Meta-analysis of Randomized Trials Comparing Carotid Endarterectomy and Endovascular Treatment

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Objective and design. In order to evaluate the comparative efficacy and safety of carotid angioplasty with or without stent placement (CAS) versus carotid endarterectomy (CEA) we performed a meta-analysis of the presently available randomized studies.

Materials and methods. A multiple electronic health database search on all randomized trials describing CAS compared with CEA in patients with symptomatic or asymptomatic carotid artery stenosis was performed.

Results. Seven trials totalling 2972 patients (1480 randomized to CEA and 1492 randomized to CAS) were included in the meta-analysis. Results significantly favoured CEA over CAS in terms of death or any stroke at 30 days after procedure; the risk of death, any stroke, or myocardial infarction at 30 days; ipsilateral ischaemic stroke at 30 days; any stroke at 30 days; death or stroke at 6 months; and the risk of procedural failure.

Conclusions. The results of this meta-analysis suggest that CEA can be performed with more safety than CAS. As a result, CEA remains the “gold standard” treatment for suitable de novo carotid stenosis and CAS should only be performed within randomized trials of stenting versus surgery.

Introduction

Carotid angioplasty with stenting (CAS) is increasingly used in the treatment of extracranial carotid atherosclerosis.1–14 In order to supersede carotid endarterectomy as the standard treatment for carotid stenosis, CAS must be shown to be at least as safe and effective as surgery. However, the exact role of CAS in the treatment of carotid stenosis, and the long-term efficacy of this technique is not yet defined.

A systematic review15 of five randomized trials comparing stenting with endarterectomy16–21 concluded that “there is currently insufficient evidence to support a widespread change in clinical practice away from recommended CEA as the treatment of choice for suitable carotid artery stenosis”. Recently, the results of two further trials were published, namely Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy trial (SPACE),22 and Endarterectomy versus Angioplasty in patients with Severe Symptomatic Stenosis (EVA-3S).23 At the moment, two more trials are ongoing in Europe24 and the United States.25

The objective of this study was to carry out a meta-analysis of all randomized trials of CAS compared with CEA in patients with carotid stenosis suitable for surgery.

Materials and Methods

Study selection

A multiple electronic health database search was performed including Medline, Embase, Ovid, Cochrane
Database of Systematic Reviews, and Cochrane Database of Abstracts of Reviews of Effectiveness (DARE), on all randomized trials published between 1966 and December 2006 describing CAS compared with CEA. These databases were searched with an unrestricted search strategy, using exploded MeSH (medical subject heading) terms (carotid arteries, stenosis, endovascular, stents, angioplasty, endarterectomy, stroke, and cerebrovascular disease).

Outcome measures

The tables and outcome definitions used were developed a priori by the investigation team, namely any stroke (disabling or non-disabling) or death within 30 days of the procedure, subsequent ipsilateral carotid territory stroke, subsequent stroke in any arterial territory, cranial neuropathy within 30 days of the procedure, other complications of the procedure, eg. myocardial infarction and restenosis rate.

Inclusion criteria

We included randomized trials (RCTs) of carotid endovascular treatment compared with carotid endarterectomy in patients of any age or sex with symptomatic or asymptomatic carotid artery stenosis who had either bilateral or unilateral procedures. Each trial was critically appraised by all investigators, using a critical review checklist for study validity as proposed by the Dutch Cochrane Collaboration, Dutch Cochrane Centre, Therapy checklist (Dutch extended version) (http://www.cochrane.nl, [accessed May 2005]).

Exclusion criteria

Non-randomized prospective trials, retrospective studies, controlled clinical trials, comparative observational studies, non-comparative observational studies, case series studies and population-based registries comparing CAS with CEA or that did not include a randomized comparison with CEA were excluded.

Quality of trials

T.L. and M.A. independently assessed the methodological quality of included trials using the checklist recommended by the Cochrane PVD Review Group. J.B. resolved any disagreements. The assessment of study quality was based on the methods described by Jadad.

Statistical analysis

Statistical analysis for categorical variables was carried out using odds ratios (ORs) as the summary statistic. An OR of less than 1 favours the CAS group, and the point estimate of the OR is considered statistically significant at the \( P < 0.050 \) level if the 95 per cent confidence interval (c.i.) does not include the value 1. To combine the OR for the outcomes of interest a Peto fixed-effects technique was used. Yates’ correction was used for those studies that contained a zero in one cell for the number of events of interest in one of the two groups. Two strategies were used to assess heterogeneity quantitatively. First, data were reanalysed using both random- and fixed-effects models. Second, graphical exploration with funnel plots for asymmetry was performed.

