Safety and Efficacy of Endovascular Treatment of Carotid Artery Stenosis Compared With Carotid Endarterectomy
A Cochrane Systematic Review of the Randomized Evidence

Lucy J. Coward, MRCP; Roland L. Featherstone, PhD; Martin M. Brown, MD, FRCP

Background and Purpose—Endovascular treatment of atherosclerotic carotid artery stenosis may be an alternative to surgical endarterectomy. To evaluate the safety and efficacy of endovascular techniques, we conducted a systematic review of randomized studies that compared endovascular treatment with surgery for carotid stenosis.

Methods—We searched the Cochrane Stroke Group trials register, the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and Science Citation Index for randomized trials of carotid angioplasty and/or stenting compared with surgery. We also contacted researchers in the field and balloon catheter and stent manufacturers.

Results—Five trials involving 1269 patients were included. Analysis of 30-day safety data found no significant difference in the odds of treatment-related death or any stroke (odds ratio [OR], endovascular surgery, 1.33; 95% confidence interval [CI], 0.86 to 2.04), death or disabling stroke (OR, 1.22; CI, 0.61 to 2.41), or death, any stroke, or myocardial infarction (OR, 1.04; CI, 0.69 to 1.57). At 1 year after randomization, there was no significant difference between the 2 treatments in the rate of any stroke or death (OR, 1.01; CI, 0.71 to 1.44). Endovascular treatment significantly reduced the risk of cranial nerve injury (OR, 0.13; CI, 0.06 to 0.25). There was substantial heterogeneity between the trials for 4 of the 5 outcomes.

Conclusions—No significant difference in the major risks of treatment was found but the wide confidence intervals indicate that it is not possible to exclude a difference in favor of one treatment. Minor complication rates favor endovascular treatment. There is currently insufficient evidence to support a widespread change in clinical practice away from recommending carotid endarterectomy as the treatment of choice for suitable carotid artery stenosis. Patients suitable for carotid endarterectomy should only be offered stenting within the ongoing randomized trials of stenting versus surgery. (Stroke. 2005;36:905-911.)

Key Words: angioplasty ■ carotid stenosis ■ endarterectomy ■ stents ■ stroke prevention

Large randomized trials have convincingly shown that carotid endarterectomy significantly reduces the long-term risk of subsequent stroke from severe carotid artery stenosis.1–4 However, surgery does have the disadvantage of requiring an incision in the neck and, in some centers, is performed under general anesthesia.

Case series evidence has accumulated to show that carotid angioplasty and stenting may offer an alternative to carotid endarterectomy.5–20 The advantages to treating carotid stenosis in this way include avoidance of general anesthesia and its complications such as myocardial infarction and pulmonary embolism. Endovascular treatment is usually performed via a femoral catheter, thus avoiding an incision in the neck and subsequent cranial and cutaneous nerve damage. Hospital admission and recovery time after endovascular treatment may be less than with surgery, therefore reducing costs. In addition, endovascular treatment may be the only treatment option for patients at high-risk after surgery because of comorbidity such as ischemic heart disease or for those with surgically inaccessible lesions.

There has been some resistance to treating carotid artery disease endovascularly because of concerns over distal embolization to the brain during passage of a catheter through a tight stenosis. However, in recent years endovascular equipment and techniques have been developed to limit this complication. Initially, percutaneous transluminal angioplasty using a balloon catheter was used to treat carotid stenosis. This procedure is known to carry a risk of arterial dissection, which may be symptomatic causing a stroke or transient ischemic attack. Stents for use in the carotid arteries were developed ~10 years ago and may be less likely to cause arterial dissection and thromboembolic symptoms when used by experienced individuals.6,14 Cerebral protection devices have also been developed to...
TABLE 1. Characteristics of the Randomized Controlled Trials Included in the Review

