Randomized Controlled Trials Comparing Endarterectomy and Endovascular Treatment for Carotid Artery Stenosis
A Cochrane Systematic Review

Jörg Ederle, MD; Roland L. Featherstone, PhD; Martin M. Brown, FRCP

Background and Purpose—Endovascular treatment of carotid stenosis may be an alternative to surgical endarterectomy. We conducted a systematic review of the randomized evidence to assess the benefits and risks of endovascular treatment compared to surgery.

Methods—Cochrane registers and online databases were searched and researchers in the field contacted. Outcome events were compared using odds ratios (ORs) calculated using the Peto fixed effect and Mantel-Haenszel random effects models if there was significant heterogeneity.

Results—Ten trials involving 3178 patients were included. Not all contributed to each analysis. The primary outcome comparison of any stroke or death within 30 days of treatment favored surgery (fixed-effects OR 1.35), the difference was not statistically significant using the random effects model. Endovascular treatment was significantly better than surgery in avoiding cranial neuropathy (OR 0.15) and myocardial infarction (OR 0.34). There was no significant difference between endovascular treatment and surgery in the following comparisons: 30-day stroke, MI, or death (OR 1.12); 30-day disabling stroke or death (OR 1.19); 30-day death (OR 0.99); 24-month death or stroke (OR 1.26); and 30-day death or stroke in endovascular patients treated with or without protection devices (OR 0.75).

Conclusions—The data are difficult to interpret because the trials are heterogeneous. Five trials were stopped early, perhaps leading to an overestimate of the risks of endovascular treatment. The results do not support a change in clinical practice away from recommending carotid endarterectomy as the treatment of choice for suitable carotid artery stenosis but support continued recruitment in the large ongoing trials. (*Stroke*. 2009;40:1373-1380.)

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

Stroke became the standard method of treating carotid stenosis when the large randomized trials were published.5–8 Interventional endovascular treatment (angioplasty and then stenting) was introduced for carotid stenosis around the same time, but has not yet been shown to be as safe or effective as carotid endarterectomy, despite many case series suggesting it provided an alternative to surgery. Carotid stenting might avoid the risks associated with carotid surgery, including cranial nerve palsy, myocardial infarction, or pulmonary embolism. This makes carotid stenting especially appealing in patients at high surgical risk. Because access to the carotid artery is through the femoral artery, there is no need of an incision in the neck with the associated risk of cranial nerve damage. Over the past 10 years, researchers have tried to add to the wealth of case series on the topic, sounder and robuster evidence in the form of randomized trials comparing carotid angioplasty with or without stenting and carotid endarterectomy, in both symptomatic and asymptomatic patients. Since the last thorough review was published in *Stroke* in 2005, two large trials have reported their results, more than doubling the number of patients included in randomized trials, and we felt it to be justified to update and extend the previous review.9

Methods

Search Strategy
A detailed search of the available literature was performed. A comprehensive search strategy was designed to search the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 1, 2007), MEDLINE (1950 to March 2007), EMBASE (1980 to March 2007), and Science Citation Index (1945 to March 2007). For the exact search strategy used to search MEDLINE and adopted to search the other databases, see the Appendix. Informal inquiries were made with individuals active in the field.

