outside the UK. The full version of the protocol is available at www.cavatas.com.[11]

Participants

Patients of either sex over the age of 40 years with symptomatic atherosclerotic stenosis of the carotid artery were included in the trial. The consent form and patient information form are shown in *Appendices 1* and *2*, respectively. The inclusion and exclusion criteria are outlined below.

Inclusion criteria

- Symptomatic, extracranial, internal or bifurcation atheromatous carotid artery stenosis suitable for both stenting and surgery, and 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 the NASCET method or non-invasive equivalent).
- Symptoms must have occurred in the 12 months before randomisation. It was recommended that the time between symptoms and randomisation should be < 6 months, but patients with symptoms occurring between 6 months and 12 months could be included if the randomising physician considered that treatment was indicated.
- The patient had to be clinically stable following their most recent symptoms attributable to the stenotic vessel.
- Patients had to be willing to have either treatment, be able to provide informed consent and be willing to participate in follow-up.
- Patients had to be able to undergo their allocated treatment as soon as possible after randomisation.
- Any patient > 40 years of age could be included.
- Patients could only be randomised if the investigator was uncertain which of the two treatments was 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 had previously had a major stroke with no useful recovery of function within the territory of the treatable artery.

- Patients with a stenosis that was 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
  - pseudo-occlusion ('string sign').
- Patients not suitable for surgery owing to anatomical factors (e.g. high stenosis, rigid neck).
- Patients in whom it was 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 CEA or stenting in the randomised artery.
- Patients in whom common carotid artery surgery was planned.
- Patients medically not fit for surgery.
- Patients who had a life expectancy of < 2 years owing to a pre-existing condition (e.g. cancer).

Interventions

Stenting protocol

Stenting was 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 was used whenever the operator thought that one could be safely deployed. Stents and other devices used in the trial had to be Conformité Européenne (CE) marked and approved by the steering committee.

Pre-medication was at the discretion of the interventionist, although the protocol recommended the combination of aspirin and clopidogrel as the antiplatelet regime of choice to cover the period of stenting and for a minimum of 4 weeks afterwards. Intra-procedural heparin was mandatory at a dose determined by the operator; post-procedural heparin could be given according to clinical requirements.

The trial protocol stated that 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 or asystole.

Angiographic images showing the stenosis at its most severe prior to stenting and the same view and any other view that demonstrated the maximum residual stenosis after stenting were collected by the trial office.

Details of the procedure, including all periprocedural complications, drug therapy and devices used in the procedure, were reported on the stenting and cerebral protection technical data sheet which was returned to the trial central office.

Endarterectomy protocol

Endarterectomy was carried out as soon as possible after randomisation by a designated consultant surgeon. It was carried out using whichever procedures were 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 could be performed. Details of the procedure, including all periprocedural complications, drug therapy and type of endarterectomy performed, were reported on the surgery technical data sheet which was returned to the trial central office.

Approval of surgeons and interventionists, and credentialing of less-experienced operatives

An accreditation committee decided if surgeons and interventionists at enrolling centres had the appropriate experience and expertise to join the study. Surgeons and interventionists were expected to show a stroke and death rate within 30 days of treatment, consistent with the centres in the European Carotid Surgery Trial who had an average rate of 7.0% with a 95% CI of 5.8% to 8.3%.[1] Surgeons were expected to have performed a minimum of 50 carotid operations with a minimum annual rate of at least 10 cases per year. Interventionists were expected to have performed a minimum of 50 stenting procedures, of which at least 10 should have been in the carotid territory. Centres that had little or no experience of carotid stenting were allowed to join ICSS for a probationary period in order to gain the minimum experience of 10 carotid stenting procedures required to join the trial fully. Stenting procedures carried out during the probationary period were proctored by an experienced carotid interventionist appointed by the trial steering committee, until the proctor was satisfied that the interventionist(s) at the centre could satisfactorily carry out procedures unproctored. Probationary interventionists became fully enrolled in ICSS when the proctor was satisfied that the interventionist could perform procedures unsupervised and the interventionist had 10 or more successfully completed cases in the trial, with an acceptable complication rate.

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

The database manager at the trial office monitored periprocedural outcome events, and if there were 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 was triggered. A blinded assessment of the relevant outcome events was submitted by the central office to the chairman of the data monitoring committee who had the power to recommend further action, such as suspending randomisation at the centre. A cumulative major event or death rate of more than 10% over 20 cases would also trigger careful assessment of the relevant outcome events.

Data collected at baseline

Baseline data collected at randomisation included demographic data; existing medical risk factors; neurological symptoms and an assessment of disability using the modified Rankin Scale (mRS); current antiplatelet therapy and blood pressure; and films and reports of pre-randomisation brain imaging and the results of duplex ultrasound (DUS).

Randomisation

Randomisation was performed by a telephone call or fax to a computerised service provided by the Oxford Clinical Trials Service Unit. It was stratified by centre with minimisation of the main risk factors and balanced between the arms. Patients who needed treatment of both carotid arteries could only be randomised for the carotid artery to be treated first. Two patients were randomised at the Service Unit by coin toss when the computerized service was not available.

Follow-up

Patients were followed up by a neurologist or a physician interested in stroke, who was not involved in the revascularisation procedure but who was not masked to group assignment, at the participating centres at 30 days after treatment, 6 months after randomisation and, then, annually after randomisation.

At each visit, levels of stroke-related disability were assessed using the mRS and any relevant outcome events notified to the central trial office. DUS examinations of the carotid arteries were carried out at each follow-up visit at centres with available facilities. Bilateral peak systolic and end diastolic velocities in the internal carotid artery and the peak systolic velocity in the common carotid artery were recorded. The data were collected on a follow-up form and an ultrasound report form (see *Appendices 3* and *4*), which were returned to the central trial office where the data were entered into a Microsoft Access (Microsoft Corporation, Redmond, WA, USA) database. In addition to the clinical data, patients were asked to complete a EuroQol European Quality of Life-5 Dimensions – 3 level response (EQ-5D-3L™) questionnaire (see www.euroqol.com) to assess quality of life and health status at baseline, after stenting or surgery at 1 month, and then at 6-month and annual follow-up visits.

Patients were followed up to the end of the trial in 2011 (a maximum of 10 years after randomisation). Patients reaching their 5-year follow-up before the end of the trial were asked if they were willing to carry on with follow-up, in which case they continued with annual follow-up until the end of the trial.

Outcomes

The following events were collected and analysed as trial outcome events:

- any stroke or death
- TIA
- MI 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 ≥ 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.

Outcome events included in the safety analysis or primary outcome (stroke, MI within 30 days of treatment, death) were documented in detail by the investigating centre, censored after receipt at the central office to remove clues as to the treatment allocated, and then adjudicated by a neurologist at the central office and by an independent external neurologist. If the external neurologist's adjudication differed from the central office, a third independent neurologist reviewed the event and the majority opinion prevailed. The major event and death forms are shown in *Appendices 5* and *6*.

Centres were asked to supply the following information for adjudication, whenever possible:

- a report of the event using the standard trial case report form
- a film copy of a computerised tomography (CT) or magnetic resonance imaging (MRI) brain scan as soon as possible after the event, together with a film copy of the pre-randomisation scan (if done) and a report of the event
- copies of discharge summaries, death certificates and post-mortem results (if relevant).

Disability after stroke and cranial nerve palsy was assessed 30 days after treatment or at onset using the mRS. Duration of symptoms was recorded and outcome events were classified as disabling if the mRS score was 3 or more at 1 month. If the patient was not seen at exactly 30 days after onset of the event, the investigator was asked to estimate the 30-day mRS.

The degree of carotid stenosis during follow-up was determined in the study central office based on flow velocity data using pre-defined criteria,[12] masked to treatment allocation and date of ultrasound follow-up. Results of carotid imaging studies ordered outside regular follow-up at the discretion of the treating clinicians (e.g. for recurrent symptoms) were also included. The main outcome event of the restenosis analysis was defined as any severe (≥ 70%) residual or recurrent stenosis, or occlusion of the carotid artery during follow-up. No correction was made for the presence of a stent when measuring stenosis severity.

Statistical methods

All analyses were conducted according to the statistical analysis plan for the short-term (safety) analysis or the long-term analysis (see *Appendix 7*), which provides a detailed and comprehensive description of the main, pre-planned analyses for the study. Analyses were performed with Stata statistical software version 12.1 or earlier (StataCorp LP, College Station, TX, USA), except for the MRI substudy and the study on the effect of white-matter lesions on periprocedural stroke, which used SPSS statistical software version 17 (SPSS Inc., Chicago, IL, USA) and version 21 (IBM Corp., Armonk, NY, USA), respectively.

The main features of the analysis plan are summarised below.

The Consolidated Standards of Reporting Trials (CONSORT) flow diagram is used to summarise representativeness of the study sample and patient throughput (see *Figure 1*). Baseline characteristics are presented by treatment group with continuous variables presented with means and standard error.

The analyses 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 with a two-sided *p*-value of 0.05 (5% level) used to declare statistical significance with a 95% CI reported throughout. Secondary analyses compare the proportions of outcome events within 30 days of treatment. All analyses are adjusted for centre and pre-determined risk factors. Subgroup analyses examine risk factors for outcome events.

Cox proportional hazard models were used to calculate the hazard ratio (HR) and 95% CI with endarterectomy as the reference group using all available follow-up data. Log-rank tests were used to compare the two survival curves. Censoring was assumed to be non-informative.

As the restenosis outcome was interval-censored it was instead analysed using a generalised non-linear model which assumes proportional hazards and whose treatment effect parameter estimate can be interpreted as a log-HR. The treatment effect *p*-value for the restenosis outcome was calculated using a likelihood ratio test. Life-table analyses were used to estimate the cumulative incidences of restenosis at 1 year and 5 years after treatment.

Interaction tests were performed to investigate whether or not the relative treatment effect for the pre-defined primary long-term outcome, as well as for procedural stroke or death or ipsilateral stroke during follow-up, differed across various patient groups. Functional ability at the final follow-up or at death was compared between treatment groups across the entire range of the mRS at 1-year and 5-year follow-up using the permutation test described by Howard *et al.*[13] Drug treatments and blood pressure at 1-year and 5-year follow-up were compared using chi-squared tests and *t*-tests at each time point, respectively.

Sample size (original and revised)

At the commencement of recruitment in 2001 we planned to recruit 2000 patients, but this was revised shortly after the start of the trial in 2003 to 1500 in response to the initial funding period and taking into account the observed recruitment rate to that date. For 1500 patients, the 95% CI was the observed difference ± 3.0 percentage points for the outcome measure of 30-day stroke, MI and death rate and ± 3.3 percentage points for the outcome measure of death or disabling stroke over 3 years' follow-up.

The difference detectable with power 80% was 4.7 percentage points for 30-day outcome and 5.1 percentage points for survival free of disabling stroke. Similar differences were detectable for secondary outcomes. In 2007, the steering committee modified the protocol to emphasise that the sample size of 1500 patients should reflect only patients recruited at experienced centres, to ensure that the study would be adequately powered to compare outcomes of stenting performed by experienced interventionists with endarterectomy. An extension of funding was therefore obtained to allow the recruitment of a total of 1700 patients, anticipating that 200 of these would come from centres with probationary investigators.

Protocol amendments

The major amendments to the protocol during the course of the trial are detailed in *Appendix 8*. In brief, in addition to the modifications to the sample size described above, in 2003, clarification of the rules governing proctoring of probationary centres and the maximum permissible delays between symptoms and randomisation were added to the protocol. In 2007, an amendment was made to state that data from patients enrolled at probationary centres would be analysed separately from data from fully enrolled experienced centres. Subsequently, the steering committee decided after completion of recruitment and initial analysis of the results that the data from probationary and fully enrolled centres should be analysed together, because there was no significant difference in the results (indeed the results were slightly better at probationary centres).

The International Carotid Stenting Study–magnetic resonance imaging substudy: symptomatic and asymptomatic ischaemic and haemorrhagic brain injury following protected and unprotected stenting versus endarterectomy

Clinical follow-up of patients in ICSS was not masked to treatment allocation and, therefore, there was the possibility of potential bias in the ascertainment of non-disabling strokes. We therefore planned a substudy of ICSS at centres with sufficient neuroimaging facilities and capacity in which we would use multimodal MRI as an additional outcome measure of procedural cerebral ischaemia that could be analysed without knowledge of treatment allocation. We aimed to compare the risk of procedural ischaemia and persistent infarction on MRI between patients randomly allocated to receive stenting or endarterectomy. Moreover, diffusion weighted imaging (DWI), a modern MRI technique, may show ischaemic lesions after carotid interventions even in patients who do not experience symptoms.[14] In previous studies, new ischaemic lesions on DWI were detected more frequently after stenting than after endarterectomy.[15–21] DWI lesions were also more frequent after unprotected stenting than after protected stenting.[22,23] However, selection bias and the use of historical controls might account for the observed differences in these non-randomised comparisons. In addition, it was 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 were needed to gain further insight into the significance of asymptomatic DWI lesions and their potential role as surrogate markers of treatment risk.

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.[24,25] Concern that stenting without cerebral protection might be associated with an increased risk of stroke led to the abandonment of unprotected procedures in one trial,[25] but in another trial, there was no difference in the risk of stenting with and without protection.[24] Although clear evidence that cerebral protection enhances treatment safety is lacking,[26] protection devices were widely used, significantly contributing to the cost of carotid stenting. We therefore planned to carry out an exploratory analysis of the MRI data to investigate the effect of cerebral protection devices on the risk of ischaemia associated with stenting.

Objectives

The primary objective of this substudy was 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 were: 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 with 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.

The ICSS–MRI substudy was designed to allow 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 was not subject to randomisation in ICSS. However, the participating centres systematically used either protected or unprotected stenting. The risk of brain injury associated with either stenting technique could, therefore, be compared with a randomised control group of patients undergoing endarterectomy.

Outcome measures and analyses were 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.

Inclusion criteria

Patients were eligible to participate in the ICSS–MRI substudy if they were enrolled in the ICSS trial and separately provided written informed consent to undergo three MRI exams.

Exclusion criteria

Patients with contraindications to MRI (e.g. pacemakers, metallic implants and claustrophobia) were excluded from the ICSS–MRI substudy.

Magnetic resonance imaging protocol

Patients enrolled in the ICSS–MRI substudy had three MRI investigations, at 1–3 days before, 1–3 days after and 30 ± 3 days after the intervention. The following sequences were performed in all three investigations:

- DWI to detect acute ischaemic brain injury associated with the procedure
- gradient echo T2 star-weighted sequences to detect haemorrhagic brain injury associated with the procedure
- T1-weighted, T2-weighted and fluid-attenuated inversion recovery sequences were used to assess whether or not acute brain lesions detected on DWI after the procedure led to permanent scarring at 1 month.

Data acquisition

Baseline data (such as age, sex, medical risk factors, degree of carotid stenosis, etc.) were collected as part of ICSS. Two researchers, one a neurologist and one a neuroradiologist, with several years of experience in assessing brain scans in patients with cerebrovascular disease independently scored the presence, size and location (vascular territory) of ischaemic and haemorrhagic lesions on the MRI scans. A third experienced researcher reviewed the scans in case of disagreement. The scans were reported and scored blind to patient identifiers, treatment, date and time of the scans. Patients were clinically examined by a neurologist at the time of MRI examination and followed up after treatment as part of ICSS to determine outcome events, including TIA, stroke, MI and death.

Statistical analysis

The rates of ischaemic and haemorrhagic brain lesions were compared between patients undergoing endarterectomy and stenting using chi-squared tests[2] and Fisher's exact tests. Significance was declared at $p < 0.05$. Exploratory analyses were performed to test the interaction between the use of cerebral protection devices and the rate of DWI lesions after stenting.

Sample size calculation

Power calculations for this substudy were based on the primary outcome measure. The two largest series reported new ischaemic lesions on DWI after CEA in 17% and 34% of patients, respectively.[27,28] 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.

Effect of white-matter lesions on the risks of periprocedural stroke after carotid artery stenting versus endarterectomy

Leukoaraiosis was associated with a higher perioperative risk of stroke or death in patients assigned to CEA in the NASCET.[29] Patients with widespread white-matter changes allocated to the best medical management group also had an increased risk of stroke or death. To the best of our knowledge, the effect of white-matter lesions on the procedural risk of stroke and death in carotid stenting has hitherto not been investigated. We therefore investigated the effect of leukoaraiosis on the risk of procedural complications in a large group of patients with recently symptomatic carotid disease randomised in ICSS in a pre-specified analysis.[30] Brain imaging by CT or MRI was needed before revascularisation.

Methods

In this study of white-matter lesions, we included all patients enrolled in ICSS in whom copies of the baseline CT or MRI done before carotid stenting or endarterectomy were available. Patients were excluded if no baseline brain imaging was available or if the quality of the images was poor. Copies of baseline brain imaging were analysed by two investigators, one a neurology research fellow and one a neuroradiologist, who were both trained in the analysis of white-matter lesions and masked to treatment and clinical outcome, for the severity of white-matter lesions using the age-related white-matter changes (ARWMC) score. Differences were resolved by consensus. Patients were divided into two groups using the median ARWMC score. We analysed the risk of stroke within 30 days of revascularisation using a per-protocol analysis. A total of 1036 patients (536 randomly allocated to CAS, 500 to CEA) had baseline imaging available. The median ARWMC score was 7, and patients were dichotomised into those with a score of 7 or more and those with a score of < 7.

Cost–utility analysis of stenting versus endarterectomy for treatment of symptomatic carotid stenosis

A cost–utility analysis with full incremental analysis was undertaken to compare the costs and outcomes associated with stenting and endarterectomy.

Methods

Outcome measure

The outcome measure was quality-adjusted life-years (QALYs), which combine length of life and quality of life; this is consistent with National Institute for Health and Care Excellence (NICE) recommendations. Cost-effectiveness was expressed as incremental net monetary benefits (NMBs). The analysis took a UK NHS and personal social services (PSS) perspective.[31] Costs are calculated in 2013–14 Great British pounds. The time horizon was 5 years, which was long enough to reflect all important differences in costs or outcomes between the two treatments. An annual discount rate of 3.5% was applied to costs and outcomes.[31]

Resource use and costs

For every patient we calculated the cost of the index procedure and the cost of follow-up using resource-use data collected prospectively in the trial. The former included surgeon and radiologist time; operating theatre time, including nursing staff, drugs, consumables and overheads; anaesthesia; materials and devices including stents, shunts, patches, cerebral protection devices, catheters, wires and sheaths; and length of hospital stay in the intensive care unit (ICU) and inpatient ward. The latter included additional carotid artery procedures; complications within 30 days of index procedure (fatal and non-fatal MI, severe haematoma and disabling cranial nerve palsy); imaging tests; drug treatment; and non-disabling, disabling and fatal strokes.

Unit costs were obtained from published and local sources,[32–35] inflated where appropriate[32] and multiplied by resource use. Unit costs of surgeon, radiologist and operating theatre times were hourly costs applied to procedure durations collected during the trial. The choice of stents was at the discretion of the interventionist. In the base-case analysis each stent was assigned an acquisition cost of £840 based on the cost of the most commonly used stent, the Carotid WALLSTENT® (Boston Scientific, Marlborough, MA, USA) at the lead centre; this was varied in sensitivity analysis. Unit costs of hospital stays were daily costs applied to length-of-stay data collected in the trial. Length of stay on the ICU was not collected for individual patients, but mean values were collected by centre. From these data we assumed that where patients were admitted to the ICU post-operatively it was for 1 day. Unit costs of additional carotid artery procedures were assumed to be equal to the mean cost of the index procedures. Unit costs of drug treatment were monthly costs applied to treatment durations collected in the trial. Stroke events were recorded in the trial, but the costs of managing them were not. These were obtained from supplementary analyses of data from a contemporaneous UK population-based study of all strokes, the Oxford Vascular (OXVASC) study,[36,37] which were used to predict care home and hospital care costs for each stroke patient as a function of their sex, age, disability before stroke, previous history of cardiovascular disease, initial stroke severity (non-disabling, disabling, fatal) and number of recurrent strokes (see *Appendix 9*).

Utilities and quality-adjusted life-years

Generic health status was described at baseline (randomisation), at 3 and 6 months, and at 1, 2, 3, 4 and 5 years post-randomisation using the EQ-5D-3L descriptive system (see www.euroqol.com), containing five dimensions (mobility, self-care, usual activities, pain and discomfort, anxiety and depression) with three levels in each dimension. Each EQ-5D-3L health state can be converted into a single summary index (utility value) by applying a formula that attaches weights to each of the levels in each dimension based on valuations by general population samples. Given the perspective of our analysis, we used a value set for the UK population to calculate utility values at each time point for every participant.[38] Utility values of 1 represent full health, values of 0 are equivalent to death, negative values represent states worse than death. Patients who died were assigned a utility value of 0 at their date of death. A utility profile was constructed for every patient assuming a straight line relation between their utility values at each measurement point. QALYs for every patient from baseline to 5 years were calculated as the area under the utility profile.

Dealing with missing data

Multiple imputation was used to impute missing data for the following variables: cost of surgeon and radiologist time; cost of operating theatre time; cost of anaesthesia; cost of stents; cost of patches; cost of cerebral protection devices; cost of other materials used in stenting; cost of length of hospital stay; cost of non-fatal MI; cost of imaging tests; costs of drug treatment; cost of strokes; total cost; utility values at baseline, 3 months and 6 months post-randomisation, and 1, 2, 3, 4 and 5 years post-randomisation; and total QALYs. The cost variables were unit costs multiplied by resource use. Age, sex, study centre and treatment allocation were included in the imputation models as additional explanatory variables. We used multivariate normal regression to impute missing values and generated 20 imputed data sets. We repeated the multiple imputation several times using different random number seeds to investigate if the conclusions of the analysis changed.

Statistical methods

Mean costs, outcomes and NMBs were compared between all patients randomly assigned to stenting and to endarterectomy, irrespective of which treatment was administered and whether or not they received additional carotid artery procedures of either type. We calculated differences in mean costs and QALYs and incremental NMBs between groups. NMBs for stenting and endarterectomy were calculated as the mean QALYs per patient multiplied by the maximum willingness to pay for a QALY minus the mean cost per patient. Incremental NMBs were calculated as the difference in mean QALYs per patient with stenting versus endarterectomy multiplied by the maximum willingness to pay for a QALY minus the difference in mean cost per patient. We used the cost-effectiveness threshold range recommended by NICE of £20,000 to £30,000[31] as the lower and upper limits of the maximum willingness to pay for a QALY. If the incremental NMB is positive (negative) then stenting (endarterectomy) was preferred on cost-effectiveness grounds. The QALYs gained were adjusted for age, sex, study centre and baseline utility values using regression analysis; the incremental costs were adjusted for age, sex and study centre. For each of the 20 imputed data sets we ran 1000 bootstrap replications and combined the results using equations described by Briggs *et al.*[39] to calculate standard errors around mean values accounting for uncertainty in the imputed values, the skewed nature of the cost data and utility values, and sampling variation. Standard errors were used to calculate 95% CIs around point estimates.

Sensitivity and subgroup analyses

A cost-effectiveness acceptability curve[40] showing the probability that stenting was cost-effective compared with endarterectomy at a range of values for the maximum willingness to pay for a QALY was generated based on the proportion of the bootstrap replications across all 20 imputed data sets with positive incremental NMBs.[41] The probability that stenting was cost-effective at a maximum willingness to pay for a QALY of £20,000 and £30,000 was reported, based on the proportion of bootstrap replications with positive incremental NMBs at these values. We undertook further sensitivity analyses to evaluate the impact of uncertainty in the following components: no adjustment for age, sex, study centre and baseline utility values; complete-case analysis without imputing missing values; univariate analyses of high- and low-cost values (unit costs multiplied by resource use) for anaesthesia, operating theatre time, surgeon and radiologist time, shunts, patches, stents, cerebral protection devices, other materials used in stenting, length of hospital stay, additional carotid artery procedures, imaging, severe haematoma, disabling cranial nerve palsy, fatal and non-fatal MI, drug treatment, treating strokes (values per patient were recalculated to be 50% higher and 50% lower than the base case); and discount rate (1.5%, 5%). No significant interactions were found in any subgroup analyses of the primary outcomes in ICSS. In post-hoc subgroup analyses we calculated cost-effectiveness results separately by sex and age ($\geq$ 70 years, < 70 years). We completed a Consolidated Health Economic Evaluation Reporting Standards statement to ensure that the cost–utility analysis was reported appropriately (see *Appendix 9*).

Chapter 3 Results

The short-term and long-term outcomes of ICSS have been reported in the literature.[42,43]

Recruitment

Figure 1 shows the CONSORT diagram of the flow of patients through the trial. Between May 2001 and October 2008, 1713 patients from 50 centres in the UK, mainland Europe, Australia, New Zealand and Canada were enrolled and randomised. The trial centres, together with the members of the trial committees, location of recruiting centres, number of patients recruited at each centre and the names of the investigators at each centre are detailed in *Appendix 10*. Three patients (two in the stenting group and one in the endarterectomy group) withdrew consent immediately after randomisation and were excluded from the intention-to-treat (ITT) analysis. In total, 1511 patients were enrolled at experienced centres and 202 at supervised probationary centres: 751 (88%) of 853 patients assigned to carotid stenting and 760 (89%) of 857 patients assigned to endarterectomy were randomised at centres classified as experienced. Most patients had their allocated treatment initiated (stenting group, $n = 828$; endarterectomy group, $n = 821$). Nine patients allocated to stenting crossed over to surgery without an attempt at the procedure and a further 16 had no attempted ipsilateral endarterectomy or stenting procedure (*Figure 1*). Fifteen patients allocated to endarterectomy crossed over to stenting without an attempt at endarterectomy and 21 had no attempted ipsilateral procedure.

Monitoring of adverse events led to concern about the stenting results of two investigators at supervised centres. These investigators were stopped from treating further patients within the trial and their centres were suspended from randomisation. All the patients allocated to stenting ($n = 11$, five with disabling stroke or death) or endarterectomy during the same time period ($n = 9$, one with fatal stroke) at these centres were included in the analyses. One of the two centres subsequently restarted randomisation with a different investigator performing stenting.

