Management strategies for asymptomatic carotid stenosis: a systematic review and meta-analysis

CRD summary
The authors concluded that evidence was not sufficiently robust, or applicable to current clinical practice, to allow the comparative effectiveness of management strategies for adults with asymptomatic carotid stenosis. These conclusions reflect the evidence presented and seem reliable.

Authors' objectives
To evaluate evidence on management strategies for asymptomatic carotid stenosis, and the incidence of ipsilateral stroke with medical therapy alone.

Searching
MEDLINE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception to December 2012, for English language studies. Search terms were reported. Bibliographies of narrative and systematic reviews and the United States Food and Drug Administration web site were also searched. Authors of eligible studies were contacted for any unpublished data.

Study selection
Eligible studies were randomised controlled trials (RCTs) or prospective/retrospective non-randomised comparative studies (NRCs), with at least 30 patients per intervention group. Studies had to compare medical therapy alone, carotid endarterectomy plus medical therapy or carotid artery stenting plus medical therapy. Participants had to be adults (aged 18 years or older) with asymptomatic carotid stenosis. Single-group, prospective cohort studies of medical therapy were also included if they had a minimum of 12 months follow-up. Eligible outcomes of interest included incidence rates of ipsilateral stroke, any stroke, mortality or their composite outcomes at 30 days and at the last follow-up.

The most commonly used techniques for diagnosis of carotid stenosis were duplex ultrasonography or digital subtraction angiography (where reported). Medical therapy included the use of antiplatelet therapy, and/or the drugs such as aspirin, statins, antihypertensive drugs and anticoagulants. Most studies defined asymptomatic status as no symptoms; some gave specific time frames for no symptoms, used diagnostic coding systems, or included other types of symptoms (such as ipsilateral/contralateral) to ascertain the status.

Multiple reviewers selected studies for inclusion in the review.

Assessment of study quality
Risk of bias for RCTs was assessed according to randomisation, allocation concealment, blinding of patients and outcome assessors, drop-out rate, statistical analysis details, and funding source. Risk of bias for NRC studies was assessed according to clarity of eligibility criteria, selection bias, description of the interventions, definitions of outcomes, baseline group comparability, statistical analysis details, and funding source. Overall risk of bias was rated as low, medium or high. Multiple reviewers performed the quality assessments.

Data extraction
Data on number of events per outcome (stated above) were extracted from individual studies to calculate risk ratios and 95% confidence intervals for RCTS and NRCs, and incidence rates and 95% confidence intervals for single cohort studies. When raw data were reported for the cohort studies, data on incidence rates was extracted from published Kaplan-Meier curves. One reviewer extracted the data; a second reviewer checked the extractions for completeness and accuracy.

Methods of synthesis
Risk ratios of RCTS and NRC studies were separately pooled using inverse variance random-effects models. Between-
study heterogeneity was assessed using I². Where populations of the studies varied considerably, narrative synthesis of their results was presented instead. Pooled incidence rates (percentage per year) of cohort studies were obtained by use of a random-intercept generalised linear model. A meta-regression analysis was conducted to explore the effect of time on the incidence rates of ipsilateral stroke.

Results of the review
Forty-seven studies in 56 publications were included in the review (number of participants 36 to 238,389). Risks of bias for studies were reported in each section of the results (below).

Carotid artery stenting plus medical therapy versus carotid endarterectomy plus medical therapy

Overall there were three RCTs and 10 NRC studies. Four NRC studies (all with a high risk of bias) demonstrated a statistically significantly increased risk for peri-procedural stroke (RR 1.74, 95% CI 1.41 to 2.16; I²=75%) and death (RR 1.43, 95% CI 1.20 to 1.71; I²=0%) with the carotid artery stenting group, compared with the carotid endarterectomy group.

Carotid endarterectomy plus medical therapy versus medical therapy alone

Overall there were three RCTs and eight NRC studies. Compared with medical therapy alone, three RCTs (all with a low risk of bias) showed that carotid endarterectomy plus medical therapy had statistically significant lower risks for long-term outcomes of ipsilateral stroke (RR 0.72, 95% CI 0.58 to 0.90; I²=0%), composite outcome of ipsilateral stroke (RR 0.69, 95% CI 0.55 to 0.87; I²=0%) and any stroke, including any death within 30 days (RR 0.68, 95% CI 0.56 to 0.82; I²=18%).

Two of these RCTs demonstrated that the risk of any stroke (at peri-procedural or 30 day endpoints) was statistically significantly greater with carotid endarterectomy plus medical therapy, than with medical therapy alone (RR 5.94, 95% CI 2.06 to 17.12; I²=0%).

Carotid artery stenting plus medical therapy versus medical therapy alone

Of the two NRC studies, one found statistically significantly decreased risks for long-term outcomes of stroke, death and a composite of these two outcomes with carotid artery stenting plus medical therapy compared with medical therapy alone. There was medium risk of bias for this NRC study.

Rate of ipsilateral stroke with medical therapy alone

Overall there were six medical therapy arms of RCTs and 20 cohort studies. The risk of bias for the 26 studies that investigated medical therapy alone was low (eight studies), medium (11 studies) or high (seven studies). The incidence rate of ipsilateral stroke was 1.68% (95% CI 1.34 to 2.11) per year of follow-up. The results were not substantially changed when studies with high risk of bias were removed from the meta-analysis. Meta-regression analyses demonstrated that the incidence of ipsilateral stroke was statistically significantly lower in studies that completed their recruitment of patients between 2000 and 2010, compared with those that completed it earlier.

No other statistically significant results were reported.

Authors’ conclusions
The authors concluded that evidence was not sufficiently robust, or applicable to current clinical practice, to allow the comparative effectiveness of management strategies for adults with asymptomatic carotid stenosis.

CRD commentary
The review question and inclusion criteria were broad and clearly defined. Relevant electronic databases were searched and attempts were made to locate grey and unpublished literature. The English language restriction may had led to some relevant studies being missed. Efforts were made throughout the review process to minimise reviewer error and bias. The quality assessment criteria seemed suitable for the study designs assessed. Results revealed that the RCTs were of low or medium risk of bias; a large proportion of NRC studies had a high risk of bias, and more mixed results were found for risk of bias in cohort studies. Study details were presented and the methods of synthesis seemed
appropriate. The authors’ conclusions reflect the evidence presented and seem reliable.

**Implications of the review for practice and research**

**Practice**: The authors did not state any implications for future practice.

**Research**: The authors stated that future RCTs of asymptomatic carotid stenosis should not only compare carotid endarterectomy with carotid artery stenting, but should also investigate whether these invasive intervention procedures give incremental benefits over the best medical therapy that was available. Additional suggestions for future research included standardisation of definitions and severity assessments for asymptomatic carotid stenosis, and evaluation of the effect of peri-procedural myocardial infarction on the long-term prognosis of patients undergoing invasive carotid artery procedures.

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