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

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## Scientific summary

### The International Carotid Stenting Study

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# 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 ($\geq 70\%$) 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.

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