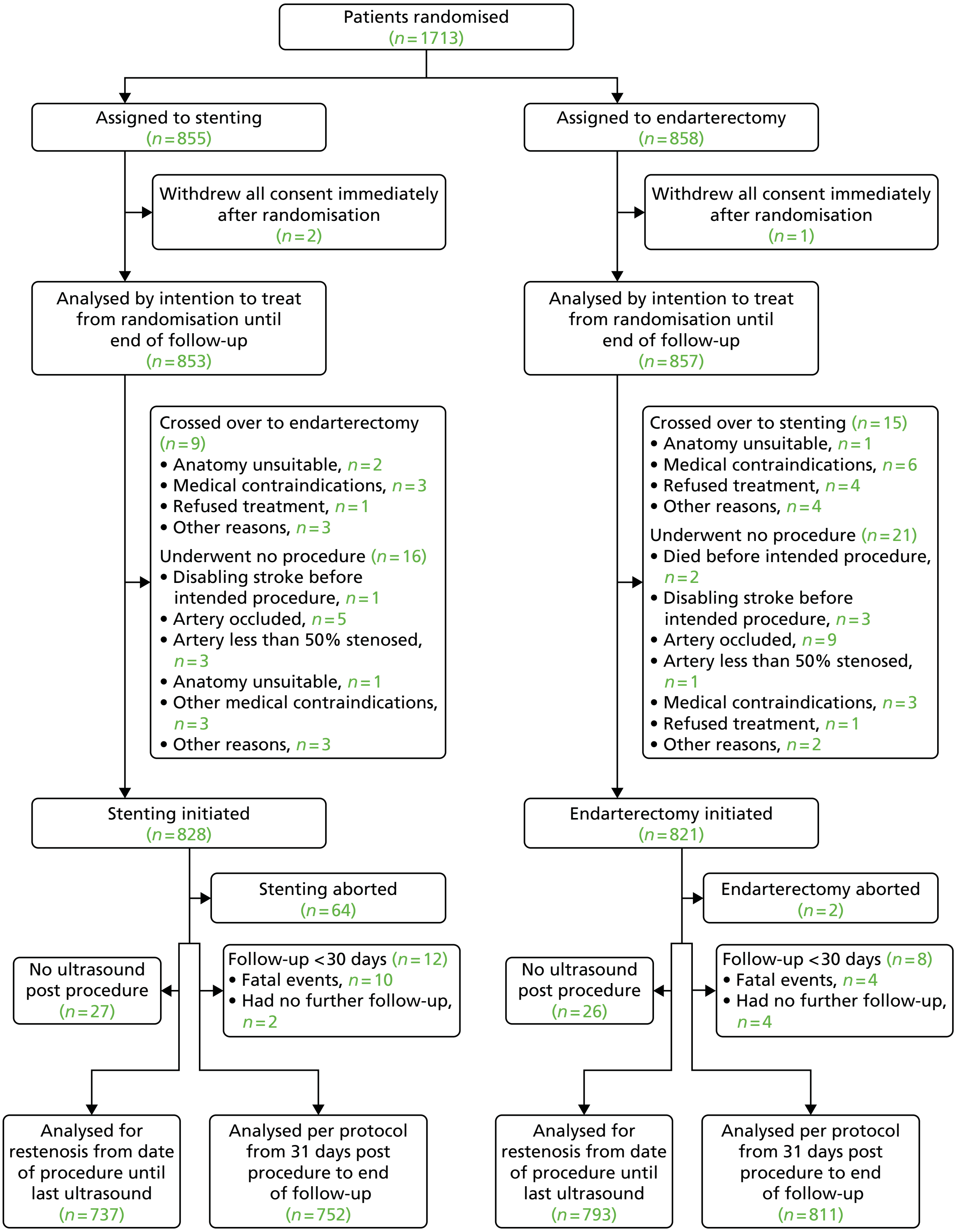


FIGURE 1 Consolidated Standards of Reporting Trials diagram for ICSS.

Baseline characteristics

Table 1 shows baseline characteristics of study participants.

Patient baseline characteristics (*Table 1*) and drug treatment during the trial (*Table 2*) were similar between the two treatment groups. At 1 year after randomisation, 97% of patients in both the stenting group and the endarterectomy group took any antiplatelet or anticoagulant; at 5 years, the percentages were 94% and 95% (*Table 2*). There were slightly more patients taking antihypertensive medications in the endarterectomy group at 1 year (71% vs. 75%; $p = 0.088$), but at 5 years the difference had reversed (83% vs. 76%; $p = 0.017$). However, this did not lead to any significant difference in systolic blood pressure or diastolic blood pressure (DBP) between groups at either time point. The majority of patients were treated with lipid-lowering medications with no significant difference between the groups (82% of patients in the CAS group vs. 84% in the CEA group at 1 year, and 87% of patients in the CAS group vs. 86% in the CEA group at 5 years).

TABLE 1 Baseline patient characteristics at randomisation by allocated treatment

Baseline patient characteristic	Stenting (*n* = 853)	Endarterectomy (*n* = 857)
Age (years), mean (SD)	70 (9)	70 (9)
Male sex, *n* (%)	601 (70)	606 (71)
Vascular risk factors		
Treated hypertension, *n* (%)	587 (69)	596 (70)
Systolic blood pressure (mmHg), mean (SD)	147 (24)	146 (24)
Diastolic blood pressure (mmHg), mean (SD)	79 (12)	78 (13)
Cardiac failure, *n* (%)	23 (3)	47 (5)
Angina in last 6 months, *n* (%)	83 (10)	77 (9)
Previous MI, *n* (%)	151 (18)	156 (18)
Previous CABG, *n* (%)	109 (13)	116 (14)
Atrial fibrillation, *n* (%)	57 (7)	59 (7)
Other cardiac embolic source, *n* (%)	19 (2)	16 (2)
Diabetes mellitus, non-insulin dependent, *n* (%)	134 (16)	147 (17)
Diabetes mellitus, insulin dependent, *n* (%)	50 (6)	41 (5)
Peripheral artery disease, *n* (%)	139 (16)	136 (16)
Current smoker, *n* (%)	205 (24)	198 (23)
Ex-smoker, *n* (%)	408 (48)	424 (49)
Treated hyperlipidaemia, *n* (%)	522 (61)	563 (66)
Total serum cholesterol (mmol/l), mean (SD)	4.8 (1.3)	4.9 (1.3)
***Degree of symptomatic carotid stenosis,* n *(%)*[a]**		
50–69%	92 (11)	76 (9)
70–99%	761 (89)	781 (91)
***Degree of contralateral carotid stenosis,* n *(%)*[a]**		
< 50%	565 (66)	561 (65)
50–69%	128 (15)	142 (17)
70–99%	105 (12)	110 (13)
Occluded	49 (6)	37 (4)
Unknown	6 (1)	7 (1)

continued

TABLE 1 Baseline patient characteristics at randomisation by allocated treatment (*continued*)

Baseline patient characteristic	Stenting ($n = 853$)	Endarterectomy ($n = 857$)
***Most recent ipsilateral event,* n *(%)*[b]**		
Ischaemic hemispheric stroke	393 (46)	376 (44)
TIA	273 (32)	303 (35)
Retinal infarction	26 (3)	23 (3)
Amaurosis fugax	148 (17)	142 (17)
Unknown	13 (2)	13 (2)
Event < 6 months prior to randomisation	826 (97)	816 (95)
Event 6–12 months prior to randomisation[c]	27 (3)	36 (4)
mRS at randomisation,* n *(%)		
0–2	756 (89)	744 (87)
3–5[d]	81 (10)	99 (12)

CABG, coronary artery bypass graft; SD, standard deviation.
a Degree of stenosis reported by randomising centre according to the measure used in the NASCET or a non-invasive equivalent.
b If two events were reported on the same day, the one higher up in the order above was counted.
c In three patients the event was more than 12 months before randomisation and in two the date was unknown.
d Some Rankin scores of ≥ 3 were caused by non-stroke disability.

TABLE 2 Drug treatment and blood pressure readings during follow-up (ITT population)

	1 year		5 years	
Drug treatment and blood pressure	**Stenting**	**Endarterectomy**	**Stenting**	**Endarterectomy**
Drug treatment (number of patients with data)	714	751	343	329
Any antiplatelet, *n* (%)	668 (94)	688 (92)	303 (88)	284 (86)
Aspirin alone, *n* (%)	401 (56)	413 (55)	197 (57)	169 (51)
Clopidogrel alone, *n* (%)	79 (11)	79 (11)	40 (12)	46 (14)
Dipyridamole + aspirin or clopidogrel, *n* (%)	130 (18)	154 (21)	48 (14)	48 (15)
Aspirin + clopidogrel, *n* (%)	55 (8)	34 (5)	14 (4)	17 (5)
Anticoagulation: vitamin K antagonists, *n* (%)	36 (5)[a]	57 (8)[a]	23 (7)	33 (10)
Other anticoagulation or antiplatelet, *n* (%)	3 (0)	10 (1)	5 (1)	4 (1)
Any anticoagulation or antiplatelet, *n* (%)	696 (97)	731 (97)	322 (94)	313 (95)
Antihypertensive, *n* (%)	510 (71)	566 (75)	286 (83)[a]	250 (76)[a]
Lipid lowering, *n* (%)	584 (82)	629 (84)	299 (87)	282 (86)
Blood pressure (*n* patients with data)	664[b]	685[b]	313[b]	302[b]
Systolic blood pressure (mmHg), mean (SD)	147 (22)[a]	144 (22)[a]	142 (22)	143 (23)
Diastolic blood pressure (mmHg), mean (SD)	79 (12)[a]	78 (11)[a]	77 (12)	76 (12)

SD, standard deviation.
a Statistical comparison between treatment groups (chi-squared test for specified drug treatments and *t*-test for blood pressures): $p < 0.05$. 'Anticoagulation' (1 year; $p = 0.046$); 'antihypertensive' (5 year; $p = 0.017$); 'systolic blood pressure' (1 year; $p = 0.011$); 'diastolic blood pressure' (1 year; $p = 0.035$).
b For diastolic blood pressure, numbers of patients with data are 663 and 684 (1 year), and 312 and 301 (5 year).

Success of procedures and cross-overs

Figure 2 shows the delay from randomisation to first initiated ipsilateral treatment in the per-protocol analysis within the first 120 days after randomisation.

Median delay from randomisation to treatment was shorter in the stenting group than in the endarterectomy group, as was the delay from most recent ipsilateral event to treatment (*Table 3*).

Of the 828 patients in whom stenting was initiated as allocated, 64 (8%) had their procedure aborted before the insertion of a stent (38 procedures were aborted because of difficulty gaining access to the stenosis; 15 were aborted because of the finding of an occluded artery, one patient had a fatal stroke, one patient had a fatal MI before completion of treatment, two had other medical complications, and further investigation in seven patients showed the artery to be < 50% stenosed). Of the 62 patients whose stenting procedure was aborted after initiation and who did not have a fatal event, 37 went on to have an ipsilateral

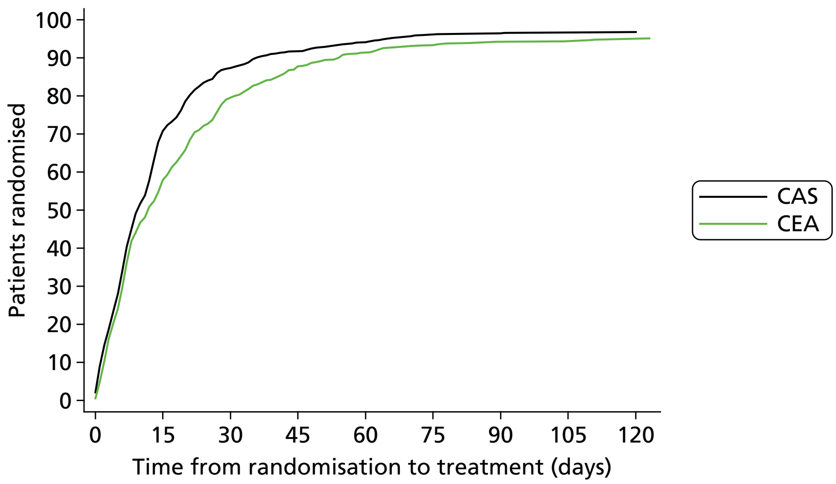


FIGURE 2 Time between randomisation and treatment. Cumulative number of patients in whom allocated treatment was initiated per protocol plotted as a proportion (%) of the total number randomised in each treatment group (*y*-axis), against the delay in days between the dates of randomisation and treatment (*x*-axis). Only allocated per-protocol treatment dates were counted.

TABLE 3 Time from randomisation and from most recent ipsilateral event to allocated treatment

	Stenting ($n = 828$)	Endarterectomy ($n = 821$)	p-value[a]
Time from randomisation to treatment (days), median (IQR)	9 (5–17)	11 (5–24)	< 0.001
≤ 14 days, *n* (%)	578 (70)	469 (57)	
> 14 days, *n* (%)	250 (30)	352 (43)	
Time from most recent event to treatment (days), median (IQR)	35 (15–82)	40 (18–87)	0.013
≤ 14 days, *n* (%)	205 (25)	151 (18)	
> 14 days, *n* (%)	623 (75)	668 (81)	

a Mann–Whitney *U*-test.
Three patients were randomised more than 12 months after symptoms in the endarterectomy group. The date of the most recent event was unknown in two patients (endarterectomy group).

endarterectomy, whereas 25 continued with best medical care only. Only two of the 821 patients whose allocated endarterectomy was initiated had their procedure aborted (one patient had an allergic reaction during general anaesthesia; the other became distressed and the endarterectomy had to be abandoned). Both patients subsequently had ipsilateral stenting.

The following stents were each used in 10% or more of the 764 patients in whom stents were inserted: Carotid WALLSTENT® (Boston Scientific), Precision (Cordis®, Freemont, CA, USA), and Protege™ (EV3®, Dublin, Ireland). The following were each used in < 10% of patients: Acculink (Guidant™, Santa Clara, CA, USA), XACT® (Abbott™, Santa Clara, CA, USA), S.M.A.R.T.® (Cordis®, Miami Lakes, FL, USA), Cristallo Ideale (Invatec, Roncadelle, Brescia, Italy), Exponent (Medtronic®, Minneapolis, MN, USA), Next Stent (Boston Scientific). Protection devices were known to have been used in 593 (72%) of 828 patients. The following protection devices were each used in 10% or more of the patients in whom stenting was attempted: FilterWire EZ™ (Boston Scientific), ANGIOGUARD® (Cordis), SpiderFX™ (EV3) and Emboshield® (Abbott). A range of other protection devices were used in < 5% of patients. In 27 patients, it was not clear whether or not a protection device was used.

Short-term outcomes

In the ITT analysis, between randomisation and 120 days, there was no significant difference in the rate of disabling stroke or death between groups (stenting group, 4.0% vs. endarterectomy group, 3.2%; *Table 4*). The risk of stroke, death or procedural MI 120 days after randomisation was significantly higher in patients in the stenting group than in patients in the endarterectomy group (8.5% vs. 5.1%), representing an estimated 120-day absolute risk difference of 3.3% (95% CI 0.9% to 5.7%) with a HR in favour of surgery of 1.69 (1.16 to 2.45, log-rank p-value = 0.006) (*Figure 3* and *Table 4*).

Most outcome events, within 120 days of randomisation in the stent and endarterectomy groups occurred within 30 days of the first ipsilateral procedure (61 of 72 events vs. 31 of 44 events). A few events occurred after randomisation but before the date of treatment (two patients vs. one patient) in patients who had no attempted ipsilateral procedure (three patients vs. six patients), or more than 30 days after treatment but within 120 days of randomisation (six patients vs. six patients). Compared with

TABLE 4 Intention-to-treat analyses: outcome measures within 120 days of randomisation

Outcome measures	CAS N = 853, n (%)	CEA N = 857, n (%)	HR (95% CI)	RD (95% CI)	p-value[a]
Main outcome					
Stroke, death or procedural MI	72 (8.5)	44 (5.2)	1.69 (1.16 to 2.54)	3.3 (0.9 to 5.7)	0.006
Secondary outcomes					
Any stroke	65 (7.7)	35 (4.1)	1.92 (1.27 to 2.89)	3.5 (1.3 to 5.8)	0.002
Any stroke or death	72 (8.5)	40 (4.7)	1.86 (1.26 to 2.74)	3.8 (1.4 to 6.1)	0.001
Any stroke or procedural death	68 (8.0)	36 (4.2)	1.95 (1.30 to 2.92)	3.8 (1.5 to 6.0)	0.001
Disabling stroke or death	34 (4.0)	27 (3.2)	1.28 (0.77 to 2.11)	0.8 (–0.9 to 2.6)	0.34
All-cause death	19 (2.3)	7 (0.8)	2.76 (1.16 to 6.56)	1.4 (0.3 to 2.6)	0.017

RD, risk difference.
a Log-rank test.
Data are number of first events (Kaplan–Meier estimate at 120 days), HRs or risk differences (95% CI). Risk differences are calculated from Kaplan–Meier estimates at 120 days.

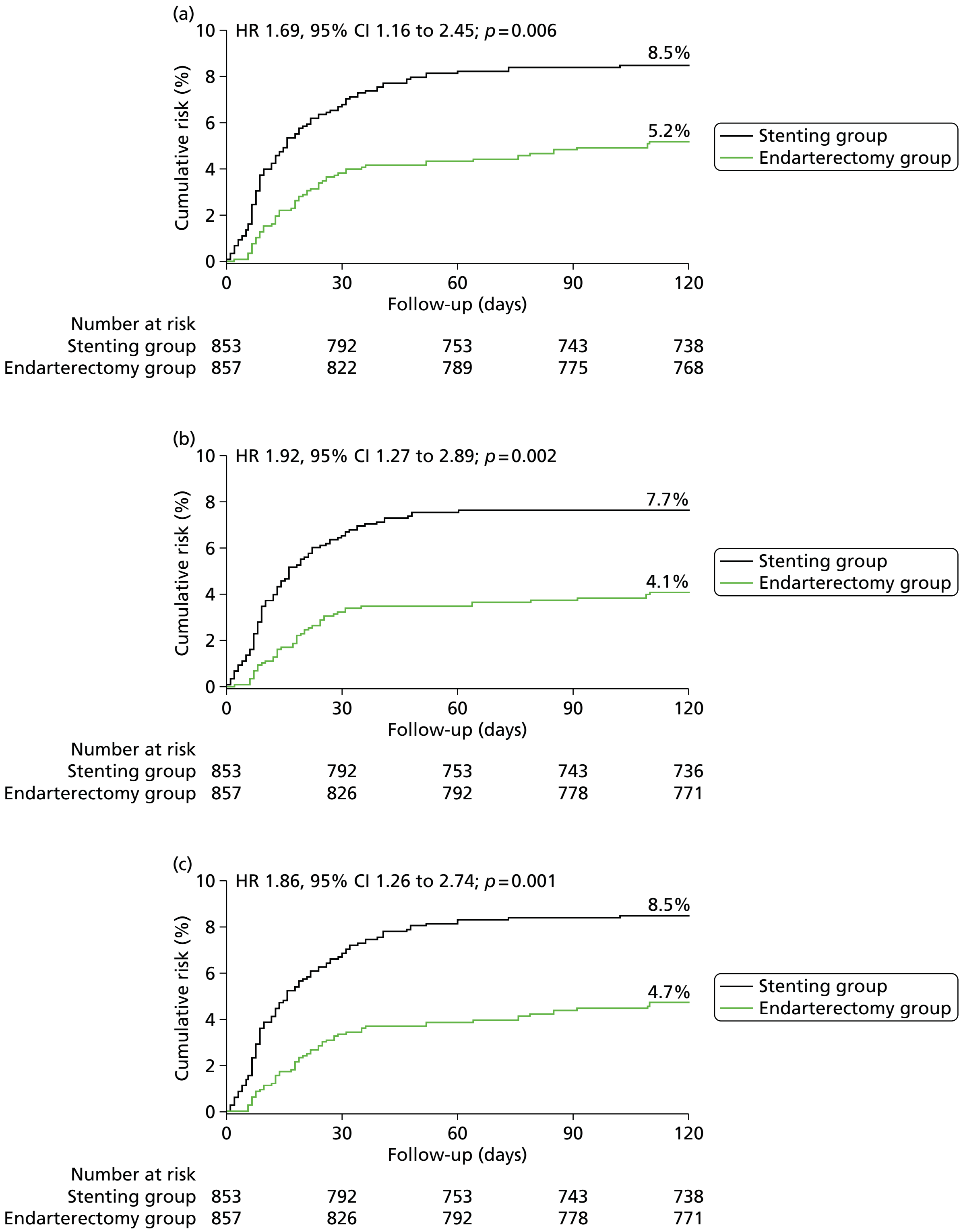
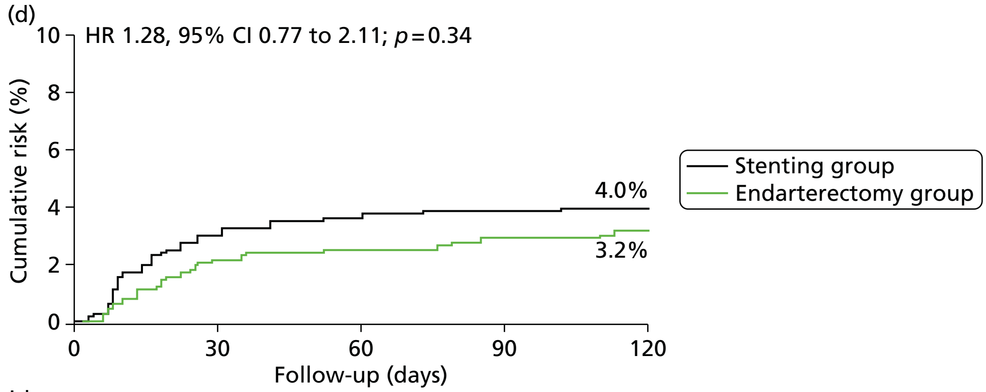
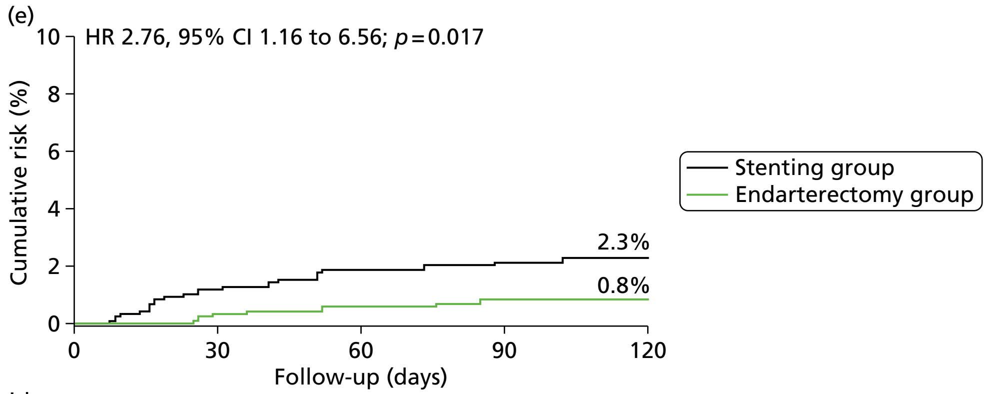


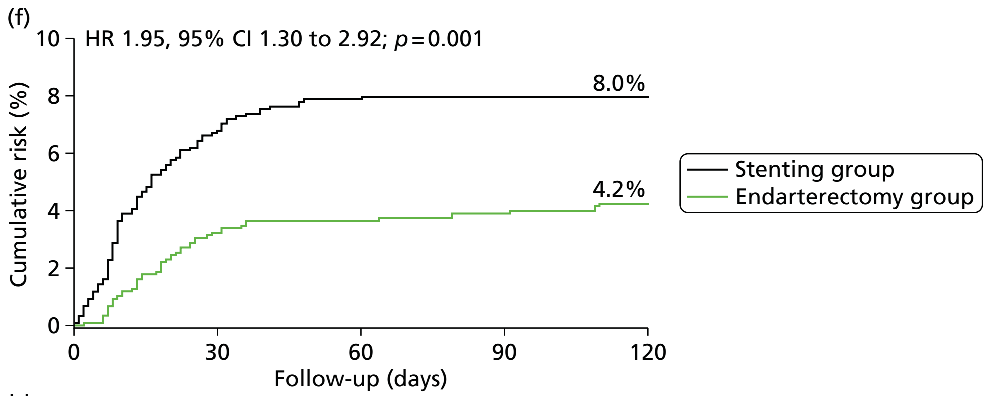
FIGURE 3 Kaplan–Meier estimates of cumulative incidence of main short-term outcome measures. Data are analysed by ITT. The numbers above the end of the lines are the incidence estimates at 120 days after randomisation. (a) Stroke, death or procedural MI (primary outcome measure); (b) any stroke; (c) stroke or death; (d) disabling stroke or death; (e) all-cause death and (f) any stroke or procedural death. (*continued*)



Number at risk					
Stenting group	853	823	790	780	775
Endarterectomy group	857	836	803	790	784



Number at risk					
Stenting group	853	837	803	793	788
Endarterectomy group	857	851	818	806	802



Number at risk					
Stenting group	853	792	753	743	738
Endarterectomy group	857	826	792	778	771

FIGURE 3 Kaplan–Meier estimates of cumulative incidence of main short-term outcome measures. Data are analysed by ITT. The numbers above the end of the lines are the incidence estimates at 120 days after randomisation. (a) Stroke, death or procedural MI (primary outcome measure); (b) any stroke; (c) stroke or death; (d) disabling stroke or death; (e) all-cause death and (f) any stroke or procedural death.

endarterectomy, allocation to stenting had a greater 120-day risk of the outcome measures of any stroke, any stroke or death, any stroke or procedural death, and all-cause death (*Table 4*).

Most strokes within 120 days of randomisation were ipsilateral to the treated carotid artery and most were ischaemic (*Table 5*). There were very few haemorrhagic strokes, with only two patients in whom the cause of the stroke was uncertain.

The observed treatment effect was largely driven by the higher number of non-disabling strokes in the stenting group, most of which had symptoms lasting for more than 7 days. There was an excess of fatal strokes in the stenting group compared with the surgery group, but little difference in the number of patients with disabling stroke within 120 days of randomisation.