Eligible Studies
Randomized trials of endovascular treatment (angioplasty or stenting) compared with endarterectomy in patients of any age or sex with symptomatic or asymptomatic carotid stenosis were selected for inclusion. Trials that allowed any acceptable technique for endovascular treatment or endarterectomy were reviewed. One reviewer...
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.</th>
<th>Randomized to Endovascular Treatment</th>
<th>Randomized to Surgery</th>
<th>Cerebral Protection Devices</th>
</tr>
</thead>
<tbody>
<tr>
<td>BACASS</td>
<td>2006</td>
<td>Single centre</td>
<td>20</td>
<td>20/0</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>CAVATAS-CEA</td>
<td>2001</td>
<td>Multicentre</td>
<td>504</td>
<td>488/16</td>
<td>251</td>
<td>55/158</td>
<td>253</td>
</tr>
<tr>
<td>EVA-3S</td>
<td>2006</td>
<td>Multicentre</td>
<td>527</td>
<td>527/0</td>
<td>265</td>
<td>262</td>
<td>227</td>
</tr>
<tr>
<td>Kentucky Symp.</td>
<td>2001</td>
<td>Single centre</td>
<td>104</td>
<td>104/0</td>
<td>53</td>
<td>51</td>
<td>0</td>
</tr>
<tr>
<td>Kentucky Asymp.</td>
<td>2004</td>
<td>Single centre</td>
<td>85</td>
<td>0/85</td>
<td>43</td>
<td>42</td>
<td>0</td>
</tr>
<tr>
<td>Leicester*</td>
<td>1998</td>
<td>Single centre</td>
<td>23</td>
<td>23/0</td>
<td>11</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>SAPPHIRE*</td>
<td>2004</td>
<td>Multicentre</td>
<td>334</td>
<td>96/238</td>
<td>167</td>
<td>167</td>
<td>167</td>
</tr>
<tr>
<td>SPACE*</td>
<td>2006, 2007</td>
<td>Multicentre</td>
<td>1196</td>
<td>1196/0</td>
<td>607</td>
<td>589</td>
<td>151</td>
</tr>
<tr>
<td>TESCAS-C</td>
<td>2006</td>
<td>Multicentre</td>
<td>166</td>
<td>NK</td>
<td>82</td>
<td>84</td>
<td>NK</td>
</tr>
<tr>
<td>WALLSTENT*</td>
<td>2001</td>
<td>Multicentre</td>
<td>219</td>
<td>219/0</td>
<td>107</td>
<td>112</td>
<td>0</td>
</tr>
</tbody>
</table>

Values are No. of patients. Symp/Asymp indicates the No. of patients who were symptomatic or asymptomatic; PTA, percutaneous transluminal angioplasty without stent.

*Trials that were stopped before reaching their calculated sample size.

(J.E.) applied the search strategy and inclusion criteria, and one reviewer (R.L.F.) double-checked the search results.

Data Extraction and Analysis

For each trial the following data were extracted: (1) the method of randomization, (2) number of patients allocated to each treatment group, (3) number of exclusions and losses to follow-up, (4) type of intervention, and (5) outcome measures and the method of measuring outcome. If provided, the stroke classification (fatal, disabling, nondisabling) was also recorded. Additionally, the following data were extracted to allow a number of subgroup analysis: The proportion of symptomatic versus asymptomatic patients, the degree of baseline stenosis for each treatment group, stents versus no stents, and the use of cerebral protection devices.

Intention-to-treat analysis was performed using the software provided by the Cochrane Collaboration (RevMan). The Peto fixed effect model was used to calculate odds ratios (OR) and 95% confidence intervals (CI). Probability values <0.05 were considered statistically significant. When the Peto fixed-effect model showed a statistically significant difference, the OR was also calculated using the Mantel-Haenszel random-effects model. Heterogeneity among trials was tested using a χ² test, probability values <0.1 were considered statistically significant.

The Peto fixed effect model is based on the assumption that the effect of intervention is the same in every study and implies that any differences among study results are attributable to chance. A random-effects model is based on the assumption that the true effect in different studies is not strictly identical. Using a random-effects model leads to a widening of the confidence interval. If the level of significance differs between the fixed-effect and the random-effects model, the result is not very robust and should be interpreted with caution.

The scope of possible outcome analyses was limited by the information provided by the different trial publication and definition of outcome measures used in each trial. To assess the safety of the procedure (within 30 days after treatment), the following outcome analyses were carried out: (1) stroke, (2) death, (3) disabling stroke, (4) stroke or death, (5) disabling stroke or death, (6) cranial neuropathy, (5) myocardial infarction, (6) myocardial infarction, stroke, or death, and (7) in patients undergoing stenting, death, or stroke with or without cerebral protection device.

To assess long-term efficacy of treatment (after the initial 30-day period), only combined end-point analyses were possible: (1) any stroke or death at 30 days plus ipsilateral stroke between 31 days and 6 months after randomization, and (2) death or stroke at 24 months after randomization.

Results

The authors identified 10 randomized trials. Five of these were completed randomized controlled trials comparing endovascular treatment of carotid stenosis with surgery (n=879 patients); the 5 other trials were stopped early (n=2299 patients).

