Carotid artery stenting vs carotid endarterectomy: meta-analysis and diversity-adjusted trial sequential analysis of randomized trials


CRD summary
The review concluded that carotid artery stenting was associated with higher rates of peri-procedural and intermediate to long term harms than carotid endarterectomy, but with fewer peri-procedural myocardial infarctions and cranial nerve injuries. Limitations in the review, which included heterogeneity between studies and use of composite outcomes across varying time frames, mean these results should be treated with some caution.

Authors' objectives
To compare the peri-procedural and intermediate to long-term benefits and harms of carotid artery stenting (CAS) and carotid endarterectomy (CEA).

Searching
PubMed, EMBASE and Cochrane Central Register of Controlled Trials were searched without language restrictions to June 2010. Search terms were reported. Reference lists of reviews, meta-analyses and primary studies were checked.

Study selection
Randomised controlled trials (RCTs) that compared CAS and CEA with or without embolic protection device in participants with symptomatic or asymptomatic carotid artery stenosis were eligible for inclusion. Eligible trials needed to report outcomes at 30 days or more post-procedure. Outcomes of interest were death, myocardial infarction and stroke or a composite of these within 30 days or in the intermediate/longer term. Cranial nerve injury and carotid restenosis were evaluated in the intermediate/longer term.

Most participants had symptomatic disease. Participants were reported to have hypertension (38% to 86%), diabetes (6% to 39%) and coronary artery disease (18% to 81%). An embolic protection device was used in about half of the studies. Mean participant age ranged from 66 to 73 years and 66% to 85% were men. Mean follow-up was 2.7 years (range four to 65 months).

Two reviewers independently selected the studies. Disagreements were resolved by consensus.

Assessment of study quality
Sequence generation, allocation concealment, blinding, completeness of outcome data, selective outcome reporting and other sources of bias were assessed. RCTs that clearly met criteria for the first three components were considered to have low risk of bias.

Two reviewers independently assessed study validity. Disagreements were resolved by consensus.

Data extraction
Odds ratios (ORs) and their 95% confidence intervals (CIs) were extracted or calculated.

Two reviewers independently extracted the data. Disagreements were resolved by consensus. Primary study authors were contacted for more information where required.

Methods of synthesis
Pooled odds ratios and 95% CIs were calculated using the Peto method, stratified by whether or not participants were symptomatic. Heterogeneity was assessed using $I^2$. Sensitivity and subgroup analyses were conducted to investigate the impact of study quality, use (or not) of an embolic protection device, study setting (USA or other), exclusion of specific
RCTs and length of follow-up. Meta-regression was used to examine the effects of age. Trial sequential analyses were conducted to calculate whether there was sufficient information to detect or reject an intervention effect of 15% or 20%. Publication bias was assessed with funnel plots and Begg and Egger tests.

Results of the review
Thirteen RCTs were included (n=7,477 participants, range 20 to 2,502). Six of the trials were rated as having low risk of bias. The authors commented that risk of bias from incomplete outcome data, selective reporting and other sources did not differ across studies. One RCT (n=1,710) apparently used per protocol analysis.

In the peri-procedural period, CAS was associated with a significantly higher risk than CEA of death, myocardial infarction or stroke (OR 1.31, 95% CI 1.08 to 1.59, I²=50%; 12 RCTs), death or stroke (OR 1.65, 95% CI 1.34 to 2.02, I²=45%; 13 RCTs) or any stroke (OR 1.67, 95% CI 1.34 to 2.08, I²=44%; 11 RCTs) and a significantly lower risk of myocardial infarction (OR 0.45, 95% CI 0.28 to 0.71, I²=0%; 10 RCTs) and cranial nerve injury (OR 0.15, 95% CI 0.10 to 0.22, I²=0%). Trial sequential analysis gave firm indication of a 20% relative risk increase for death or stroke and a relative risk reduction of 15% for myocardial infarction associated with CAS.

In the intermediate and longer terms (including peri-procedurally), CAS was associated with a significantly higher risk than CEA of various definitions of the composite of death/stroke/myocardial infarction (OR 1.19, 95% CI 1.02 to 1.38, I²=26%; 12 RCTs), peri-procedural death or stroke plus ipsilateral stroke thereafter (OR 1.38, 95% CI 1.16 to 1.64, I²=49%; 12 RCTs), death or any stroke (OR 1.24, 95% CI 1.05 to 1.47, I²=38%; 10 RCTs), any stroke (OR 1.48, 95% CI 1.24 to 1.77, I²=16%; 11 RCTs) and restenosis (OR 2.80, 95% CI 1.96 to 4.00, I²=0%). Trial sequential analysis gave firm indication of a 20% relative risk increase for any stroke associated with CAS; there were no firm indications for the other outcomes evaluated.

Analysis of intermediate and longer term outcomes for other than peri-procedural events showed no significant difference between CAS and CEA for any outcome evaluated. There was no evidence of publication bias. Other results were reported in the review.

Authors’ conclusions
CAS was associated with a higher rate of peri-procedural and intermediate to long term harms than CEA, but with fewer peri-procedural myocardial infarctions and cranial nerve injuries.

CRD commentary
The objectives and inclusion criteria of the review were clear. Relevant sources were searched for studies. There were no restrictions by language and publication status. Appropriate tests were used to assess publication bias and none was evident. Steps were taken to minimise the risk of reviewer bias and error by having more than one reviewer independently select studies, undertake validity assessment and extract data. Study quality was mixed. Some important aspects of study quality (such as drop-out rates) were not reported clearly. Appropriate statistical methods were used to combine the studies and investigate differences between them. Pooled results were derived from clinically heterogeneous studies. Most used a range of composite outcomes. Some analyses pooled differing outcomes. Therefore, the clinical value and generalisability of these results was uncertain. Significant differences were observed only when peri-procedural outcomes were included in analyses; there were no significant differences in intermediate/longer term outcomes when analysed separately. The effect of including a large study that reported events per protocol was not investigated.

The authors’ conclusions reflected the results for analyses where peri-procedural and intermediate/longer term outcomes were combined, but not the results for intermediate/longer term outcomes when analysed separately. This and methodological limitations in the included studies, pooling of clinically heterogeneous studies and reliance on a variety of composite outcomes mean the results should be treated with some caution.

Implications of the review for practice and research
Practice: The authors stated that emphasis should be placed on reducing events in the periprocedural period after CAS or CEA.
Research: The authors stated a need to identify subsets of individuals at low risk with CAS and identify which individuals benefit most from CAS or CEA. RCTs were required to examine the effects of operator experience, patient selection and optimal use of embolic protection devices.

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