TABLE 5 Number of outcome events recorded between randomisation and 120 days in the ITT analysis, and between initiation of treatment and 30 days after treatment in the per-protocol analysis

	ITT analysis: events up to 120 days after randomisation, *n* (%)		Per-protocol analysis: events between 0 days and 30 days after treatment, *n* (%)	
Outcome events	Stenting, (*N* = 853)	Endarterectomy, (*N* = 857)	Stenting, (*N* = 828)	Endarterectomy, (*N* = 821)
Any stroke	65 (7.6)[a]	35 (4.1)	58 (7.0)[a]	27 (3.3)
Ipsilateral stroke	58 (6.8)	30 (3.5)	52 (6.3)	25 (3.0)
Ischaemic stroke	63 (7.4)	28 (3.3)	56 (6.8)	21 (2.6)
Haemorrhagic stroke	3 (0.4)	5 (0.6)	2 (0.2)	5 (0.6)
Uncertain pathology	0	2 (0.2)	0	1 (0.1)
Non-disabling stroke	39 (4.6)	14 (1.6)	36 (4.6)	11 (1.3)
Lasting < 7 days	9 (1.1)	5 (0.6)	8 (1.0)	5 (0.6)
Lasting > 7 days	31 (3.6)[b]	9 (1.1)[c]	29 (3.5)[b]	6 (0.7)[c]
Disabling stroke	17 (2.0)[d]	20 (2.3)	14 (1.7)	14 (1.7)
Fatal stroke	9 (1.1)	2 (0.2)	8 (1.0)	3 (0.4)
Procedural MI	3 (0.4)	4 (0.5)	3 (0.4)	5 (0.6)
Non-fatal MI	0	4 (0.5)	0	5 (0.6)[e]
Fatal MI	3 (0.4)	0	3 (0.4)	0
Non-stroke, non-MI death	7 (0.8)	5 (0.6)	1 (1.0)	1 (0.1)
Cranial nerve palsy	1 (0.1)[f]	45 (5.5)	1 (1.0)[f]	45 (5.5)
Disabling cranial nerve palsy	1 (0.1)[f]	1 (0.1)	1 (1.0)[f]	1 (0.1)
Haematoma	31 (3.6)	50 (5.8)	30 (3.6)	50 (6.0)
Severe haematoma[g]	9 (1.1)	28 (3.3)	8 (1.0)	28 (3.4)

a In two patients this was retinal infarction.
b One patient had a subsequent fatal MI and one patient also had a non-disabling stroke that lasted for more than 7 days.
c One patient had a subsequent disabling stroke.
d Two patients subsequently died of non-stroke, non-MI cause.
e One patient had a non-fatal MI within 30 days of their first procedure, which was performed > 120 days after randomisation. This MI was therefore excluded from the ITT analysis (which stopped at 120 days) but was included in the per-protocol 30-day analysis which included all first ipsilateral allocated procedures.
f The cranial nerve palsy in this patient allocated CAS, which was initiated but aborted, occurred after CEA carried out within 30 days of the stent procedure.
g Severe haematoma was defined as one that required surgical evacuation or blood transfusion, or resulted in prolonged hospital stay.

The per-protocol analysis included 1649 patients (stenting group, $n = 828$; endarterectomy group, $n = 821$). Results for 30-day procedural risk mirrored the results of the ITT analysis. Risk of stroke, death or procedural MI was higher in the stenting group than in the endarterectomy group (30-day risk 7.4% vs. 4.0%) [risk difference (RD) 3.3%, 95% CI 1.1% to 5.6%; risk ratio (RR) 1.83, 95% CI 1.21 to 2.77; χ^2 $p = 0.003$] (*Table 6*). Risk of any stroke or death up to 30 days after treatment remained significantly higher in patients in whom stenting was initiated than in patients with surgery initiated, but there was no significant difference in the risk of disabling stroke or death between treatment groups. There were more fatal strokes in the stenting group than in the endarterectomy group (eight vs. three), but difference in the risk of death alone was no longer significant (see *Table 5*). Forty-three (74%) of 58 strokes in the stenting group and 12 (44%) of 27 strokes in the endarterectomy group occurred on the day of the procedure. There was no difference in the numbers of strokes occurring between day 2 and day 30 between the two treatments (15 vs. 15).

Few procedural MIs were recorded (three in the stenting group, all of which were fatal, compared with five in the endarterectomy group). Cranial nerve palsies were almost completely avoided by stenting (RR 0.02, 95% CI 0.00 to 0.16; $p < 0.0001$) (see *Table 5*). The one cranial nerve palsy recorded in the stenting group occurred as a complication of an endarterectomy performed within 30 days of stenting. This patient and one additional patient in the endarterectomy group required percutaneous endoscopic gastrostomy feeding as a result of the cranial nerve palsies, which was classified as disabling. There were also fewer haematomas of any severity in the stenting group than in the endarterectomy group (RR 0.59, 95% CI 0.38 to 0.93; $p = 0.0197$), and fewer severe haematomas requiring surgical intervention, blood transfusion or extended hospital stay (RR 0.28, 95% CI 0.13 to 0.62; $p = 0.0007$) (see *Table 5*). A post-hoc sensitivity analysis was undertaken to examine if the results of the per-protocol analysis were affected by inclusion of patients in whom the allocated procedure was initiated but not completed. Exclusion of the 64 patients allocated to stenting and two patients allocated to endarterectomy in whom the procedures were aborted after initiation (i.e. including only patients in whom the allocated procedure was completed as planned) made little difference to the results (30-day risk of stroke, death or procedural MI of 7.6% in the stenting group vs. 4.0% in the endarterectomy group) (RD 3.6%, 95% CI 1.3% to 5.9%; RR 1.88, 95% CI 1.24 to 2.86; $p = 0.002$).

TABLE 6 Per-protocol analysis of procedural risk: outcome measures between initiation of treatment and 30 days after treatment

Outcome measures	CAS $N = 828$, n (%)	CEA $N = 821$, n (%)	RR (95% CI)	RD (95% CI)	p-value[a]
Main outcome					
Stroke, death or MI	61 (7.4)	33 (4.0)	1.83 (1.21 to 2.77)	3.3 (1.1 to 5.6)	0.003
Secondary outcomes					
Any stroke	58 (7.0)	27 (3.3)	2.13 (1.36 to 3.33)	3.7 (1.6 to 5.8)	0.001
Any stroke or death	61 (7.4)	28 (3.4)	2.16 (1.40 to 3.34)	4.0 (1.8 to 6.1)	0.0004
Disabling stroke or death	26 (3.1)	18 (2.2)	1.43 (0.79 to 2.59)	0.9 (–0.6 to 2.5)	0.23
Procedural death	11[b] (1.3)	4 (0.5)	2.73 (0.87 to 8.53)	0.8 (–0.1 to 1.8)	0.072

a Chi-squared test.
b One patient had a fatal stroke but died more than 30 days after the procedure. The event is therefore counted in the fatal stroke outcome but not the procedural death outcome.

We undertook exploratory analyses of the composite outcome of stroke, death or procedural MI for pre-defined subgroups (*Figure 4*). These analyses suggested that carotid stenting might have a similar risk to endarterectomy in women, but that the intervention was more hazardous than endarterectomy in men. The difference was mainly caused by a higher risk of stroke, death or procedural MI in women assigned to endarterectomy than in men (7.6% vs. 4.2%). However, the difference between the HRs comparing the risk of stenting with endarterectomy in men and women only reached borderline significance (interaction $p = 0.071$). Stenting was more hazardous, and endarterectomy less hazardous, in patients not taking medication for hypertension at baseline than in patients taking medication for hypertension (see *Figure 4*). There was also a suggestion that patients who presented with multiple ipsilateral symptoms had a similar risk of stroke death, or procedural MI with stenting and endarterectomy. However, when compared with patients with only one event before randomisation, the difference in the HRs only reached borderline significance (interaction $p = 0.055$). There was no evidence that the relative increase in the hazard of an event in the stenting group compared with the endarterectomy group differed significantly across any other subgroups.

Subgroup	Stenting: Number of events/number of patients (%)[a]	Endarterectomy: Number of events/number of patients (%)[a]	HR (95% CI)	Interaction *p*-value
Age (years)				
<70	21/394 (54)	15/404 (3.7)	1.46 (0.75 to 2.84)	0.62
≥70	51/459 (11.2)	29/453 (6.5)	1.79 (1.14 to 2.83)	
Sex				
Male	52/601 (8.7)	25/606 (4.2)	2.17 (1.35 to 3.50)	0.071
Female	20/252 (8.0)	19/251 (7.6)	1.05 (0.56 to 1.97)	
Diabetes[b]				
No	51/659 (7.8)	32/663 (4.9)	1.64 (1.05 to 2.55)	0.97
Yes	19/184 (10.4)	12/187 (6.5)	1.67 (0.81 to 3.43)	
Treated hypertension[b]				
No	25/256 (9.8)	8/255 (3.2)	3.25 (1.46 to 7.20)	0.039
Yes	45/587 (7.7)	36/595 (6.1)	1.29 (0.83 to 2.00)	
Ipsilateral stenosis				
50–69%	4/92 (4.4)	3/76 (4.0)	1.13 (0.25 to 5.04)	0.584
70–99%	68/761 (9.0)	41/781 (5.3)	1.75 (1.19 to 2.58)	
Contralateral stenosis				
0–49%	45/565 (8.0)	27/561 (4.8)	1.70 (1.05 to 2.73)	0.741
50–69%	14/128 (11.0)	8/142 (5.7)	2.04 (0.85 to 4.85)	
70–99%	9/105 (8.7)	7/110 (6.4)	1.37 (0.51 to 3.68)	
Occluded	2/49 (4.3)	1/37 (2.7)	1.51 (0.14 to 16.61)	
Type of most recent event				
Stroke	45/419 (10.8)	21/399 (5.3)	2.12 (1.26 to 3.55)	0.157
TIA	24/273 (8.8)	16/303 (5.3)	1.71 (0.91 to 3.22)	
Amaurosis fugax	3/148 (2.0)	5/142 (3.5)	0.57 (0.14 to 2.40)	
Multiple ipsilateral symptoms				
No	52/523 (10.0)	25/540 (4.7)	2.22 (1.38 to 3.58)	0.055
Yes	20/330 (6.1)	19/317 (6.0)	1.03 (0.55 to 1.92)	
Centre experience				
Experienced	65/751 (8.7)	38/760 (5.0)	1.78 (1.19 to 2.65)	0.444
Supervised	7/102 (6.9)	6/97 (6.6)	1.13 (0.38 to 3.35)	
Centre recruitment				
<50 patients	33/302 (11.0)	14/307 (4.6)	2.51 (1.35 to 4.70)	0.102
≥50 patients	39/551 (7.1)	30/550 (5.5)	1.32 (0.82 to 2.12)	
Time from event to treatment[c]				
≤14 days	15/205 (7.3)	5/151 (3.3)	2.21 (0.82 to 5.95)	0.68
>14 days	46/623 (7.4)	28/668 (4.2)	1.76 (1.12 to 2.78)	

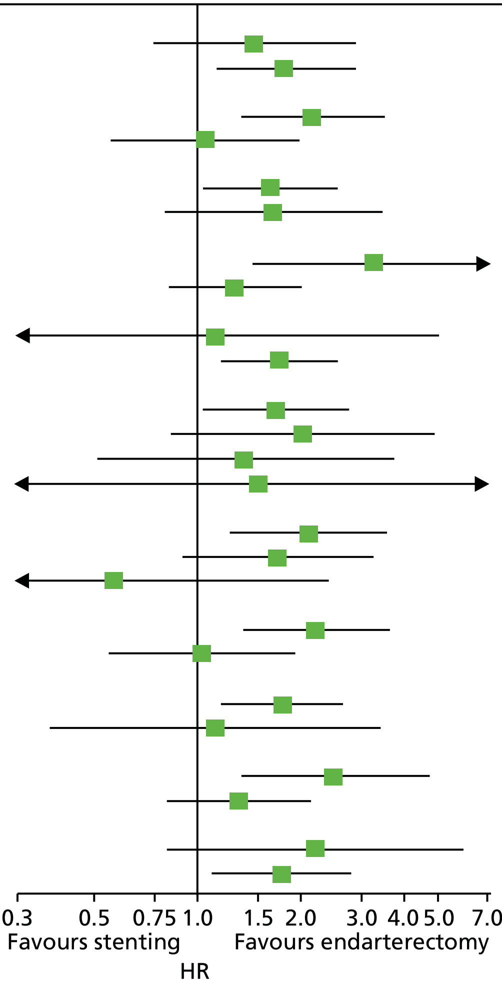


FIGURE 4 Comparison of the short-term rate of stroke, death, or procedural myocardial infarction. Subgroups are defined according to baseline characteristics and analysed by intention to treat up to 120 days after randomisation, apart from time from event to treatment, which is analysed per protocol. *p*-values are associated with treatment-covariate interaction tests. a, Data are number of events of first stroke, death or procedural myocardial infarction within 120 days of randomisation/number of patients (Kaplan–Meier estimate at 120 days). b, Patients with missing information were excluded from the analysis. c, Time from the most recent ipsilateral event before randomisation to the date of treatment, analysed per protocol for 30-day procedural events only (results are relative risk and 95% CI at 30 days after treatment).

Duration of follow-up in the International Carotid Stenting Study

Figure 5 shows the number of patients remaining in follow-up in ICSS plotted against time from randomisation. Patients were followed up for a maximum of 10 years after randomisation with a median of 4.2 years and an interquartile range of 3.0–5.2 years. This amounted to 7355 patient-years of follow-up, without any difference between the two arms.

Long-term primary and secondary outcomes

In the ITT analysis, the primary outcome event, fatal or disabling stroke between randomisation and the end of follow-up, occurred in 52 patients in the stenting group, corresponding to a cumulative 5-year risk of 6.4%, and in 49 patients in the endarterectomy group (5-year risk *n*, 6.5%), without any evidence for a difference in time to first occurrence of an event (HR 1.06, 95% CI 0.72 to 1.57; $p = 0.76$) (*Table 7* and *Figure 6*).

The following secondary outcome events occurred significantly more often in the stenting group in the ITT analysis between randomisation and the end of follow-up: any stroke (5-year risks 15.2% vs. 9.4%) (HR 1.71, 95% CI 1.28 to 2.30; $p = 0.0003$); any stroke or death (27.5% vs. 22.6%) (HR 1.34, 95% CI 1.11 to 1.63; $p = 0.003$); the combination of any procedural stroke, procedural death or ipsilateral stroke during follow-up (11.8% vs. 7.2%) (HR 1.72, 95% CI 1.24 to 2.39; $p = 0.001$). There was no difference in all-cause mortality between treatment groups (17.4% vs. 17.2%) (HR 1.17, 95% CI 0.92 to 1.48; $p = 0.19$).

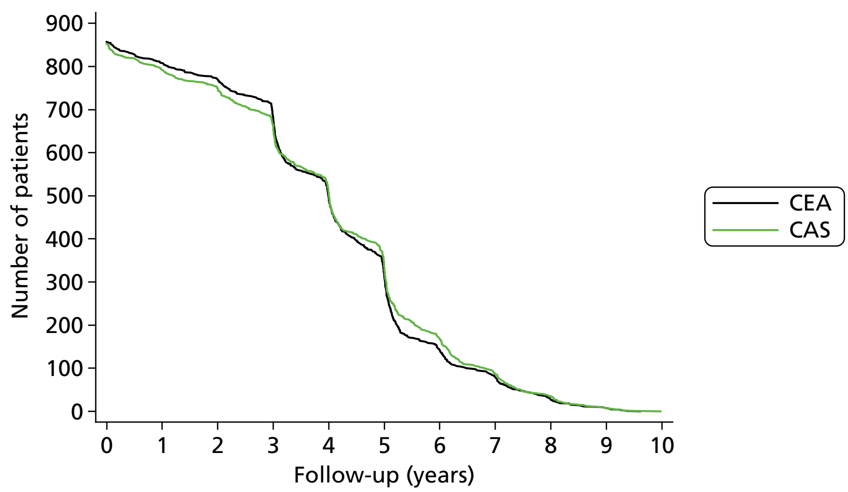


FIGURE 5 Patients remaining in each arm of the study (per protocol) are plotted against year of follow-up. In total, there are 7354.45 patient-years of follow-up until time of last follow-up or death. CAS ($n = 853$): median follow-up = 4.2 years, interquartile range (IQR) 3.0–5.4 years (maximum = 10.0 years, 153 deaths); CEA ($n = 857$): median follow-up = 4.2 years, IQR 3.0–5.2 years (maximum = 9.6 years, 129 deaths).

TABLE 7 Intention-to-treat analysis of cumulative risks and HRs of main outcome events during the entire study period

	Stenting ($n = 853$)			Endarterectomy ($n = 857$)				Absolute risk difference, % (95% CI)	
Outcome events	*n* events[a]	Cumulative 1-year risk, % (SE)	Cumulative 5-year risk, % (SE)	*n* events[a]	Cumulative 1-year risk, % (SE)	Cumulative 5-year risk, % (SE)	HR[a] (95% CI); *p*-value	At 1 year	At 5 years
Fatal or disabling stroke (primary outcome measure)	52	3.9 (0.7)	6.4 (0.9)	49	3.2 (0.6)	6.5 (1.0)	1.06 (0.72 to 1.57); 0.77	0.7 (–1.0 to 2.5)	–0.2 (–2.8 to 2.5)
Any stroke	119	9.5 (1.0)	15.2 (1.4)	72	5.1 (0.8)	9.4 (1.1)	1.71 (1.28 to 2.30); 0.0003	4.4 (1.9 to 6.9)	5.8 (2.4 to 9.3)
Procedural stroke or death, or ipsilateral stroke during follow-up	95	9.0 (1.0)	11.8 (1.2)	57	4.7 (0.7)	7.2 (0.9)	1.72 (1.24 to 2.39); 0.001	4.2 (1.9 to 6.6)	4.6 (1.6 to 7.6)
All-cause death	153	4.9 (0.7)	17.4 (1.5)	129	2.3 (0.5)	17.2 (1.5)	1.17 (0.92 to 1.48); 0.19	2.6 (0.8 to 4.4)	0.2 (–4.0 to 4.4)

SE, standard error.
p-value: calculated by log-rank test.
a The number of events and the HRs are calculated using the first occurrence of the relevant outcome event from randomisation until the end of follow-up.

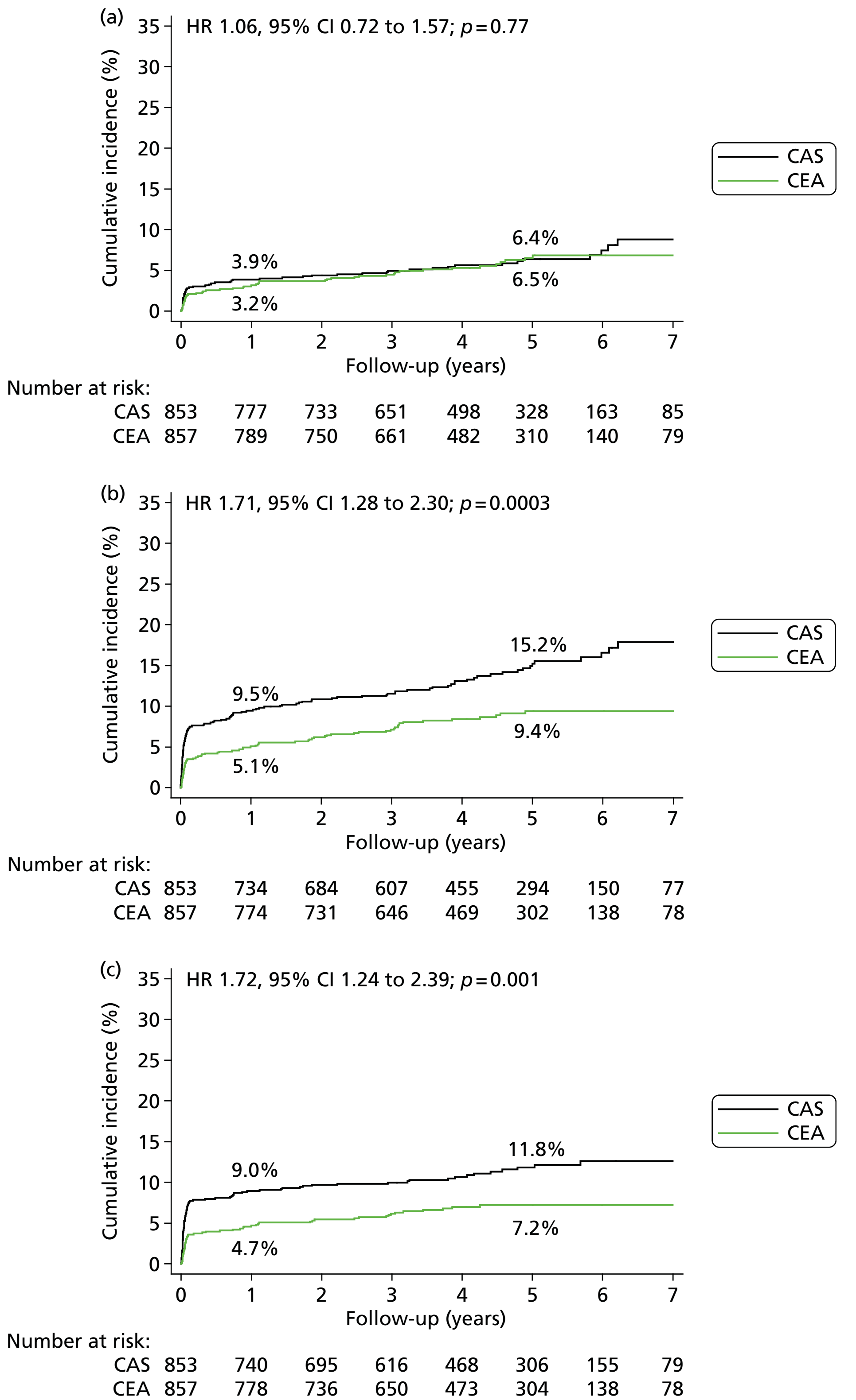


FIGURE 6 Kaplan–Meier estimates of cumulative incidence of major long-term outcome measures. (a) Fatal or disabling stroke; (b) any stroke; (c) procedural stroke or death, or ipsilateral stroke during follow up; (d) any stroke > 30 days after treatment; (e) ipsilateral stroke > 30 days after treatment; (f) contralateral carotid or vertebrobasilar stroke > 30 days after treatment; (g) ipsilateral carotid stenosis (≥ 70%) or occlusion during follow-up; and (h) all-cause death. Data were analysed by ITT from randomisation except for parts (d) to (f), which are analysed in the per-protocol population from 30 days post procedure, and part (g) which is analysed in the per-protocol population from treatment. The numbers on the lines are the estimated 1-year and 5-year cumulative incidences. The graphs have only been plotted to 7 years' follow-up because the numbers with longer follow-up were < 100. However, the HRs were calculated using all relevant outcome events until the end of follow-up (maximum 10 years). (*continued*)

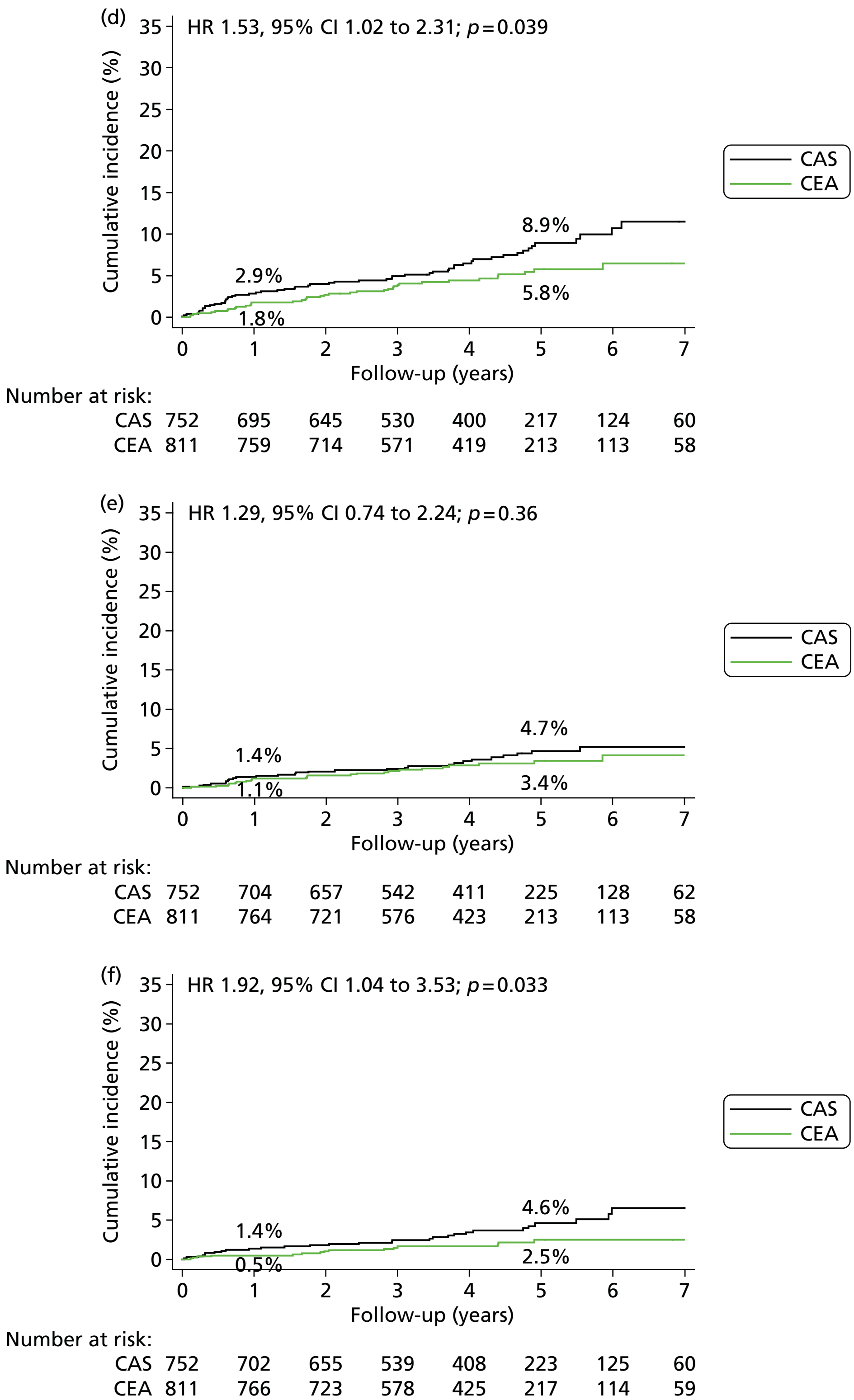
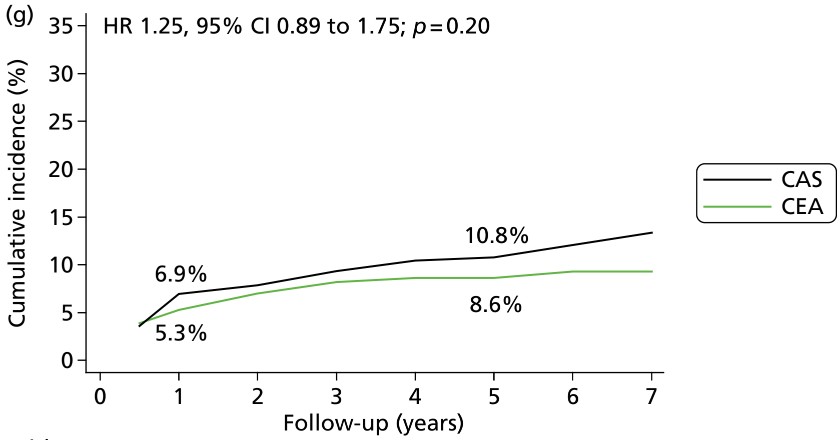
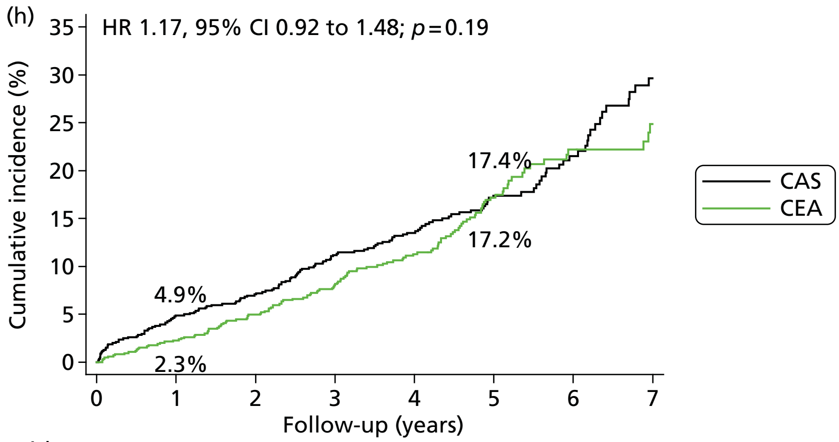


FIGURE 6 Kaplan–Meier estimates of cumulative incidence of major long-term outcome measures. (a) Fatal or disabling stroke; (b) any stroke; (c) procedural stroke or death, or ipsilateral stroke during follow up; (d) any stroke > 30 days after treatment; (e) ipsilateral stroke > 30 days after treatment; (f) contralateral carotid or vertebrobasilar stroke > 30 days after treatment; (g) ipsilateral carotid stenosis (≥ 70%) or occlusion during follow-up; and (h) all-cause death. Data were analysed by ITT from randomisation except for parts (d) to (f), which are analysed in the per-protocol population from 30 days post procedure, and part (g) which is analysed in the per-protocol population from treatment. The numbers on the lines are the estimated 1-year and 5-year cumulative incidences. The graphs have only been plotted to 7 years' follow-up because the numbers with longer follow-up were < 100. However, the HRs were calculated using all relevant outcome events until the end of follow-up (maximum 10 years). (*continued*)



Number at risk:

CAS	737	638	547	455	347	190	91	44
CEA	793	681	611	483	330	187	89	45



Number at risk:

CAS	853	792	749	663	510	337	168	86
CEA	857	809	770	682	498	319	142	80

FIGURE 6 Kaplan–Meier estimates of cumulative incidence of major long-term outcome measures. (a) Fatal or disabling stroke; (b) any stroke; (c) procedural stroke or death, or ipsilateral stroke during follow up; (d) any stroke > 30 days after treatment; (e) ipsilateral stroke > 30 days after treatment; (f) contralateral carotid or vertebrobasilar stroke > 30 days after treatment; (g) ipsilateral carotid stenosis (≥ 70%) or occlusion during follow-up; and (h) all-cause death. Data were analysed by ITT from randomisation except for parts (d) to (f), which are analysed in the per-protocol population from 30 days post procedure, and part (g) which is analysed in the per-protocol population from treatment. The numbers on the lines are the estimated 1-year and 5-year cumulative incidences. The graphs have only been plotted to 7 years' follow-up because the numbers with longer follow-up were < 100. However, the HRs were calculated using all relevant outcome events until the end of follow-up (maximum 10 years).

