Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial

CAVATAS investigators*

Summary

Background Percutaneous transluminal angioplasty and stenting (endovascular treatment) can be used to treat carotid stenosis, but risks and benefits are uncertain. We therefore compared endovascular treatment with conventional carotid surgery.

Methods In a multicentre clinical trial, we randomly assigned 504 patients with carotid stenosis to endovascular treatment (n=251) or carotid endarterectomy (n=253). For endovascular patients treated successfully, we used stents in 55 (26%) and balloon angioplasty alone in 158 (74%). An independent neurologist followed up patients. Analysis was by intention to treat.

Findings The rates of major outcome events within 30 days of first treatment did not differ significantly between endovascular treatment and surgery (6·4% vs 5·9%, respectively, for disabling stroke or death; 10·0% vs 9·9% for any stroke lasting more than 7 days, or death). Cranial neuropathy was reported in 22 (8·7%) surgery patients, but not after endovascular treatment (p=0·001). Major groin or neck haematoma occurred less often after endovascular treatment than after surgery (three [1·2%] vs 17 [6·7%], p=0·0015). At 1 year after treatment, severe (70–99%) ipsilateral carotid stenosis was more usual after endovascular treatment (25 [14%] vs seven [4%], p=0·001). However, no substantial difference in the rate of ipsilateral stroke was noted with survival analysis up to 3 years after randomisation (adjusted hazard ratio=1·04, 95% CI 0·63–1·70, p=0·9).

Interpretation Endovascular treatment had similar major risks and effectiveness at prevention of stroke during 3 years compared with carotid surgery, but with wide CIs. Endovascular treatment had the advantage of avoiding minor complications.

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See Commentary page 1722

*Members listed at the end of the report

Introduction

Atherosclerotic stenosis of the carotid artery, which is close to the carotid bifurcation in the neck, causes about 20% of all ischaemic strokes and transient ischaemic attacks. In patients with a short-term history of symptoms associated with severe carotid stenosis, the risk of recurrent stroke in the following 2 years is 20% or more if they are treated medically. Findings from two large randomised clinical trials, European Carotid Surgery Trial (ECST)1 and North American Symptomatic Carotid Endarterectomy Trial (NASCET),2 have shown that the risks of stroke are significantly reduced by carotid surgery in suitable patients with recent symptoms and severe carotid stenosis. The results of these trials have convincingly established carotid surgery as the standard treatment for severe symptomatic carotid artery stenosis. However, surgery has the disadvantage of an incision in the neck that could lead to cranial or superficial nerve injury and wound complications.3 Although such treatment has overall benefits, there is also a risk of a stroke, which might be fatal. Additionally, there is a small risk of myocardial infarction, because many patients with carotid stenosis also have ischaemic heart disease. Carotid surgery is often done under general anaesthesia, increasing the potential for complications.

Treatment of carotid stenosis by endovascular techniques (balloon dilation or use of a stent) is advantageous because it avoids surgical incision and requires only local anaesthetic for insertion of the catheter in the groin. The costs may be less than those of surgery, because of a shorter hospital stay and the reduced use of high dependency or intensive care beds. However, the procedure also carries a risk of stroke. Although early series suggested that endovascular treatment had an acceptable complication rate,4 there remained concern that the risks would be much greater than those in surgery in patients who were fit for an operation.5 One small randomised trial6 of carotid stenting at a single centre in Leicester, UK, was stopped after only 20 patients had been recruited, because of an unacceptable stroke rate at the time of stenting. Unlike carotid endarterectomy, endovascular techniques do not remove the atheromatous plaque, and the long-term efficacy of these techniques in prevention of stroke was unknown. We therefore established the Carotid and Vertebral Artery Transluminal Angioplasty Study, (CAVATAS), a randomised multicentre clinical trial to investigate the risks and benefits of endovascular treatment for carotid and vertebral artery stenosis compared with conventional treatment. Our hypothesis was that endovascular treatment would have the same major complication rates and less minor morbidity than surgery. We report the main results of our analysis of the
safety of treatment and rate of major events up to 3 years after randomisation in patients with carotid stenosis suitable for surgery. We also separately randomly assigned patients with carotid artery stenosis or vertebral artery stenosis, who were not suitable for surgery, to endovascular treatment or medical care alone. Only a few patients were randomly assigned in these two groups and the results will be the subject of a future report.