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Type</th>
<th>No. of Patients</th>
<th>Symp/ Asymp (No.)</th>
<th>Randomized to Endovasc. (No.)</th>
<th>Received Endovasc. (No.)</th>
<th>Stent/PTA</th>
<th>Endovasc Technical Success</th>
<th>Randomized to Surgery (No.)</th>
<th>Treated Surgery (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAVATAS</td>
<td>2001</td>
<td>Multicenter</td>
<td>504</td>
<td>488/16</td>
<td>251</td>
<td>240</td>
<td>55/158</td>
<td>89%*</td>
<td>253</td>
<td>246</td>
</tr>
<tr>
<td>Kentucky A</td>
<td>2001</td>
<td>Single center</td>
<td>104</td>
<td>104/0</td>
<td>53</td>
<td>53</td>
<td>All stents</td>
<td>NK</td>
<td>51</td>
<td>51</td>
</tr>
<tr>
<td>Kentucky B</td>
<td>2004</td>
<td>Single center</td>
<td>85</td>
<td>0/85</td>
<td>43</td>
<td>43</td>
<td>All stents</td>
<td>NK</td>
<td>42</td>
<td>42</td>
</tr>
<tr>
<td>Leicester</td>
<td>1998</td>
<td>Single center</td>
<td>23</td>
<td>23/0</td>
<td>11</td>
<td>7</td>
<td>All stents</td>
<td>100%*</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>WALLSTENT</td>
<td>2001</td>
<td>Multicenter</td>
<td>219</td>
<td>219/0</td>
<td>107</td>
<td>NK</td>
<td>All stents</td>
<td>97%†</td>
<td>112</td>
<td>NK</td>
</tr>
<tr>
<td>SAPHIRE</td>
<td>2004</td>
<td>Multicenter</td>
<td>334</td>
<td>96/238</td>
<td>167</td>
<td>159</td>
<td>All stents</td>
<td>95.6%</td>
<td>167</td>
<td>151</td>
</tr>
</tbody>
</table>

Values are numbers or percentage (%) of patients.

*Success defined as completion of the procedure as far as dilating a balloon across the stenosis at least once or use of a stent.
†Success defined as post-stent stenosis of <30%.
Symp/Asymp indicates the portion of the patients who were symptomatic or asymptomatic; endovasc, endovascular; NK, not known; PTA, percutaneous transluminal angioplasty without stent.

Materials and Methods

Search Strategy
An extensive search of the literature was performed using the Cochrane Groups’ Specialized Register of Trials (last searched September 2003) using a search strategy designed to identify all relevant trials. The Cochrane Central Register of Controlled Trials (The Cochrane Library, Issue 3, 2003) was also searched for all possibly relevant trials. In addition, all publications describing relevant trials were sought through EMBASE (1980 to October 2004) using the following key words in various combinations: carotid arteries, stenosis, endovascular, stents, angioplasty, endarterectomy, stroke, and cerebrovascular disease. This strategy was modified for use with MEDLINE (1966 to October 2004) and Science Citation Index (1981 to October 2004). Ongoing trials were identified from conference proceedings and personal contact with individuals active in the field. Informal inquiries were made with balloon catheter and stent manufacturers.

Eligible Studies
We selected for inclusion randomized trials of carotid endovascular treatment compared with carotid endarterectomy in patients of any age or sex with symptomatic or asymptomatic carotid artery stenosis. We included patients who had bilateral and unilateral procedures. Trials that allowed any acceptable technique for carotid endarterectomy (for example, use of a shunt or not, patching or not, local or general anesthesia) and that allowed any acceptable endovascular technique for treatment of carotid stenosis (for example, use of a simple balloon catheter or stent and use of cerebral protection or not) were reviewed. Two reviewers (L.J.C. and R.L.F.) independently applied the inclusion criteria, extracted data, and assessed trial quality.

Data Extraction and Analysis
For each study, the following data were extracted: (1) method of randomization and whether the randomizing doctor was blinded to the treatment allocated; (2) number of patients originally allocated to each treatment group and the outcome of every patient to allow an intention to treat analysis; (3) method of measuring outcome and whether outcome assessment was independent and/or blinded; (4) number of exclusions and losses to follow up; (5) intervention characteristics; and (6) outcome measures, such as any stroke (disabling or non-disabling) or death within 30 days of procedure; subsequent ipsilateral carotid territory stroke; subsequent stroke in any arterial territory; cranial neuropathy within 30 days of procedure; other complications of the procedure, eg, myocardial infarction; and restenosis rate.