A total of 752 patients in the stenting group (88.2% of the ITT population) and 811 patients in the endarterectomy group (94.6%) were included in the per-protocol analysis of clinical outcome events. In the per-protocol analysis of events occurring more than 30 days after completed treatment up to the end of follow-up, there was no significant difference in the long-term risks of fatal and disabling stroke after stenting compared with endarterectomy (5-year risk 3.4% vs. 4.3%) (HR 0.93, 95% CI 0.53 to 1.60; $p = 0.78$) (*Table 8*). There was also no significant difference in the rates of ipsilateral stroke in the territory of the treated carotid artery (4.7% vs. 3.4%) (HR 1.29, 95% CI 0.74 to 2.24; $p = 0.36$). However, stroke of any severity occurred more often after stenting (8.9% vs. 5.8%) (HR 1.53, 95% CI 1.02 to 2.31; $p = 0.039$) (*Figure 6* and *Table 8*). This difference was largely attributable to stroke occurring in the territory of the contralateral carotid artery or the vertebrobasilar circulation among patients treated with stents (5-year risks 4.6% vs. 2.5%) (HR 1.92, 95% CI 1.04 to 3.53; $p = 0.033$) and the majority were non-disabling.

A total of 737 (98.0%) patients in the stenting group and 793 (97.8%) in the endarterectomy group were followed up with carotid ultrasound for a median of 4.0 years (interquartile range, 2.3–5.0 years) after treatment. There was no significant difference in long-term rates of severe carotid restenosis ($\geq 70\%$) or occlusion, which occurred in 72 patients in the stenting group (5-year risk 10.8%) and in 62 patients in the endarterectomy group (5-year risk 8.6%) (HR 1.25, 95% CI 0.89 to 1.75; $p = 0.20$; see *Table 8* and *Figure 6*).

Exploratory subgroup analyses showed no significant modification of the HR of the primary outcome event (*Figure 7*), nor of the combined outcome of procedural death or stroke, or non-procedural ipsilateral stroke by any of the evaluated variables (*Figure 8*).

TABLE 8 Per-protocol analysis of cumulative risks and HRs of major non-procedural outcome events occurring > 30 days after treatment

Outcome events	Stenting ($n=752$)			Endarterectomy ($n=811$)				Absolute risk difference, % (95% CI)	
	n events[a]	Cumulative 1-year risk, % (SE)[a]	Cumulative 5-year risk, % (SE)[a]	*n* events	Cumulative 1-year risk, % (SE)[a]	Cumulative 5-year risk, % (SE)[a]	HR[b] (95% CI); *p*-value	At 1 year	At 5 years
Fatal or disabling stroke	24	0.9 (0.4)	3.4 (0.8)	27	1.4 (0.4)	4.3 (0.9)[a]	0.93 (0.53 to 1.60); 0.78	–0.5 (–1.5 to 0.6)	–0.9 (–3.2 to 1.4)
Any stroke	56	2.9 (0.6)	8.9 (1.2)	39	1.8 (0.5)	5.8 (1.0)	1.53 (1.02 to 2.31); 0.039	1.1 (–0.4 to 2.6)	3.1 (0.0 to 6.2)
Ipsilateral carotid stroke	28	1.4 (0.4)	4.7 (0.9)	23	1.1 (0.4)	3.4 (0.8)	1.29 (0.74 to 2.24); 0.36	0.2 (–0.9 to 1.3)	1.2 (–1.1 to 3.6)
Contralateral carotid or vertebrobasilar stroke	29	1.4 (0.4)	4.6 (0.9)	16	0.5 (0.3)	2.5 (0.7)	1.92 (1.04 to 3.53); 0.033	0.9 (–0.1 to 1.8)	2.1 (–0.2 to 4.3)
Severe carotid restenosis (≥ 70%) or occlusion	72/737	6.9 (1.0)	10.8 (1.3)	62/793	5.3 (0.8)	8.6 (1.1)	1.25 (0.89 to 1.75); 0.20	1.7 (–0.8 to 4.1)	2.2 (–1.1 to 5.4)

SE, standard error.
a Cumulative risks are 1 year and 5 years after the procedural period for the first four outcomes and 1 year and 5 years after treatment for the last outcome.
b HR calculated using all outcome events from > 30 days after completed treatment for the first four outcomes and from completed treatment for the last outcome, until the end of follow-up. *p*-value calculated by log-rank test.

Subgroup	CAS: Number of events/number of patients (%)[a]	CEA: Number of events/number of patients (%)[a]	HR (95% CI)	Interaction *p*-value
Age				
<70 years	20/395 (4.9)	16/404 (4.5)	1.26 (0.65 to 2.43)	0.520
≥70 years	32/458 (7.7)	33/453 (8.4)	0.96 (0.59 to 1.56)	
Sex				
Male	33/601 (5.6)	29/606 (5.3)	1.15 (0.70 to 1.90)	0.584
Female	19/252 (8.2)	20/251 (9.4)	0.92 (0.49 to 1.73)	
Treated hypertension				
No	16/256 (6.0)	12/255 (5.1)	1.39 (0.65 to 2.95)	0.340
Yes	34/587 (6.4)	37/596 (7.2)	0.90 (0.57 to 1.44)	
Treated hyperlipidaemia				
No	21/321 (6.7)	17/288 (6.8)	1.07 (0.57 to 2.04)	0.821
Yes	29/522 (5.9)	32/563 (6.5)	0.98 (0.59 to 1.62)	
Diabetes				
No	36/669 (5.6)	40/669 (6.8)	0.91 (0.58 to 1.42)	0.175
Yes	16/184 (9.4)	9/188 (5.2)	1.72 (0.76 to 3.91)	
Ipsilateral stenosis				
50–69%	4/92 (3.9)	7/76 (9.6)	0.47 (0.14 to 1.59)	0.155
70–99%	48/761 (6.7)	42/781 (6.2)	1.17 (0.77 to 1.77)	
Contralateral stenosis				
0–49%	31/565 (5.7)	33/561 (7.1)	0.92 (0.56 to 1.50)	0.835
50–69%	10/128 (9.2)	6/142 (3.7)	2.09 (0.75 to 5.80)	
70–99%	7/105 (6.2)	7/110 (7.0)	0.96 (0.33 to 2.78)	
Occluded	2/49 (4.1)	2/37 (6.2)	0.73 (0.10 to 5.18)	
Type of most recent event				
Stroke	32/419 (8.7)	22/399 (6.5)	1.37 (0.80 to 2.36)	0.217
TIA	17/273 (5.6)	21/303 (7.6)	0.96 (0.50 to 1.82)	
AFX	2/148 (1.6)	5/142 (3.6)	0.34 (0.07 to 1.76)	
Time from event to procedure[b]				
≤14 days	15/205 (7.7)	7/151 (6.6)	1.56 (0.63 to 3.82)	0.390
>14 days	34/623 (5.7)	36/668 (6.2)	1.00 (0.63 to 1.60)	

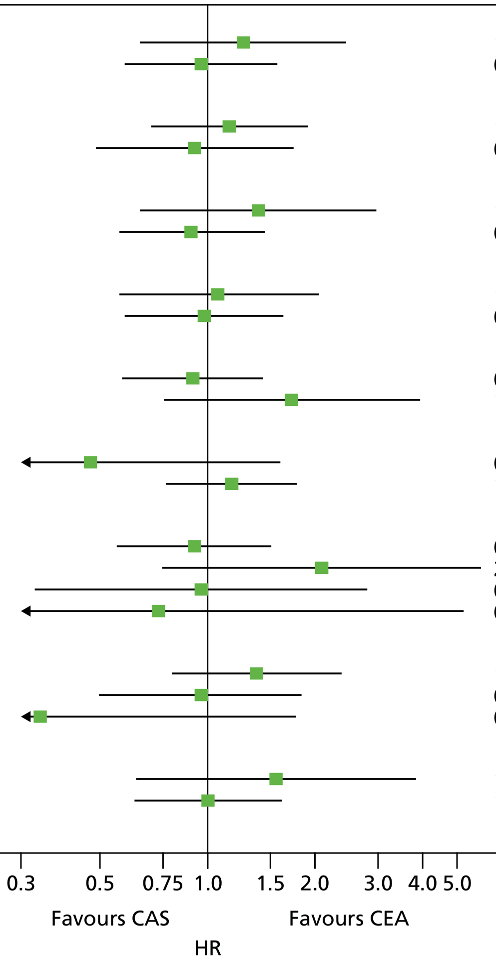


FIGURE 7 Hazard ratios of fatal or disabling stroke between randomisation and end of follow-up in various patient subgroups. Subgroups are defined according to baseline characteristics and analysed by ITT for all available follow-up, apart from time from event to procedure, which is analysed per protocol. *P*-values are associated with treatment–covariate interaction tests. a, Data are number of events of first fatal or disabling stroke/number of patients, and Kaplan–Meier estimate of cumulative risk at 5 years. Patients with missing information were excluded from the analysis. b, Time from most recent ipsilateral event before randomisation to the date of treatment, analysed per protocol from the time of procedure. All subgroups for analysis were pre-specified except for treated hyperlipidaemia which was added post hoc. AFX, amaurosis fugax.

Subgroup	CAS Number of events/ number of patients (%)[a]	CEA Number of events/ number of patients (%)[a]	HR (95% CI)	Interaction p-value
Age				
<70 years	35/395 (9.1)	22/404 (6.0)	1.65 (0.97 to 2.81)	0.836
≥70 years	60/458 (14.2)	35/453 (8.3)	1.77 (1.17 to 2.69)	
Sex				
Male	65/601 (11.3)	32/606 (5.9)	2.12 (1.39 to 3.23)	0.110
Female	30/252 (13.0)	25/251 (10.4)	1.22 (0.72 to 2.07)	
Treated hypertension				
No	28/256 (11.3)	12/255 (4.9)	2.43 (1.24 to 4.78)	0.213
Yes	65/587 (12.0)	45/596 (8.3)	1.50 (1.02 to 2.19)	
Treated hyperlipidaemia				
No	35/321 (11.7)	17/288 (6.7)	1.89 (1.06 to 3.38)	0.646
Yes	58/522 (11.7)	40/563 (7.6)	1.61 (1.07 to 2.40)	
Diabetes				
No	65/669 (10.1)	44/669 (7.1)	1.52 (1.04 to 2.23)	0.214
Yes	30/184 (18.3)	13/188 (7.7)	2.44 (1.27 to 4.67)	
Ipsilateral stenosis				
50–69%	5/92 (6.0)	6/76 (8.8)	0.70 (0.21 to 2.28)	0.118
70–99%	90/761 (12.5)	51/781 (7.1)	1.87 (1.33 to 2.63)	
Contralateral stenosis				
0–49%	62/565 (11.9)	35/561 (6.8)	1.80 (1.19 to 2.72)	0.371
50–69%	17/128 (14.0)	9/142 (6.5)	2.22 (0.99 to 4.97)	
70–99%	12/105 (11.1)	10/110 (10.1)	1.32 (0.57 to 3.04)	
Occluded	2/49 (4.1)	2/37 (6.2)	0.74 (0.10 to 5.23)	
Type of most recent event				
Stroke	59/419 (15.1)	29/399 (8.0)	2.01 (1.29 to 3.13)	0.618
TIA	28/273 (10.3)	22/303 (7.7)	1.48 (0.84 to 2.58)	
AFX	7/148 (5.7)	5/142 (3.7)	1.32 (0.42 to 4.15)	
Time from event to procedure[b]				
≤14 days	22/205 (12.0)	5/151 (3.8)	3.32 (1.26 to 8.77)	0.172
>14 days	67/623 (11.6)	44/668 (7.1)	1.66 (1.14 to 2.43)	

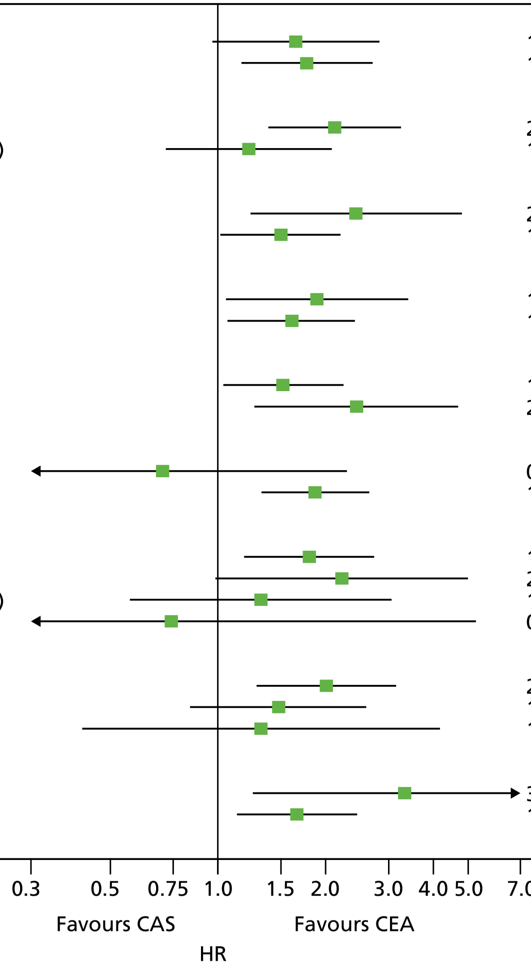


FIGURE 8 Hazard ratios of procedural stroke, death or ipsilateral stroke between randomisation and end of follow-up in various patient subgroups. Subgroups are defined according to baseline characteristics and analysed by ITT for all available follow-up, apart from time from event to procedure, which is analysed per protocol. *P*-values are associated with treatment–covariate interaction tests. a, Data are number of events of first ipsilateral stroke or procedural stroke or death/number of patients, and Kaplan–Meier estimate of cumulative risk at 5 years. Patients with missing information were excluded from the analysis. b, Time from most recent ipsilateral event before randomisation to the date of treatment, analysed per protocol from the time of procedure. AFX, amaurosis fugax.

Long-term functional outcome

There was no difference in distribution of functional disability as measured by the mRS scores at the end of follow-up, nor was there any significant difference 1 or 5 years after randomisation (*Figure 9*).

Findings of the magnetic resonance imaging substudy

The MRI substudy has been previously published in detail.[44] A total of 231 patients (124 in the stenting group and 107 in the endarterectomy group) had MRI before and after treatment. Sixty-two (50%) of 124 patients in the stenting group and 18 (17%) of 107 patients in the endarterectomy group had at least one new DWI lesion detected on post-treatment scans done a median of 1 day after treatment [adjusted odds ratio (OR) 5.21, 95% CI 2.78 to 9.79; $p < 0.0001$]. At 1 month, there were changes on fluid-attenuated inversion recovery sequences in 28 (33%) of 86 patients in the stenting group and

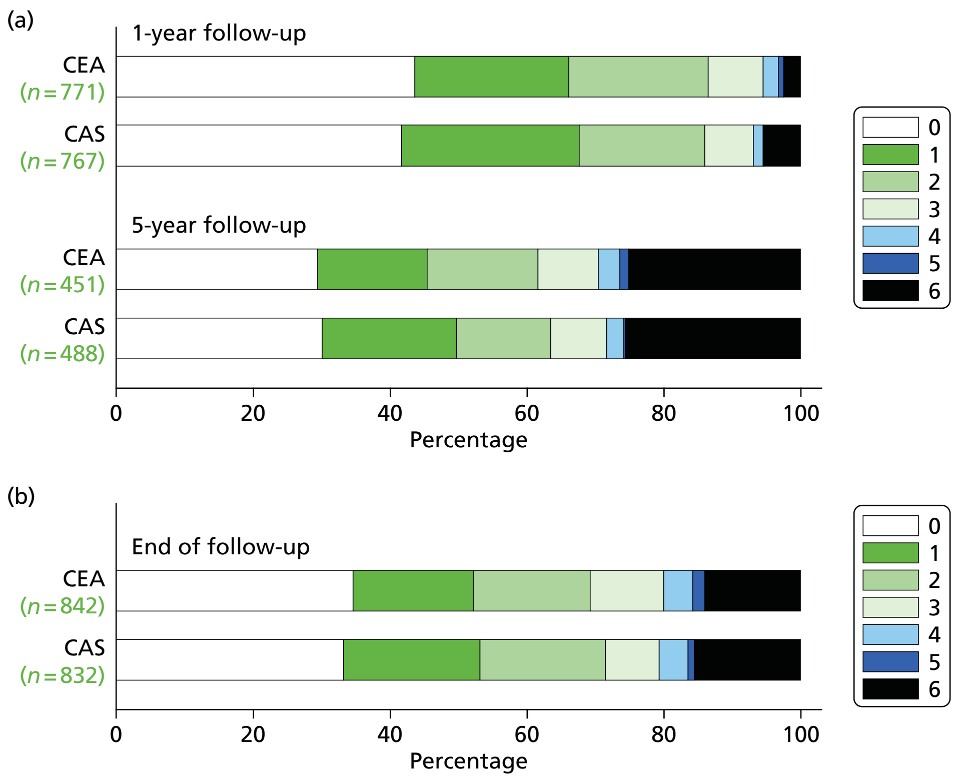


FIGURE 9 The distribution of scores on the mRS: (a) after 1-year and 5-year follow-up in patients allocated CAS or CEA using the Rankin scores in patients still surviving and in follow-up or who had died before at the indicated time points [permutation test comparing Rankin scores between the two groups at 1 year (unadjusted $p = 0.70$, adjusted for baseline mRS $p = 0.11$), at 5 years (unadjusted $p = 0.54$, adjusted for baseline mRS $p = 0.98$)[13]]; (b) at the last follow-up recorded for the patient, regardless of duration (unadjusted, $p = 0.49$; adjusted for baseline mRS score, $p = 0.24$).

six (8%) of 75 in the endarterectomy group (adjusted OR 5.93, 95% CI 2.25 to 15.62; $p = 0.0003$). In patients treated at a centre with a policy of using cerebral protection devices, 37 (73%) of 51 in the stenting group and eight (17%) of 46 in the endarterectomy group had at least one new DWI lesion on post-treatment scans (adjusted OR 12.20, 95% CI 4.53 to 32.84), whereas in those treated at a centre with a policy of unprotected stenting, 25 of 73 patients (34%) in the stenting group and 10 of 61 (16%) in the endarterectomy group had new lesions on DWI (adjusted OR 2.70, 95% CI 1.16 to 6.24; interaction $p = 0.019$).

Studies on the predictors of risk of individual procedures

Findings of study on the effect of white-matter lesions on the risk of periprocedural stroke

This analysis has been published in detail elsewhere.[30] Patients were divided into two groups using the median ARWMC. We analysed the risk of stroke within 30 days of revascularisation using a per-protocol analysis. A total of 1036 patients (536 randomly allocated to CAS, 500 to CEA) had baseline imaging available. Median ARWMC score was 7, and patients were dichotomised into those with a score of 7 or more and those with a score of < 7. In patients treated with CAS, those with an ARWMC score of 7 or more had an increased risk of stroke compared with those with a score of < 7 (HR for any stroke 2.76, 95% CI 1.17 to 6.51; $p = 0.021$; HR for non-disabling stroke 3.00, 95% CI 1.10 to 8.36; $p = 0.031$). However, we did not see a similar association in patients treated with CEA (HR for any stroke 1.18, 95% CI 0.40 to 3.55; $p = 0.76$; HR for disabling or fatal stroke 1.41, 95% CI 0.38 to 5.26; $p = 0.607$). Carotid artery stenting was associated with a higher risk of stroke compared with CEA in patients with an ARWMC score of 7 or more (HR for any stroke 2.98, 95% CI 1.29 to 6.93; $p = 0.011$; HR for non-disabling stroke 6.34, 95% CI 1.45 to 27.71; $p = 0.014$), but there was no risk difference in patients with an ARWMC score of < 7.

Findings of the analysis of the effect of baseline characteristics on the risk of stenting

This analysis has been published in detail elsewhere.[45] We examined the influence of baseline patient characteristics influencing the risk of stroke, MI or death within 30 days of CAS in a regression model, including only patients allocated to stenting in whom the procedure was actually initiated (per-protocol analysis). Patients who crossed over to CAS, received CAS after an attempt at endarterectomy or received medical therapy instead of CAS were excluded. Risk factors were examined using binomial regression. A multivariable model was developed using a forward stepwise approach. Independent predictors of risk were age (RR 1.17 per 5 years of age, 95% CI 1.01 to 1.37), a right-sided procedure (RR 0.54, 95% CI 0.32 to 0.91), aspirin and clopidogrel prior to CAS (compared with any other antiplatelet regimen) (RR 0.59, 95% CI 0.36 to 0.98), smoking status and the severity of index event. In patients in whom a stent was deployed, use of an open-cell stent conferred higher risk than use of a closed-cell stent (RR 1.92, 95% CI 1.11 to 3.33). The use of a cerebral protection device did not modify the risk.

Incidence, impact and predictors of cranial nerve palsy and haematoma following carotid endarterectomy

This analysis has been published in detail elsewhere.[46] We analysed the effects of patient factors and surgical technique on the risk, and impact on disability, of cranial nerve palsy or haematoma in the surgical arm, including only patients allocated to endarterectomy in whom the procedure was actually initiated (per-protocol analysis). Patients who crossed over to CEA, received CEA after an attempt at CAS or received medical therapy instead of CAS were excluded. Forty-five of 821 (5.5%) patients undergoing CEA developed cranial nerve palsy, one instance of which was disabling (mRS of 3 at 1 month). Twenty-eight (3.4%) patients developed severe haematoma; 12 patients with haematoma also had cranial nerve palsy, a significant association ($p < 0.01$). Independent risk factors modifying the risk of cranial nerve palsy in the multivariate analysis were cardiac failure (RR 2.66, 95% CI 1.11 to 6.40), female sex (RR 1.80, 95% CI 1.02 to 3.20), the degree of contralateral carotid stenosis and time from randomisation to treatment > 14 days

(RR 3.33, 95% CI 1.05 to 10.57). The risk of haematoma was increased in women, by the prescription of anticoagulant drugs pre-procedure and in patients with atrial fibrillation, and was decreased in patients in whom a shunt was used and in those with a higher baseline cholesterol level.

Findings of the analysis of the effect of baseline characteristics on the risks of procedural stroke, myocardial infarction or death after endarterectomy

This analysis has been published in detail elsewhere.[47] We examined the influence of baseline patient characteristics influencing the risk of stroke, MI or death within 30 days of endarterectomy in a regression model, including only patients allocated CEA in whom the procedure was actually initiated (per-protocol analysis). Patients who crossed over to CEA, received CEA after an attempt at CAS or received medical therapy instead of CAS were excluded. Demographic and technical risk factors for these procedural complications were analysed sequentially in a binomial regression analysis and, subsequently, in a multivariable model. The risk of stroke, MI or death within 30 days of CEA was higher in female patients (RR 1.98, 95% CI 1.02 to 3.87; $p = 0.05$), and with increasing baseline DBP (RR 1.30 for each 10 mmHg increase, 95% CI 1.02 to 1.66; $p = 0.04$). In a multivariable model, only DBP remained a significant predictor. The risk was not related to the type of surgical reconstruction, anaesthetic technique or perioperative medication regimen. A total of 21.2% of events occurred on or after the day of discharge.