**Methods**

**Trial centres**

22 centres in Europe, Australia, and Canada collaborated in the random assignment of patients with carotid stenosis (see end of this report). Centres were required to have a designated vascular surgeon or neurosurgeon with expertise in carotid endarterectomy, a designated radiologist (or radiologists) who had received training in neuroradiology and the techniques of angioplasty (but not necessarily in the carotid artery), and a consultant neurologist or physician with an interest in cerebrovascular disease. All investigators were required to submit details of their practical experience of carotid surgery or angioplasty techniques, as well as full curriculum vitae to meet the subcommittee’s requirement that investigators had the appropriate knowledge and expertise to join the study. Centres with little skill in cerebrovascular angioplasty received training and assistance from a radiologist from the more experienced centres. Each centre had local ethical approval.

**Patients**

For inclusion in the study patients had to have stenosis of the common carotid artery, carotid bifurcation, or internal carotid artery that investigators believed needed treatment and was suitable for both carotid endarterectomy and endovascular treatment. Investigators included patients only if the best treatment was unclear—ie, patients were randomly assigned only if they and their carotid stenosis were equally suitable for both surgery and endovascular treatment. Exclusion criteria included patients thought to be unsuitable for surgery because of medical or surgical risk factors (eg, recent myocardial infarction, poorly controlled hypertension or diabetes mellitus, renal disease, respiratory failure, inaccessible carotid stenosis, or severe cervical spondylosis). We also excluded patients if they were unwilling to undergo either procedure, were unable to give informed consent, or if they had a disabling stroke with no useful recovery of function within the region supplied by the treatable artery. Patients were not eligible for the study if angiography showed thrombus in the carotid artery, severe intracranial carotid artery stenosis beyond the skull base, or a stenosis unsuitable for endovascular treatment—eg, because of tortuous vascular anatomy. However, patients did not need to have catheter angiography if a reliable non-invasive investigation had confirmed carotid stenosis. We did not exclude patients if contraindications were noted after random assignment. There was no age limit.

Investigators used their own protocol to establish the presence of clinically important carotid stenosis before treatment. Most chose to confirm preliminary ultrasound findings before random assignment by conventional digital subtraction angiography with aortic arch or selective carotid artery contrast injections. Investigators at individual centres were allowed to assign patients after non-invasive techniques, including magnetic resonance angiography (MRA), computed tomographic angiography (CTA), or ultrasound (usually in combination). Investigators could then randomly assign patients only if their non-invasive investigation protocol had a high degree of accuracy, as assessed by audit, compared with conventional angiography. Centres submitted copies of angiographic or non-invasive carotid investigations to the central office for concealed review and measurement of stenosis. One investigator (MMB) measured with a micrometer the severity of stenosis of both carotid arteries before treatment on the best available angiogram. Carotid artery stenosis was calculated by the common carotid method—ie, percentage of stenosis = 100 (1-A/C), where A=diameter of the residual lumen at point of maximum stenosis, C=width of disease-free common carotid artery, below the bifurcation, at a point where the walls were about parallel. We chose this method because it is more reproducible than those of ECST or NASCET. The measurement of severity of the ipsilateral carotid artery stenosis was taken from catheter angiography in 216 and 217 patients randomly assigned to endovascular treatment or surgery, respectively. In patients for whom only MRA or CTA films were available (34 and 28, respectively), we used the common carotid method to calculate stenosis severity from views of the carotid artery. In cases where both MRA and digital subtraction angiography (DSA) were available for the same patient (30) a concealed comparison showed that measurements of stenosis severity from MRA films consistently overestimated severity by an average of 8·5% compared with DSA. We therefore used this factor to adjust the final assessment of stenosis severity in patients with MRA measurements alone. Similarly, if MRA or CTA showed complete signal drop out due to turbulence, the severity of stenosis was taken as 86·5%. In one (0·4%) endovascular patient and six (2%) surgical patients in whom only ultrasound data were available, we estimated stenosis severity from standard ultrasound criteria.10

After researchers at every centre obtained informed consent, patients were randomly assigned to a treatment group, in equal proportions, by telephone call or fax to the randomisation centre at the Clinical Trial Service Unit in Oxford, UK, between March 1, 1992, and July 31, 1997. We randomly assigned patients by computer with a minimisation algorithm, which took account of centre and timing of symptoms, to help to ensure balance of numbers of patients in each group—ie, those with symptoms within 6 months before randomisation, those with distant symptoms (more than 6 months before), and those without symptoms. If more than one artery was treated, the side treated first was taken as the randomised side. All patients gave written informed consent.

