Safety of carotid artery stenting for symptomatic carotid artery disease: a meta-analysis

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Aims
Clinical trials comparing carotid artery stenting (CAS) with carotid endarterectomy (CEA) for patients with symptomatic carotid artery disease have produced conflicting results. We performed a meta-analysis to systematically evaluate currently available data by comparing CAS with CEA in patients with symptomatic carotid artery disease.

Methods
We searched MEDLINE, Embase, ISI Web of Knowledge, Current Contents, International Pharmaceutical Abstracts databases, the Cochrane Central Register of Controlled Trials, and scientific meeting abstracts up to 31 October 2006 and then calculated summary risk ratios (RRs) for mortality, stroke, disabling stroke, and death using random- and fixed-effect models. Data from five trials with 2122 patients were pooled. There was no difference in risk of 30-day mortality (summary RR 0.57, 95% CI 0.22–1.47, P = 0.25), stroke (summary RR 1.64, 95% CI 0.67–4.00, P = 0.34), disabling stroke (summary RR 1.67, 95% CI 0.50–5.62, P = 0.50), death and stroke (summary RR 1.54, 95% CI 0.81–2.92, P = 0.19), or death and disabling stroke (summary RR 1.19, 95% CI 0.57–2.51, P = 0.64) among patients randomized to CAS, compared with CEA.

Conclusions
No significant differences could be identified between CAS and CEA in the treatment of patients with symptomatic carotid artery disease. Larger randomized controlled trials are warranted to compare the two strategies.

Keywords
Carotid artery disease • Carotid endarterectomy • Carotid stenting • Meta-analysis

Introduction
The efficacy of carotid endarterectomy (CEA) in patients with symptomatic carotid artery disease has been established in several large randomized clinical trials.1–4 Although endovascular therapy for carotid artery stenosis has been used for many years in certain centres, its use has become more prevalent recently5 and carotid artery stenting (CAS) has been advocated as a viable alternative to CEA in some patients.6 However, recent clinical trials comparing the two strategies have showed disparate results, and the role of CAS in symptomatic carotid artery disease has been questioned.7–10 The purpose of this meta-analysis is to systematically evaluate currently available data by comparing CAS with CEA in patients with symptomatic carotid artery disease.

Methods
We performed a computerized search to identify relevant articles from 1990 to 31 October 2006 in MEDLINE, Embase, ISI Web of Knowledge, Current Contents, International Pharmaceutical Abstracts databases, and the Cochrane Central Register of Controlled Trials. We combined exploded medical subject headings and keyword searches for stroke, carotid artery, stent, angioplasty, endovascular, endarterectomy, and revascularization. Abstract lists from the 2005 and 2006 scientific meetings of the American Heart Association, the American College of Cardiology, the European Society of Cardiology, and the Transcatheter Cardiovascular Therapeutics were also searched. Published review articles, editorials, and internet-based sources of information (www.tctmd.com and www.theheart.org) were also reviewed.

A study was included if it randomized patients with symptomatic carotid artery disease to CAS or CEA and provided information on 30-day outcomes. Trials enrolling less than 50 patients were excluded. Patients were considered symptomatic if there was a history of a stroke or transient ischaemic attack ascribed to the carotid artery stenosis in the preceding 120 days. Information was abstracted using a standardized form that included data on the study population and protocol (mean age, proportion of women; endovascular approach and technique; use of embolic protection devices (EPDs) as well as...
30-day outcomes of death, stroke, myocardial infarction (MI), and a composite of death, stroke, or MI). Given the implications of a disabling stroke on patient quality of life, we evaluated the incidence of this endpoint separately in trials in which these data were available. We also assessed quality of the trial by evaluating specific elements of study design (i.e. concealment of allocation during randomization, number of patients screened before enrolment, independent neurological evaluation, and proportion of follow-up), but a quality score was not used.