Strokes were classified if possible as fatal, disabling (requiring help with activities of daily living for >1 month after onset), or nondisabling (symptoms lasted >7 days but patient was independent at 30 days).

Results were reported as odds ratios (ORs) (ie, the odds of an unfavorable outcome among patients treated by endovascular intervention compared with the corresponding odds among patients treated surgically) and were calculated using the Peto fixed-effect method. Heterogeneity between trial results was tested for using a standard χ² test.

Included Studies
The main characteristics of the included studies are shown in Table 1. In total, 1269 patients with mainly symptomatic (75% of patients) carotid artery stenosis were treated within these 5 trials. None of the trials specifically excluded patients with nonatheromatous carotid stenosis. In Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPHIRE), 23% of included patients had restenosis after previous endarterectomy but exact numbers of patients with nonatheromatous disease in the other 4 trials were not reported. Because of study design and the nature of the interventions, health workers, patients, and assessors were not blinded to treatment or outcome in any of the trials.

CAVATAS
The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) is an international multicenter trial in
which long-term follow-up (>5 years) is ongoing. Patients with symptomatic or asymptomatic carotid stenosis who were equally suitable for endovascular treatment or surgery could be randomized. Surgery could be performed using any acceptable technique. All endovascular techniques were allowed. If the patient was unsuitable for surgery (eg, because of unacceptably high anesthetic risk factors), randomization could be between endovascular treatment and medical care. The number of patients randomized in this arm was small and the data have not yet been published. In total, 504 patients with carotid stenosis suitable for surgery were randomized to endovascular treatment (N=251) or surgery (N=253); 90% of patients had symptoms within 6 months before randomization. The trial found no significant difference in the rates of major outcome events within 30 days of endovascular or surgical treatment (10.0% versus 9.9% for any stroke lasting >7 days or death).27

Kentucky
The Kentucky study was a single-center randomized trial comparing carotid angioplasty and stenting with carotid endarterectomy. The trial comprised a symptomatic arm in which 104 patients who had experienced symptoms and/or signs of cerebral ischemia confined to the ipsilateral carotid artery within the 3 months before randomization were included.28 These patients were randomized between stenting (N=53) and surgery (N=51), and all had an ipsilateral internal carotid artery stenosis of >70%. In addition, there was an asymptomatic arm in which 85 patients with no symptoms of cerebrovascular ischemia and with internal carotid artery stenosis of >80% were randomized between stenting (N=43) and surgery (N=42).29 In the symptomatic arm of this study, 1 patient died as a consequence of myocardial infarction immediately after carotid endarterectomy. There were no other deaths or strokes in symptomatic or asymptomatic patients treated with stenting or surgery.28,29

Leicester
In the single-center Leicester study, all patients with symptomatic severe internal carotid artery stenosis (>70%) who consented to be included in the study were randomized to stenting or surgery.30 The trial was stopped after 23 patients had been randomized to treatment. Only 17 of the randomized patients had received their allocated treatment at the time the trial was suspended. Ten carotid endarterectomies proceeded without complication, but 5 of the 7 patients who underwent stenting had a stroke. Three patients were excluded from the trial after randomization (1 patient occluded the carotid artery asymmetrically before admission and 2 patients refused to undergo their allocated treatment after admission). The final 3 patients had not yet been admitted for treatment when the trial was stopped.30

WALLSTENT
The WALLSTENT study was another multicenter trial and randomized patients with symptomatic internal carotid artery stenosis (transient ischemic attack or completed stroke within 120 days of randomization, with at least 60% stenosis) to either stenting or carotid endarterectomy.31 Two hundred nineteen patients were randomized to stenting (N=107) or surgery (N=112). The 30-day peri-procedure complication rate (any stroke or death) was significantly higher in the stented group than in those who underwent carotid endarterectomy (12.1% versus 4.5%; P=0.049).37 Further results from this trial have not been published.