Our protocol specified that patients should be treated as soon as possible after random assignment. Surgeons did carotid endarterectomy by the technique that they routinely used, and requirements for use of anaesthesia, shunts or patches, or heparin during the procedure were not specified. All patients assigned to endovascular treatment before 1994 underwent percutaneous transluminal angioplasty with balloon catheters. Stents suitable for use in the carotid artery were developed during the course of the study, and stenting was allowed from 1994 onwards when the radiologist believed this treatment necessary. The stents used were Wallstent (Schneider, USA), Streker (Medi-Tech, USA), and Palmaz (Johnson and Johnson, USA). Investigators could use stents either as a secondary procedure after unsatisfactory balloon dilation or as a primary procedure in which the decision was to stent the lesion without attempting full balloon dilation first. Radiologists used
their preferred type and manufacturer of guide wires, catheters, and stents. Our protocol specified that patients should be given aspirin (minimum dose 150 mg daily) or an alternative antiplatelet agent, for at least 24 h before endovascular treatment, followed by systemic heparin for anticoagulation at the time of the procedure and for a minimum of 24 h afterwards, unless contraindicated. Treatment with atropine was recommended before balloon inflation or stent use to prevent bradycardia. Antiplatelet therapy was continued throughout follow-up in both groups.

Follow-up
Patients were followed up at 1 month after treatment, and then at 6 months, 12 months, and yearly after random assignment by the independent participating neurologist or clinician, who had not been directly involved in the surgical or endovascular treatment. Researchers reported outcome events and sent copies of relevant radiological investigations, post-mortem reports, or both to the central CAVATAS office. Patients were flagged at the UK Office for National Statistics, Census, Population, and Health to identify all deaths in trial patients within the UK. Details revealing treatment group were removed from reports of all stroke and death outcome events in the central office. Researchers at the central office, who were unaware of treatment group, then independently confirmed the classification of the event, by review of the other clinical details, CT scan, or necropsy report (if available). Two independent external adjudicators decided the classification if there was any doubt about the nature of the event or a difference of opinion between the central office and the reporting investigator.

Stroke outcome events were classified as fatal if death occurred as a direct result of stroke at any time after the event, or as disabling if survivors required help from another person as a result of stroke to undertake every day activities for more than 30 days after the onset of symptoms (equivalent to modified Rankin grade three or worse). The remainder of stroke outcome events were classified as non-disabling if symptoms lasted more than 7 days. We specified before analysis that we would not count events reported as transient ischaemic attack or strokes with symptoms lasting 7 days or less. This specification was made to match the criterion used for stroke in the ECST,1 and to avoid bias related to the potential under-reporting of transient and short-lived neurological events in surgical patients who are operated on under general anaesthesia and then returned to intensive care units or surgical wards. In these wards they were not routinely examined by neurologists before follow-up at 1 month. We reasoned that events lasting for a few days and minor neurological events would be more likely to be detected and recorded after endovascular treatment because the procedure was always done under local anaesthesia and patients were usually returned to a neurological ward. Thus, to avoid bias, we prospectively chose not to measure the frequency of transient ischaemic attack and stroke lasting less than 7 days.

Where reliable facilities were available, researchers did carotid duplex ultrasound with doppler measurement of flow velocities to establish the patency of the treated carotid artery at 1 year. Ultrasound measurements were assigned with standard ultrasound criteria into one of four categories of stenosis: mild (<50%), moderate (50–69%), severe (70–99%), and occluded (100%).10 If more than one ultrasound was done we analysed the carotid ultrasound examination closest to 1 year after treatment within the range of 181–540 days. Ultrasound follow-up was not mandatory because not all investigators had access to ultrasound at the start of the study in 1992.

Statistical analysis
The study was planned as an exploratory trial. No formal sample size calculations were done. Duration of funding, recommendations of the data monitoring committee, and the investigators’ view that results of the trial were needed to guide further development of endovascular treatment determined sample size and duration of follow-up before analysis. All data were analysed and are shown by intention to treat. The primary outcome variable was specified as disabling stroke or death. Analysis was by Cox’s regression, with adjustment for sex, age as a continuous variable, and trial centre as a categorical variable. Secondary analyses were done in the same way for any ipsilateral stroke lasting more than 7 days and for death or ipsilateral disabling stroke. Analyses of events within 30 days of treatment were done by χ2 tests. All analyses were done with Stata (Stata Corp, College Station, TX, USA).