Included Studies

Trial characteristics are displayed in Table 1. Because of the nature of the interventions and study design, health professionals, 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) was an international multicenter study incorporating 2 separate randomized trials of the treatment of carotid stenosis as measured by the common carotid method. Long-term follow-up for more than 5 years continued until 2007. Patients with symptomatic and asymptomatic carotid stenosis suitable for endovascular treatment and surgery were included. 504 patients were randomized between endovascular treatment and carotid endarterectomy (CAVATAS-CEA). The trial found no significant difference in the rate of major outcome events within 30 days of endovascular treatment or endarterectomy (10.0% versus 9.9% for any stroke lasting more than 7 days or death, Table 2).

BACASS

The single center Basel Carotid Artery Stenting Study (BACASS) was carried out by one of the centers that had collaborated in CAVATAS. 20 patients were randomized to compare carotid endarterectomy and endovascular treatment. Inclusion criteria were similar to CAVATAS-CEA, and the study used the same criteria to establish the degree of stenosis as CAVATAS. One patient in the surgery group had an ipsilateral nondisabling stroke within 30 days of the procedure. No patient in the endovascular treatment group experienced symptoms of TIA or stroke within 2 years of randomization.
Table 2. Outcome Event Rate in the Individual Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>30-Day Death or Stroke</th>
<th>30-Day Death or Disabling Stroke</th>
<th>30-Day Stroke</th>
<th>30-Day Death</th>
<th>30-Day Disabling Stroke</th>
<th>30-Day Death or Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Endovasc Surgery</td>
<td>Endovasc Surgery</td>
<td>Endovasc</td>
<td>Endovasc</td>
<td>Endovasc</td>
<td>Endovasc Surgery</td>
</tr>
<tr>
<td>BACASS</td>
<td>0 (0)</td>
<td>1 (10)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>CAVATAS-CEA*</td>
<td>25 (10)</td>
<td>25 (10)</td>
<td>16 (6.4)</td>
<td>15 (5.9)</td>
<td>18 (7.1)</td>
<td>21 (8.3)</td>
</tr>
<tr>
<td>EVA-3S</td>
<td>25 (9.4)</td>
<td>10 (3.8)</td>
<td>9 (3.4)</td>
<td>4 (1.5)</td>
<td>23 (8.7)</td>
<td>7 (2.7)</td>
</tr>
<tr>
<td>Kentucky Symp.</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Kentucky Asymp.</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Leicester</td>
<td>5 (45.5)</td>
<td>0 (0)</td>
<td>3 (27.3)</td>
<td>0 (0)</td>
<td>5 (45.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>SAPPHIRE</td>
<td>8 (4.8)</td>
<td>9 (5.4)</td>
<td>4 (2.4)</td>
<td>7 (4.2)</td>
<td>6 (3.6)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>SPACE</td>
<td>42 (6.9)</td>
<td>38 (6.5)</td>
<td>30 (4.9)</td>
<td>22 (3.7)</td>
<td>44 (7.2)</td>
<td>37 (6.3)</td>
</tr>
<tr>
<td>TESCAS-C</td>
<td>NK</td>
<td>NK</td>
<td>NK</td>
<td>NK</td>
<td>NK</td>
<td>NK</td>
</tr>
<tr>
<td>WALLSTENT</td>
<td>13 (12.1)</td>
<td>5 (4.5)</td>
<td>NK</td>
<td>NK</td>
<td>NK</td>
<td>NK</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>30-Day Cranial Neuropathy</th>
<th>30-Day Myocardial Infarction, Stroke, or Death</th>
<th>30-Day Myocardial Infarction</th>
<th>24-Month Death or Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Endovasc Surgery</td>
<td>Endovasc Surgery</td>
<td>Endovasc Surgery</td>
<td>Endovasc Surgery</td>
</tr>
<tr>
<td>BACASS</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>CAVATAS-CEA*</td>
<td>0 (0)</td>
<td>22 (8.7)</td>
<td>3 (1.2)</td>
<td>25 (9.9)</td>
</tr>
<tr>
<td>EVA-3S</td>
<td>3 (1.1)</td>
<td>20 (7.6)</td>
<td>1 (0.4)</td>
<td>26 (9.8)</td>
</tr>
<tr>
<td>Kentucky Symp.</td>
<td>0 (0)</td>
<td>4 (7.8)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Kentucky Asymp.</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Leicester</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NK</td>
<td>5 (45.5)</td>
</tr>
<tr>
<td>SAPPHIRE</td>
<td>0 (0)</td>
<td>8 (4.8)</td>
<td>4 (2.4)</td>
<td>10 (5.9)</td>
</tr>
<tr>
<td>SPACE</td>
<td>NK</td>
<td>NK</td>
<td>NK</td>
<td>8 (9.7)</td>
</tr>
<tr>
<td>TESCAS-C</td>
<td>NK</td>
<td>NK</td>
<td>NK</td>
<td>8 (9.7)</td>
</tr>
<tr>
<td>WALLSTENT</td>
<td>NK</td>
<td>NK</td>
<td>NK</td>
<td>NK</td>
</tr>
</tbody>
</table>