Findings of the cost–utility analysis

Resource use and costs

The cost–utility economics analysis has been published elsewhere.[48] Mean index procedure duration was 107 minutes [standard deviation (SD) 47 minutes] in the endarterectomy group ($n = 700$) and 68 minutes (SD 33 minutes) in the stenting group ($n = 691$; see *Appendix 9*). Eighty-two per cent of endarterectomy patients ($n = 794$) had general anaesthetic compared with 0% of stenting patients ($n = 853$). Eighteen per cent of endarterectomy patients had local anesthetic compared with 100% of stenting patients. In the endarterectomy group a shunt was used in 40% of patients ($n = 818$) and a patch in 66% ($n = 693$). In the stenting group a stent was deployed in 92% of patients ($n = 816$) and a cerebral protection device was used in 71% ($n = 824$). Sixty-four per cent of endarterectomy patients ($n = 813$) were admitted to the ICU post-operatively versus 52% in the stenting group ($n = 808$). Length of stay on the ward was 5.7 days (SD 9.4 days) for endarterectomy ($n = 803$) and 5.1 days (SD 10.8 days) for stenting ($n = 789$). In patients randomised to endarterectomy the mean number of additional endarterectomies during follow-up was 0.039 (SD 0.193) and the mean number of stents was 0.023 (SD 0.159). In patients randomised to stenting, the figures were 0.066 (SD 0.257) and 0.028 (SD 0.172), respectively. No patients in the endarterectomy group had a fatal MI during the first 30 days after treatment, compared with three patients in the stenting group; five patients had a non-fatal MI in the endarterectomy group compared with none in the stenting group; 28 patients in the endarterectomy group had severe haematoma compared with eight patients in the stenting group; one patient in each group had disabling cranial nerve palsy. Patients in both groups underwent a range of imaging tests; ultrasound was the most common in the endarterectomy group (234 tests; $n = 857$) compared with intra-arterial angiography in the stenting group (352 tests; $n = 853$). Drug usage 1 month after treatment was similar for both endarterectomy ($n = 785$) and stenting ($n = 781$) groups. Seventy-one patients (8%) in the endarterectomy group had one or more strokes during the 5-year time horizon compared with 114 patients (13%) in the stenting group; a higher proportion of strokes in the stenting group were non-disabling (61% vs. 37%).

Accounting for missing data using multiple imputation, mean total costs per patient were £6762 (95% CI £6154 to £7369) in the endarterectomy group ($n = 857$) and £7351 (95% CI £6786 to £7915) in the stenting group ($n = 853$) (*Table 9*). In both groups, approximately two-thirds of the total costs were for the index procedure and one-third for follow-up. Values were similar for complete-case analysis (see *Appendix 9*).

TABLE 9 Mean utility values, QALYs and costs per patient

	Endarterectomy ($n=857$)		Stenting ($n=853$)	
Variable	Mean	95% CI	Mean	95% CI
Cost of index procedure, £	4558	4319 to 4797	4787	4548 to 5026
Cost of follow-up, £	2204	1696 to 2711	2563	2114 to 3013
Total cost, £	6762	6154 to 7369	7351	6786 to 7915
Utility values				
Baseline	0.758	0.743 to 0.774	0.776	0.761 to 0.790
3 months	0.779	0.763 to 0.795	0.777	0.759 to 0.795
6 months	0.763	0.746 to 0.780	0.754	0.735 to 0.773
1 year	0.739	0.721 to 0.758	0.737	0.718 to 0.757
2 years	0.709	0.688 to 0.729	0.710	0.689 to 0.732
3 years	0.677	0.655 to 0.699	0.674	0.650 to 0.698
4 years	0.628	0.602 to 0.653	0.648	0.622 to 0.675
5 years	0.594	0.563 to 0.625	0.609	0.578 to 0.641
QALYs	3.228	3.150 to 3.306	3.247	3.160 to 3.333
NMB				
£20,000	£57,793	£55,994 to £59,592	£57,580	£55,699 to £59,461
£30,000	£90,070	£87,520 to £92,621	£90,046	£87,329 to £92,762

Costs are in 2013–14 Great British pounds (£). Data include values imputed using multiple imputation. The 95% CIs were derived from 1000 bootstrap replications of each of the 20 imputed data sets.The NMB is calculated at a maximum willingness to pay for a QALY of £20,000 and £30,000.

Utility values and quality-adjusted life-years

Mean utility values at each follow-up point were similar for the two groups and there was a decline over time. Accounting for missing data, mean utility values per patient increased from 0.758 (95% CI 0.743 to 0.747) in the endarectomy group at baseline to 0.779 (95% CI 0.763 to 0.795) at 3 months and then declined to 0.594 (95% CI 0.563 to 0.625) at 5 years (*Table 9*). In the stenting group, the values were 0.776 (95% CI 0.761 to 0.790) at baseline, 0.777 (95% CI 0.759 to 0.795) at 1 month and 0.609 (95% CI 0.578 to 0.641) at 5 years. Mean total QALYs per patient were 3.228 (95% CI 3.150 to 3.306) in the endarterectomy group and 3.247 (95% CI 3.160 to 3.333) in the stenting group. Utility values and QALYs were similar for complete cases (see *Appendix 9*).

Cost–utility analysis

Mean NMBs for endarterectomy and stenting were £57,793 (95% CI £55,994 to £59,592) and £57,580 (95% CI £55,699 to £59,461) at a maximum willingness to pay for a QALY of £20,000, and £90,070 (95% CI £87,520 to £92,621) and £90,046 (95% CI £87,329 to £92,762) at a maximum willingness to pay for a QALY of £30,000 (*Table 9*). In the base-case analysis there were no significant differences in costs between the two groups (mean incremental costs for stenting versus endarterectomy £537, 95% CI –£238 to £1312) or in outcomes (mean QALYs gained –0.010, 95% CI –0.117 to 0.097; *Table 10*). The incremental NMB for stenting versus endarterectomy was not significantly different from zero at a maximum willingness to pay for a QALY of £20,000 (mean –£723, 95% CI –£3134 to £1670) or £30,000 (mean –£830, 95% CI –£4265 to £2605).

We repeated the analysis several times using alternative versions of the multiple imputation process using different random number seeds to investigate if the conclusions of the analysis changed; in every case the results were qualitatively the same (i.e. there were no significant differences between the two groups in terms of costs, QALYs and NMBs).

TABLE 10 Incremental cost-effectiveness of stenting vs. endarterectomy: base-case and subgroup analyses

					Incremental NMB, £					
	Incremental cost, £		QALYs gained		£20,000		£30,000		Probability stenting cost-effective	
Scenario	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	£20,000	£30,000
Base case[a]	537	–238 to 1312	–0.010	–0.117 to 0.097	–732	–3134 to 1670	–830	–4265 to 2605	0.27	0.31
No adjustment[b]	589	–202 to 1380	0.019	–0.098 to 0.135	–213	–2821 to 2395	–25	–3761 to 3712	0.43	0.49
Complete-case analysis[c]	533	–836 to 1902	0.006	–0.194 to 0.206	–415	–4669 to 3840	–355	–6538 to 5827	0.42	0.45
Subgroup analyses[d]										
Men	337	–471 to 1145	–0.055	–0.185 to 0.076	–1431	–4278 to 1417	–1977	–6096 to 2142	0.17	0.18
Women	787	–808 to 2382	0.103	–0.098 to 0.304	1256	–3334 to 5864	2291	–4234 to 8815	0.71	0.75
Age ≥ 70 years	779	–323 to 1881	–0.061	–0.219 to 0.097	–1993	–5474 to 1489	–2599	–7607 to 2408	0.13	0.16
Age < 70 years	143	–713 to 999	0.057	–0.094 to 0.208	992	–2234 to 4219	1560	–3139 to 6259	0.73	0.75

a Data include values imputed using multiple imputation. The 95% CIs were derived from 1000 bootstrap replications of each of the 20 imputed data sets. The QALYs gained are adjusted for age, sex, centre and baseline utility values. The incremental costs are adjusted for age, sex and centre. The incremental NMB and the probability stenting is cost-effective are based on the adjusted QALYs gained and incremental costs, and calculated at a maximum willingness to pay for a QALY of £20,000 and £30,000. The QALYs gained, incremental cost and incremental NMB figures are for stenting minus endarterectomy; to compute analogous figures for endarterectomy minus stenting multiply the figures by minus one. The probability endarterectomy is cost-effective is one minus the probability stenting is cost-effective.
b As for the base-case analysis, except that the QALYs gained and the incremental costs are unadjusted.
c As for the base-case analysis, except that there is no multiple imputation of missing values and the 95% CIs were derived from 1000 bootstrap replications of a single data set containing endarterectomy patients ($n = 202$) and stenting patients ($n = 254$) with no missing values.
d As for the base-case analysis but run on patients within each subgroup. Among the endarterectomy patients ($n = 857$) 606 are men, 251 are women, 453 are aged ≥ 70 years and 404 are < 70 years. Among the stenting patients ($n = 853$) the respective figures are 601, 252, 458 and 395.

Sensitivity and subgroup analyses

The cost-effectiveness acceptability curve shows that at a maximum willingness to pay for a QALY of £20,000 the probability that stenting is cost-effective was 0.27; at a maximum willingness to pay for a QALY of £30,000 the probability that stenting is cost-effective was 0.31 (*Table 10* and *Figure 10*).

Incremental costs, QALYs gained and incremental NMBs for stenting versus endarterectomy remained not significantly different from zero when rerunning the base-case analysis without adjustment and using complete cases (see *Table 10*). At a maximum willingness to pay for a QALY of £20,000 the incremental NMB for stenting versus endarterectomy was most sensitive to the cost of stents, cost of operating theatre time, cost per hospital day and cost of treating stroke (*Figure 11*), but in every case the incremental NMB was not significantly different from zero. Similar findings were obtained using a maximum willingness to pay for a QALY of £30,000 (see *Appendix 9*). In women and patients aged < 70 years, the mean QALYs gained from stenting versus endarterectomy were positive, whereas in men and patients ≥ 70 years they were negative, but in all cases the differences were not significantly different from zero, neither were the incremental costs and the incremental NMBs.

Future planned analyses

In addition to the data presented in this report further analyses planned include:

- analysis of the carotid artery 'in-stent' stenosis measurements with DUS versus computerised tomography angiography substudy
- analysis of the relation between restenosis and recurrent stroke
- a more detailed analysis of the mRS as an index of disability during follow-up.

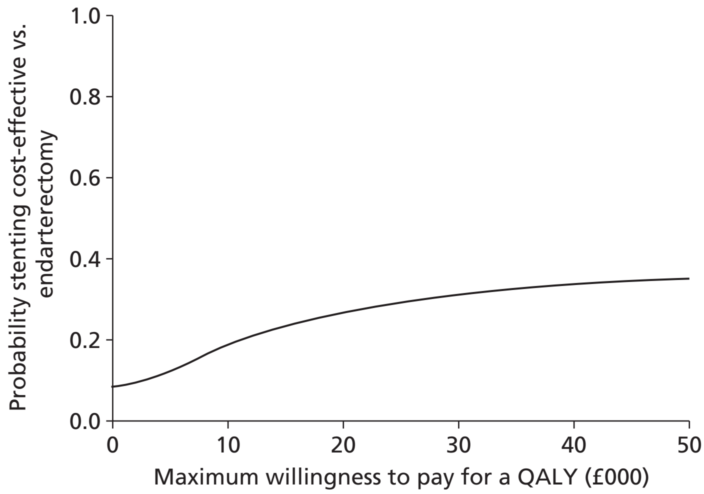


FIGURE 10 Cost-effectiveness acceptability curve. Cost-effectiveness acceptability curve showing the probability that stenting is cost-effective vs. endarterectomy at different values of the maximum willingness to pay for a QALY. The probability that endarterectomy is cost-effective is one minus the probability stenting is cost-effective at each value of the maximum willingness to pay for a QALY.

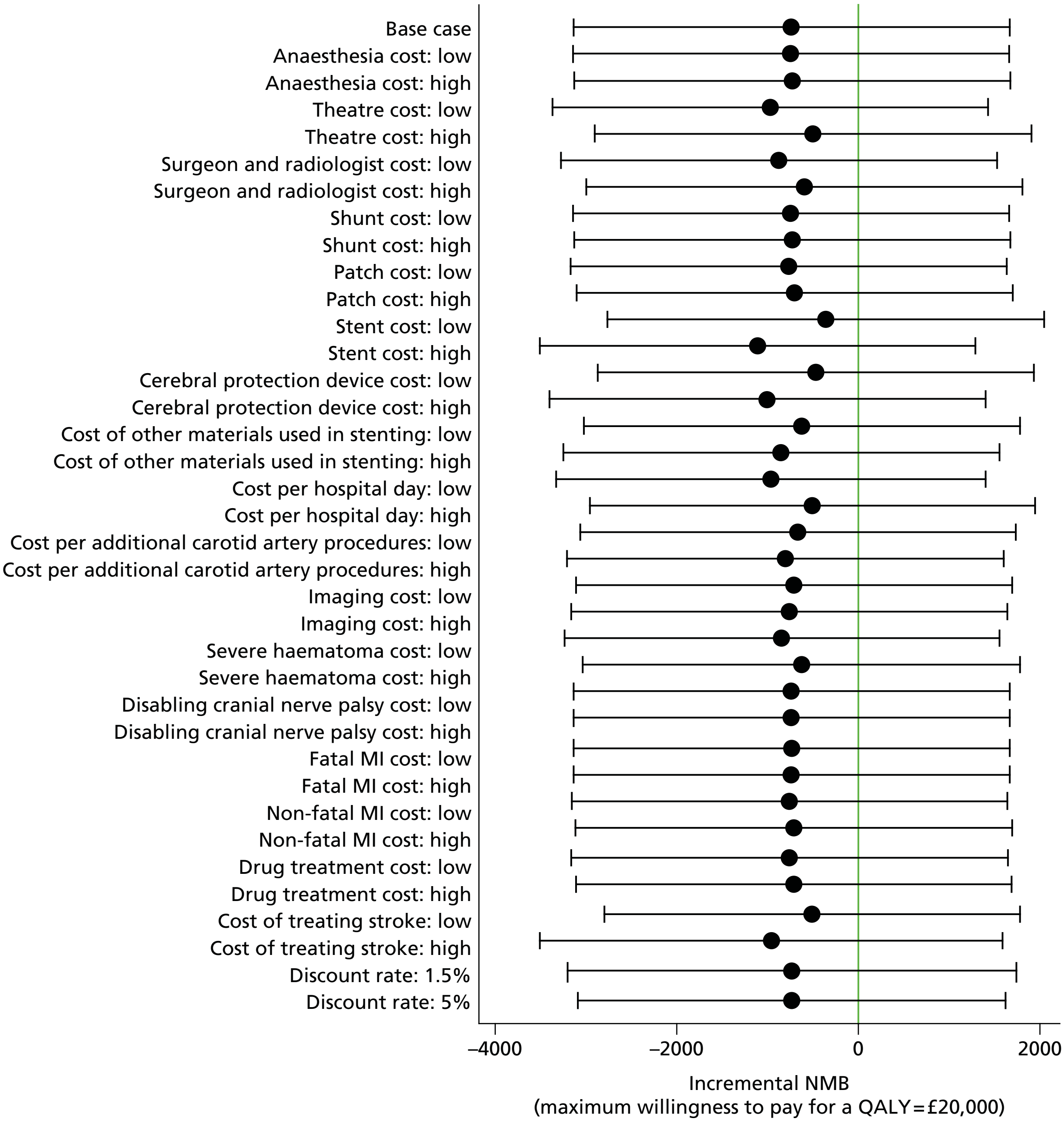


FIGURE 11 Univariate sensitivity analysis. All analyses are as for the base-case analysis with univariate adjustment of the parameters listed. Results are point estimates of the incremental NMB of stenting vs. endarterectomy (circles) and 95% CIs (capped spikes). The incremental NMB is calculated at a maximum willingness to pay for a QALY of £20,000 (see *Figure 12* in *Appendix 9* for results calculated at a maximum willingness to pay for a QALY of £30,000).

Chapter 4 Discussion

Main findings

Carotid artery stenting has a higher short-term (periprocedural) risk than CEA in terms of stroke, but has a lower rate of MI and severe haematoma, and avoids injury to cranial nerves during endarterectomy. The additional short-term risk associated with CAS is largely attributable to non-disabling strokes, and the absolute difference in the risk of any stroke during the whole of follow-up in ICSS was small, with the 47 additional strokes in the stenting group translating to one extra stroke (typically non-disabling) for every 156 patient-years of follow-up. The primary analysis of the trial showed that stenting is equivalent to endarterectomy in preventing fatal or disabling stroke up to 10 years after treatment. Severe restenosis or occlusion of the treated carotid artery was rare, with no difference between treatment groups. Stenting also appeared to be as effective as endarterectomy in preventing ipsilateral stroke occurring during follow-up after the 30-day procedural period. Importantly, there was no difference in functional outcome of patients allocated stenting compared with endarterectomy as assessed by the distribution of mRS scores at 1 year, 5 years or the end of follow-up. Moreover, there were no differences in costs or QALYs between the treatments.

Comparison with other trials

Previous data on prevention of strokes in patients with symptomatic carotid stenosis comparing stenting with endarectomy have been available from three trials reporting near- and mid-term follow-up only, two of which had stopped recruitment before reaching the full sample size.[49,50]

The Endarterectomy versus Stenting in Patients with Symptomatic Severe Carotid Stenosis trial (EVA-3S) was stopped early because of a significantly lower rate of periprocedural stroke or death in the endarterectomy group than in the stenting group.[25,49] However, it showed no significant differences in cumulative 4-year rates of fatal or disabling stroke between stenting (6.3%) and endarterectomy (4.0%).[51] The Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial in symptomatic patients was stopped early on grounds of cost and futility, but did not show non-inferiority of stenting compared with endarterectomy within 30 days after treatment.[50] In SPACE, ipsilateral disabling stroke within 2 years, or death or disabling stroke in any territory within 30 days of treatment, was recorded in 5.7% patients randomised to stent treatment and in 4.7% of patients allocated to surgery.[52]

In the Carotid Revascularisation Endarterectomy versus Stenting Trial (CREST), there was a trend of an increased risk for major ipsilateral stroke in the stent group (1.4%) compared with the endarterectomy group (0.5%) occurring up to 4 years after treatment ($p = 0.05$), and including both patients with symptomatic and asymptomatic carotid stenosis.[53] This inclusion of asymptomatic patients in CREST probably also accounts for the lower overall event rates reported in that trial. The data from ICSS support these findings; the risk of having a severe stroke remains low after endarterectomy or stenting even after the first 2–4 years of follow-up and, in ICSS, does not differ between stenting and endarterectomy up to 10 years after randomisation.

ICSS is also in agreement with other randomised trials that have previously reported increased risks in procedure-related strokes that did not lead to disability associated with stenting,[49,50,53] and in the MRI substudy of ICSS there was a higher incidence of cerebral infarction 1 month after stenting compared with endarterectomy, even where this was not associated with a clinical event.[44] This excess of periprocedural non-disabling strokes accounts for the difference in the combined outcome measure of procedural stroke or death, or stroke in the ipsilateral carotid territory thereafter, in favour of surgery. However, if we consider all strokes occurring in the territory of the treated carotid artery after the procedural period, these were no more frequent after stenting than endarterectomy. It is these strokes that the procedure is designed to prevent and, in these terms, stenting can be considered to be as effective as surgery. However, we observed a small increase in risk in non-procedural stroke occurring in the contralateral carotid or vertebrobasilar territory in the stenting group compared with the endarterectomy group. It is possible that endarterectomy has a beneficial effect in preventing strokes occurring outside the territory of the revascularised artery, possibly through improvement in collateral flow. However, the most likely explanation is that the difference in non-ipsilateral strokes between CAS and CEA in ICSS represents a chance finding.

No other trials have reported the impact of stenting versus endarterectomy on long-term functional outcome measured using the mRS. We have previously reported that the impact of the excess of non-disabling stroke on the mRS scores at 30 days after stenting in ICSS patients was balanced by the impact of the excess of MI, cranial nerve palsy and haematoma on mRS scores after endarterectomy (data not shown). The fact that there was no long-term difference in the distribution of mRS scores at 1 year, 5 years and at the end of follow-up implies that the differences in the various outcomes, including stroke, between the two treatments also balance each other in the long term.

Secondary outcomes and substudies

Restenosis

The SPACE trial reported higher cumulative rates of severe restenosis 2 years after stenting (10.7%) compared with the endarterectomy group (4.6%).[52] In contrast, there was no significant difference in severe restenosis between stenting and endarterectomy in the EVA-3S trial at 3 years (3.3% vs. 2.8%), nor in CREST at 2 years (6.0% vs. 6.3%).[54,55] ICSS with cumulative 5-year rates of 11.8% and 8.6% for CAS and CEA, respectively, supports the view that completed stent treatment is as effective as endarterectomy in preventing residual or recurrent narrowing or occlusion of the carotid artery.

White-matter lesions and periprocedural stroke risk

Carotid artery stenting was associated with a higher risk of stroke compared with CEA in patients with an ARWMC score of 7 or more, but there was no risk difference in patients with an ARWMC score of < 7.[30] This implies that the presence of white-matter lesions on brain imaging should be taken into account when selecting patients for CAS, which should be avoided in patients with extensive white-matter lesions, but might be an acceptable alternative to CEA in patients with less-extensive lesions.

Magnetic resonance imaging substudy

Approximately three times more patients in the stenting group than in the endarterectomy group had new ischaemic lesions on DWI on post-treatment scans.[44] This suggests that the difference in periprocedural clinical stroke risk in ICSS is not likely to have been caused by ascertainment bias. In fact, there is a higher incidence of ischaemic lesions seen on MRI than of recorded clinical events (stroke/TIA). Whether these excess 'silent' lesions have any functional consequence for the patient (e.g. cognitive impairment or increased susceptibility to vascular dementia) is an issue not addressed by ICSS, but the fact that there was no difference in functional outcome between the two treatment groups makes it unlikely that the excess of 'silent' lesions had any long-term consequences.

Subgroup analysis of procedural events

An exploratory analyses of the composite outcome of stroke, death or procedural MI for pre-defined subgroups suggested that carotid stenting might have a similar risk to endarterectomy in women, but that the intervention was more hazardous than endarterectomy in men. However, the difference between the HRs comparing the risk of stenting with endarterectomy in men and women only reached borderline significance (interaction $p = 0.071$). Stenting was more hazardous, and endarterectomy less hazardous, in patients not taking medication for hypertension at baseline than in patients taking medication for hypertension.

Subgroup analysis: long-term primary outcome

Exploratory subgroup analyses showed no significant modification of the HR of the primary outcome event or of the combined outcome of procedural death or stroke or non-procedural ipsilateral stroke by any of the evaluated variables.

Cost–utility analysis

Our economic analysis showed that stenting and endarterectomy had similar costs (index procedure costs, follow-up costs and total costs) and outcomes (utility values, QALYs). This was despite the finding in the trial of higher rates of non-disabling strokes in the stenting group. Comprehensive sensitivity analyses showed little uncertainty in this finding. Non-significant differences in utility values and QALYs mirror differences in mRS scores and all-cause mortality found in the trial. The findings mean that there is no reason to prefer either stenting or endarterectomy on the basis of differences in quality of life or on economic grounds; other factors should be taken into account when deciding which option to use to treat patients with symptomatic carotid stenosis (e.g. the age of the patient or imaging features).

Strengths, weaknesses and generalisability

Because of the nature of the interventions in ICSS, it is not possible for either patients or researchers to be blinded to allocated treatment. However, the Chief Investigator and the steering committee remained blinded to the cumulative event rate throughout the trial and the outcome events that were independently assessed according to the following procedure: the events were documented in detail by the investigating centre, censored after receipt at the central office to remove clues as to the treatment allocated, and then adjudicated by an independent neurologist. Furthermore, the results of the imaging substudies were all assessed blinded to treatment.

A range of imaging techniques, including DUS, was allowed in the trial to assess the degree of carotid stenosis prior to randomisation, according to standard practice at the specific centre. Bilateral DUS scan alone was allowed by the protocol only if it was standard practice to treat on the basis of ultrasound alone in individual centres. The number of patients not having a procedure initiated because initial imaging appeared to have misclassified the severity of the stenosis was low (three patients in the CAS arm and one in the CEA arm were found to have < 50% stenosis after randomisation). Fourteen patients did not have a procedure because the stenosis was found to have progressed to occlusion after randomisation (five patients in the CAS arm and nine in the CEA arm). A number of initiated stenting procedures were aborted because the stenosis was found to be < 50% (seven cases) or occlusion was found to be present (15 cases) when angiography was performed immediately prior to attempting to place the stent. Obviously such cases would not have been detected in surgical patients, where the procedure would have gone ahead without knowledge of the exact degree of stenosis immediately prior to the surgery. We can assume, therefore, that the total rate of stenosis found to be inappropriate at procedure in the trial is accurately reflected by the figures for the stenting arm [i.e. a total of 10 cases found to have < 50% stenosis (1.2% of 853 patients randomised to stenting) and perhaps also the 20 cases of occlusion (2.3%)]. However, the proportion of patients who developed occlusion after randomisation (and who were therefore appropriately randomised) is unknown. Thus, despite the leeway allowed in the approach to measuring baseline stenosis in ICSS, at least 96.5% of patients were correctly identified in terms of their degree of stenosis as being suitable for inclusion in the trial (50–99%).

Inevitably in ICSS, which started when stenting was a relatively new treatment, the experience of the interventionists in carotid stenting was less than that of the surgeons in CEA. However, the risk of outcome events associated with stenting was lower in inexperienced, supervised centres than in more experienced centres (see *Figure 4*) and there was no significant difference in the excess hazard of stenting compared with endarterectomy between supervised and experienced centres, or between centres recruiting more or less than 50 patients; therefore, inexperience is not a major determinant of our results. However, the HR was lower among patients treated at the larger centres than in the smaller centres, which might indicate some effect of procedural volume on technical expertise. A pooled analysis of stenting outcomes by the Carotid Stenting Trialists' Collaboration showed lower procedural stroke or death risks among patients treated by interventionists with higher annual in-trial procedure volumes, indicating that regular practice in carrying out the procedure matters more than individual total experience or centre volumes.[56]

The trial was an international, multicentre study, so patients were included at centres with a range of experience (above the minimum necessary for trial entry) and standards of practice, and a variety of stents and protection devices were used in the trial. Overall, this should mean that the results of ICSS may be taken as being widely applicable in patients and at centres who match the criteria for inclusion in the study.

In terms of the cost–utility analysis, the main strength is that it is based on a large, international, multicentre, randomised trial with detailed information on resource use, utility values and mortality for a median follow-up period of 4.2 years. There are several limitations. First, data on costs of managing strokes were not collected in the trial. However, rather than simply extrapolating from averaged external cost data for stroke, as is done in the vast majority of health economic analyses of large trial cohorts, given the specific nature of the strokes occurring in our particular population, we used individual patient data from the OXVASC study to predict these costs at the patient-level. These were, therefore, detailed contemporaneous UK-specific costs matched to patients in the trial according to significant cost drivers, and blinded as to treatment allocation, but they do not reflect the actual costs incurred by each patient. Nevertheless, when we adjusted these costs in sensitivity analyses the results did not change appreciably. Second, the analysis took a UK NHS/PSS perspective on costs, and utility values were calculated using a UK population value set. Results may differ for other countries depending on the relative value of unit costs and the value set used to generate utility values. Third, a wider perspective (e.g. societal) could have been taken to measure costs, including impacts on the rest of society, including patients, families and businesses. Given that the trial found no differences in mortality or disability, it is unlikely that this would affect the incremental costs, although total costs associated with each treatment may change. Fourth, the time horizon was 5 years. We could have taken a longer time horizon, but there were no differences in costs or benefits between groups at this point, so this would not have affected the results of the incremental analyses.

