Effects of statin therapy on the progression of carotid atherosclerosis: a systematic review and meta-analysis

Kang S, Wu Y, Li X

CRD summary
This review determined the efficacy and safety of statin therapy on the rate of carotid atherosclerosis progression. The authors concluded that conventional statin therapy is efficient and safe in reducing the rate of carotid atherosclerosis progression, but more research is needed on the long-term safety of aggressive therapy. Methodological limitations and apparent clinical and statistical differences in the studies weaken this conclusion.

Authors' objectives
To determine the efficacy and safety of statin therapy on the rate of carotid atherosclerosis progression.

Searching
MEDLINE (from 1980 to November 2003), EMBASE (from 1985 to September 2003), the Cochrane Controlled Trials Register, the Science Citation Index (December 2003) and PubMed (updated to December 2003) were searched for relevant articles published in English; the search terms were reported. The reference lists of all relevant articles and reviews were checked, and unpublished material were sought through searches of meeting reports, letters and private communication.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies of statin therapy were eligible for inclusion. The statins assessed were lovastatin, pravastatin, atorvastatin, simvastatin and fluvastatin. The dosages ranged from 20 to 80 mg/day; these were categorised as conventional (20 to 40 mg/day) or aggressive (80 mg/day) doses. The comparator of interest was placebo or conventional statin therapy. Statin therapy was not restricted by the follow-up period, and the duration of the intervention ranged from 1 to 4 years.

Participants included in the review
Studies of symptomatic or asymptomatic early-stage carotid atherosclerosis patients with hypercholesterolaemia or familial hypercholesterolaemia were eligible for inclusion. The participants were aged from 30 to 70 years.

Outcomes assessed in the review
Studies that reported the progression of carotid atherosclerosis and plaques through the measurement of B-mode ultrasound were eligible for inclusion. The measurements used in the included studies were change in intima-media thickness (IMT), change in total cholesterol and change in low-density lipoprotein cholesterol. Other outcomes were clinical events and adverse effects.

How were decisions on the relevance of primary studies made?
Two reviewers selected primary studies for inclusion in the review. The authors did not report whether this process was conducted independently or how any disagreements were settled.

Assessment of study quality
The quality of the primary studies was assessed using the Jadad scale, which evaluates the reporting of randomisation, blinding and withdrawals. Two reviewers independently assessed the methodological quality of the primary studies. Any disagreements were resolved by consensus with a third reviewer.
Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

For each study, the mean IMT was transformed into the rate of carotid IMT progression (micrometre/year). This enabled the calculation of the difference in mean IMT in the treatment and control groups at the end of the intervention.

Methods of synthesis
How were the studies combined?
The studies were combined using a fixed-effect meta-analysis. A weighted mean difference (WMD) with 95% confidence intervals (CIs) was calculated separately for comparisons versus placebo or conventional statin therapy. Where heterogeneity was found, the analysis was repeated using a random-effects model. Funnel plots were used to assess the possibility of publication bias.

How were differences between studies investigated?
The studies were stratified by the difference in control groups and statistical heterogeneity was assessed using the chi-squared test.

Results of the review
Ten RCTs (n=2,299) were included in the review.

Two studies received a quality score of 5, six received a quality score of 4, and two received a quality score of 3.

Statin therapy was associated with a reduction in carotid progression when compared with placebo (8 studies; WMD -22.35, 95% CI: -26.56, -18.14). There was evidence of statistical heterogeneity (P<0.001).

Aggressive statin therapy was associated with a greater reduction in carotid progression when compared with conventional statin therapy (2 studies; WMD -63.26, 95% CI: -71.08, -55.14). There was evidence of statistical heterogeneity (P=0.053).

No statistically significant difference was shown between the control and intervention groups in terms of the number of withdrawals or adverse events (P>0.05).

The authors do not report the results of the funnel plot carried out to assess publication bias.

Authors’ conclusions
Conventional statin therapy is efficient and safe for the reduction of the rate of carotid atherosclerosis progression. Long-term and aggressive statin therapy may provide superior efficacy for carotid atherosclerosis regression, but more research is needed to assess the safety of aggressive statin use in the long term.

CRD commentary
The review question was supported by clear inclusion and exclusion criteria. Several databases were searched, although the search strategy was limited by language. In addition, unpublished data were sought, thus reducing the likelihood of publication bias. The methods of study selection and data extraction were not well described and, therefore, the potential for reviewer error or bias cannot be assessed. The validity of the primary studies was assessed, but the quality rating may not best reflect the potential for bias in the included trials.

The statistical pooling of efficacy outcomes might not have been appropriate given the measures used, clinical heterogeneity and evidence of statistical heterogeneity between the primary studies. Inconsistencies in the reporting of study withdrawals precluded the pooling of outcomes relating to participant withdrawal and adverse events; a narrative summary was appropriately reported. Owing to the above considerations and poor reporting of the review process, the
authors’ conclusions should be viewed with some caution.

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

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

**Research:** The authors suggested that further well-conducted research is required to assess the safety of aggressive statin therapy in the long term.

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