Analysis was conducted using the statistical software Statistical Package for Social Sciences (SPSS 12.0, Chicago, IL, USA) for Windows and Review Manager Version 4.2 (The Cochrane Collaboration, Update Software, Oxford, UK).

Results

Studies selected

The electronic literature search yielded 16 papers that were retrieved for full text appraisal; of these, 7 randomized studies fulfilled all inclusion criteria, and were included in the meta-analysis (Table 1). A total of 2972 patients (1480 randomized to CEA and 1492 randomized to CAS) were analyzed. Four of the seven studies included only patients with symptomatic carotid stenosis. Three trials (CAVATAS, Kentucky, SAPPHIRE) analyzed patients with symptomatic and asymptomatic stenosis. One trial (SAPPHIRE) included only patients considered at high surgical risk for CEA.

In the latter three of the seven trials (SPACE, EVA-3S, SAPPHIRE) a distal protection device was used either in all CAS patients or a part thereof. The rate of successful deployment of the stent ranged from 89% to 100%. In all studies, an additional stent was used after primary angioplasty. Blinding of health workers, patients, and assessors to treatment or outcome was not feasible because of study design and the nature of the interventions.
<table>
<thead>
<tr>
<th>Study/Jadad Score</th>
<th>Inclusion criteria</th>
<th>Follow-up</th>
<th>CAS technique</th>
<th>CEA technique</th>
<th>CAS No of pat.</th>
<th>CEA No of pat.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naylor et al., 1998, Score 3</td>
<td>≥70% symptomatic ICA stenosis</td>
<td>24 hours after intervention, at 30 days after treatment, and for a total of 2 years</td>
<td>Wallstent, aspirin before and after, TCD monitoring, IV dextran-40</td>
<td>Discretion of surgeon with patch graft, shunting, TCD monitoring, IV dextran-40</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Alberts et al., for WALLSTENT trial, 2001, Score 3</td>
<td>≥60% symptomatic ICA stenosis</td>
<td>24 hours after procedure, then again at 6 and 12 months, and then annually.</td>
<td>Wallstent, aspirin and ticlopidine 72 h before and 30 days after, aspirin indefinitely after Stents in 26% of patients and included Wallstent, Streker, and Palmaz; aspirin or other antiplatelet agent at least 24 before and after</td>
<td>Discretion of surgeon; aspirin indefinitely after</td>
<td>107</td>
<td>112</td>
</tr>
<tr>
<td>CAVATAS, 2001, Score 3</td>
<td>Presence of clinically important stenosis determined by local criteria</td>
<td>1 month after treatment and then again at 6 months, 12 months, and yearly after randomization</td>
<td>Discretion of surgeon</td>
<td>251</td>
<td>253</td>
<td></td>
</tr>
<tr>
<td>Brooks et al., 2001, Score 1</td>
<td>≥70% symptomatic ICA stenosis</td>
<td>24 hours after procedure and again at 1, 3, 6, 12, and 24 months</td>
<td>Wallstent; aspirin and clopidogrel before</td>
<td>CEA under General anesthesia and EEG monitoring; aspirin and clopidogrel before</td>
<td>53</td>
<td>51</td>
</tr>
<tr>
<td>Link et al., 2000, Score 3</td>
<td>≥70% symptomatic ICA stenosis</td>
<td>30 days, 6 months, 1 year (completed), and then annually</td>
<td>Wallstent; aspirin before and indefinitely after and clopidogrel 24 h before</td>
<td>Discretion of surgeon; aspirin 72 h before and indefinitely after</td>
<td>12 (8 followed-up)</td>
<td>11 (5 followed-up)</td>
</tr>
<tr>
<td>Yadav et al., for SAPPHIRE, 2003, Score 3</td>
<td>≥50% symptomatic ICA stenosis or ≥80% asymptomatic ICA stenosis and ≥1 high-risk surgical criteria</td>
<td>7 and 30 days, and after 6, 12, and 24 months after treatment</td>
<td>Stents were Carotid Wallstent, Precise, Acculink, embolic protection devices were PercuSurge GuardWire, FilterWire EX, AngioGuard, NeuroShield, and CarotidTrap (use of protection devices, predilation, and balloon size were left to the discretion of the interventional physician, 100 mg aspirin plus 75 mg clopidogrel daily for at least 3 days before and 30 days after the intervention</td>
<td>Surgeons used their usual operative technique, 100 mg aspirin before, during, and after surgery, Shunting during surgery was optional</td>
<td>599</td>
<td>584</td>
</tr>
<tr>
<td>SPACE Score 3</td>
<td>Symptomatic stenosis of carotid bifurcation or internal-carotid artery of at least 70%, corresponding to stenosis level of at least 70% according to ECST or at least 50% according to NASCET</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>EVA-3S Score 3</td>
<td>Stenosis of 60 to 99% in the symptomatic carotid artery, as determined by the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method. The degree of stenosis warranting treatment, set at 70% or more at the start of the trial, was subsequently (in October 2003) set at 60% or more because endarterectomy was shown to benefit patients with symptomatic stenosis of 50 to 69%.</td>
<td></td>
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<tr>
<td>Independent study neurologist</td>
<td>In January 2003, the safety committee recommended the systematic use of stents with cerebral protection devices because of a higher risk of stroke in patients treated without cerebral protection; centers began using them on February 1, 2003. The daily use of aspirin (100 to 300 mg) and clopidogrel (75 mg) or ticlopidine (500 mg) for 3 days before and 30 days after stenting was also recommended. Stents used: Carotid Wallstent Monorail (Boston Scientific), Acculink (Abbott), Precise RX (Cordis), Carotid Wallstent OTW (Boston Scientific), Zilver (Cook) Protection devices used: GuardWire Plus (Medtronic), FilterWire EZ (Boston Scientific), Spider RX (ev 3), EmboShield (Abbott), Angioguard RX (Cordis), Spider (ev3) Accunet (Abbott).</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endarterectomy according to customary practice</td>
<td>261 259</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Kentucky B Score 1 | Asymptomatic carotid stenosis of more than 80% |
| An independent neurologist (TLC) and a clinical coordinator (LB) provided neurological examinations and independent oversight before and after each procedure and at specified intervals in conjunction with carotid duplex scanning. | All patients received 325 mg aspirin and 75 mg clopidogrel before CAS or CEA. CAS was performed as described previously (Wallstent). |
| All patients received 325 mg aspirin and 75 mg clopidogrel before CAS or CEA. CEA was performed by standard techniques under general anesthesia with electroencephalographic monitoring. | 43 42 |
Assessment of functional outcome