SAPPHIRE
A multicenter randomized trial based in the US compared stenting with cerebral protection with endarterectomy in patients at high surgical risk.32 Patients had >50% symptomatic stenosis (or >80% asymptomatic stenosis) plus one or more comorbidity conditions (eg, congestive heart failure, left ventricular dysfunction, recent myocardial infarction, or severe pulmonary disease). Three hundred thirty four patients were randomized to stenting with cerebral protection (N=167) or surgery (N=167). The majority of patients (71%) were asymptomatic in this study. In our original Cochrane review, only 30-day results were available from this trial;39 however, data from 1-year follow-up have recently been published and have now been included.32 The primary end point of the trial (cumulative incidence of death, stroke, or myocardial infarction within 30 days of the procedure or death or ipsilateral stroke between 31 days and 1 year) occurred in 12.2% patients randomized to stenting and in 20.1% patients randomized to surgery (P=0.05, log-rank test for superiority).32 The trial was terminated early because recruitment slowed after nonrandomized stent registries were established; therefore, the power of the study and interpretation of results may have been influenced by this fact.

Randomization Method
The method of randomization was given for all trials. For each trial, allocation concealment was judged to be adequate. In one trial, patients were randomly assigned treatment by computer after a telephone call or fax to a randomization center.37 A minimization algorithm taking account of center and timing of symptoms was used. Patients were allocated treatment on the basis of sealed envelopes in 2 trials.28–30 In one study, randomization of patients was performed using a computerized number generator, sequentially numbered sealed envelopes, and each center was assigned its own randomization sequence.31 Randomization in the final trial was performed with the use of a pseudo-random number generator and was stratified according to clinical center and according to whether the patient had symptomatic or asymptomatic disease. Numbers were distributed by an automated centralized telephone response system.32

Follow-up
In CAVATAS, patients were followed-up 1 month after treatment and then again at 6 months, 12 months, and yearly after randomization by the independent participating neurologist or clinician who was not directly involved in treatment. The mean duration of follow-up was 1.95 years (interquartile range, 1.0 to 2.2) in the endovascular and 1.98 years (1.0 to 2.8) in the surgery group at the time the interim data were published.27 In the Leicester study, patients were re-examined by a consultant neurologist 24 hours after intervention, at 30
Assessment of Functional Outcome

The assessment of functional outcome was by the Oxford Handicap Stroke score in one trial. Three trials used a combination of the Barthel, Rankin, and National Institutes of Health Stroke Scale scores to measure outcome: a combination of the Barthel, Rankin, and National Institutes of Health Stroke Scale scores were used. In CAVATAS, 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 everyday activities for 30 days after the onset of symptoms (equivalent to modified Rankin grade 3 or worse). The remainder of stroke outcome events were classified as nondisabling if symptoms lasted >7 days.

Analysis of Data

Two trials specified that analysis was by intention to treat (an actual treatment analysis was also performed in SAPPHIRE). The Leicester study only reported results from patients who underwent treatment. It was possible to perform intention-to-treat analysis on all trials as the number of patients originally allocated to each treatment was extracted and the outcome of all patients (including those who did not undergo treatment within the trial) was known.

Ongoing Trials

We are aware of 4 trials currently ongoing comparing carotid endovascular treatment with endarterectomy: the International Carotid Stenting Study (ICSS), Carotid Revascularization Endarterectomy versus Stenting Trial (CREST), Stent-protected Percutaneous Angioplasty of the Carotid versus Endarterectomy (SPACE), and Endarterectomy versus Angioplasty in patients with Severe Symptomatic Stenosis (EVA-3S).

Meta Analysis

Table 2 shows the rates of outcome events for each of the included studies. Meta-analysis of the data found no significant difference between the odds of death or any stroke at 30 days after procedure (OR for endovascular surgery, 1.33; 95% confidence interval [CI], 0.86 to 2.04) (Figure 1). The odds of death or disabling stroke at 30 days were similar in the endovascular and surgical group (OR, 1.22; CI, 0.61 to 2.41) (Figure 2). At 1 year after the procedure, there was no significant difference between the 2 groups in preventing any stroke or death (OR, 1.01; CI, 0.71 to 1.44) (Figure 3). Endovascular treatment significantly reduced the risk of cranial neuropathy (OR, 0.13; CI, 0.06 to 0.25) (Figure 4). There was no significant difference between the 2 groups when the risk of death, any stroke, or myocardial infarction was considered (OR, 1.04; CI, 0.69 to 1.57) (Figure 5).