Numbers of patients (percentage); NK indicates not known; n/a, all patients treated with protection device.
*CAVATAS analyzed only strokes lasting more than 7 days.

Kentucky
Two single-center randomized trials were conducted by the Kentucky group.11,12 The first trial compared carotid angioplasty and stenting with endarterectomy in 104 patients who had experienced symptoms or signs of cerebral ischemia confined to the ipsilateral carotid artery within the previous 3 months and with an ipsilateral carotid stenosis of greater than 70% (measured by NASCET criteria).11 One patient died of myocardial infarction immediately after carotid endarterectomy. No other deaths or strokes were reported.

Patients with a carotid stenosis >80% and no symptoms or signs of cerebral ischemia were randomized between stenting and surgery (n=84 patients).12 No events occurred in these patients.

TESCAS-C
The Trial of Endarterectomy versus Stenting for the treatment of Carotid Atherosclerotic Stenosis in China (TESCAS-C) reported results of 166 patients randomized between carotid endarterectomy and endovascular treatment. The cumulative incidence of death, stroke, or myocardial infarction within 30 days of intervention or death or ipsilateral stroke between 31 days and 6 months of endovascular treatment and surgery was similar (22.0% versus 19.1%).14

Leicester
In a single-center study carried out in Leicester, patients with symptomatic severe internal carotid stenosis >70% (peak systolic velocity <200 cm/s on ultrasound) were randomized to stenting or surgery.17 The trial was stopped early after only 23 patients had been randomized to treatment and only 17 had received their allocated treatment. Whereas the carotid endarterectomies (n=10) proceeded without any complications, 5 of the 7 patients who underwent stenting had a subsequent stroke.

WALLSTENT
WALLSTENT was an industry-sponsored multicenter randomized trial which randomized patients with symptomatic carotid artery stenosis >60% and symptoms within 120 days before randomization between surgery and stenting.15 219 patients were randomized. The 30-day periprocedural com-
plication rate (any stroke or death) was significantly higher in the stented group compared to the surgery group (12.1% versus 4.5%, \( P=0.049 \)). The trial was stopped early, not by the independent data-monitoring committee, but the trial sponsor well before the targeted sample size. Further results have not been published in a peer-reviewed journal.

**SAPPHIRE**

The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial included only patients with a high surgical risk (n=334 patients). The majority of patients randomized in the trial were asymptomatic. The eligible degree of stenosis depended on whether a patient was symptomatic (\( \geq 60\% \)) or asymptomatic (\( \geq 80\% \)). The majority of patients included in SAPPHIRE had asymptomatic carotid stenosis. The degree of stenosis was based on ultrasound flow velocity criteria. The trial used cerebral neuroprotection devices in the stenting group. The cumulative incidence of a major cardiovascular event at 1 year after the procedure was lower in the stenting group (12.2% versus 20.1%). The trial was terminated early because of a slowdown in recruitment. Subsequently, it emerged that SAPPHIRE’s Principle Investigator received undeclared royalties from sales of the protection device used in the trial.