No uniform assessment of the neurological status was performed in the various trials. In the Leicester study functional outcome was assessed by the Oxford Handicap Stroke score. In Kentucky A, Kentucky B, Wallstent, and SAPPHIRE a combination of the Barthel, Rankin, and National Institutes of Health Stroke Scale scores was used, the so called >1 scale to measure outcome. 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. In EVA-3S, the degree of disability from stroke and functional disability from cranial-nerve injury was assessed by the study neurologist. In SPACE, stroke outcome was assessed by independent neurologists. Disabling ipsilateral stroke was defined by a score on the modified Rankin scale of at least 3.

Restenosis rates

CAVATAS was the only study that explicitly reported restenosis rates. In that study, ipsilateral stenosis of >70% 1 year after treatment was more common after CAS than CEA (14% compared with 4%; P < 0.001), where the low rate of stent use has to be considered.

Meta-analysis

Intention-to-treat analysis could be performed on all trials (Figs. 1a–2a). The rates of the major outcomes for each of the included studies are depicted in Table 2.

Results significantly favoured CEA over CAS for death or any stroke at 30 days after the procedure (OR 1.39 (95 per cent c.i. 1.05 to 1.84)), ipsilateral ischaemic stroke at 30 days after the procedure (OR 1.48 (95 per cent c.i. 1.05 to 2.07)), any stroke at 30 days after the procedure (OR 1.50 (95 per cent c.i. 1.05 to 2.16)), death or stroke at 6 months after the procedure (OR 1.99 (95 per cent c.i. 1.09 to 3.62)), and the risk of procedural failure (OR 3.42 (95 per cent c.i. 2.03 to 5.79)).

There was, however, a significantly reduced risk of cranial neuropathy at 30 days after the procedure for CAS (OR 0.15 (95 per cent c.i. 0.09 to 0.26)).

There was no significant difference between CAS and CEA groups in the odds of death or stroke at 1 year after the procedure (OR 1.01 (95 per cent c.i. 0.71 to 1.44)) or ipsilateral intracerebral bleeding at 30 days after the procedure (OR 0.57 (95 per cent c.i. 0.17 to 1.87)).

Publication bias

To test whether publication bias was present within the above sample included in the meta-analysis, a funnel plot was undertaken. (Figs. 1b–2b). None of the studies lies outside the limits of the 95 per cent c.i. The funnel plot shows no publication bias, all studies being equally distributed around the vertical axis.