Results
505 patients were randomly assigned in the group of patients with carotid stenosis fit for surgery. One patient was included in error, after angiography had shown carotid occlusion, not stenosis. This patient was therefore excluded from the analysis, which left 251 patients randomly assigned to endovascular treatment and 253 to surgery (figure 1).

Table 1 shows the most severe previous ischaemic cerebrovascular symptoms which could be due to a disorder of the treated artery, within 6 months before randomisation. In patients with occlusion of the contralateral carotid artery, symptoms from ischaemia in either eye or brain hemisphere were judged as being within the area of the treated artery. 452 (90%) patients had symptoms within 6 months before randomisation, 36 (7%) had symptoms more than 6 months before, and only 16 (3%) had no symptoms. Vascular risk factors at randomisation were present in most patients (table 2).

Most patients had severe carotid stenosis measured by the common carotid method on the treated side, with a mean stenosis of 86–4% (SD 9–1) in the endovascular and

Figure 1: Trial profile

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artefacts and were treated only medically (two refused any treatment and two were deemed unsuitable for surgery after group assignment). These patients were censored observations in the Cox regression analysis.

The number of strokes in any arterial territory lasting more than 7 days and deaths from any cause occurring within 30 days after first treatment analysed by intention to treat were identical in the two groups (table 3). The rates of disabling stroke or death did not differ between patients in the endovascular group and those in the surgery group (p=0.8, 2 test). Within 30 days after treatment the rate of death or any stroke (lasting more than 7 days) was the same in the two groups (p=0.98, 2 test). All seven deaths within 30 days of treatment in the endovascular group were the result of fatal stroke. Four deaths in the surgical group within 30 days of treatment were caused by fatal stroke, ruptured aortic aneurysm, respiratory arrest from neck haematoma, and pulmonary embolus.

In the endovascular group, stroke within 30 days of treatment was caused by cerebral infarction in 22 patients and primary intracerebral haemorrhage in three (all fatal). In the surgery group, the causes were cerebral infarction in 20 patients and primary intracerebral haemorrhage in two (both non-disabling). All but one of the strokes in the endovascular group and all strokes in the surgery group were ipsilateral to the treated artery. The same number of strokes (16) occurred in the two groups on the day of treatment (risk on day of treatment, 6-4% in the endovascular and 6.3% in the surgery group) (figure 3). Three of these strokes in the endovascular group occurred before balloon dilation (catheterisation stroke rate, 1.2%). The remaining 13 strokes occurred immediately or soon after balloon dilation or stenting. Nine (36%) of the 25 strokes that occurred within 30 days of treatment had an onset after the day of endovascular treatment, and six (27%) of 22 took place after surgery. All but one of these strokes occurred within the first 12 days after treatment (figure 3); this one stroke was judged treatment related because it took place on the 21st day after endovascular treatment. All the cerebral

### Table 1: Baseline cerebrovascular symptoms within 6 months before randomisation

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Endovascular treatment</th>
<th>Surgical treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 251)</td>
<td>(n = 253)</td>
</tr>
<tr>
<td>Uncertain symptoms</td>
<td>6 (24%)</td>
<td>63 (25%)</td>
</tr>
<tr>
<td>No symptoms</td>
<td>9 (4%)</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>Minor</td>
<td>19 (8%)</td>
<td>20 (8%)</td>
</tr>
<tr>
<td>Major, non-disabling</td>
<td>32 (13%)</td>
<td>28 (11%)</td>
</tr>
<tr>
<td>Major, disabling</td>
<td>11 (4%)</td>
<td>18 (7%)</td>
</tr>
<tr>
<td>Symptoms more than 6 months before randomisation</td>
<td>21 (8%)</td>
<td>15 (6%)</td>
</tr>
<tr>
<td>No symptoms</td>
<td>9 (4%)</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>Uncertain symptoms</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