Trial Heterogeneity

Significant heterogeneity was found in the 2 main safety outcome measures, for which data were available from all 5 trials, namely: (1) 30-day risk of any stroke or death \( \chi^2 = 10.35 \) \( P = 0.035 \); and (2) 30-day risk of stroke or myocardial infarction or death \( \chi^2 = 14.96 \) \( P = 0.0048 \). Data
Restenosis Rates

There was insufficient data from most of the included trials to perform any analysis on re-stenosis rates after endovascular treatment compared with those after surgery. In CAVATAS, ipsilateral stenosis of >70% 1 year after treatment was more common after endovascular treatment than carotid endarterectomy (14% compared with 4%; P<0.001), but no difference in the rate of ipsilateral stroke was noted in the survival analysis up to 3 years after randomization. The patency of treated arteries in the Kentucky study was reported to be “satisfactory” 2 years after either endovascular or surgical treatment as determined by sequential ultrasound examination; however, the mean degree of residual stenosis in each group was not given.

Discussion

Some evidence of the benefits and risks of carotid endovascular intervention comes from nonrandomized case series. We identified reports of >5000 carotid angioplasty and stenting procedures while identifying studies for this review. The 30-day risk of stroke or death from these reports ranged from 2% to 9%, with an average rate of 4.7%. There was insufficient data from most of the included trials to perform any analysis on restenosis rates after endovascular treatment compared with those after surgery. In CAVATAS, ipsilateral stenosis of >70% 1 year after treatment was more common after endovascular treatment than carotid endarterectomy (14% compared with 4%; P<0.001), but no difference in the rate of ipsilateral stroke was noted in the survival analysis up to 3 years after randomization. The patency of treated arteries in the Kentucky study was reported to be “satisfactory” 2 years after either endovascular or surgical treatment as determined by sequential ultrasound examination; however, the mean degree of residual stenosis in each group was not given.

![Figure 2](http://stroke.ahajournals.org/)

**Figure 2.** The effect of endovascular treatment versus carotid endarterectomy for patients with carotid artery stenosis on the combined outcome “death or disabling stroke within 30 days of procedure.” Results are expressed as Peto OR with a fixed effects model. OR <1 suggests endovascular treatment to be superior to endarterectomy.

<table>
<thead>
<tr>
<th>Study</th>
<th>Endovascular n/N</th>
<th>Surgery n/N</th>
<th>Peto OR (95% CI Fixed)</th>
<th>Weight %</th>
<th>Peto OR (95% CI Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAVATAS 2001</td>
<td>36/255</td>
<td>34/253</td>
<td>0.39 (0.22, 0.70)</td>
<td>30.7</td>
<td>0.39 (0.22, 0.70)</td>
</tr>
<tr>
<td>SAPPHIRE 2004</td>
<td>22/187</td>
<td>33/187</td>
<td>0.57 (0.34, 0.95)</td>
<td>23.4</td>
<td>0.57 (0.34, 0.95)</td>
</tr>
<tr>
<td>Vesslens 2001</td>
<td>12/107</td>
<td>4/112</td>
<td>0.30 (0.05, 1.86)</td>
<td>12.8</td>
<td>0.30 (0.05, 1.86)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>71/525</td>
<td>71/532</td>
<td>1.00 (0.71, 1.41)</td>
<td>0.11</td>
<td>1.00 (0.71, 1.41)</td>
</tr>
</tbody>
</table>

**Figure 3.** The effect of endovascular treatment versus carotid endarterectomy for patients with carotid artery stenosis on the combined outcome “death or any stroke at 1 year”. Results are expressed as Peto OR with a fixed effects model. OR <1 suggests endovascular treatment to be superior to endarterectomy.
infarction was defined as creatine kinase level >2-times the upper limit of normal with a positive myocardial bound fraction and patients did not have to have characteristic electrocardiogram changes. When the outcome 30-day stroke or death was analyzed, no significant difference between the treatments was found. We included stopped and completed trials in the review because it was felt that the results from these trials should be considered, although the impact of the stopped trials on the meta-analysis is likely to be minimal given the small numbers of patients involved.