Sensitivity analysis

We performed sensitivity analysis to test the results under varied conditions such as the exclusion of trials that contributed the most number of patients. After exclusion of SPACE or CAVATAS the results remained significant; however, after exclusion of EVA-3S or all three studies the Peto odds ratios for the effect size showed no significant difference between CAS and CEA.

In three of the seven studies included cerebral protection devices were used. After exclusion of these trials, the sensitivity analysis could not demonstrate any significant difference concerning the Peto odds ratio for CAS versus CEA. A subgroup analysis only for patients with symptomatic carotid stenosis still demonstrated significant differences of composite rates of stroke or death among patients in the CAS group compared with the CEA group.

Using a random-effects model instead of a fixed-effects model, evaluating the Peto odds ratios during sensitivity between CAS and CEA a nonsignificant difference of relative risk for 30-day rates of stroke and death was observed (P = 0.14). For sensitivity analysis, evaluation of the relative risk difference for the effect size of all studies a fixed-effects model was also applied. The fixed-effects model recorded a significant increase of 30-day rates of stroke or death (P = 0.02) (Table 3).

Discussion

Nonrandomized experience originating from over 5000 carotid angioplasty and stenting procedures for carotid stenosis in high-risk and even in patients without increased surgical risk2–14,31 suggested, that CAS would be associated with acceptable periprocedural complication rates as the 30-day risk of stroke or death ranged from 2% to 9%, with an average rate
of 4.7%. An essential shortcoming of the CAS case series mentioned above is their non-randomized study design with the potential risk of bias due to heterogeneity of patient selection and severity of the lesions. Furthermore, outcome was assessed by independent neurologists or physicians in very few studies (see Table 1). Thus randomized controlled trials were required to assess the outcome of carotid stenting by comparison to endarterectomy.32,33

A recent meta-analysis15 of five prospective randomized trials comparing stenting with endarterectomy16–20,34 by analyzing a total of 1269 patients demonstrated a 30-day odds of stroke or death after CAS of the carotid artery of 8.1% (51 of 632 patients; range, 0.0 to 12.1%), and for CEA a 30-day odds of death or any stroke of 6.3% (40 of 637 patients; range, 0.0 to 9.9%). However, the difference between the two treatments was not statistically significant. On the basis of the bottom-line conclusion of this meta-analysis, the authors stated that there was no evidence to support a shift from the recommendation of CEA as the standard treatment for carotid stenosis.15–20,34 On the contrary, this meta-analysis only offers Phase I-type evidence that CAS can be performed relatively
Table 2. Rates of outcome events in the individual trial

<table>
<thead>
<tr>
<th>Study</th>
<th>30-Day Death or Stroke</th>
<th>30-Day Death or Disabling Stroke</th>
<th>1-Year Death or Stroke</th>
<th>30-Day Cranial Nerve Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Endovasc No. (%)</td>
<td>Surgery No. (%)</td>
<td>Endovasc No. (%)</td>
<td>Surgery No. (%)</td>
</tr>
<tr>
<td>CAVATAS</td>
<td>25 (10)</td>
<td>25 (9.9)</td>
<td>16 (6.4)</td>
<td>15 (5.9)</td>
</tr>
<tr>
<td>Kentucky A</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Kentucky B</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>
</tr>
<tr>
<td>WALLSTENT</td>
<td>13 (12.1)</td>
<td>5 (4.5)</td>
<td>NK</td>
<td>NK</td>
</tr>
<tr>
<td>SAPPHIRE</td>
<td>8 (4.8)</td>
<td>9 (5.4)</td>
<td>NK</td>
<td>NK</td>
</tr>
<tr>
<td>SPACE</td>
<td>46 (7.7)</td>
<td>38 (6.5)</td>
<td>28 (4.7)</td>
<td>22 (3.8)</td>
</tr>
<tr>
<td>EVA-3S</td>
<td>25 (9.6)</td>
<td>10 (3.9)</td>
<td>9 (3.4)</td>
<td>4 (1.5)</td>
</tr>
</tbody>
</table>

Values are numbers or percentage (%) of patients.
MI indicates myocardial infarction; NK, not known.
safely. In the present meta-analysis, the two completed and last published series (SPACE, EVA-3S) have been added and provide us with additional material.

**SPACE**

The SPACE investigators randomized 1183 symptomatic patients within 180 days of transient ischaemic attack or moderate stroke (modified Rankin scale of ≤3) and reported a 30-day stroke and death rate of 6.34% for CEA and 6.84% for CAS, which was not statistically significantly different ($p = 0.89$).