**EVA-3S**

The multicenter randomized Endarterectomy versus Angioplasty in patients with Severe carotid Stenosis Study (EVA-3S) only included symptomatic patients with carotid stenosis greater than 70% (NASCET criteria). Later the threshold was reduced to >60%. Symptoms had to have occurred within 120 days before randomization. 527 patients were randomized between stenting and surgery. The trial was put on hold 3 years after the start of randomization. The use of cerebral protection devices was then made mandatory. The incidence of any stroke or death was higher in the endovascular group compared to surgery at 30 days (9.6% versus 3.9%) and 6 months after treatment (11.7% versus 6.1%). Recruitment into the trial was stopped early after a safety analysis by the data-monitoring committee.

**SPACE**

The multicenter Stent-Protected Angioplasty versus Carotid Endarterectomy in symptomatic patients (SPACE) trial enrolled only patients with symptomatic carotid stenosis greater 70% (measured using NASCET criteria). 1200 patients were randomized between stenting and surgery. The rate of death or ipsilateral ischemic stroke 30 days after endovascular treatment or surgery was similar (6.84% versus 6.34%). This trial was terminated early after interim analysis showed that a much larger sample size would be needed to prove equivalence, and funds were not available to support further recruitment.

**Randomization Method**

The method of randomization was given for 7 trials and allocation concealment was judged to be adequate. Patients were randomly assigned treatment by computer after a telephone call to a randomization center using a minimization algorithm in 1 trial. In 2 trials, sealed envelopes were used for randomization. Four trials used a pseudonumber generator, a computer-generated random allocation schedule or a computer-generated sequence.

For 3 trials the method of randomization could not be obtained, and therefore allocation concealment was judged to be unclear.

**Follow-Up**

Most trials reported short-term outcome events at 1 month after treatment. However, long-term follow-up varied greatly between trials. Some trials did not report any long-term follow-up. Follow-up information from 3 trials were included in this review: 2-year results were available from 2 studies, and 3 trials contributed to the combined safety/efficacy outcome measure. CAVATAS-CEA provided the longest follow-up to 11 years, but final long-term results await publication. The 3-year follow-up results recently published from SAPPHIRE were not included in the review because the published data were not reconcilable with the chosen outcome measures.

**Functional Outcome**

The assessment of functional outcome was by the Oxford Handicap Stroke score in 1 trial. Three trials used one or more methods of assessing functional outcome: Barthel score, modified Rankin scale, and National Institute of Health Stroke Score. In CAVATAS-CEA, strokes were only counted if they lasted more than 7 days. Strokes were classified as disabling if the patient required help undertaking activities of daily living for more than 30 days and nondisabling if help was not required at 30 days. The remaining trials did not specify the method of assessing functional outcome.

**Analysis of Data**

Because the authors of this report did not have access to individual patient data, the authors had to rely on the published data, limiting the available end-point analyses, and not all trials contributed to each analysis.

**Ongoing Trials**

The authors were aware of 3 trials of endovascular treatment versus endarterectomy that were randomizing patients with symptomatic carotid stenosis at the time of preparing the review. One of these trials was also recruiting asymptomatic patients. The authors are aware of 3 trials of endovascular versus endarterectomy for asymptomatic stenosis in progress.

**Meta-Analysis: Symptomatic Carotid Stenosis**

**Safety**

Using a fixed-effect model, the odds ratio (OR) for the combined outcome of death or any stroke was significantly in favor of carotid endarterectomy (OR endovascular:surgery 1.40, 95% CI 1.04 to 1.88, \( P=0.03 \)). While the completed trials did not favor either treatment (OR 0.93, 95% 0.52 to 1.64, \( P=0.79 \)), the stopped trials significantly favored sur-
gery (OR 1.63, 95% CI 1.15 to 2.30, \(P = 0.0006\)). However, the \(\chi^2\)-test revealed statistically significant heterogeneity among the stopped trials (\(\chi^2 = 10.12, P = 0.03\)) and the whole group of trials (\(\chi^2 = 14.83, P = 0.02\), Figure 1). The use of a random-effects model led to a widening of the confidence interval, and the overall difference between surgery and endovascular was no longer statistically significant (OR 1.53, 95% CI 0.89 to 2.62, \(P = 0.12\)).