**Statistical analysis**

From each trial, results were organized into a two-by-two table to permit calculation of effect sizes for CAS in comparison with CEA in regard to each outcome. Data on the results were collected on an intention-to-treat basis. Patients who were assigned to a particular therapy, but received no therapy or crossed over to the alternate strategy, were considered to belong to the group randomized to the original therapy. When the outcome did not occur in either group, we were unable to calculate effect sizes because of the empty cells and data were excluded from that particular trial. Summary risk ratios (RR) with 95% confidence intervals were calculated by combining results across the trials using fixed- and random-effect models. Cochran’s Q-test was used to assess heterogeneity. P-values less than 0.05 were considered significant. All analyses were performed using Stata, version 9.0 (Stata Corporation, College Station, TX, USA).

**Results**

Our search identified six trials that randomized patients with symptomatic carotid artery disease to CAS vs. CEA. Of these, four had been published in peer-reviewed journals, whereas one had been published only as an abstract with information on limited endpoints (Figure 1). The Stenting and Angio- plasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial enrolled both symptomatic and asymptomatic patients. Although the results of the symptomatic cohort were presented in the original publication, specific outcome data from patients with symptomatic carotid disease were obtained from the study investigators. Given its small size (17 treated patients), data from the Leicester trial were excluded from the analysis. We also excluded data from the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) trial, as stenting was used in only a small fraction of the patients randomized to the endovascular arm. A total of 2122 patients in five trials made up our final study population.

The baseline characteristics of the patient population, the inclusion criteria for degree of stenosis, type of stent used in the CAS arm, the proportion of patients treated with EPD, and the reason for trial termination are listed in Table 1. Three trials allowed the use of only a single stent, whereas two trials permitted the use of multiple stent delivery systems. EPDs were not used in two trials,11–13 were mandatory in SAPPHIRE, and based on operator discretion in Stent-Supported Percutaneous Angioplasty of the Carotid Artery Versus Endarterectomy (SPACE).7 The Endarterectomy Versus Stenting in patients with Symptomatic Severe Carotid Stenosis (EVA-3 S) trial originally permitted the use of EPDs at the discretion of the operator, but the protocol was modified to mandate routine EPD use following high risk of
stroke in patients treated without EPDs. Owing to the nature of the procedures, the patients, operators, and the neurologists assessing for neurological events were not blinded to the treatment arm in any of the studies.

Borderline evidence for statistical heterogeneity was noted for some endpoints. For this reason, we report results from the more conservative random effects models, although fixed-effect models were also performed and generated similar results (Table 2). The raw event rates for each trial are listed in Table 3.

Mortality in the trials ranged from 0 to 0.76% in the CAS arm and from 0 to 6.5% in the CEA arm. In the pooled estimate, 30-day death occurred in six (0.62%) patients in the CAS group and 12 (1.26%) patients in the CEA group. There was no difference in mortality between the two strategies (summary RR 0.57, 95% CI 0.22–1.47, \( P = 0.25 \), Figure 2). The incidence of stroke ranged from 0 to 8.81% in the CAS arm and from 0 to 6.16% in the CEA arm. Overall, stroke occurred in 68 (7.06%) patients in the CAS group and 44 (4.68%) patients in the CEA group. There was no difference in the likelihood of stroke (summary RR 1.64, 95% CI 0.67–4.00, \( P = 0.34 \), Figure 3). The incidence of disabling stroke ranged from 0 to 4.00% in the CAS arm and from 0 to 2.91% in the CEA arm. Overall, disabling strokes occurred in 31 (3.21%) patients in

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**Table 1** Key features of trials included in the meta-analysis