### Table 2: Baseline characteristics of patients

<table>
<thead>
<tr>
<th>Demography</th>
<th>Endovascular group (n = 251)</th>
<th>Surgical group (n = 253)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean [SD], years)</td>
<td>67 (8.3)</td>
<td>67 (8.5)</td>
</tr>
<tr>
<td>Vascular risk factors at randomisation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>132 (53%)</td>
<td>144 (58%)</td>
</tr>
<tr>
<td>Systolic blood pressure (mean [SD] mm Hg)</td>
<td>151 (8) (21.6)</td>
<td>152 (6) (20.1)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mean [SD] mm Hg)</td>
<td>83 (5) (11.8)</td>
<td>83.9 (10.7)</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>95 (39%)</td>
<td>92 (37%)</td>
</tr>
<tr>
<td>Previous history of myocardial infarction</td>
<td>43 (19%)</td>
<td>40 (17%)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>60 (24%)</td>
<td>55 (20%)</td>
</tr>
<tr>
<td>Insulin dependent diabetes mellitus</td>
<td>8 (3%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Non-insulin dependent diabetes mellitus</td>
<td>27 (11%)</td>
<td>26 (11%)</td>
</tr>
<tr>
<td>Ex smoker</td>
<td>69 (28%)</td>
<td>67 (27%)</td>
</tr>
<tr>
<td>Cholesterol &gt;6.5 mmol/L</td>
<td>67 (34%)</td>
<td>62 (32%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>12 (5%)</td>
<td>12 (5%)</td>
</tr>
<tr>
<td>Other cardiac embolic source</td>
<td>2 (1%)</td>
<td>5 (2%)</td>
</tr>
</tbody>
</table>

**Values are numbers of patients (% of known data), unless otherwise indicated.**

**Angiographic characteristics**

| Percentage ipsilateral carotid stenosis (mean [SD])* | 86.4% (9%) | 85.1% (10%) |
| Contralateral carotid artery occlusion | 24 (10%) | 20 (8%) |

*Measured by common carotid method.
haemorrhages occurred between 2 and 9 days after treatment. Although heparin was used routinely in the endovascular group for 24–48 h after treatment, none of the cerebral haemorrhages was related to anticoagulation. The rate of treatment related stroke did not change significantly in either group over time and was not significantly different between centres.

Table 3 shows other treatment related outcomes. Cranial neuropathy was seen in 22 (9%) surgical patients, but not in the endovascular group (p<0.001). Major neck or groin haematoma (defined as requiring surgery or extending hospital stay) was more frequent in the surgical than in the endovascular group. 14 of 17 neck haematomas in the surgical group required re-exploration, and one was associated with the onset of disabling stroke. One surgical haematoma was fatal. None of the groin haematomas in the endovascular group required surgery. Peripheral nerve palsy, myocardial infarction, pulmonary embolus, and fatal respiratory failure related to treatment were also reported only in the surgical group. None of the myocardial infarcts in the surgical group was fatal, but one of the two patients with pulmonary emboli died.

The mean duration of follow-up was 1.95 years (IQR 1.0–2.2) in the endovascular and 1.98 years (1.0–2.8) in the surgical group. Although heparin was used routinely in the endovascular arm, six patients had new ipsilateral strokes (two fatal, two disabling, six non-disabling) between 30 days after endovascular treatment and the end of follow-up. In the surgery arm, ten patients had new ipsilateral strokes (two fatal, two disabling, six non-disabling) during the same follow-up period (not significant).

Results from the survival analyses showed that both surgery and endovascular treatment were equally effective at preventing stroke. Only 96 surviving patients had more than 3 years’ follow-up, and the event rate in these patients remained very low. The survival analysis was therefore limited to the 3 years after randomisation. The rates of death or disabling stroke in any vascular territory and in the rate of any ipsilateral stroke did not differ between the groups (figure 4). At 3 years’ follow-up, the rate of death or disabling stroke (any territory) including treatment related events was 14·3% in the endovascular group and 14·2% in the surgery patients. Survival analyses were done by Cox’s proportional hazards regression, with adjustment for sex, age, and trial centre. For any disabling stroke or death, the hazard ratio (endovascular treatment/surgery) was 1.03 (95% CI 0·64–1·64, p=0·9). Secondary analyses were done for two other survival outcomes. For ipsilateral stroke lasting more than 7 days, the hazard ratio was 1·04 (0·63–1·70, p=0·9). For disabling or fatal ipsilateral stroke, with other causes of treatment related death excluded, the hazard ratio was 1·22 (0·63–2·36, p=0·4).