No statistically significant difference was found for the combined outcome of disabling stroke or death (OR 1.30, 95% CI 0.87 to 1.96, \(P = 0.21\)) using the Peto fixed-effect model.

Endovascular treatment was equally effective in preventing the combined outcome of myocardial infarction, stroke, or death within 30 days of treatment as surgery (fixed OR 1.37, 95% CI 0.91 to 2.08, \(P = 0.14\)).

Endovascular treatment was not statistically significant different from surgery, when the OR was calculated for stroke alone (1.37, OR 0.99 to 1.90, \(P = 0.06\), disabling stroke (OR 1.51, 95% CI 0.95 to 2.41, \(P = 0.08\)), and death (OR 1.14, 95% CI 0.54 to 2.40, \(P = 0.73\)). The \(\chi^2\)-test revealed statistically significant heterogeneity among trials when calculating the OR for stroke (\(\chi^2 = 13.57, P = 0.009\)).

The odds ratio for cranial neuropathy was significantly in favor of endovascular treatment using both the Peto fixed-effect model (OR 0.16, 95% CI 0.09 to 0.28, \(P = 0.00001\); Figure 2) and the random-effects model (OR 0.10, 95% CI 0.04 to 0.29, \(P = 0.0001\)).

Endovascular treatment did not differ in avoiding myocardial infarction within 30 days of treatment, calculating the odds ratio using the Peto fixed-effect model (OR 0.24, 95% CI 0.05 to 1.04, \(P = 0.06\); Figure 3).

Comparing patients stented with the use of a cerebral protection device and those stented without a protection device, the OR was not significantly different (OR [protection: no protection] 0.75, 95% CI 0.38 to 1.45, \(P = 0.39\)); however, there was significant heterogeneity between trials (\(\chi^2 = 5.63, P = 0.02\)).

### Efficacy

The odds ratio for death or stroke at 24 months after randomization was not statistically significant (OR 1.26, 95% CI 0.83 to 1.90, \(P = 0.28\)).

### Combined Safety and Efficacy

Trial data from 3 studies were included in this analysis. The odds ratio for any stroke or death at 30 days plus ipsilateral stroke between 31 days and 6 months after randomization calculated using the Peto fixed-effect model, significantly favored surgery (OR 1.53, 95% CI 1.14 to 2.05, \(P = 0.005\); Figure 4). Applying the random-effects model led to a widening of the confidence interval, but the result remained statistically significant (OR 1.58, 95% CI 1.07 to 2.35, \(P = 0.02\)).

### Meta-Analysis: Asymptomatic Carotid Stenosis

Only 1 trial compared endovascular treatment and surgery in patients with asymptomatic stenosis alone. No outcome events were recorded but the number of patients included in the trial was very small.\(^{12}\) One further study was primarily conducted in asymptomatic patients but did not report results for the cohort of asymptomatic patients separately and therefore did not contribute to the analysis of asymptomatic carotid stenosis.\(^{19}\) No odds ratios were therefore calculated.

### Discussion

Randomized controlled trials have shown that the addition of carotid endarterectomy to medical therapy is effective in reducing the risk of stroke among selected patients with carotid stenosis. Data from nonrandomized studies suggest that carotid angioplasty and stenting may be performed with risks and benefits comparable to surgery. However, nonrandomized studies do not provide a direct comparison between the treatment modalities in matched patients. Data from