<table>
<thead>
<tr>
<th></th>
<th>Wallstent</th>
<th>Kentucky</th>
<th>SAPPHIRE</th>
<th>SPACE</th>
<th>EVA-3S</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CAS</td>
<td>CEA</td>
<td>CAS</td>
<td>CEA</td>
<td>CAS</td>
</tr>
<tr>
<td><strong>n</strong></td>
<td>107</td>
<td>112</td>
<td>53</td>
<td>51</td>
<td>50</td>
</tr>
<tr>
<td><strong>Male (%)</strong></td>
<td>66</td>
<td>62</td>
<td>NA(^a)</td>
<td>NA(^a)</td>
<td>70</td>
</tr>
<tr>
<td><strong>Mean age (years)</strong></td>
<td>66.5</td>
<td>70</td>
<td>66.4</td>
<td>69.6</td>
<td>73</td>
</tr>
<tr>
<td><strong>Inclusion stenosis (angiographic)</strong></td>
<td>&gt;60% Wallstent</td>
<td>&gt;70% Wallstent</td>
<td>&gt;50% Wallstent</td>
<td>Precise</td>
<td>&gt;50% Wallstent, Precise, Aculink</td>
</tr>
<tr>
<td><strong>EPD strategy</strong></td>
<td>None</td>
<td>None</td>
<td>Routine</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EPD used</strong></td>
<td>None</td>
<td>None</td>
<td>AngioGuard</td>
<td>Percusurge Guardwire, AngioGuard, Filterwire EZ, Spider, Emboshield, Acunet</td>
<td></td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>NA</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Independent neurological evaluation</strong></td>
<td>NA</td>
<td>yes</td>
<td>yes</td>
<td></td>
<td>yes</td>
</tr>
<tr>
<td><strong>Termination</strong></td>
<td>Premature termination based on futility analysis</td>
<td>Trial completion</td>
<td>Premature termination secondary to declining enrolment</td>
<td>Premature termination secondary to futility in meeting endpoint of non-inferiority</td>
<td>Premature termination secondary to futility and safety concerns</td>
</tr>
</tbody>
</table>

\(^a\)The manuscript did not provide the number of men and women, but described the proportion as not different.

**Table 2** Risk ratios of mortality, stroke, disabling stroke, and composite endpoints generated using random- and fixed-effect models

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Summary risk ratio (random-effect model)</th>
<th>Summary risk ratio (fixed-effect model)</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0.57 (95% CI 0.22–1.47)</td>
<td>0.52 (95% CI 0.21–1.30)</td>
<td>0.71</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.64 (95% CI 0.67–4.00)</td>
<td>1.50 (95% CI 1.04–2.16)</td>
<td>0.07</td>
</tr>
<tr>
<td>Disabling stroke</td>
<td>1.67 (95% CI 0.50–5.62)</td>
<td>1.57 (95% CI 0.90–2.74)</td>
<td>0.21</td>
</tr>
<tr>
<td>Death or stroke</td>
<td>1.54 (95% CI 0.81–2.92)</td>
<td>1.44 (95% CI 1.04–1.99)</td>
<td>0.08</td>
</tr>
<tr>
<td>Death or disabling stroke</td>
<td>1.19 (95% CI 0.57–2.51)</td>
<td>1.19 (95% CI 0.75–1.90)</td>
<td>0.27</td>
</tr>
</tbody>
</table>
Table 3 30-day event rates in each arm across the trials included in the meta-analysis

<table>
<thead>
<tr>
<th></th>
<th>Wallstent CAS (n = 107)</th>
<th>Wallstent CEA (n = 112)</th>
<th>Kentucky CAS (n = 53)</th>
<th>Kentucky CEA (n = 51)</th>
<th>SAPPHIRE CAS (n = 50)</th>
<th>SAPPHIRE CEA (n = 46)</th>
<th>SPACE CAS (n = 599)</th>
<th>SPACE CEA (n = 584)</th>
<th>EVA-3S CAS (n = 261)</th>
<th>EVA-3S CEA (n = 259)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, n (%)</td>
<td>NA</td>
<td>NA</td>
<td>0 (0)</td>
<td>1 (2.0)</td>
<td>0 (0)</td>
<td>3 (6.5)</td>
<td>4 (0.67)</td>
<td>5 (0.86)</td>
<td>2 (0.77)</td>
<td>3 (1.16)</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>NA</td>
<td>NA</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (2.2)</td>
<td>45 (7.5)</td>
<td>36 (6.2)</td>
<td>23 (8.81)</td>
<td>7 (2.70)</td>
</tr>
<tr>
<td>Disabling stroke, n (%)</td>
<td>NA</td>
<td>NA</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (2.2)</td>
<td>24 (4.0)</td>
<td>17 (2.91)</td>
<td>7 (2.7)</td>
<td>1 (0.38)</td>
</tr>
<tr>
<td>Death + stroke, n (%)</td>
<td>13 (12.2)</td>
<td>5 (4.5)</td>
<td>0 (0)</td>
<td>1 (2.0)</td>
<td>0 (0)</td>
<td>3 (6.5)</td>
<td>46 (7.7)</td>
<td>38 (6.5)</td>
<td>25 (9.6)</td>
<td>10 (3.9)</td>
</tr>
<tr>
<td>Death + disabling stroke, n (%)</td>
<td>NA</td>
<td>NA</td>
<td>0 (0)</td>
<td>1 (2.0)</td>
<td>0 (0)</td>
<td>3 (6.5)</td>
<td>28 (4.7)</td>
<td>22 (3.8)</td>
<td>9 (3.4)</td>
<td>4 (259 (1.5)</td>
</tr>
</tbody>
</table>

