Risks associated with statin therapy: a systematic overview of randomized clinical trials

CRD summary
This review evaluated the risk of adverse events among patients taking statins. The authors concluded that statin therapy in carefully selected patients is associated with low adverse event rates in clinical trials. The reliability of the results is unclear given the lack of detail about the review process and potential for bias.

Authors' objectives
To evaluate the risk of adverse events associated with statin therapy.

Searching
MEDLINE (1966 to December 2005), EMBASE (1980 to December 2005), the Cochrane Library (Controlled Trials Register and Database of Systematic Reviews; all years), ClinicalTrials.gov, the Food and Drug Administration's website and relevant bibliographies were searched for studies in English; the search terms were reported.

Study selection
Study designs of evaluations included in the review
Double-blinded studies that randomly allocated 100 patients or more to statin monotherapy versus placebo were eligible for inclusion.

Specific interventions included in the review
Studies investigating statin monotherapy versus placebo were eligible for inclusion. The studies included compared placebo with the following statins: atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin. The statin doses ranged from 0.025 to 80 mg. Studies of the withdrawn statin, cerivastatin, were analysed separately.

Participants included in the review
Studies of adults aged 18 years or older with hyperlipidaemia were eligible for inclusion. Studies limited to specific patient populations were excluded. The mean age range in the included studies was unclear; the tables indicated it was 22 to 81 years whereas the main text stated a range of 49 to 81 years. The proportion of males varied from 25 to 100% and the participants were predominantly white. The participants had a history of coronary heart disease, hypertension and diabetes mellitus, and the proportion of smokers ranged from 4 to 80%.

Outcomes assessed in the review
Studies reporting adverse effects of statins were eligible for inclusion. The outcomes included in this review were myalgias, creatine kinase (CK) elevation, rhabdomyolysis, transaminase elevation and discontinuation due to any adverse event. The follow-up period ranged from 1.5 to 64.8 months.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The methodological quality of each study was assessed in terms of randomisation, blinding and drop-outs using the Jadad scale to obtain a quality score out of 5. The authors did not state how the validity assessment was performed.

Data extraction
Paired reviewers independently extracted the data. Any discrepancies were resolved by consensus. The risk difference (RD) per 1,000 patients and relative risk (RR), along with 95% confidence intervals (CIs), were calculated for each end point. To account for varying follow-up periods in the included studies, the end points were also evaluated as the RD per 1,000 patient-years of therapy and the number-needed-to-treat per 1,000 patients.

Methods of synthesis
How were the studies combined?
The RRs and RDs were pooled in a random-effects meta-analysis using the DerSimonian and Laird method, which incorporated weighting based on inverse variance. Publication bias was checked using funnel plots.

How were differences between studies investigated?
Statistical heterogeneity was assessed using a chi-squared test.

**Results of the review**

Thirty-five randomised controlled trials involving 74,102 participants were included in this review.

The average Jadad score of the included studies was 4.1.

The incidence of transaminase elevation (reported in 28 studies) was significantly higher in patients receiving statin therapy compared with placebo (RR 1.30, 95% CI: 1.06, 1.59); this was noted particularly in patients receiving fluvastatin and lovastatin. The absolute risk of transaminase elevations was an increase of 4.3 patients per 1,000 treated.

In an analysis of cerivastatin alone compared with placebo, there was a significant increase in the incidence of rhabdomyolysis (RD 12.4, 95% CI: 5.4, 19.3, p<0.01) and transaminase elevations (RD 10.0, 95% CI: 5.1, 14.9, p<0.01).

There was no significant difference in the incidence of myalgias in patients on statin therapy compared with placebo. However, when individual statins were evaluated, there was a statistically significant increase in risk of myalgias in patients that took atorvastatin compared with placebo (RD 31.9, 95% CI: 2.1, 61.6, p=0.04).

There was no significant difference in the incidence of CK elevation, rhabdomyolysis and discontinuation due to adverse events in patients on statin therapy compared with placebo. No significant difference was found in the incidence of myalgias, CK elevation or discontinuation due to adverse events for cerivastatin compared with placebo.

The authors reported that there was no significant evidence of publication bias in pooled analyses or any of the individual listed end points. The funnel plots were not presented in this paper.

Tests for heterogeneity did not reveal any statistically significant differences between the studies.

**Authors’ conclusions**
The use of statins in carefully selected patients is associated with low adverse event rates in clinical trials.

**CRD commentary**
The review question was well defined and the inclusion criteria were clear with regard to the study design, intervention, participants and outcomes. The search involved relevant electronic databases and included unpublished studies, thereby decreasing the chance of publication bias. Publication bias was assessed but details of this were not provided. However, the authors only searched for reports in English, which might have introduced language bias into the review. The validity of the studies and statistical heterogeneity were adequately assessed. The data extraction was performed by paired reviewers, thus minimising the potential for bias. As details of the study selection and validity assessment were not given, it is not known whether steps were taken to reduce bias in these processes. The conclusions reflect the evidence presented, but the extent to which they are reliable is unclear when considering the lack of detail about the review process and the potential for bias.

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

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

**Research:** The authors stated that further research is needed in older patients, patients with more severe co-morbid conditions and those that receive higher statin doses than in clinical trials, in order to determine whether the results seen in trials are similar to those seen in clinical practice. Further studies to investigate the increased incidence of
rhabdomyolysis in patients that take cerivastatin are also needed.

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**Other publications of related interest**
This additional published commentary may also be of interest.

Bronson DL. Review: statin monotherapy is safe in hyperlipidemia except for increased risk for transaminase elevation. ACP J Club 2007;146:70.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.