---

### Figure 1.
Stroke or death within 30 days of treatment of symptomatic stenosis (fixed effect model).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Endovascular Events</th>
<th>Surgery Events</th>
<th>Total</th>
<th>Weight</th>
<th>Peto Odds Ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leicester</td>
<td>5</td>
<td>11</td>
<td>0</td>
<td>12</td>
<td>2.3</td>
<td>1998</td>
</tr>
<tr>
<td>Wallstreet</td>
<td>11</td>
<td>107</td>
<td>5</td>
<td>112</td>
<td>9.5</td>
<td>2003</td>
</tr>
<tr>
<td>Kentucky 2001</td>
<td>0</td>
<td>53</td>
<td>1</td>
<td>51</td>
<td>0.6</td>
<td>2001</td>
</tr>
<tr>
<td>CAVATAS-CEA</td>
<td>25</td>
<td>251</td>
<td>25</td>
<td>253</td>
<td>25.8</td>
<td>2003</td>
</tr>
<tr>
<td>EVA-3S</td>
<td>25</td>
<td>263</td>
<td>10</td>
<td>262</td>
<td>18.7</td>
<td>2006</td>
</tr>
<tr>
<td>SPACE</td>
<td>42</td>
<td>607</td>
<td>38</td>
<td>589</td>
<td>42.6</td>
<td>2006</td>
</tr>
<tr>
<td>BACAS</td>
<td>0</td>
<td>10</td>
<td>1</td>
<td>10</td>
<td>0.5</td>
<td>2006</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>1304</strong></td>
<td><strong>1289</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>1.40 (1.04, 1.88)</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Total events      | 110                 |                           | 80   |       |                |      |
| Heterogeneity: Chi² = 14.83, df = 6 (P = 0.02); I² = 60% |
| Test for overall effect: Z = 2.22 (P = 0.03) |

### Figure 2.
Cranial neuropathy within 30 days of treatment of symptomatic stenosis (fixed effect model).
randomized controlled trials provide such data, but to date no single trial has been large enough to provide a convincing result. The meta-analysis we describe here combines the data from the individual randomized trials but the results are difficult to interpret in a single conclusion. The main reason for this difficulty is the considerable clinical and statistical heterogeneity between the trials.

Heterogeneity was found for several outcome analyses and there are several possible explanations for this. The endovascular technique used was not the same for all the trials. Trials carried out in the early stage of the development of the technique used devices no longer in use and without cerebral protection. There may also be significant heterogeneity among baseline characteristics of the included patients, with varying degrees of baseline stenosis and time since symptom onset being considered for treatment. Heterogeneity may also arise because stopped and completed trials were analyzed together. Three trials were stopped prematurely because of concerns over the safety of stenting.

Our meta-analysis of the data concerning the safety of treatment in symptomatic patients available from all the randomized controlled trials showed a significantly higher risk of stroke or death within 30 days of treatment in patients treated endovascularly compared to those treated surgically, when analyzed using the Peto fixed-effect model. The confidence interval was wide and applying the Mantel-Haenszel random-effects model to the same data increased the confidence interval even further and showed no statistically significant difference between the treatments. This reduces the weight that can be placed on these findings and suggest that the data are not very robust. Furthermore, only trials that were stopped early for one reason or another favored surgery. There was no difference between endovascular treatment and surgery in the completed trials. This highlights the problem of stopping trials early because of a perceived higher risk in one group compared to the other. If this higher rate of unfavorable outcome is attributable to chance it will lead to bias against endovascular treatment that might not be justified. Analyzing stroke, disabling stroke, and death separately, no difference between endovascular treatment and surgery was found. However, endovascular treatment was significantly better than surgery in preventing cranial nerve damage using both the Peto fixed-effect and the Mantel-Haenszel random-effects model.

Long-term efficacy was difficult to assess because outcome measures differed greatly between trials and there was no consistency in the length of reported follow-up. Few trials reported long-term follow-up beyond 1 year. It was only possible to calculate odds ratios for combined end points. The interpretation of combined outcomes is difficult unless the relative contribution of each of the component is known. In the case of the included studies this was not possible. However, the odds ratio for death or stroke at 24 months in the endovascular group was similar to the surgery group but only 1 moderately sized trial and 1 very small trial contributed to this analysis.

In contrast to expectations, we found no significant difference in the 30-day rate of stroke or death in endovascular patients treated with or without a protection device. However, only 2 trials included data regarding the use of cerebral protection devices. It has to be noted that the use of protection devices was not allocated randomly and selection bias may be operating, and the result of the comparison is therefore not conclusive. Our result does not exclude a benefit of protection devices, but implies that a randomized trial assessing the value of protection devices would be justified.

The number of patients and outcome events in the cohort of patients with asymptomatic stenosis was too small to justify a detailed meta-analysis.