Only eight patients received the alternative method of treatment without any initial attempt at giving the assigned treatment (crossover rate 1·6%). Of these, six patients who were assigned endovascular treatment received surgery instead (four because of patient choice, one because of contrast allergy, and one because of the need for carotid treatment before cardiac surgery). Two patients assigned to surgery crossed over to endovascular treatment (one because of patient choice, one because of an unacceptable waiting list for surgery). One patient who crossed from endovascular treatment had a fatal cerebral haemorrhage. Day 1=day of treatment.

<table>
<thead>
<tr>
<th>Major outcome events</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>NS</td>
</tr>
<tr>
<td>Disabling stroke</td>
<td>NS</td>
</tr>
<tr>
<td>Non-disabling stroke</td>
<td>NS</td>
</tr>
<tr>
<td>Death or disabling stroke</td>
<td>NS</td>
</tr>
<tr>
<td>Death or any stroke</td>
<td>NS</td>
</tr>
</tbody>
</table>

The rates of death or disabling stroke (any territory) did not differ significantly in either group over time and was not significantly different between centres.

<table>
<thead>
<tr>
<th>Other outcome events</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial nerve palsy</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>Peripheral nerve palsy</td>
<td></td>
</tr>
<tr>
<td>Haematoma (requiring surgery or extending hospital stay)</td>
<td>&lt;0·0015</td>
</tr>
<tr>
<td>Myocardial infarction (non-fatal)</td>
<td>NS</td>
</tr>
<tr>
<td>Pulmonary embolus</td>
<td>NS</td>
</tr>
</tbody>
</table>

Patients were analysed by intention to treat. Values are numbers (%). NS=non-significant. *Fatal in one patient and analysed as a death.

Table 3: Outcome events within 30 days after first treatment

Figure 4: Death or disabling stroke in any vascular territory (upper) or ipsilateral stroke lasting more than 7 days (lower)
stroke after carotid endarterectomy, and one who crossed over from surgery had a disabling stroke during balloon angioplasty. The number of strokes and deaths within 30 days after the first treatment, analysed by actual treatment received, remained identical to the results of the intention-to-treat analysis.

Four surgical patients had bilateral carotid endarterectomy, with intervals between treatment to each side ranging from 7 to 17 months. Two endovascular patients had bilateral treatment during one session on the same day, and three patients had bilateral endovascular treatment with intervals between treatment to each side ranging from 14 days to 2 years.

We used general anaesthetic in 229 (93%) cases and local anaesthesia in 17 (7%) for carotid surgery cases. Perioperative shunts and patches were used in 157 (64%) and 155 (63%) of the surgical operations, respectively.

We used local anaesthesia in all patients treated by endovascular techniques. Endovascular treatment was technically successful in 213 (89%) of 240 treated patients at the first attempt. Success was defined as completion of the procedure as far as dilating a balloon across the stenosis at least once or use of a stent (table 4). Four of the unsuccessful endovascular attempts were complicated by stroke. Stents were used during the first attempt at endovascular treatment in 55 (26%) of 213 of all the patients in whom endovascular treatment was technically successful. In four of these 55 patients, we did stenting as a rescue procedure after the onset of stroke caused by balloon dilation. Of the patients stented 53% had Wallstents, 34% had Palmaz stents, and 13% had Strecker stents. The remainder were treated by balloon angioplasty alone. Endovascular treatment was tried on another occasion in four patients after the initial failure, but was only successful in two. 14 patients, in whom the initial attempts at endovascular treatment were unsuccessful, subsequently had carotid surgery without a major outcome event.

Post-hoc subgroup analysis was done to examine the rate of stroke associated with stenting. Only one (2%) of 55 stented patients had a stroke when the stent was used. However, two (4%) of the ischaemic strokes and two (4%) of the cerebral haemorrhages occurred in stented patients between 2 and 11 days after the procedure. There were no strokes in stented patients more than 11 days after the procedure during the remainder of follow-up.

Ultrasound follow-up at around 1 year after treatment was done in 173 and 174 patients in the endovascular and surgery groups, respectively (figure 5). Severe stenosis (70–99%) was more common on ultrasound at 1 year in the endovascular group than in the surgical group (25 [14%] vs seven [4%], respectively, p<0.001). There were also seven (4%) patients in the endovascular group with carotid occlusion at 1 year, compared with only two (1%) surgical patients, but the difference was not significant. Thus, severe stenosis or occlusion was noted at 1 year in 32 (18%) endovascular patients, compared with nine (5%) surgical patients (p<0.001). In the subgroup of patients treated by stenting, severe stenosis or occlusion at 1 year was found in nine (22%) of 41 patients who had ultrasound follow-up compared with 23 (17%) of 132 patients treated by balloon angioplasty without stenting (not significant).