**EVA-3S**

The EVA-3S trial, instead, showed a stroke and death rate of 3.9% for CEA and 9.6% for CAS by studying 527 symptomatic patients ($p < 0.02$). This trial was stopped before the estimated patient recruitment was completed. Half the strokes in the patients who did not have a protection device occurred during the first postoperative day ($N = 2$) and the other half evolved on the day of treatment ($N = 2$). Deficient methods and lack of experience on the part of the endovascular operator may have undermined the results of EVA-3S. The results of the EVA-3S trial underscore the need to standardize the training and performance of operators of carotid artery stenting.

The present meta-analysis combined the results of all seven completed or stopped randomized trials that compared CAS with CEA between 1998 and 2006. The results significantly favoured CEA over CAS with respect to the combined and separate 30-day risk of death or any stroke, but also death or stroke at 6 months after the procedure. The risk of procedural failure was also greater in the CAS group, whereas the risk of cranial neuropathy at 30 days was lower but this is not surprising, considering the nature of the CAS technique and that of CEA.

We did not observe any significant difference between CAS and CEA when looking at the composite end point death or stroke at 1 year after the procedure, or ipsilateral intracerebral bleeding at 30 days after the procedure. CAS may only be beneficial for a particular group of patients. Relative to CEA, the results of CAS seem favorable only in the setting of some anatomic conditions that render surgery technically difficult, such as restenosis after prior CEA, prior radical neck surgery, and previous radiation therapy involving the neck and in patients with severe concomitant cardiac disease. The findings of this analysis as compared to that of Coward and colleagues suggest increasing evidence for an advantage of endarterectomy over carotid stenting.

At present carotid-artery stenting should be performed in high volume, specialized centers, where tailored carotid artery stenting procedures are performed according to the specific characteristics of the patient and lesion and continuously registered. Perhaps the safety and efficacy of carotid stenting will be proved in appropriately selected patients.

**Limitations/heterogeneity of included studies**

There are a number of limitation in our present ability to compare endarterectomy and stenting based on this meta-analysis. Completed and stopped studies were included in the meta-analysis.

In addition carotid stenting is an evolving procedure being compared with an established treatment

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### Table 3. Sensitivity analysis

<table>
<thead>
<tr>
<th></th>
<th>Fixed-effects model, Peto odds ratio</th>
<th>Random-effects model, Peto odds ratio</th>
<th>Fixed-effects model, relative risk</th>
<th>Exclusion of large trials</th>
<th>Exclusion of trials with the use of distal protection systems (SPACE, EVA-3S, SAPPHIRE)</th>
<th>Exclusion of studies with asymptomatic patients (CAVATAS, Kentucky B, SAPPHIRE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day risk of any stroke or death</td>
<td>$\chi^2 = 14.77, P = 0.02$</td>
<td>$\chi^2 = 11.3, P = 0.14$</td>
<td>$\chi^2 = 0.02$</td>
<td>Exclusion of SPACE: $\chi^2 = 9.52, P = 0.02$</td>
<td></td>
<td>$\chi^2 = 10.4, P = 0.03$</td>
</tr>
<tr>
<td>data available from 7 studies</td>
<td>$\chi^2 = 11.3, P = 0.08$</td>
<td></td>
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</tbody>
</table>

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**Meta-analysis of Carotid Stenting Versus Surgery**
and follow-up time has been limited in the present assessed trials.

However, for most of the outcomes analyzed, in our meta-analysis the confidence intervals surrounding the ORs were more narrow than in the recent meta-analysis by Coward15 or in the SPACE or EVA-3S trial. These findings suggest that with larger patient numbers the advantage of CEA over CAS will become more significant.

Ongoing studies

Currently, there are two more ongoing trials comparing carotid endovascular treatment with endarterectomy: the International Carotid Stenting Study (ICSS),24 and the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST),25 adding another 4000 patients to future analyses.

Long-term follow-up results and subgroup analyses are needed to determine whether CAS really is durable and long-lasting in terms of stroke prevention. This question will be more precisely addressed when the data from a larger number of patients with a more extensive follow-up period are available from the ongoing multicenter prospective randomized trials. The results of these studies hopefully will provide us with evidence to allow surgeons and other specialists an opportunity to construct valid guidelines for individual patients.

Summary

There appears to be growing evidence in favour of a significant better primary outcome after CEA compared to CAS. As a result, CEA presently remains the ‘gold standard’ treatment for suitable carotid stenoses. CAS should only be offered within the ongoing trials of stenting versus surgery. A general shift in the attitude towards the treatment of carotid disease cannot be recommended based on the presently available data.

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References


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