Authors' objectives
To assess the value of carotid endarterectomy for prevention of stroke in patients with asymptomatic carotid stenosis.

Searching
MEDLINE (1 January 1966 to 30 January 1988) was searched using the following search terms: carotid stenosis, endarterectomy, carotid, asymptomatic, clinical trial, and randomised controlled trial. Trials published in any language were included. The Cochrane Controlled Trials Register and the Ottawa Stroke Trials Register were also searched (dates not stated). Current Contents was handsearched from 1 January 1995 to 30 January 1997. The New England Journal of Medicine, Stroke, and JAMA were searched from 1 January 1991 to 30 January 1997. The reference lists of all retrieved articles were reviewed. Authorities in the speciality were contacted, including the corresponding authors of several of the included trials.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials (RCTs) were included in the review. Follow-up periods ranged from 2 to 5 years.

Specific interventions included in the review
Carotid endarterectomy versus or added to medical treatment.

Participants included in the review
Patients with asymptomatic carotid stenosis determined by carotid ultrasound or arteriography, either with no history of cerebrovascular disease or with previous stroke or transient ischaemic attack in vertebrobasilar circulation or contralateral carotid territory, and patients who had undergone contralateral carotid endarterectomy.

All trials included patients with greater than or equal to 50% carotid stenosis. The proportion of men in the included studies ranged from 58% to 100% and the mean age ranged from 64 to 67 years.

Outcomes assessed in the review
The four outcome measures were: ipsilateral stroke plus perioperative stroke or death, ipsilateral stroke plus perioperative ipsilateral stroke, all stroke plus perioperative stroke or death and perioperative stroke or death.

How were decisions on the relevance of primary studies made?
Two authors selected the trials to be included in the review, and disagreements were resolved by consensus.

Assessment of study quality
Validity was assessed using a three item scale that assigns two points each for describing aspects of randomisation, and double blinding, and one point for withdrawals and drop outs. The scale ranged from zero to five, with higher scores indicating more complete reporting. Included trials were graded independently by two of the authors.

Data extraction
Two authors extracted the data independently, and disagreements were resolved by consensus.

Methods of synthesis
How were the studies combined?
Odds ratios were calculated by using Peto's fixed-effect model. Publication bias was evaluated by using the inverted
funnel plot approach recommended for meta-analyses with few studies.

How were differences between studies investigated?
Heterogeneity between studies was assessed using the Breslow-Day test for homogeneity.

Sensitivity analyses were performed investigating random-effects models (DerSimonian and Laird method), trial quality (equality weight), publication status (published versus unpublished) and trial size (largest versus the others).

Results of the review
Five trials, involving 2440 participants were included in the review.

Three studies received a quality rating of 3, and one was rated 2 (one study was not rated).

Ipsilateral strokes plus all perioperative strokes or deaths: The risk among patients allocated to carotid endarterectomy was clearly reduced (odds ratio (OR) = 0.62; 95% CI: 0.44, 0.86), with no significant heterogeneity across the five trials (p=0.07). The adjusted rate of these outcomes was 6.4% for the medically treated patients, and 4.4% for the surgical group, yielding an absolute reduction after carotid endarterectomy of about 2% over a mean follow up of about 3 years. With 3 years of follow up, about 50 patients would need to undergo the operation to prevent one event (including disabling or non-disabling stroke).

Sensitivity analyses were conducted with the assumption that, firstly, two thirds of all perioperative strokes in the asymptomatic carotid atherosclerosis study occurred around the operated vessel, secondly; all were ipsilateral, and, thirdly, none were ipsilateral; all three yielded similar results. Sensitivity analysis that excluded one unpublished trial also yielded similar results, and analysis by quality weighting did not change these results. Sensitivity analysis which excluded the results of a large asymptomatic carotid atherosclerosis study showed very similar reduction in ipsilateral stroke plus perioperative stroke or death (OR = 0.60; 95% CI: 0.36, 1.01).

Ipsilateral strokes plus perioperative stroke: Carotid endarterectomy yielded a significant reduction (OR = 0.46; 95% CI: 0.32, 0.66) compared to the medical group, with no significant heterogeneity among the trials (p=0.13). The fail safe method indicated that 19 randomised controlled trials of similar sizes with inconclusive results would need to be added to the present analysis to change this conclusion. Sensitivity analyses that excluded the large asymptomatic carotid atherosclerosis study, and, separately, the unpublished trial, yielded similar results.

All strokes (regardless of vascular territory) plus perioperative stroke or death: The risk among patients who received carotid endarterectomy was reduced (OR = 0.68; 95% CI: 0.51, 0.90) with no significant heterogeneity (p=0.15). Sensitivity analysis that excluded the asymptomatic carotid atherosclerosis study again showed a similar, although nonsignificant reduction (OR = 0.67; 95% CI: 0.42, 1.08). Sensitivity analysis that excluded the unpublished trial did not alter the results.

Perioperative stroke or death: Patients receiving carotid endarterectomy had a fourfold risk of stroke or death in the 30 days after treatment assignment (OR = 4.51; 95% CI: 2.36, 8.64). In two studies, several strokes occurred during angiography, and these events were included in this analysis.

Authors' conclusions
Carotid endarterectomy in patients with asymptomatic carotid stenosis unequivocally reduces the incidence of ipsilateral stroke, though the absolute benefit is relatively small. Given the modest benefit of surgery for unselected patients with asymptomatic carotid artery stenosis, carotid endarterectomy cannot be routinely recommended for these patients pending reliable identification of high risk subgroups. Medical management is a sensible alternative or most patients.

CRD commentary
The review focuses on a well defined question. Inclusion criteria were clearly reported, and appropriate. The validity of individual studies was adequately assessed. A thorough literature search was conducted. Potential publication bias was
evaluated by using the inverted funnel plot, but the results of this were not reported. Sufficient details of the individual studies were reported.

Although individual studies were combined appropriately, the authors note that the lack of uniformity in the measurement of carotid stenosis may have led to the pooling of subgroups of patients at different risk for stress.

This is a thorough meta-analysis, and the conclusions follow from the results.

Implications of the review for practice and research
Practice: The authors suggest that carotid endarterectomy cannot be routinely recommended for unselected patients with asymptomatic carotid stenosis. The incidence of ipsilateral stroke was relatively low in those patients who did not undergo the operation, and hence the benefit of carotid endarterectomy will remain small until high risk subgroups can be identified. Medical management is a sensible alternative for most patients.

Research: The authors suggest that future research should investigate the identification of high-risk subgroups. They note that a large ongoing randomised trial of carotid stenosis may shed some light on this issue when the results become available (See Other Publications of Related Interest).

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