Figure 2 Forest plot of risk ratios of mortality. Sizes of data markers are proportional to the weight of each study in the meta-analysis. Horizontal bars = 95% CI

Figure 3 Forest plot of risk ratios of stroke. Sizes of data markers are proportional to the weight of each study in the meta-analysis. Horizontal bars = 95% CI

Figure 4 Forest plot of risk ratios of disabling stroke. Sizes of data markers are proportional to the weight of each study in the meta-analysis. Horizontal bars = 95% CI

Figure 5 Forest plots of risk ratios of composite endpoint of death or stroke. Sizes of data markers are proportional to the weight of each study in the meta-analysis. Horizontal bars = 95% CI
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Discussion

The key finding of our analysis is that there is no significant difference between CEA and CAS for symptomatic patients. Although there is a trend favouring CEA for stroke or disabling stroke, there is a trend in favour of CAS for death and no difference in the composite endpoint of death and disabling stroke. Although there were no definite statistical differences found that can support one strategy over another, the results of our meta-analysis reveal insights into recent concerns raised following the publication of SPACE and EVA-3S trials and provide an opportunity to identify targets to refine CAS by reducing stroke risk.

First, the risk of mortality and cardiovascular complications after CEA remains an important concern. Although early trials suggested a lower risk of mortality, most contemporary data suggest a mortality hazard of ~1% in both symptomatic and asymptomatic patients. The risk of mortality with CAS has been consistently low and this may be particularly important in patients deemed to be at high peri-operative mortality risk. This lower procedural mortality provides an important reason to refine rather than abandon CAS and also provides a quality target for CEA.

Early peri-procedural risk for stroke hazard after CAS has been highlighted in the past and remains the key shortcoming of this procedure. Many of the trials included in our meta-analysis had important limitations that likely increased the peri-procedural stroke hazard and thus may not reflect an accurate comparison of CAS and CEA. Strokes after CAS may be secondary to embolization at the time of the procedure, delayed embolization after the procedure (likely from plaque prolapse and secondary embolization), and haemorrhagic strokes related to hyperperfusion. Given these varied putative mechanisms, strategies to prevent or reduce incidence of stroke will need to focus on each of these factors. Prevention of procedural stroke mandates complete emboli protection for the entirety of the procedure. Although EPD use has been advocated as a preventive measure, there are no randomized trials evaluating such a strategy.

Many of the trials included in our meta-analysis preceded availability of EPD, did not use EPD in all patients, or used a variety of EPDs. Although lack of EPD use exposes the patient to a high risk of distal embolization and stroke, selective use cannot be advocated to protect high-risk patients. Although the high risk of stroke in patients treated with EPDs in the SPACE trial has been used as an argument against use of EPDs, this is more likely a reflection of a selection bias. The increased stroke rate in these patients could reflect the high-risk characteristics that influenced operator choice towards EPDs, rather than being secondary to their use. Indirect evidence for such an effect comes from trials of platelet glycoprotein (GP) IIb/IIIa inhibitors, in which bail out use of GP IIb/IIIa inhibitors has always been associated with a higher risk of complications when compared with routine use.