Implications for health care

Stroke is the major cause of acquired adult physical disability and is responsible for 12% of all deaths in the UK. Atherosclerotic stenosis of the carotid artery is an important cause of stroke, and the risk of recurrent stroke in recently symptomatic patients with severe carotid stenosis is as high as 28% over 2 years. Therefore, revascularisation offers an important means to reduce the burden of stroke in the population. The results of ICSS taken with those of other trials demonstrate that CAS is as effective as endarterectomy in preventing ipsilateral stroke during long-term follow-up. Carotid stenting carries a higher risk of periprocedural stroke, which is largely accounted for by an excess of non-disabling stroke, and more patients in the stenting group than in the endarterectomy group had new ischaemic lesions on post-treatment MRI scans. This excess of non-disabling stroke and new lesions associated with stenting does not translate into a significant difference between stenting and endarterectomy in long-term functional outcomes as assessed by the mRS, quality of life as assessed by the EQ-5D-3L, or a difference in costs as assessed by the economics analysis. The mRS is not a precise measure of the level of independence, and we cannot rule out subtle differences in cognitive outcome or subjective perception of wellbeing between the two treatment groups not captured by these scales. However, it is notable that a substudy of ICSS, carried out at two ICSS centres in which 177 patients enrolled in ICSS had detailed neuropsychological examination, showed no significant difference in cognition 6 months after stenting compared with endarterectomy, despite double the number of new ischaemic lesions on MRI after stenting.[57] Thus, the evidence from ICSS indicates that any impact of the excess of non-disabling stroke and asymptomatic infarction associated with stenting is limited and short-lasting.

We have shown that the severity of white-matter disease is an important modifier of risk with stenting, but not with endarterectomy. In a separate analysis restricted to ICSS patients who were randomised to and completed stenting treatment, age was an independent predictor of the risk of stroke, MI or death within 30 days of stenting. In an analysis of CREST, age also significantly modified the risk of stenting versus endarterectomy,[53] whereas a pooled analysis of the data from ICSS with data from EVA-3S and SPACE, as well as a meta-analysis of all the existing trials, have confirmed that patients over the age of 70 years have a higher risk of stroke or death with stenting, but patients below the age of 70 have a similar risk with stenting compared with endarterectomy.[58,59]

The analysis of the risk of baseline and procedural-related factors in ICSS showed that the use of an open-cell stent conferred higher risk than use of a closed-cell stent (RR 1.92, 95% CI 1.11 to 3.33), but the use of a cerebral protection device did not modify the risk. Although this was not a randomised comparison, the findings are in keeping with results from the SPACE study and large observational studies.[60,61] This effect of stent design may reflect the benefit of closed-cell stents providing greater coverage of the atheromatous lesion and implies that, in general, closed-cell stents should be preferred to open-cell stents.

The multivariate analysis showed that DBP at baseline was a significant predictor of the risk of stroke, MI or death within 30 days of CEA, implying that control of hypertension pre-operatively is an important aspect of ensuring the safety of surgery. Our analysis confirmed that cranial nerve palsy remains an important complication of endarterectomy, but cranial nerve palsy recovered in almost all patients. Thus, the risk of cranial nerve injury should not influence the choice between CAS and CEA in patients who have not had previous carotid surgery, unless other features favour stenting.

We therefore conclude that the data from ICSS together with data from the other randomised trials show that the choice between stenting and endarterectomy should take into account the different procedural risks of these treatments related to individual patient characteristics. Endarterectomy remains the treatment of choice for older patients and those with extensive white-matter disease, but stenting is an appropriate treatment alternative for patients with symptomatic carotid stenosis if the risk of periprocedural stroke is low, for example in younger patients and those with lower levels of pre-existing white-matter disease. Such patients should be offered stenting after informed consent giving full consideration of the overall periprocedural risks. Considerations of cost and cost-effectiveness should not affect the decision about which of these two treatments to use. In addition to taking into account clinical and imaging features, treatment decisions should take into account patient preferences, with reference to the differing nature of the risks with the two procedures.

Implications for research

The impact of the treatments on patients' cognitive function was not assessed as part of the main protocol in ICSS (or any of the other reported trials). Given the effect of stenting on silent infarction noted in ICSS MRI substudy, measurement of cognitive function should be an important part of any future study of stenting and/or CEA as this might be an important consideration in choosing between stenting and endarterectomy.

Other important areas for future studies include assessing the morphology and stability of the carotid plaque using modern imaging techniques prior to intervention, and identifying the clinical characteristics of patients that determine how likely they are to benefit from revascularisation in the context of modern optimised medical therapy in lower-risk symptomatic and asymptomatic patients.

Acknowledgements

The ICSS Trial Steering Committee wishes to express its gratitude to all of the principal investigators and researchers (listed in *Appendix 9*), and the patients and their families whose hard work and commitment were vital to the success of ICSS. Professor Peter Rothwell and Dr Ramon Luengo-Fernandez kindly contributed to the cost-effectiveness evaluation using information from the OXVASC study.

This study was funded by grants from the Medical Research Council (MRC), the Stroke Association, Sanofi-Synthélabo, and the European Union. The funding from the MRC was managed by the National Institute for Health Research (NIHR) on behalf of the MRC–NIHR partnership. MMB's Chair in Stroke Medicine is supported by the Reta Lila Weston Trust for Medical Research. JE and RLF were supported by a grant from the MRC. LHB was supported by grants from the Swiss National Science Foundation (PBBSB-116873) and the University of Basel. This work was supported by researchers at the NIHR University College London Hospitals Biomedical Research Centre.

Contributions of authors

Roland L Featherstone is the trial manager of ICSS and maintained the trial database with day-to-day responsibility for data collection and completeness. He prepared the data for analysis.

Joanna Dobson, the trial statistician, contributed to the design of the study, its conduct and analysis.

Jörg Ederle contributed to the data analysis and had particular responsibility for the white-matter analysis.

David Doig contributed to the data analysis and interpretation.

Leo H Bonati contributed to analysis and interpretation of data, and led the MRI substudy.

Stephen Morris and **Nishma V Patel** were responsible for the cost–utility analysis.

Martin M Brown led the development of the protocol and had ongoing oversight and management of the study; he had the final responsibility for the analyses and the manuscript content as the chief investigator of ICSS.

All the authors contributed to drafting the manuscript or revising it critically for important intellectual content.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Data sharing statement

All available data can be obtained from the corresponding author.

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Appendix 1 Consent form

CONSENT FORM

Patient ID for this trial __ __ __ __ **Centre Number __ __ __ __ __** **Project ID__ __ __ __**

Title of project: International Carotid Stenting Study (ICSS)

Name of researcher:

Please initial box

1) I confirm that I have read and understood the information sheet dated 19/07/2004 (version 2.21) for the above study and have had the opportunity to ask questions. ☐

2) I confirm that I have had sufficient time to consider whether or not I want to be included in the study. ☐

3) I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

4) I understand that sections of any of my medical notes may be looked at by responsible individuals from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐

5) I understand that information held by the NHS and records maintained by the General Register Office may be used to keep in touch with me and follow up my health status ☐

6) I agree to take part in this study. ☐

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

1 copy for patient, 1 copy for researcher, 1 copy to be kept with hospital notes
Version 2.21 31/10/04

Appendix 2 Patient information sheet

International Carotid Stenting Study (ICSS)

You are invited to participate in a research project we are running to compare the risks and benefits of two treatments for carotid artery narrowing. Before you decide it is important for you to understand why the research is being done and what it will involve. 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 that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study? Narrowing of one of the carotid arteries in the neck, which supply blood to the brain, is an important cause of stroke. It is therefore important to remove this narrowing to prevent stroke. The traditional method of treatment is a surgical operation (endarterectomy), often performed under a general anaesthetic, in which the diseased part of the artery is cut out through an incision in the neck. We are studying a new treatment in which is a small tube made of wire mesh, called a stent, is placed inside the narrowed artery in the neck. The stent is placed into the artery through a small tube (catheter) inserted in the groin under local anaesthetic. Injections of dye will be made through the catheter to take Xray pictures of the narrowing. This is called angiography. Once in position across the narrowing the stent is opened out where it acts like a spring to keep the artery open. This new treatment is known as carotid artery stenting. Stenting has been used successfully in the arteries supplying the heart and the legs. Stenting avoids the discomforts of surgery and risks of general anaesthesia but we do not know which treatment is better overall for the patient.

Why I have I been chosen? You have been chosen because the tests that you have had reveal you may benefit from either surgery or the insertion of a stent.

Do I have to take part? Your participation in the trial is entirely voluntary. It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive.

What will happen to me if I take part? To find out which treatment is better, half the patients entering the study will be allocated to be treated with surgery and the other half to be treated by stenting. The treatment is allocated by a computer, which chooses the treatment for each individual by chance. This will allow us to compare the benefits and risks of the two treatments fairly. All patients entering the study will receive the best possible medical treatment, including aspirin or similar tablets, if tolerated, and careful treatment of high blood pressure or raised blood fats. If you agree to join the study your GP will be informed and you will be seen by a neurologist approximately 30 days after your treatment, after six months and then annually after entering the study for up to 5 years. At each visit a carotid ultrasound (a non-invasive sound picture of the arteries which does not use radiation) will be performed to assess the degree of narrowing. You will be asked to fill in a questionnaire about your health and how you feel about yourself before your allocated treatment and at follow-up visits.

What will happen if I am allocated surgery? You will be scheduled to have surgery as soon as routinely possible and the operation will be performed by an experienced surgical team. You may need to have a general anaesthetic to put you to sleep during the operation. An angiogram may be performed before or after the procedure. You will usually have to stay in hospital for several days after surgery.

What will happen if I am allocated carotid stenting? You will have a fine wire and tube inserted into an artery in the groin, which will be used to feed the stent up the artery and into the neck, so that it can be placed across the narrowing in the carotid artery. This is normally done following a local anaesthetic injection into the groin area, but you will stay awake during the procedure. A balloon or filter device may also be fed up the artery to collect any debris that may be dislodged during the stenting procedure. X ray pictures (angiography) will taken immediately before, during and after stenting the artery to make sure the wire and stent are in the correct place. In a small percentage of patients, the angiography may show that stenting is not possible. In this case, you will be referred for surgery instead. If you are well after the stenting procedure you will be able to go home the day afterwards.

What are the possible disadvantages and risks of taking part? Both surgical endarterectomy and stenting carry a risk of causing a stroke at the time of the treatment. Previous trials showed a significant risk of stroke or death at the time of surgery or stenting of between 6 and 10 in every 100 patients. There is a small risk of about one in a hundred that angiography will cause a stroke. Stroke caused by surgery, stenting or angiography may recover, cause permanent disablement or be fatal. However, you are being considered for the study because the risks of strokes resulting from surgical or stenting treatment are believed to be less than leaving the carotid artery narrowing untreated. Treatment is not always successful and the narrowing may recur and require further treatment or the artery may become blocked.

What are the other main risks of surgery? Surgery also has a risk of causing a heart attack. About one in ten patients has temporary tongue or facial weakness. A large blood clot (haematoma) may form at the site of incision, which may require removal. Surgery results in a permanent scar in the neck.

What are the other main risks of stenting? Angiography and stenting may also result in bruising or haematoma at the site of injection (usually in the groin) and can cause temporary discomfort or pain in the neck. There is a small risk of allergic reactions to the dye.

What are the possible benefits of taking part? All patients taking part in the trial will receive careful follow-up and the opportunity to benefit from advances in treatment. Overall, treating carotid narrowing will reduce your chances of subsequent strokes.

What if something goes wrong? If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for taking legal action but you may have to pay the legal costs. Regardless of this, if you wish to complain, or have any concerns about this study, the normal National Health Service complaints mechanism should be available to you.

Will my taking part in this study be kept confidential? Information relevant to your medical condition will be collected as part of the study. Medical information about yourself and your treatment will be kept in the central study office in the Institute of Neurology, University College London, England for analysis. Professor Martin M Brown, the Principal Investigator, will be responsible for the security and access to the information. All information regarding your medical records will be treated as strictly confidential and will only be used for medical research on the factors that influence the diagnosis of or outcome from stroke. The data may be used for future research on stroke by other research institutions in the UK but again your confidence will be strictly maintained. Your medical records may be inspected by competent authorities and properly authorised persons, but if any information is released outside the trial office this will be done so in coded form with your name removed from the records so that your confidentiality is strictly maintained. The results of the study will be published in medical journals or other public sites. Information regarding the study will be stored on a secured computer database for a minimum of 15 years.

Who is organizing and funding the study? The study is organized by the Stroke Research Unit at the Institute of Neurology, UCL and funded by grants from The Stroke Association, Sanofi Synthelabo and the European Union.

Who has reviewed the study? The NorthWest Multi-Centre Research Ethics Committee reviewed this study.

Thank you for taking time to consider participating in this study. If you agree to take part, you will be given a copy of this information sheet and a copy of the signed consent form.

Further information can be obtained from:

[redacted]

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Appendix 3 International Carotid Stenting Study follow-up form

ICSS FOLLOW UP FORM

(Please ask the patient to complete form EQ5D at same time)

Centre .... Investigator .... ICSS No __ __ __ __
Family Name .... Forename .... D o B __ __/__ __/__ __
day/month/year

Follow up (time since randomisation): 1mth ☐ 6mth ☐ 1yr ☐ 2yr ☐ 3yr ☐ 4yr ☐ 5yr ☐
Extra ☐
(follow up dates should be calculated from date of randomisation except one month which is calculated from date of treatment)

Date of follow up __ __/__ __/__ __
day/month/year

EVENTS SINCE LAST FOLLOW UP

	Yes	No	Date most recent day/month/year	Duration of symptoms (999 if persisting)
Death ✞	☐	☐	__ __/__ __/__ __	
Left carotid ischaemic stroke (symptoms >24hrs)*	☐	☐	__ __/__ __/__ __	__ __ __ days
Right carotid ischaemic stroke (symptoms >24hrs)*	☐	☐	__ __/__ __/__ __	__ __ __ days
Vertebrobasilar ischaemic stroke (symptoms >24hrs)*	☐	☐	__ __/__ __/__ __	__ __ __ days
Left retinal infarction. (symptoms >24hrs)*	☐	☐	__ __/__ __/__ __	__ __ __ days
Right retinal infarction (symptoms >24hrs)*	☐	☐	__ __/__ __/__ __	__ __ __ days
Intracerebral haemorrhage (symptoms >24hrs)*	☐	☐	__ __/__ __/__ __	__ __ __ days
Subarachnoid haemorrhage (symptoms >24hrs)*	☐	☐	__ __/__ __/__ __	__ __ __ days
Left carotid TIA (symptoms <24hrs)	☐	☐	__ __/__ __/__ __	
Right carotid TIA (symptoms <24hrs)	☐	☐	__ __/__ __/__ __	
Vertebrobasilar TIA (symptoms<24hrs)	☐	☐	__ __/__ __/__ __	
Left carotid amaurosis fugax (symptoms <24hrs)	☐	☐	__ __/__ __/__ __	
Right carotid amaurosis fugax (symptoms<24hrs)	☐	☐	__ __/__ __/__ __	
Non fatal M I**	☐	☐	__ __/__ __/__ __	
Other medical events (give details)	☐	☐	__ __/__ __/__ __	

Details ....

✞ Please complete death report
*** Please complete major event report, **complete major event report if within 30 days of stenting/surgery**

Modified RANKIN on day of follow up:

0 ☐ Asymptomatic
1 ☐ Non-disabling symptoms which do not interfere with lifestyle
2 ☐ Minor disability-symptoms which lead to some restriction in lifestyle but do not interfere with the patients 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** but does not need constant attention day and night.
5 ☐ Severely disabled-totally dependent requiring constant attention day and night.
6 ☐ Dead

Is any disability rated above caused by medical condition/s other than stroke Yes☐ No ☐

If Yes give details...

	Yes	No
Smoking currently	☐	☐
Blood pressure	Systolic __ __ __ mmHg	Diastolic __ __ __ mm Hg

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ICSS No

PROCEDURES PERFORMED SINCE LAST FOLLOW UP (OR RANDOMISATION IF 1 MONTH FOLLOW UP)

	Yes	No	Date performed day/month/year
Left carotid endarterectomy*	☐	☐	__ __/__ __/__ __
Right carotid endarterectomy*	☐	☐	__ __/__ __/__ __
Left carotid angioplasty/stenting**	☐	☐	__ __/__ __/__ __
Right carotid angioplasty/stenting **	☐	☐	__ __/__ __/__ __
Left vertebral angioplasty/stenting **	☐	☐	__ __/__ __/__ __
Right vertebral angioplasty/stenting **	☐	☐	__ __/__ __/__ __
Other surgery (give details)	☐	☐	__ __/__ __/__ __ Details.................

………

* **Ensure surgery technical data form is completed**

MEDICATION AT TIME OF FOLLOW UP:
Warfarin ☐ Heparin ☐ Aspirin ☐ Ticlopidone ☐ Clopidogrel ☐ Dipyridamole ☐ Other anticoagulant/antiplatelet agent ☐ (specify) **…………**
Statin therapy ☐
Antihypertensive treatment ☐

IMAGING - N.B. CAROTID ULTRASOUND SHOULD BE PERFORMED ANNUALLY:

		Yes	No	Date day/month/year
Carotid Ultrasound performed		☐	☐	__ __/__ __/__ __
CT performed		☐	☐	__ __/__ __/__ __
MRI performed		☐	☐	__ __/__ __/__ __
Angiography	IA	☐	☐	__ __/__ __/__ __
	IVDSA	☐	☐	__ __/__ __/__ __
	MRA (non-enhanced)	☐	☐	__ __/__ __/__ __
	CEMRA	☐	☐	__ __/__ __/__ __
	CTA	☐	☐	__ __/__ __/__ __

Please send copy of all FILMS and REPORTS to ICSS office

Now please check patient has completed form EQ5D **Yes** ☐

Please arrange next follow up appointment – this should be 6 months after randomisation then at annual intervals calculated from randomisation date. If patient has a stroke during follow up please arrange extra follow up appointments 30 days and 6 months after the event.

Next appointment arranged **Yes** ☐ **No** ☐

Form completed by (PRINT)..Date __ __/__ __/__ __
day/month/year

PLEASE COPY FOR YOUR FILES THEN POST OR FAX THIS FORM TO THE ICSS OFFICE TOGETHER WITH COPIES OF THE EQ5D AND ANY RELEVANT IMAGING FILMS AND/OR REPORTS.

[redacted]

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Appendix 4 International Carotid Stenting Study ultrasound form

ICSS ULTRASOUND FORM

Centre ____

Investigator ____

ICSS No __ __ __ __

Patient's Family Name ____________________ Forename _____________________

Patient's DoB __ __/__ __/__ __
day/month/year

DATE OF ULTRASOUND: __ __/__ __/__ __
day/month/year

	Right carotid artery	**Left carotid artery**
CCA PSV		
ICA PSV		
ICA EDV		

Form completed by (PRINT) ___________________________________ Date __ __/__ __/__ __

day/month/year

PLEASE POST OR FAX THIS FORM TO THE ICSS OFFICE
TOGETHER WITH COPIES OF THE ULTRASOUND REPORT
[redacted]

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Appendix 5 Major event report

ICSS MAJOR EVENT REPORT
(Stroke or Myocardial infarction)
Please complete this form, AS WELL AS A FOLLOW UP FORM, for any patient having a stroke or MI

Centre .... Investigator .... ICSS No __ __ __ __
Family Name .... Forename ....D o B __ __/__ __/__ __

day/month/year

Please complete all sections as appropriate.

STROKE REPORT
Date of onset day__ __/month__ __/year__ __
Was the stroke: Non-fatal ☐ Fatal ☐ (complete death report)

Pathology of stroke	**Yes**	**No**
Was CT/MRI scan done to confirm diagnosis	☐	☐
Ischaemic stroke[1]	☐	☐
Intracerebral haemorrhage	☐	☐
Subarachnoid haemorrhage	☐	☐
Subdural haematoma	☐	☐

[1]If stroke was ischaemic then please give classification, TOAST Criteria (please tick one box):

Large vessel atherosclerosis ☐
Small-vessel occlusion (lacunar) ☐
Cardioembolic ☐
Other determined cause ☐ Give details of type……………………………
Unknown cause ☐

NB Haemrrhagic transformation of an initial infarction should be classified as an ischaemic stroke

Precipitating Events (please tick probable event):
Complication of angiography ☐
Complication of carotid procedure (surgery or stenting) ☐
Hypotension or cardiac arrhythmia ☐

Territory of stroke (please tick probable territory, or territories - if more than one):
Right retinal/ophthalmic artery ☐
Left retinal/opthalmic artery ☐
Right middle or anterior cerebral artery ☐
Left middle or anterior cerebral artery ☐
Right posterior cerebral artery ☐
Left posterior cerebral artery ☐

Vertebrobasilar artery (excluding posterior cerebral artery) ☐
Unknown territory ☐

HYPERPERFUSION SYNDROME
Was syndrome non fatal ☐ fatal ☐ **(Please complete death report)**
Was syndrome complicated by stroke **Yes** ☐ **No** ☐

If yes complete section above for stroke

IMAGING PERFORMED AFTER STROKE ONSET OR HYPER PERFUSION SYNDROME:

		Yes	No	Date day/month/year
Carotid Ultrasound performed		☐	☐	__ __/__ __/__ __
CT performed		☐	☐	__ __/__ __/__ __
MRI performed		☐	☐	__ __/__ __/__ __
Angiography	IA	☐	☐	__ __/__ __/__ __
	IVDSA	☐	☐	__ __/__ __/__ __
	MRA (non-enhanced)	☐	☐	__ __/__ __/__ __
	CEMRA	☐	☐	__ __/__ __/__ __
	CTA	☐	☐	__ __/__ __/__ __

Please complete ultrasound form (if done)

Please send copy of all FILMS and REPORTS to ICSS office

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ICSS No __ __ __ __

Modified RANKIN scale at 30 days after event (estimate if not seen then): Date:__/__/__ :

0 ☐ Asymptomatic
1 ☐ Non-disabling symptoms which do not interfere with lifestyle
2 ☐ Minor disability-symptoms which lead to some restriction in lifestyle but do not interfere with the patients 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** but does not need constant attention day and night.

5 ☐ Severely disabled-totally dependent requiring constant attention day and night

6 ☐ Dead

Is any disability rated above caused by medical condition/s other than stroke Yes☐ No ☐

If Yes give details…………………………………………………………………..………………………

Was the patient seen more than 6 months after event Yes☐ No ☐
If yes give modified Rankin score at 6 months (estimate if not seen then)
1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐
If No please schedule follow up for 6 months after stroke onset

MYOCARDIAL INFARCTION REPORT Date of event __ __/__ __/__ __
Was MI: Non-fatal ☐ Fatal ☐ (please complete death report)

	Yes	**No**
Cardiac enzymes elevated 2x normal	☐	☐
Chest discomfort for >than 30 minutes	☐	☐
Diagnostic ECG	☐	☐
Other reasons for diagnosis	☐	☐ If yes give

details………………………..
NB. Two out of three of above required for diagnosis (see protocol)

Description of outcome event: Please give brief description of onset, duration and results of relevant investigations especially CT and MRA findings and any evidence indicating aetiology. **If stroke occurred within thirty days of surgery or stenting** please describe;

1) If anything unusual was noted (e.g. blood pressure, results of monitoring etc.)
2) Exactly what was being done when the stroke occurred if it did so during the procedure
3) Whether the stroke could be attributed to any particular technical factor or complication

………
………
………
………
………
………
………………………………………………

Form completed by (PRINT) .... Date __ __/__ __/__ __

PLEASE COPY FOR YOUR FILES THEN POST OR FAX THIS FORM TO THE ICSS OFFICE TOGETHER WITH COPIES OF ANY RELEVANT IMAGING FILMS AND/OR REPORTS.
[redacted]

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Appendix 6 Death report

ICSS Death Report

Centre .... Investigator .... ICSS No __ __ __ __

Family Name .... Forename ....D o B __ __/__ __/__ __

day/month/year
Date of Death __ __/ __ __/ __ __
Day /Month /Year

Underlying cause of death (main event leading to death)

	Tick
Stroke	☐ (complete major event form)
Myocardial Infarction	☐ (complete major event form if within 30 days
surgery/stenting)	
Sudden death, probably cardiovascular	☐
Pulmonary embolism	☐
Other vascular (e.g. aortic aneurism)	☐ Details:

………………………………………………………
……
……
………………………………………………………………………………………………

Non-vascular cause ☐Details:
………………………………………………………
……
………………………………………………………………………………………………………

Brief description of events leading to death:…………………………………………………………………...
……
……
……
……
……
…………………………………………………………………………..

Documentation

Was post-mortem examination (autopsy) performed? Yes ☐ (**please enclose PM/autopsy report**) No ☐

Please obtain copies of death certificate (**please translate into English, if relevant**)

Diagnosis on death certificate:

1. Primary cause of death ……………………………………………………………
2. Contributing cause of death ……………………………………………………………

Form completed by (PRINT): …………………………………………… **Date:** __ __/ __ __/ __ __

Day/month/year

PLEASE COPY FOR YOUR FILES THEN POST OR FAX THIS FORM TO THE ICSS OFFICE TOGETHER WITH COPIES ANY RELEVANT IMAGING FILMS AND/OR REPORTS.

[redacted]

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Appendix 7 Statistical analysis plan

ICSS Safety (30 day) Results – Statistical Analysis Plan

Background:

ICSS is a randomised controlled trial of carotid artery stenting (CAS) versus carotid endarterectomy (CEA) for the long term prevention of disabling and fatal stroke in patients with symptomatic carotid artery stenosis. A total of approximately 1700 patients will be randomised; 1500 from centres which are 'non-probationary' and 200 from centres which are 'probationary' (i.e. do not yet satisfactorily meet the CAS and/or CEA 'previous experience' criteria as a centre overall). This statistical analysis plan is limited to the main secondary endpoint of the trial - morbidity and mortality during the 30-day post procedural period – which will be published prior to the primary analysis results.

Section 1: PLANNED TIMING OF DATASET CLOSURE FOR 30 DAY RESULTS

- Only CEA and CAS procedures that have taken place up to 90 days after the last patient has been randomised into ICSS will be included in the main paper results.

- The dataset for analysis will be locked approximately 5.5 months after the last patient was randomised (17th April 2009).

Section 2: KEY DEFINITIONS

- **Probationary patients**

  These are defined as ALL patients within a centre (whether allocated to CEA or to CAS) randomised into ICSS whilst the whole centre has a 'probationary' status. In the case of probationary centres which lack the necessary experience in CAS only, a centre is promoted to being a non-probationary centre after a total of 10 CAS procedures have been performed with a complication rate of less than 7 % (i.e. all 10 CAS procedures must be successful). Probationary and non-probationary patients will be identified prior to analysis of the safety results.

- **Procedure initiation**

  A patient is considered to have had an ipsilateral procedure if the procedure has been 'initiated' (i.e. the patient has been given either local or general anaesthetic), even if the procedure is subsequently aborted. Any events occurring within 30 days of initiated but aborted procedures will therefore be included in the main analyses as post-procedural events.