**Conclusion**

The data available contributing to this meta-analysis are limited in terms of number of outcome events available for analysis, and conflicting in terms of 30-day complication rate. Some safety analyses of events within 30 days of treatment favored endovascular treatment (eg, cranial nerve palsy and...
myocardial infarction), some favored surgery (eg, any stroke or death), and some suggested equivalence between the procedures (eg, the combined outcome event of any stroke, MI, or death within 30 days). The overall estimates of effect were both imprecise and difficult to interpret because of substantial heterogeneity among the trials, probably because of different patients, endovascular procedures, and duration of follow-up. In general the trials compared experienced carotid surgeons against less experienced interventionists, and 5 trials were stopped early. Combining all the trials together in a meta-analysis may therefore have led to an overestimate of the risks of endovascular treatment. The fact that the risks of stroke or death within 30 days of treatment were very similar when only the completed trials were combined supports this interpretation. Only 1 trial provided follow-up data beyond 2 years. The long-term efficacy of stenting versus surgery therefore remains unknown. Overall, the data are insufficient to support a change from routine clinical practice in the types of patient for which carotid endarterectomy is the current standard treatment. The results of the analysis support the continuing inclusion of patients within randomized clinical trials between endovascular and surgical treatment for carotid artery stenosis.

Appendix: Medline Search Strategy

1. carotid artery diseases/ or carotid artery thrombosis/ or carotid stenosis/
2. carotid arteries/ or carotid artery, common/ or carotid artery, external/ or carotid artery, internal/
3. constriction, pathological/
4. 2 and 3
5. (carotid adj5 (stenosis or thrombosis or disease$ or narrow$ or plaque$ or arteriosclerosis$ or atherosclerosis$)). tw.
6. 1 or 4 or 5
7. angioplasty/ or angioplasty, balloon/ or angioplasty, balloon. Laser-assisted/
8. Balloon Dilatation/
9. Stents/
10. (angioplasty or stent$ or endovascular). tw
11. (balloon adj5 (dilat$ or catheter$)). tw
12. (endoluminal or transluminal) adj5 repair$. tw
13. 7 or 8 or 9 or 10 or 11 or 12
14. 6 and 13
15. Randomized Controlled Trials/
16. random allocation/
17. Controlled Clinical Trials/
18. control groups/
19. clinical trials/ or clinical trials, phase i/ or clinical trials, phase ii/ or clinical trials, phase iii/
20. double-blind method/
21. single-blind method/
22. Therapies, Investigations/
23. Research Design/
24. Randomized controlled trial. pt
25. Controlled clinical trial. pt
26. clinical trial. pt
27. random$. tw
28. (controlled adj5 (trial$ or study$)). tw
29. (clinical$ adj5 trial$). tw
30. ((control or treatment or experiment$ or intervention or surgical) adj5 (group$ or subject$ or patient$)). tw
31. (quasi-random$ or quasi random$ or pseudorandom$ or pseudo random$). tw
32. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)). tw
33. (sing$ or doubl$ or trip$ or trebl$) adj5 (blind$ or mask$). tw
34. (coin adj5 (flip or flipped or toss$)). tw
35. latin square. tw
36. versus. tw
37. controls. tw
38. or/15 to 37
39. 14 and 38
40. limit 39 to humans

Acknowledgments

This article is based on a more extensive review available in the Cochrane Library,1 supported by a grant from the Department of Health, which has been updated with the latest results from SPACE.2 Previously unpublished data from CAVATAS-CEA, and additional outcome measures. The authors thank the Cochrane Stroke Group Editorial Team for advice and support.

Sources of Funding

This work was undertaken at UCLH/UCL, who received a proportion of funding from the Department of Health’s NIHR Biomedical Research Centres funding scheme. M.M.B.’s Chair in Stroke Medicine at UCL is supported by the Reta Lila Weston Trust for Medical Research. J.E. and R.L.F. are funded by a grant from the Medical Research Council.

Disclosures

None.

References


Randomized Controlled Trials Comparing Endarterectomy and Endovascular Treatment for Carotid Artery Stenosis: A Cochrane Systematic Review
Jörg Ederle, Roland L. Featherstone and Martin M. Brown

*Stroke*. 2009;40:1373-1380; originally published online February 19, 2009;
doi: 10.1161/STROKEAHA.108.531228

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://stroke.ahajournals.org/content/40/4/1373