One surgical patient with restenosis had two subsequent carotid endarterectomies for recurrent myointimal hyperplasia. One patient was retreated by stenting, 4 months after balloon angioplasty because of a suboptimum result. Two patients, initially treated by balloon angioplasty, had retreatment by the same method in one case and stenting in the other because of restenosis associated with recurrent symptoms (transient ischaemic attacks and minor ischaemic stroke, respectively). The remaining patients with restenosis did not receive further surgical or endovascular treatment. There was no association between the severity of stenosis at 1 year and the small number of recurrent ipsilateral strokes in either treatment group.

**Discussion**

Our findings showed no difference in the major risks of endovascular treatment (balloon angioplasty or stenting) compared with carotid surgery. The risk of stroke or death within 30 days of treatment was almost identical in both groups. The time to death or disabling stroke or any ipsilateral stroke during follow-up in the primary analysis
did not differ between groups after correction for stenosis severity, age, sex, and trial centre. Although CAVATAS included substantially more patients, the major outcome measures of stroke and death were nearly identical in the two groups. We cannot exclude, however, a clinically important difference in favour of either treatment.

Our results lend support to the concept that endovascular techniques are better than surgery because they avoid risks related to the incision in the neck and the use of general anaesthesia. The avoidance of morbidity related to these factors is an important advantage of endovascular techniques, if there is no difference in the major risks of stroke or death with either treatment. Another advantage of endovascular techniques was that the economic costs, assessed at the two UK centres recruiting the most patients, were about half those of surgery (data not shown). However, this economic advantage might disappear if stents and protection devices are used routinely.

The rate of stroke and death within 30 days of treatment in CAVATAS was higher in both groups than reported in the two much larger randomised trials of carotid endarterectomy, ECST and NASCET (table 5). However, the rate of stroke over 3 years, including perioperative events, was still about half the expected rate calculated from these trials if the patients in CAVATAS had been treated medically. Moreover, the risks of treatment in our trial were well within the range of risks of carotid endarterectomy reported by Rothwell and colleagues.12 Nevertheless, the perioperative rate of stroke and death in the surgical group is greater than the rate reported as achievable in some centres.13 Prospective examination of all patients by a neurologist at 1 month after treatment in our trial might account for some of the difference between our treatment related stroke rates and those of others, but it is unlikely to be the only reason for a higher complication rate in CAVATAS. In ECST, which also excluded minor strokes lasting less than a week, the 30-day stroke and death rate in patients in the surgical group was 7.0%.1

There are several possible explanations for the higher rate of procedural stroke in CAVATAS than in these other studies. First, the higher morbidity of surgery and endovascular treatment in CAVATAS than in ECST and NASCET might merely be due to chance, judging from the statistical tests (table 5). Second, this difference is unlikely to be due to variation in surgical skills, because there was no evidence, on subgroup analysis, of any significant difference in outcome between centres. Many of these centres had collaborated in ECST and one in NASCET. The rates in CAVATAS of cranial neuropathy, wound haematoma, and myocardial infarction were very similar to those in NASCET.5,14 Therefore, surgeons and anaesthetists in the two trials were likely to have had similar skill and used similar techniques. Third, the most likely explanation for the high morbidity rate in both groups is the inclusion of patients at higher than average risk from treatment. Case mix is one of the major factors in risk of carotid surgery,15 which has been confirmed by a further analyses of the surgical risks in ECST and NASCET.5,16 Doctors became enthusiastic for operating on patients with severe symptomatic carotid stenosis after ECST and NASCET, and this enthusiasm might have led to an increase in the rate of referrals of less fit patients. Also, the availability of endovascular treatment in the trial centres might have encouraged the inclusion of less fit patients for surgery. In accordance with this explanation, there were substantially more patients with vascular risk factors, particularly ischaemic heart disease, assigned to surgery in CAVATAS than in ECST (table 5). Patients included in NASCET were also highly selected, whereas there were few exclusion criteria in CAVATAS. We did not routinely seek data on non-randomised patients treated at our centres.