- **Procedure timing**

  All first ipsilateral procedures (see definition of procedure completion above) will be analysed irrespective of time from randomisation.

- **Procedural event**

A procedural event is one that occurs 0 to 30 days after the procedure (day 0 = day of the procedure).

- **Fatal, disabling and non-disabling stroke events**
  A fatal event is one that leads directly to the death of the patient (within 30 days of the event). For this analysis, a stroke will be classified as disabling if the Rankin score is ≥ 3 for 30 or more days after onset.

- **Cranial nerve palsy severity**
  Disability after cranial nerve palsies will be assessed in the same way as for stroke events (see above).

- **Per protocol analysis**
  Secondary per protocol analysis of the ITT Kaplan Meier analysis will be performed. A patient will be excluded in the per-protocol analyses if they:
    - Did not receive the allocated procedure as their first ipsilateral procedure after randomisation.
    - Are known to have been entered into ICSS contrary to inclusion and exclusion criteria at the time of randomisation e.g. Rankin score >=4 at randomisation

- **Primary endpoint**

  The primary endpoint for the 30 day results analyses will be "any stroke, death or peri-operative MI" (non-fatal MI only collected during 30 days post procedure)

- **Secondary endpoints**

  Secondary endpoints will include the following:
    - Any stroke or death
    - Any stroke or death (excluding non-disabling strokes lasting < 7 days)
    - Any stroke / Fatal or disabling stroke / Fatal stroke / Disabling stroke / Non-disabling stroke
    - Any perioperative MI / Fatal perioperative MI
    - Non-stroke, non-MI death
    - All cause death
    - Cranial nerve palsies (disabling and non-disabling)
    - Haematoma requiring surgery, transfusion or prolonging hospital stay
    - All neurological events
    - Rankin score at 30 days post-procedure

Section 3: ANALYSES – KEY POINTS

- **Primary Analyses**

  1) Procedural risk analysis:
    - Excluding those who never had (or are not yet known to have had) a procedure AND those that did not receive the allocated procedure as their first ipsilateral procedure after randomisation
    - The main outcome is risk of an event within 30 days post-procedure (so only follow-up after the procedure is considered and hence pre-procedural events are excluded).
    - The main statistical results will be absolute risk differences, risk ratios and 95% confidence intervals.
    - Any patients with a non-fatal pre-procedural (but post-randomisation) event that go on to have the ipsilateral procedure will still be considered at risk and included in the analysis.
    - All patients (probationary and non-probationary) will be included (see Definitions section above).
    - All first allocated ipsilateral procedures will be included (at any point after randomisation) except where first crossed-over to best medical treatment.

  2) Kaplan- Meier plot

    - Time to event from randomisation by allocated treatment group (ITT) with censoring at 120 days after randomisation if the patient has been followed up for 120 days and is event free (so any pre-procedure and > 30 days post-procedure but < 120 days post-randomisation events will be included). Patients without an event and with <120 days of follow-up will be censored on date of last known event status.
    - The main statistical results will be a KM plot, log rank test and Cox model hazard ratio plus 95% confidence interval. Absolute risk differences at 120 days with 95% CI (from KM plots) may also be estimated.
    - All patients (probationary and non-probationary) will be included (see Definitions section above).

- **Secondary Analyses**

  3) Kaplan-Meier - per protocol:
    - Repeat of Kaplan-Meier plot analyses set out in 2) above, but for the 'per-protocol' population of patients only (see Definitions section above).

  4) Pre-defined treatment by risk factor interaction analyses:
    - Repeat primary ITT analysis with sub-group analysis (based on HR and interaction test) using the following pre-defined baseline risk factor

subgroups (categories may be collapsed or changed prior to analysis if numbers of events are small):

- ✓ Age (<70 and >=70 years: approx. median age)
- ✓ Gender (Male, Female)
- ✓ Time from most recent pre-randomisation event to procedure (<=14 days, >14 days)
- ✓ Type of most recent event prior to randomisation (TIA, stroke, AF)
- ✓ More than one event of any type prior to randomisation (Yes, No)
- ✓ Stroke prior to most recent event pre-randomisation (Yes, No) – only if sufficient numbers
- ✓ Ipsilateral stenosis (50-69%, 70-99%)
- ✓ Status of contralateral artery at randomisation (0-49%, 50-69%, 70-99%, Occluded)
- ✓ Size of centres (<50 , >=50 patients)
- ✓ Diabetes
- ✓ Hypertension

5) Adjustment for pre-determined risk factors:

- o For all these 30 day analyses, there will be no adjustment for pre-determined risk factors. A sensitivity analysis controlling for predetermined risk factors e.g. age (<60, 60-69, 70+), sex, contralateral occlusion, side of artery will also be performed. An additional analysis adjusting for centre will also be performed. As there are 50 centres, a modified 'centre' variable will be used instead of the centre variable itself e.g. countries stratified by probationary status of centres.

6) Probationary patients:

- o Using dataset with probationary + non-probationary patients, perform treatment x probationary status interaction tests to identify whether any evidence of a difference in treatment effect by probationary status (but probably small numbers).
- o A sensitivity analysis of the primary analyses (with non-probationary patients and probationary patients combined) will be performed where the 2 centres that were stopped to poor results will be excluded.

7) Meta-analysis

- o A provisional literature based meta-analysis of the stroke or death 30 day outcome may be performed.

8) Learning curve:

- o Analysis of learning curve of surgeons and interventionalists. This will be a separate analysis and paper and as such will have a separate statistical analysis plan. (NB/ could extract information from files on prior experience of interventionalists taking part in the trial)

Section 4: ADDITIONAL ANALYSES

- CONSORT trial flow diagram.

The following analyses will all be performed by allocated treatment:

- Tabulation of summary statistics for baseline characteristics (demography, medical risk factors, severity of stenosis, disability).
- Tabulation of summary statistics for baseline cerebrovascular symptoms, by allocated treatment.
- Tabulation of summary statistics for time from randomisation to first ipsilateral treatment and from index event to first ipsilateral treatment.
- Tabulation of summary statistics for technical information on the first ipsilateral procedure (types of stents, protection device used [y/n], type of protection device, time from procedure to discharge for those without an event).

ICSS Safety Long-term Results – Statistical Analysis Plan

Background:

ICSS is a randomised controlled trial of carotid artery stenting (CAS) versus carotid endarterectomy (CEA) for the long term prevention of disabling and fatal stroke in patients with symptomatic carotid artery stenosis. A total of approximately 1700 patients have been randomised; 1500 from centres which are 'non-probationary' and 200 from centres which are 'probationary' (i.e. do not yet satisfactorily meet the CAS and/or CEA 'previous experience' criteria as a centre overall). This statistical analysis plan describes the long-term analyses of the trial.

Section 1: TRIAL POPULATION

Individuals randomised in the study excluding those randomised to the MRI sub-study after randomisation in the main study was completed.

Section 2: PLANNED TIMING OF DATASET CLOSURE FOR LONG-TERM RESULTS

- **July 2011-28th February 2012**
    - Data cleaning and final collecting
- **Oct 2011 -28th February 2012**
    - Steering committee teleconference Nov 21st
        - Primary and secondary outcomes finalised and agreed upon
    - Internal adjudication
        - Strokes
        - Other deaths
    - Send to external adjudication
        - Strokes
    - **End of follow-up: 31st December 2011**

- **Database locked: 28th February 2012** (to allow two months for final adjudication and cleaning)
- i.e. Centres will be asked to return all data by 31st December 2011 in order that cleaning and final checks be performed by 28th February 2012
- Statistical analysis code pre-planning and testing of analyses in SAP using a cut of the data from January 2012

- **March 2012 – May 2012**
  - Data analysis
  - Note: A minimum of 3 months (i.e. of a part-time statistician) is required for analysis when a CLEAN final data set has been received i.e. For a CLEAN data set (i.e. with all events adjudicated) received on 1st March 2012, results would be anticipated for June 1st 2012.

Section 3: KEY DEFINITIONS

- **Probationary patients**
  These are defined as ALL patients within a centre (whether allocated to CEA or to CAS) randomised into ICSS whilst the whole centre has a 'probationary' status. In the case of probationary centres which lack the necessary experience in CAS only, a centre is promoted to being a non-probationary centre after a total of 10 CAS procedures have been performed with a complication rate of less than 7 % (i.e. all 10 CAS procedures must be successful). Probationary and non-probationary patients were identified prior to interim analyses and will be described in the final analysis. All probationary patients will be included in the final analyses.

- **Procedure initiation**
  A patient is considered to have had an ipsilateral procedure if the procedure has been 'initiated' (i.e. the patient has been given either local or general anaesthetic), even if the procedure is subsequently aborted.

- **Procedure timing**
  All first ipsilateral procedures will be analysed irrespective of time from randomisation according to the definition used for the short-term paper (i.e. no additional procedures will be included over and above those already considered in that paper).

- **Procedural event**
  A procedural event is one that occurs 0 to 30 days after the procedure (day 0 = day of the procedure).

- **Fatal, disabling and non-disabling stroke events**
  A fatal event is one that leads directly to the death of the patient (within 30 days of the event). For this analysis, a stroke will be classified as disabling if the Rankin score is ≥ 3 at 30 days after onset and is one which has increased by at least 1 point compared to

the Rankin score before onset where the increase is attributable to stroke. Note that the ICSS protocol mentions disability at 6 months but the TSC felt that disability at 1 month was preferable. Note further that, although worded here slightly differently for clarity, this definition is that used for all analyses in the short-term results paper.

- **Cranial nerve palsy (CNP) severity**
  Disability after cranial nerve palsies will be assessed in the same way as for stroke events (see above). [Note: any other disability will be defined accordingly.]

- **Per protocol, post-treatment analysis (modified per-protocol)**
  Secondary per protocol, post treatment analysis will be performed to compare non-procedural outcomes in patients whose allocated procedure was completed (i.e. not aborted). This analysis 'starts' at 31 days after the allocated ipsilateral procedure i.e. it includes all follow-up from this point onwards, and excludes the following patients:
  - those that did not have their allocated procedure initiated (i.e. either x BMT or x CEA/CAS without an attempt at their allocated procedure)
  - those whose allocated procedure was initiated but the stent was not deployed or the surgery was aborted
  - those that died between randomisation and 30 days after the allocated ipsilateral procedure
  - those that left follow-up between randomisation and 30 days after the allocated ipsilateral procedure
  - those that had a fatal event during 30d but died > 30 days after procedure

Patients with earlier non-fatal strokes are therefore included (and any second events they have) although a sensitivity analysis will be performed in which patients with an earlier non-fatal stroke are excluded.
Note, this is a NON-RANDOMISED comparison between treatment groups (i.e. it is a selected group of patients and thus there may differences in patient characteristics between the treatment groups that are not due to chance).

- **Outcome events of interest**

  - Ipsilateral Stroke
  - Stroke (any territory)
  - Death
  - Vascular death
  - Myocardial Infarction death
  - TIA

- **Primary endpoint for analysis**

  Fatal or disabling stroke (in any territory).

  Note that this as stated in the ICSS short-term results paper and the protocol. It will not include other peri-procedural non-stroke deaths.

- **Timepoint for Kaplan-Meier vs time-point for estimates for primary analyses**

    - KM plots will be provided up to a point in time for which there are a reasonable number of events which the TSC agreed will likely be at 8 years of follow-up
        - It was noted at the TSC that it preferable to include as much of the data as possible despite caveats about not plotting KM plots when few events/patients remain. (See Pocock, Clayton and Altman, Lancet 2002; 359:1686-89.) Numbers at risk in each treatment arm will be provided for each year of follow-up.
        - Cumulative outcomes (i.e. risk differences) will be reported at 8 years subject to sufficient data (See Pocock, Clayton and Altman), whereas hazard ratios from Cox PH model will use all data up to locking of database (see below). Such comparisons will also be presented at 1- and 5-years.
    - Cox PH estimates
        - All clean follow-up events (for events prior to 31st Dec 2011) up to database locking on February 2012 will be included (i.e. including follow-up data beyond that shown in KM plots) except, of course, for events for individuals who have formally withdrawn from ICSS. Specifically, such patients will be considered censored from the day after withdrawal so that even if data on death is available from ONS such events will not be included.
            - A further note on the use of ONS data: blinded assessment of the patterns of visit follow-up will be considered to ascertain how many deaths would be identified only from ONS (i.e. not reported by recruiting centres). It is anticipated that all such data on deaths would be included, at least up to 12 months after last known follow-up.
        - A concern could be non-proportionality because of few individuals and few events later on. Such assumptions will be checked but it is not anticipated that events later on will affect this assumption.

- **Secondary endpoints for analysis**

    - Any stroke or death
    - Death of any cause
    - Any stroke
    - Ipsilateral stroke / Non-ipsilateral stroke
    - Ipsilateral stroke and peri-procedural stroke or death
    - Vascular death
        - Note: these are neither internally nor externally adjudicated
    - Myocardial Infarction death
        - Note: these are not externally adjudicated with internal adjudication only up to 30 days

- TIA
  - Note: these are not adjudicated
- Further treatment of the randomised artery by interventional radiology techniques or surgery after the initial attempt
- Modified Rankin score at set time periods e.g. 1, 5 and 8 years
- Note: restenosis and quality of life will each form the basis of separate papers hence will not be reported in the ICSS long-term results.

Section 4: ANALYSES – KEY POINTS

- **Primary Analyses**

1) ITT analysis:

- Time to event from randomisation by allocated treatment group (ITT). All follow-up time will be used (see specifics for KM plot below). Patients without an event will be censored on date of last known event status.
- The main statistical results will be
  1. KM plot
  2. Log rank test
  3. Cox model hazard ratio plus 95% confidence interval. Model proportionality assumption will checked with appropriate techniques e.g. Schoenfeld residuals
  4. Absolute risk differences at 1, 5 and 8 years with 95% CI (from KM plots) in line with timings reported above.
- All patients (probationary and non-probationary) will be included (see Definitions section above).

- **Secondary Analyses**

2) Per-protocol, post treatment analysis (modified per-protocol):

- Same analysis as 1) but restricting to 'modified per protocol' population as defined in section 3.

3) Characterisation of timing of events

- Only first events will be considered except for the modified Rankin score for which we would like to know whether changes in Rankin scores between time points is caused by new events.
  - Note: Rankin score will form the basis of another paper with simple summary measures only reported in the main paper
  - It is anticipated that the full frequency distribution will be included.
- A table like Table 2 included in the EVA-3S long-term paper (*Lancet Neurol* 2008;7:885–892) will be included which splits events in to peri-procedural and non-procedural. Note that for ICSS, there will be less information in the table since the primary endpoint does not include peri-procedural deaths due to causes other than stroke.

4) Pre-defined treatment by risk factor interaction analyses:

Interaction analyses will be undertaken as for interim analyses: i.e. for ITT only from time of randomisation, except for time from event to treatment, which is analysed per protocol (here defined as from time of treatment for all patients whose allocated treatment was initiated).

Subgroups to analyse in ITT analyses (except for time to treatment which will be per-protocol) are those included in the interim analyses, specifically:

- ✓ Age (<70 and >=70 years: approx. median age)
- ✓ Gender (Male, Female)
- ✓ Time from most recent pre-randomisation event to procedure (<=14 days, >14 days)
- ✓ Type of most recent event prior to randomisation (TIA, stroke, AF)
- ✓ More than one event of any type prior to randomisation (Yes, No) (Multiple ipsilateral symptoms)
- ✓ Stroke prior to most recent event pre-randomisation (Yes, No) – only if sufficient numbers
- ✓ Ipsilateral stenosis (50-69%, 70-99%)
- ✓ Status of contralateral artery at randomisation (0-49%, 50-69%, 70-99%, Occluded)
- ✓ Size of centres i.e. centre recruitment (<50 , >=50 patients)
- ✓ Diabetes
- ✓ Treated Hypertension
- ✓ Centre experience (probationary, non-probationary)

5) Adjustment for pre-determined risk factors:

- For all these long-term analyses, there will be no adjustment for pre-determined risk factors. A sensitivity analysis controlling for predetermined risk factors e.g. age (<60, 60-69, 70+), sex, contralateral occlusion, side of artery will also be performed. An additional analysis adjusting for centre will also be performed. As there are 50 centres, a modified 'centre' variable will be used instead of the centre variable itself e.g. countries stratified by probationary status of centres.

6) Exclusion of stopped centres:

- No sensitivity analyses excluding the stopped centres will be performed as all the problems were periprocedural.

7) Meta-analysis

  - Meta-analysis is required by the Lancet as part of their recommendations for reporting of clinical trials.
  - However, since it is anticipated that a revised Cochrane review of CAS vs. CEA will be completed before publication of the ICSS long-term results, we could simply add the ICSS data to the long-term meta-analysis in the Cochrane review

Section 5: ADDITIONAL ANALYSES

- CONSORT trial flow diagram.
- Summary statistics for length of follow-up during trial e.g. median duration of follow-up.

Since the goal of the long-term results paper is as a stand-alone paper, the following analyses will all be performed by allocated treatment (even though some of them were reported in short-term results paper).

- Tabulation of summary statistics for baseline characteristics (demography, medical risk factors, severity of stenosis, disability).
- Tabulation of summary statistics for baseline cerebrovascular symptoms, by allocated treatment.

Additionally, the following table by treatment will be created:

- A table of treatment during follow-up – e.g. proportion of patients comparing the 2 arms receiving BP treatment, antiplatelet agents, statins and data on their blood pressure readings during follow-up.

- Since information concerning medications will be collected at different times during follow-up and may change over the course of follow-up, comparisons between the two treatment arms will be performed at fixed time points like those defined above (anticipated to be 1 year, 5 years and 8 years). A table like Table 3 in the SPACE long-term paper (*Lancet Neurol* 2008;7:893–902) will be produced.

ICSS Effect of white-matter lesions on the risk of periprocedural stroke – Statistical Analysis Plan

We will test two hypotheses using the methods and analyses described before any results are analysed.

1 Compared with less extensive white-matter lesions, more extensive white-matter lesions are associated with an increased risk of procedural stroke after treatment of carotid artery disease by either carotid artery stenting or carotid endarterectomy.
2 The increase in procedural risk would differ in patients treated by carotid artery stenting compared with carotid endarterectomy.

The analyses to be done for the following outcome measures: any stroke, non-disabling stroke, and disabling or fatal stroke.

Data will be analysed per protocol—i.e., the analysis will include only patients who received the allocated treatment as their first ipsilateral revascularisation procedure. Patients who received the alternative revascularisation procedure as their first treatment (cross-overs), or who received no revascularisation treatment, will be excluded from this analysis.

All outcome events occurring within 30 days after initiation of the first allocated treatment will be included.

Patients to be dichotomised into two groups at the median value for the age-related white-matter changes score. The median has been chosen as the cut-point for the analysis to ensure equal-sized groups of patients for the comparisons and to avoid the risk of the bias introduced by selecting an optimum cut point after initial analysis of the data.

The baseline characteristics in the two treatment groups will be compared according to whether their ARWMC score is lower than 7 versus 7 or greater using Pearson's $\chi 2$ test or analysis of variance.

We will compare the 30-day risk of the various outcome events between the two treatment groups using a Cox proportional hazards model. We will estimate the cumulative incidences of the different outcome measures using Kaplan-Meier analysis and compare them using log-rank tests stratified by treatment with ARWMC score dichotomised at the median.

All analyses will be adjusted for age, sex, and vascular risk factors

Appendix 8 Protocol amendment details

Original ethical approval for ICSS was received on 4 October 2000 and randomisation commenced in May 2001 using protocol version 2.00.

Protocol Version 3.1 was introduced after receiving ethical approval on 31 October 2003. The main changes from version 2.00 were:

- The rules governing proctoring and probationary centres, in particular under what conditions a centre may make the transition from probationary to full, were made more explicit.
- The inclusion criteria were clarified (making it explicit that it is atheromatous stenosis being studied) and modified (the degree of stenosis warranting treatment set at 50% or greater by the NASCET criteria) to reflect current generally accepted practice in the assessment and treatment of stenosis.
- The nature of symptomatic disease in the inclusion criteria was defined so that: '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.'
- Exclusion criteria were extended to include non-atheromatous disease, previously treated artery, planned major surgery (especially CABG) within 1 month of proposed carotid intervention, or planned common carotid surgery.
- Procedures for dealing with suspected problems with surgical or stenting technique at individual centres were included in the protocol.
- The projected sample size was reduced from 2000 to 1500.
- For the primary outcome measure the wording was altered to clarify that non-stroke deaths will be censored in the primary outcome analysis.
- The EQ-5D-3L became the only measure of quality of life – the Short Form questionnaire-36 items (SF-36) was dropped. Details of the arrangements for payments to centres and the responsibilities of centres with regard to indemnity were included.

Protocol Version 3.2 was introduced after receiving ethical approval on 22 November 2007. The main changes from version 3.10 were:

- Sample size: the protocol was clarified to make it plain that 1500 patients will be enrolled at full centres – data from patients enrolled at probationary centres to be analysed separately.
- The duration of follow-up will now exceed 5 years for some patients: 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.
- Two substudies were appended to the main protocol: a restenosis substudy involving an additional investigation (computerised tomography angiography of the carotid) at 1 year after randomisation and a MRI substudy involving three MRI investigations (one before and two after treatment). Consent and patient information forms for these substudies were included with this notification.

Appendix 9 Further details of the cost–utility analysis

1. Prediction of hospital and care home costs in ICSS stroke patients using OXVASC study data.
2. Summary of data used in cost–utility analysis.
3. Additional results for univariate sensitivity analysis.
4. Consolidated Health Economic Evaluation Reporting Standards statement.

Prediction of hospital and care home costs in the International Carotid Stenting Study stroke patients using Oxford Vascular study data

Hospital and care home costs for patients who had one or more strokes in ICSS were predicted using the results from multivariate regression analyses aimed at determining the predictors of hospital and care home costs in patients enrolled in the OXVASC study.[36,37]

Oxford Vascular study

The OXVASC study population comprises over 91,000 patients registered in nine general practices across Oxfordshire, UK. Briefly, patient registration began on April 2002 and is ongoing. Only consenting TIA or stroke patients recruited from 1 April 2002 to 31 March 2007 were included in this analysis.

Patients were followed up from the first TIA or stroke in the study period for which the patient sought medical attention, referred to here as the index event. Surviving patients were followed up by a research nurse at 1, 6, 12, 24 and 60 months after the event. Data were collected on patients' living arrangements, risk factor changes and disability (measured using the mRS). Patients were also followed up via their general practitioner and hospital records, recurrent vascular events were identified by ongoing ascertainment, and all patients had mortality follow-up.

Impairment was measured using the National Institutes of Health Stroke Scale (NIHSS), which was used to categorise event severity. Non-disabling events were defined as NIHSS scores of ≤ 3, and disabling events were those with scores of ≥ 4. Case fatality was defined as death within 30 days of index event. Long-term institutionalisation was defined as admission into a nursing or residential care home. Patients' hospital records from the Oxford Radcliffe Hospitals NHS Trust were reviewed for any accident and emergency visit, emergency transport, outpatient care visit, day case or hospitalisation from the date of first TIA or stroke within the OXVASC study period (i.e. index event) and for up to 5 years.

Costs

Long-term institutionalisation was costed as the cost per week in a private nursing home, which in 2013 was £750 per week.[32] All hospital care resource use was priced using reference costs for NHS trusts and NHS trust financial returns for the year 2009.[34] These costs were then updated to 2013 prices using the Hospital and Community Health Services pay and price inflation index.[32]

Statistical analysis

Nursing/residential care home admission

A Cox proportional hazards model was used to assess the predictors of 6-month admission into a nursing or residential care home. We only assessed admission within 6 months of first stroke to avoid over-estimation of costs owing to non-related conditions. The analysis excluded all patients who had died within 30 days of index event, as no patient with a case fatal event was admitted into a care home in

OXVASC study. Independent variables included in the analysis were age at time of event; sex; previously disabled before the event; previous history of MI, angina, TIA, stroke or atrial fibrillation (AF); index event type (TIA or stroke); index event severity (non-disabling or disabling); and number of recurrent strokes up to 5 years after the index event (*Table 11*).

A 6-month risk of admission into a care home in ICSS stroke patients was predicted based on the results of the regression analyses presented in *Table 11*. We multiplied this predicted risk by £19,740, which was the mean 1-year care home cost for a stroke patient admitted within 6 months to a nursing or residential care home. Given that no OXVASC study patient was admitted into a care home after a case fatal event, ICSS patients with a fatal event as their first stroke were assigned a cost of £0.

Hospital care

A generalised gamma linear model assuming a log identity was used to determine the predictors of 5-year hospital care costs. Independent variables included in the analysis were: age at time of event; sex; previously disabled before the event; previous history of each of MI, angina, peripheral vascular disease (PVD), hypertension, TIA, stroke or atrial fibrillation; index event type (TIA or stroke); index event severity (non-disabling, disabling, fatal); and, number of recurrent strokes up to 5 years after the index event (*Table 12*).

TABLE 11 Predictors of 6-month care home admission

Characteristic	HR	*p*-value	95% CI
Age	1.088	< 0.001	1.044 to 1.134
Sex			
Female	Reference		
Male	0.687	0.245	0.365 to 1.293
Previously disabled	3.514	< 0.001	1.866 to 6.620
History of:			
MI	0.515	0.212	0.182 to 1.458
TIA	0.319	0.037	0.109 to 0.935
Stroke	0.687	0.460	0.667 to 2.448
Angina	1.222	0.634	0.535 to 2.791
AF	2.567	0.003	1.374 to 4.797
Index event			
TIA	Reference		
Stroke	1.138	0.794	0.432 to 2.996
Index event severity			
Non-disabling	Reference		
Disabling	4.590	< 0.001	2.164 to 9.735
Number of recurrent strokes	1.372	0.149	0.893 to 2.107
Observations		1046	

TABLE 12 Predictors of hospital care costs after stroke

Predictors	Coefficient	p-value	95% CI
Age	0.019	< 0.001	0.013 to 0.026
Sex			
Female	Reference		
Male	–0.207	0.010	–0.364 to –0.050
Previously disabled	0.229	< 0.001	0.034 to 0.424
History of:			
MI	0.037	0.777	–0.220 to 0.294
TIA	–0.224	0.036	–0.433 to –0.014
Stroke	0.083	0.388	–0.105 to 0.270
PVD	0.335	0.012	0.734 to 0.598
Angina	0.045	0.708	–0.191 to 0.282
Hypertension	0.017	0.838	–0.144 to 0.177
AF	0.159	0.116	–0.040 to 0.358
Index event			
TIA	Reference		
Stroke	0.203	0.049	0.001 to 0.406
Index event severity			
Non-disabling	Reference		
Disabling	0.676	< 0.001	0.486 to 0.865
Fatal	–1.608	< 0.001	–1.912 to –1.304
Number of recurrent strokes	0.309	< 0.001	0.200 to 0.419
Constant	7.988	< 0.001	7.427 to 8.550
Observations		1205	

The 5-year costs estimated using this model were assumed to be distributed across each year using the proportions reported in Luengo-Fernandez *et al.*[36] We applied these proportions and matched the resulting cost profile to the stroke patients in the ICSS data set based on the year of follow-up in which the event occurred, omitting costs that occurred outside the 5-year time horizon of the economic evaluation.