Cerebral Protection

Cerebral protection devices are designed to be placed distal to the stenosis and collect the embolic debris before it enters the intracranial circulation. There are now several case series reporting experience of endovascular treatment with cerebral protection. A recent systematic review of the nonrandomized single-center evidence on early outcome after carotid angioplasty and stenting with and without cerebral protection devices found that the use of cerebral protection devices appears to reduce the risk of thromboembolic complications during endovascular treatment. However, there is as yet no evidence from completed randomized trials comparing stenting with or without cerebral protection. Furthermore, the protection device must usually be passed through the arterial stenosis itself and therefore carries the risk of dislodging thrombotic material. Despite this uncertainty, in practice, cerebral protection devices are becoming increasingly popular with interventionists.

News From Ongoing Studies

The 4 ongoing trials of carotid stenting compared with surgery are not due to report for several years. However, a recent clinical alert from the EVA-3S trial warrants discussion. The trial reported a higher rate of stroke within 30 days of carotid stenting in the patients who underwent stenting without cerebral protection (N=15) compared with those in whom cerebral protection was used (N=58; OR, 3.9; 95% CI, 0.9 to 16.7). The trial safety committee recommended stopping stenting without cerebral protection on the basis of this interim result. However, this decision has been criticized for several reasons in a recent letter to Stroke. In the first instance, the trial was not designed as a randomized trial of stenting with or without protection and the number of patients that had received treatment at the time of the report was small. Secondly, the difference between treatment with and without protection did not reach statistical significance. In addition, the patients who received stenting without cerebral protection were significantly older than those who underwent stenting with protection (72.7 versus 66.0 years; P=0.013), a factor that has been shown previously to be a risk factor for carotid stenting. Moreover, only strokes at the time of the procedure could be expected to be prevented by the protection device; however, in the unprotected patients within EVA-3S, half the strokes occurred after the day of treatment (N=2) and half occurred on the day of treatment (N=2). Therefore, it was perhaps premature for the safety committee to recommend stenting only be performed with cerebral protection at this stage of the trial.

Conclusion

As yet, there is no evidence on long-term efficacy of angioplasty and stenting available from any of the studies. Given at least similar safety to surgery and the potential advantages outlined previously, it is ethical and necessary that randomized trials comparing endovascular treatment with surgery continue to recruit patients. In the mean time, there is insufficient evidence to support a move away from recommending carotid endarterectomy as the treatment of choice for suitable carotid stenosis. Stenting should only be offered within the ongoing trials of stenting versus surgery. These trials will provide valuable data on the safety and efficacy of stenting compared with surgery and the benefits or otherwise of cerebral protection devices.

Figure 4. The effect of endovascular treatment versus endarterectomy for patients with carotid artery stenosis on the combined outcome "cranial neuropathy within 30 days of procedure." Results are expressed as Peto OR with a fixed effects model. OR <1 suggests endovascular treatment to be superior to endarterectomy.

Figure 5. The effect of endovascular treatment versus endarterectomy for patients with carotid artery stenosis on the combined outcome "death or stroke or myocardial infarction within 30 days of procedure." Results are expressed as Peto OR with a fixed effects model. OR <1 suggests endovascular treatment to be superior to endarterectomy.
Acknowledgments

We thank the Cochrane Stroke Group Editorial Team for advice and support throughout the review process. This article is based on a review available in the Cochrane Library but has been updated with the published results of SAPPHIRE and the asymptomatic arm of the Kentucky study. M.M.B.’s Chair in Stroke Medicine at University College London is supported by the Reta Lila Weston Trust for Medical Research.

References

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