One contribution to our high rate of 30-day outcome events could be that about 30% of the treatment related strokes occurred several days after treatment. This fact has not been widely investigated, although delayed intracranial haemorrhage is known to be a complication of carotid surgery and has also been reported after carotid angioplasty and stenting.17 Delayed ischaemic stroke is usually thought to be rare, but the NASCET investigators have reported that 30% of surgical outcome events were delayed between the second and 28th postoperative day.1

There were few strokes during follow-up after successful treatment in either arm, which was striking. Carotid endovascular treatment seemed as effective as surgery at prevention of subsequent stroke, at least in the 2–3 years after treatment, despite the fact that the effectiveness of surgery was not removed by the interventional procedure. The very few strokes on the treated side during follow-up in the surgical arm confirm the effectiveness of surgery recorded in ECST and NASCET. There were even fewer of these strokes in the patients treated by balloon angioplasty during follow-up after treatment and no strokes in the patients treated by stenting. But follow-up was limited to fewer patients in the stented group. However, our finding that almost 20% of patients treated by angioplasty or stenting had severe stenosis or occlusion on ultrasound at about 1 year, compared with only 5% in the surgical group, is a concern. Most of these patients are likely to have had restenosis, but in some this finding might have been related to persistent residual stenosis after inadequate dilation.

Findings from a study of a small subgroup of patients randomly assigned in CAVATAS at one centre show that substantially more microscopic embolism to the brain occurs after a carotid angioplasty detected by transcranial doppler ultrasound, than after surgery.18 The importance of this finding was uncertain, because the size or nature of the particulate material (air, thrombus, or atheromatous debris) could not be distinguished. However, substantial reduction in the middle cerebral artery blood flow during the procedure was significantly more frequent during surgery.19 The overall results of CAVATAS show that neither of these findings translate into a major difference in the risks of symptomatic stroke. Microembolism could still result in subclinical brain damage. However, extensive neuropsychological tests in two large subgroups of patients in CAVATAS at two centres did not show any significant differences in the neuropsychological sequelae of endovascular treatment and surgery at 6 months after treatment, which provides reassurance with respect to the safety of treatment in patients without symptomatic stroke.18,20

We do not propose the widespread introduction of endovascular techniques for the treatment of carotid stenosis as an alternative to surgery, because the 95% CI surrounding the 10% risk of any stroke within 30 days of treatment in the endovascular and surgical groups is wide. Nevertheless, our results lend support to the use of endovascular treatment in selected patients at centres with skilled doctors. The interventional technique used to treat carotid stenosis has developed during the 7 years
since we started CAVATAS. We used simple inflatable balloon catheters at the beginning of the trial and the use of stenting increased towards the end. Initially, stents were used only as a secondary procedure after full balloon inflation for inadequate vessel dilation or complications of treatment. Our intention to prevent these complications and the improved early results in stented patients has led to the increasing use of primary stenting, of which the aim is to use a device in every patient before full dilation of the artery. Primary stenting is now accepted as best practice and has become the radiological technique of choice for carotid stenosis, replacing balloon angioplasty alone in most cases. However, it is essential that investigators considering carotid stenting should be trained properly in the technique.

Most strokes after carotid angioplasty are the result of plaque fracture in the carotid artery at the time of balloon inflation with subsequent thrombosis and embolism. Stents will also prevent a free intimal flap from dissection, additionally, the stent mesh limits the size of any thrombus or atheromatous debris that may be dislodged from the plaque at the time of dilation of the artery. Improved dilation achieved by stenting than with balloon angioplasty might also reduce the rate of stroke in the short-term after treatment. Individual case series suggest that carotid stenting and carotid surgery have similar rates of procedural stroke.21,22 Wholey and colleagues23 reported 2048 patients from 24 centres who had carotid stenting with a complication rate of stroke and death within 30 days of treatment of 5.8%.

Although the case series and registry data suggest an acceptable complication rate at the time of stenting, primary stenting has not been shown reliably to prevent stroke, which is the aim of treatment. Our subgroup analysis suggested that stenting will not avoid the risk of delayed stroke in the few days after the procedure, and in particular there seems to be a small risk, similar to that of carotid surgery, of delayed cerebral haemorrhage, which is probably related to cerebral hyperperfusion. Stenting does not remove atheromatous plaque and the rate of restenosis is likely to be greater after stenting than after carotid surgery, which could result in an unacceptable rate of long term stroke recurrence. There is an important need to establish the efficacy and safety of carotid stenting by comparison with surgery, before the technique is widely introduced without adequate trial based evidence.

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