Given that stroke is associated with old age and often occurs in patients with other comorbidities, such patients are likely to consume substantial health-care resources regardless of event onset. Therefore, the predicted costs that can be estimated from *Table 12* include costs incurred owing to conditions unrelated to stroke. As a result, to better quantify the impact of stroke on costs, we estimated the pre-morbid annual costs (i.e. costs before the initial stroke) and subtracted these from the hospital care costs incurred at each year of follow-up. A similar regression model to that presented in *Table 12* was used to estimate pre-morbid costs each year (*Table 13*). However, we assumed that all costs associated with a fatal event were attributable to the initial stroke. The data used in the cost-utility analysis are summarised in *Table 14*. The additional results for univariate sensitivity analysis calculated at a maximum willingness to pay for a QALY of £30,000 are shown in *Figure 12*. The Consolidated Health Economic Evaluation Reporting Standards statement is given in *Table 15*.

TABLE 13 Predictors of hospital care costs in the year before stroke

Predictors	Coefficient	*p*-value	95% CI
Age	0.019	0.004	0.006 to 0.032
Sex			
Female	Reference		
Male	–0.090	0.590	–0.416 to 0.236
Previously disabled	1.880	< 0.001	1.425 to 2.333
History of:			
MI	0.436	0.074	–0.043 to 0.914
TIA	0.150	0.546	–0.337 to 0.637
Stroke	–0.091	0.682	–0.528 to 0.345
PVD	0.624	0.041	0.026 to 1.221
Angina	0.591	0.008	0.156 to 1.028
Hypertension	–0.099	0.564	–0.436 to 0.238
AF	0.512	0.006	0.144 to 0.880
Index event			
TIA	Reference		
Stroke	0.226	0.169	–0.096 to 0.548
Index event severity			
Non-disabling	Reference		
Disabling	0.253	0.266	–0.192 to 0.698
Constant	4.813	< 0.001	3.769 to 5.856
Observations		1096	

Summary of data used in cost–utility analysis

TABLE 14 Resource use, costs, utility values and QALYs

	Endarterectomy		Stenting		
Variable	Value (£)	*N*	Value (£)	*N*	Unit cost/source
Procedure duration (minutes), mean (SD)	107 (47)	700	68 (33)	691	
Consultant vascular surgeon, *n*	1		0		£140 per hour/reference[32]
Consultant interventional radiologist, *n*	0		1		£140 per hour/reference[32]
Surgical registrar, *n*	1		0		£59 per hour/reference[32]
Consultant anaesthetist, *n*[a]	1		1		£140 per hour/reference[32]
Theatre[b]					£743 per hour/reference[32]

TABLE 14 Resource use, costs, utility values and QALYs (*continued*)

Variable	Endarterectomy		Stenting		Unit cost/source
	Value (£)	*N*	Value (£)	*N*	
Type of anaesthesia, %		794		853	
Local anaesthetic	18		100		£9/reference[33]
General anaesthetic	82		0		£30/reference[33]
Shunt used, %	40	818			£38/University College London Hospitals NHS Foundation Trust
Patch used, %	66	693			£96/University College London Hospitals NHS Foundation Trust
Stent deployed, %			92	816	£840/University College London Hospitals NHS Foundation Trust
Cerebral protection device used, %			71	824	£780/University College London Hospitals NHS Foundation Trust
Other materials used in stenting[c]					£232/University College London Hospitals NHS Foundation Trust
Admitted to ICU post-operatively, %	64	813	52	808	
Length of stay on ICU if admitted (days)	1		1		£661 per day/reference[34]
Length of stay on ward (days), mean (SD)	5.7 (9.4)	803	5.1 (10.8)	789	Endarterectomy £339 per day, stenting £301 per day/reference[34]
Additional carotid artery procedures, mean (SD)		857		853	
Endarterectomy	0.039 (0.193)		0.066 (0.257)		Mean cost of index procedure
Stenting	0.023 (0.159)		0.028 (0.172)		Mean cost of index procedure
Fatal MI in first 30 days, *n* (%)	0 (0)	857	3 (0.35)	853	£1485/reference[35]
Non-fatal MI in first 30 days, *n* (%)	5 (1)	857	0 (0)	853	£5665 in first year, £218 each year thereafter/reference[35]
Severe haematoma in first 30 days, *n* (%)[d]	28 (3)	857	8 (1)	853	£9302/reference[34]
Disabling cranial nerve palsy in first 30 days, *n* (%)	1 (0)	857	1 (0)	853	£6964/reference[34]
Imaging tests, *n*[e]		857		853	
CEMRA	14		13		£208/reference[34]
CT scan	156		171		£88/reference[34]
CTA	54		93		£110/reference[34]
Intra arterial angiography	43		352		£112/reference[34]
Intravenous DSA	4		16		£150/reference[34]
MRA	17		23		£157/reference[34]
MRA/CTA	34		48		£267/reference[34]
MRI	123		119		£157/reference[34]
Ultrasound	234		192		£67/reference[34]

continued

TABLE 14 Resource use, costs, utility values and QALYs (*continued*)

Variable	Endarterectomy		Stenting		Unit cost/source
	Value (£)	*N*	Value (£)	*N*	
Drug treatment at 1 month after treatment, *n* (%)		785		781	
Aspirin	653 (83)		698 (89)		£2.57 per month/reference[62]
Clopidogrel	136 (17)		426 (55)		£1.83 per month/reference[62]
Dipyridamole	161 (21)		94 (12)		£5.29 per month/reference[62]
Antihypertensive	556 (71)		479 (61)		£9.61 per month/reference[62]
Statin	634 (81)		601 (77)		£2.12 per month/reference[62]
Anticoagulant (vitamin K antagonist)	50 (6)		37 (5)		£0.96 per month/reference[62]
Stroke during 5 year follow-up, *n* (%)	71 (8)	857	114 (13)	853	
Stroke severity, *n* (% strokes)		71		114	
Non-disabling	26 (37)		70 (61)		
Disabling	35 (49)		27 (24)		
Fatal	10 (14)		17 (15)		
Recurrent strokes, *n* (% strokes)		71		114	
0	62 (87)		102 (89)		
1	7 (10)		10 (9)		
2	1 (1)		2 (2)		
3	1 (1)		0 (0)		
Cost per patient of treating stroke, mean (SD)		71		114	
First year	7281 (5627)		5792 (5726)		Mean predicted costs/OXVASC Study
Second year	1398 (1398)		1079 (1628)		Mean predicted costs/OXVASC Study
Third year	2050 (1929)		1602 (2034)		Mean predicted costs/OXVASC Study
Fourth year	1522 (1615)		1178 (1702)		Mean predicted costs/OXVASC Study
Fifth year	1831 (1795)		1426 (1894)		Mean predicted costs/OXVASC Study
Cost of index procedure, mean (SD)	4501 (3570)	586	4724 (3293)	660	
Cost of follow-up, mean (SD)	2187 (4522)	389	2401 (5115)	424	
Total costs, mean (SD)	6851 (7403)	274	6994 (7913)	340	

TABLE 14 Resource use, costs, utility values and QALYs (*continued*)

	Endarterectomy		Stenting		
Variable	Value (£)	*N*	Value (£)	*N*	Unit cost/source
Utility values, mean (SD)					
Baseline	0.758 (0.231)	846	0.775 (0.212)	841	
3 months	0.779 (0.233)	805	0.779 (0.255)	810	
6 months	0.768 (0.247)	764	0.759 (0.279)	774	
1 year	0.745 (0.272)	775	0.743 (0.296)	777	
2 years	0.720 (0.302)	741	0.720 (0.305)	744	
3 years	0.685 (0.333)	722	0.675 (0.341)	735	
4 years	0.619 (0.361)	589	0.635 (0.363)	620	
5 years	0.564 (0.396)	461	0.575 (0.393)	498	
QALYs	3.189 (1.204)	329	3.164 (1.364)	362	

CEMRA, contrast enhanced magnetic resonance angiography; CTA, computerised tomography angiography; DSA, digital subtraction angiography; MRA, magnetic resonance angiography.
a The consultant anaesthetist is assumed to spend an additional 30 minutes per patient before and after each procedure.
b Including nursing staff, drugs, consumables and overheads.
c Including catheters, wires and sheaths.
d Requiring surgical evacuation or blood transfusion, or resulting in extended hospital stay.
e Patients may have more than one of each type of test.
Costs are in 2013–14 Great British Pounds (£). All data are raw data with no imputed values.

Additional results for univariate sensitivity analysis

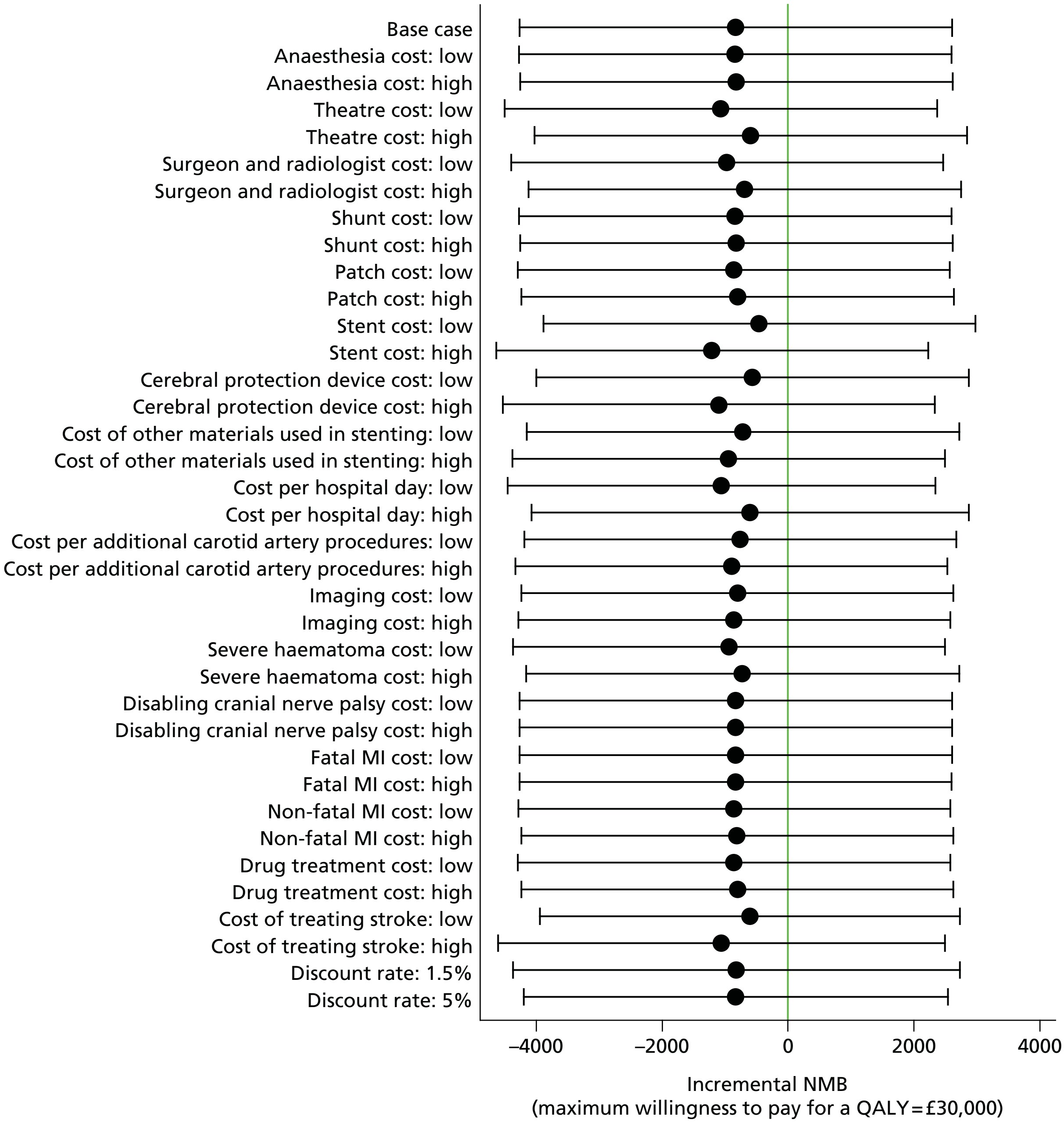

FIGURE 12 Univariate sensitivity analysis: results calculated at a maximum willingness to pay for a QALY of £30,000. All analyses are as for the base-case analysis with univariate adjustment of the parameters listed. Results are point estimates of the incremental NMB of stenting vs. endarterectomy (circles) and 95% CIs (capped spikes). The incremental NMB is calculated at a maximum willingness to pay for a QALY of £30,000.

Consolidated Health Economic Evaluation Reporting Standards statement

TABLE 15 Consolidated Health Economic Evaluation Reporting Standards statement

Section	Item number	Reported on
Title and abstract		
Title	1	The title of *Cost–utility analysis of stenting versus endarterectomy for treatment of symptomatic carotid stenosis* identifies the study as an economic analysis and describes the interventions being evaluated
Abstract	2	A structured summary is provided in the *Scientific summary*
Introduction		
Background and objectives	3	The broader context for the study, and the research question and its rationale, are described in *Cost–utility analysis of stenting versus endarterectomy for treatment of symptomatic carotid stenosis*
Methods		
Target population and subgroups	4	The target population is described in *Chapter 2*
Setting and location	5	The setting and location of the trial are described in *Chapter 2*
Study perspective	6	The study perspective is described in the first part of *Cost–utility analysis of stenting versus endarterectomy for treatment of symptomatic carotid stenosis*
Comparators	7	The comparators are described and justified in the first part of *Cost–utility analysis of stenting versus endarterectomy for treatment of symptomatic carotid stenosis*
Time horizon	8	The time horizon is described and justified in the first part of *Cost–utility analysis of stenting versus endarterectomy for treatment of symptomatic carotid stenosis*
Discount rate	9	The discount rate for costs and outcomes is described and justified in the first part of *Cost–utility analysis of stenting versus endarterectomy for treatment of symptomatic carotid stenosis*
Choice of health outcomes	10	The outcome measure is described and justified in the first part of *Cost–utility analysis of stenting versus endarterectomy for treatment of symptomatic carotid stenosis*
Measurement of effectiveness	11a	The clinical trial used to measure effectiveness is described in *Chapter 2*
Measurement and valuation of preference-based outcomes	12	Methods used to measure and value preference-based outcomes are described in the *Utilities and QALYs* subsection of *Cost–utility analysis of stenting versus endarterectomy for treatment of symptomatic carotid stenosis*
Estimating resources and costs	13a	Methods used to estimate resources and costs are described in the *Resource use and costs* subsection of *Cost–utility analysis of stenting versus endarterectomy for treatment of symptomatic carotid stenosis*
Currency, price date, and conversion	14	Currency, price date and conversion are described in the first part of *Cost–utility analysis of stenting versus endarterectomy for treatment of symptomatic carotid stenosis*
Choice of model	15	We explain that extrapolation beyond the end of the trial using decision–analytical modelling was not undertaken in the first part of *Cost–utility analysis of stenting versus endarterectomy for treatment of symptomatic carotid stenosis*
Assumptions	16	All assumptions used in the analysis are described throughout *Cost–utility analysis of stenting versus endarterectomy for treatment of symptomatic carotid stenosis* and *Appendix 9*
Analytical methods	17	Analytical methods are described in the *Dealing with missing data* and *Statistical methods* subsections in *Cost–utility analysis of stenting versus endarterectomy for treatment of symptomatic carotid stenosis*

continued

TABLE 15 Consolidated Health Economic Evaluation Reporting Standards statement (*continued*)

Section	Item number	Reported on
Results		
Study parameters	18	The main study parameters are in *Table 9* in *Findings of the cost–utility analysis* and *Appendix 9*
Incremental costs and outcomes	19	Incremental costs and outcomes are reported in *Tables 9* and *10* and *Appendix 9* and discussed throughout *Findings of the cost–utility analysis*
Characterising uncertainty	20a	Methods used in the sensitivity analyses are described in the *Sensitivity and subgroup analyses* subsection in *Cost–utility analysis of stenting versus endarterectomy for treatment of symptomatic carotid stenosis*. The results are presented in *Table 10* and *Figures 10* and *11*, and discussed in the *Sensitivity and subgroup analyses* subsection in *Findings of the cost–utility analysis*
Characterising heterogeneity	21	Methods used in the subgroup are described in the *Sensitivity and subgroup analyses* subsection in the *Cost–utility analysis of stenting versus endarterectomy for treatment of symptomatic carotid stenosis*. The results are presented in *Table 10* and discussed in the *Sensitivity and subgroup analyses* subsection in *Findings of the cost–utility analysis*
Discussion		
Study findings, limitations, generalisability and current knowledge	22	Study findings, limitations, generalisability and comparisons with current knowledge are discussed in *Chapter 4*
Other		
Source of funding	23	The funding source is in the *Acknowledgements*. The role of the funder is described in the *Role of the funding source*
Conflicts of interest	24	Conflicts of interests are described in the *Competing interests*

Appendix 10 International Carotid Stenting Study investigators and recruiting centres

Steering Committee

A Algra, J Bamford (chairperson), J Beard, M Bland, AW Bradbury, MM Brown (chief investigator), A Clifton, P Gaines, W Hacke, A Halliday, I Malik, JL Mas, AJ McGuire, P Sidhu and G Venables.

Credentialling Committee

A Bradbury, MM Brown, A Clifton and P Gaines.

Data Monitoring Committee

R Collins, A Molyneux, R Naylor and C Warlow (chairperson).

Outcome Event Adjudication Committee

JM Ferro and D Thomas.

Central office staff at University College London Institute of Neurology

LH Bonati, L Coward, J Dobson (trial statistician), D Doig, J Ederle, RF Featherstone (trial manager), F Kennedy, H Tindall, E Turner, DJH McCabe and A Wallis.

Location of International Carotid Stenting Study recruiting centres

The numbers of patients recruited at each centre (in square brackets) and investigators at each centre are recorded; PI, local principal investigator.

Australia

Austin Health, Heidelberg [46]: M Brooks, B Chambers (PI), A Chan, P Chu, D Clark, H Dewey, G Donnan, G Fell, M Hoare, M Molan, A Roberts and N Roberts.

Box Hill Hospital (Monash University), Melbourne [25]: B Beiles, C Bladin (PI), C Clifford, G Fell, M Grigg and G New.

Monash Medical Centre, Clayton [26]: R Bell, S Bower, W Chong, M Holt, A Saunder and PG Than (PI).

Princess Alexandra Hospital, Brisbane [48]: S Gett, D Leggett, T McGahan (PI), J Quinn, M Ray, A Wong and P Woodruff.

Repatriation General Hospital, Daw Park, Adelaide [6]: R Foreman, D Schultz (PI), R Scroop and B Stanley.

Royal Melbourne Hospital, Melbourne [57]: B Allard, N Atkinson, W Cambell, S Davies (PI), P Field, P Milne, P Mitchell, B Tress and B Yan.

The Royal Hobart Hospital, Hobart [18]: A Beasley, D Dunbabin, D Stary and S Walker (PI).

Belgium

Antwerp University Hospital, Antwerp [10]: P Cras, O d'Archambeau, JMH Hendriks (PI) and P Van Schil.

AZ St Blasius, Dendermonde [5]: M Bosiers (PI), K Deloose and E van Buggenhout.

AZ Sint Jan Brugge-Oostende, Campus Brugge, Brugges [18]: J De Letter, V Devos, J Ghekiere and G Vanhooren (PI).

Cliniques Universitaires St Luc, Bruxelles [1]: P Astarci, F Hammer, V Lacroix, A Peeters (PI) and R Verhelst.

Imelda Ziekenhuis, Bonheiden [3]: L DeJaegher (PI), A Peeters and J Verbist.

Canada

Centre hospitalier de l'université de Montréal/Notre-Dame Hospital, Montreal [30]: J-F Blair, JL Caron, N Daneault, M-F Giroux, F Guilbert, S Lanthier, L-H Lebrun, V Oliva, J Raymond, D Roy (PI), G Soulez and A Weill.

Foothills Medical Centre, Calgary [4]: M Hill (PI), W Hu, M Hudion, W Morrish, G Sutherland and J Wong.

Finland

Helsinki University Central Hospital, Helsinki [33]: A Albäck, H Harno, P Ijäs, M Kaste (PI), M Lepäntalo, S Mustanoja, T Paananen, M Porras, J Putaala, M Railo, T Sairanen, L Soinne, A Vehmas and P Vikatmaa.

Germany

Otto von Guericke University, Magdeburg [9]: M Goertler (PI), Z Halloul and M Skalej.

Ireland

Beaumont Hospital, Dublin [4]: P Brennan, C Kelly, A Leahy, J Moroney (PI) and J Thornton.

New Zealand

Auckland City Hospital, Auckland [40]: PA Barber, R Bourchier, A Hill, A Holden and J Stewart (PI).

Norway

Rikshospitalet University Hospital, Oslo [16]: SJ Bakke (PI), K Krohg-Sørensen, M Skjelland and B Tennøe.

Poland

Institute of Psychiatry and Neurology (2nd Department of Neurology and Department of Neuroradiology) and Medical University of Warsaw (2nd Department of General, Vascular and Oncological Surgery), Warsaw [20]: P Bialek, Z Biejat, W Czepiel, A Czlonkowska (PI), A Dowzenko, J Jedrzejewska, A Kobayashi, M Lelek and J Polanski.

Slovenia

University Medical Centre, Ljubljana [12]: J Kirbis, Z Milosevic and B Zvan (PI).

Spain

Hospital Clinic, Barcelona [18]: J Blasco, A Chamorro (PI), J Macho, V Obach, V Riambau and L San Roman.

Parc Taulí Sabadell Hospital, Barcelona [33]: J Branera, D Canovas (PI), Jordi Estela, A Gimenez Gaibar and J Perendreu.

Sweden

Malmö University Hospital, Malmö [67]: K Björses, A Gottsater (PI), K Ivancev, T Maetzsch and B Sonesson.

Sodersjukhuset, Stockholm [55]: B Berg, M Delle, J Formgren, P Gillgren, T-B Kall, P Konrad (PI), N Nyman and R Takolander.

The Karolinska Institute, Stockholm [5]: T Andersson, J Malmstedt, M Soderman, C Wahlgren and N Wahlgren (PI).

Switzerland

Centre Hospitalier Universitaire Vaudois, Lausanne [12]: S Binaghi, L Hirt, P Michel (PI) and P Ruchat.

University Hospital Basel, Basel [94]: LH Bonati, ST Engelter, F Fluri, L Guerke, AL Jacob, E Kirsch, PA Lyrer (PI), E-W Radue, P Stierli, M Wasner and S Wetzel.

University Hospital of Geneva, Geneva [16]: C Bonvin, A Kalangos, K Lovblad, N Murith, D Ruefenacht and R Sztajzel (PI).

The Netherlands

Academic Medical Centre, Amsterdam [56]: M Koelemaij, PJ Nederkoorn (PI), J Reekers and YB Roos.

Erasmus Medical Centre, Rotterdam [75]: JM Hendriks, PJ Koudstaal (PI), PMT Pattynama, A van der Lugt, LC van Dijk, MRHM van Sambeek, H van Urk and HJM Verhagen.

The Haga Teaching Hospitals, The Hague [45]: CMA Bruijninckx, SF de Bruijn, R Keunen, B Knippenberg, A Mosch (PI), F Treurniet, L van Dijk, H van Overhagen and J Wever.

Isala Klinieken, Zwolle [14]: FC de Beer, JSP van den Berg (PI), BAAM van Hasselt and DJ Zeilstra.

Medical Centre Haaglanden, The Hague [3]: J Boiten (PI), JCA de Mol van Otterloo, AC de Vries, GJ Lycklama a Nijeholt and BFW van der Kallen.

UMC St Radboud, Nijmegen [13]: JD Blankensteijn, FE De Leeuw, LJ Schultze Kool (PI) and JA van der Vliet.

University Medical Centre, Utrecht [270]: GJ de Borst, GAP de Kort, LJ Kapelle (PI), TH Lo, WPThM Mali, F Moll, HB van der Worp and H Verhagen.

UK

Addenbrookes Hospital, Cambridge [5]: N Higgins, PJ Kirkpatrick, P Martin (PI) and K Varty.

Birmingham Heartlands Hospital, Birmingham [11]: D Adam, J Bell, AW Bradbury, P Crowe, M Gannon, MJ Henderson, D Sandler, RA Shinton (PI), JM Scriven and T Wilmink.

Lancashire Teaching Hospitals NHS Trust, Preston [2]: S D'Souza, A Egun, R Guta, S Punekar, DM Seriki (PI) and G Thomson.

Liverpool Royal Infirmary [21] and The Walton Centre, Liverpool [7]: JA Brennan, TP Enevoldson, G Gilling-Smith (PI), DA Gould, PL Harris, RG McWilliams, H-C Nasser and R White.

Manchester Royal Infirmary, Manchester [2]: KG Prakash, F Serracino-Inglott, G Subramanian (PI), JV Symth and MG Walker.

Newcastle Acute Hospitals NHS Foundation Trust, Newcastle-Upon-Tyne [108]: M Clarke, M Davis, SA Dixit, P Dorman (PI), A Dyker, G Ford, A Golkar, R Jackson, V Jayakrishnan, D Lambert, T Lees, S Louw, S Macdonald, AD Mendelow, H Rodgers, J Rose, G Stansby and M Wyatt.

North Bristol NHS Trust, Frenchay Hospital, Bristol [13]: T Baker, N Baldwin (PI), L Jones, D Mitchell, E Munro and M Thornton.

Royal Free Hospital, London [1]: D Baker, N Davis, G Hamilton (PI), D McCabe, A Platts and J Tibballs.

Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield [151]: J Beard, T Cleveland, D Dodd, P Gaines, R Lonsdale, R Nair, A Nassef, S Nawaz and G Venables (PI).

St George's University of London and St George's NHS Healthcare Trust, London [58]: A Belli, A Clifton, G Cloud, A Halliday, H Markus (PI), R McFarland, R Morgan, A Pereira and A Thompson.

St Mary's Hospital, Imperial College Healthcare NHS Trust, London [13]: J Chataway (PI), N Cheshire, R Gibbs, M Hammady, M Jenkins, I Malik and J Wolfe.

University College London Hospitals NHS Foundation Trust, London [51]: M Adiseshiah, C Bishop, S Brew, J Brookes, MM Brown (PI), R Jäger and N Kitchen.

University Hospital of South Manchester, Wythenshawe, Manchester [58]: R Ashleigh, S Butterfield, GE Gamble, C McCollum (PI), A Nasim, P O'Neill and J Wong.

Western Infirmary, Glasgow [5]: RD Edwards, KR Lees, AJ MacKay, J Moss (PI) and P Rogers.

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