Although a large number of EPDs have been released for clinical use, there are no clinical data to compare these devices. Preclinical studies suggest that there may be significant differences between the devices available. Scientific rigour demands that any new device released in the market be compared directly with surgery or with devices that have demonstrated superiority or non-inferiority to surgery. Unfortunately, given the current regulatory climate, there is little incentive for device manufacturers to do so and new devices keep appearing in the market based on comparisons with
Prevention of delayed embolization requires adequate plaque scaffolding and appropriate antithrombotic and antiplatelet therapy. Currently, there is no clear-cut strategy for comparing the plaque scaffolding ability of different stents and no regulatory requirement for newly released stents to be compared with previously available stents in the market. This factor becomes especially important for the carotid bed, where stents not only need to show immediate safety but should also carry a low risk of restenosis and stroke on long-term follow-up. Another factor that may explain the high risk of delayed strokes in the CAS patients in these studies may relate to inadequate platelet inhibition. Appropriate platelet inhibition is pivotal in preventing thrombo-embolic complication in the coronary bed and has been incorporated in contemporary endovascular therapy of carotid disease.21,22 However, 17% of patients in the EVA-3S trial were treated with a single antiplatelet agent only and this may have contributed to the high stroke risk.

These data highlight that a number of factors need to be considered when faced with a patient with symptomatic carotid artery stenosis. Although on surface, the trend towards lower risk of stroke with CEA in this meta-analysis may suggest that CEA may be preferable to CAS; the CAS strategy in these trials was limited by inadequate operator experience, lack of routine emboli protection device use, heterogeneous equipment choice, and substandard antiplatelet therapy (in some patients). Furthermore, despite these limitations, the composite of death and disability stroke, arguably the most important endpoint for such a comparison, did not differ between the two strategies.

Although the body of currently available literature favours CEA in most patients who have ‘average’ surgical risk, protected CAS remains a viable alternative in high-risk surgical patients when a skilled operator is available. Given that CAS is associated with a lower mortality, further efforts are required to diminish the stroke hazard associated with the procedure. Further refinement in technology, scrupulous operator credentialing, appropriate patient selection, and adequate peri-procedural therapy will be key to enhancing procedural safety. Furthermore, we need to move away from registries to randomised controlled trials (RCTs) as the evidence base for the evaluation of therapeutic strategies for carotid disease. This would require concerted efforts on the part of the medical community, device manufacturers, regulatory authorities, and third-party payers to ensure that availability of registries does not sabotage enrolment in RCTs.

**Limitations**

Our analysis encompasses trials that have wide variation in endovascular technology and their relevance to contemporary practice may be limited. The current analysis only compares 30-day outcome and hence safety of the two procedures; there are relatively little data on long-term efficacy of CAS relative to CEA or medical therapy. Further, the total number of trials was small and there was borderline statistical heterogeneity for some of the outcome measures. A major limitation of the trials included in our analysis is that five of the six trials were terminated for futility or difficulty in enrolment. Thus, our results cannot supplant a large adequately powered clinical trial.

**Conclusions**

Currently available data suggest a trend towards higher peri-procedural stroke and lower mortality with CAS when compared with CEA. However, several limitations prevent wider generalizability of the results and there is no definitive evidence favouring one strategy over another. Given the absence of data to the contrary, use of CAS as a routine procedure for low-risk symptomatic carotid artery disease cannot be advocated at this point. We would like to conclude by echoing recent appeals supporting patient enrolment into the ongoing trials of CEA vs. CAS.8,9

**Conflict of interest:** J.Y. is the inventor of the Angioguard emboli-protection device used in the SAPPHIRE trial and was a shareholder in Angioguard, Inc. at the time of purchase by Johnson&Johnson in 1999. He receives recurring payments from Johnson&Johnson as a former shareholder of Angioguard, Inc. He does not own any shares of stock in Johnson&Johnson. H.S.G. has been named as an inventor on patents filed by the University of Michigan for devices that could be used for carotid artery interventions. B.K.N. has no conflict of interest.

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