Meta-analysis of large randomized controlled trials to evaluate the impact of statins on cardiovascular outcomes
Cheung B M, Lauder I J, Lau C P, Kumana C R

CRD summary
This review assessed the effects of statins used in people at risk of cardiovascular events. Statins were found to reduce cardiovascular events overall and in subgroups, but the risk of non-cardiovascular death remained unchanged. Although the evidence presented appears to support the author's conclusions, the methods of the review were not described so the reliability of the findings could not be assessed.

Authors' objectives
To estimate the effects of statins on cardiovascular events and mortality, and in different subgroups of people.

Searching
PubMed was searched from January 1990 to April 2003; the search terms were given. The reference lists of identified articles were also checked. Only English language papers were eligible for inclusion.

Study selection
Study designs of evaluations included in the review
Only randomised placebo-controlled studies lasting at least 3 years were eligible for inclusion. In addition, the outcome assessors had to be blinded to the treatment allocation.

Specific interventions included in the review
The intervention of interest was statin treatment, as compared with placebo. In addition, there should have been no other difference in treatment between the two groups (treatment and control).

Participants included in the review
Studies on people at risk of cardiovascular events were sought. Some of the included studies were on primary prevention, whilst others were on participants who had coronary heart disease, cardiovascular disease, hypertension or myocardial infarction (MI). Between 0 and 52% of the participants in the studies were women and the mean age, where stated, ranged from 55 to 75 years. The baseline total cholesterol ranged from 5.2 to 7.0 mmol/L, and low-density lipoprotein ranged from 3.4 to 5.0 mmol/L.

Outcomes assessed in the review
The inclusion criteria specified that a cardiovascular event had to be the primary or secondary end point of the study, and that at least 100 major coronary events had to occur during the study. In the included studies a major coronary event included coronary death, nonfatal MI, unstable angina and resuscitated cardiac arrest. In one study silent MIs were included as part of the primary outcome, but these were ignored in the analyses in the review. The reported outcomes were coronary events, mortality, non-cardiovascular mortality and stroke (transient ischaemic attacks were excluded from the definition of stroke). The primary outcome of major coronary events was also reported according to gender, smoking status, hypertension status, and the presence or absence of diabetes. The effect of pravastatin was analysed separately to other statins.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected studies for inclusion. Any differences were resolved by consensus.

Assessment of study quality
The authors did not state that they assessed validity.
**Data extraction**
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Relative risk ratios (RRRs) and numbers-needed-to-treat were calculated for events in different treatment arms in the individual studies.

**Methods of synthesis**

**How were the studies combined?**
The RRRs were combined using the random-effects model of DerSimonian and Laird; 95% confidence intervals (CIs) were reported. Pre-defined subgroup analyses were performed (by gender, smoking, diabetes, hypertension, and pravastatin versus other statins).

**How were differences between studies investigated?**
The authors did not state a method for assessing any differences between the studies. However, they appear to have investigated heterogeneity as they reported on the effect of the one additional study on heterogeneity. Where this was non-sigificant they included this study in the analyses. Pooled RRRs were calculated with and without data from this one study in which the inclusion criteria were not fully met (not placebo-controlled). Separate analyses were performed for pravastatin versus other statins.

**Results of the review**
Ten trials (79,494 participants) were included. Of these, 9 trials (69,139 participants) met the inclusion criteria. The remaining trial (10,355 participants) was considered a large and important study but it was not placebo-controlled; it was only included in some of the analyses.

Heterogeneity was not significant when the additional study was included in the analyses for non-cardiovascular mortality and for stroke, so this study was included in these analyses. However, heterogeneity was significant for the outcomes of coronary events and for all-cause mortality, so this study was not included in these analyses.

Coronary events (9 studies): statins reduced coronary events (RRR 0.73, 95% CI: 0.70, 0.77).

Mortality (9 studies): statins reduced all-cause mortality (RRR 0.85, 95% CI: 0.79, 0.92). There was no significant change in non-cardiovascular mortality (10 studies; RRR 0.96, 95% CI: 0.90, 1.03).

Stroke (8 studies): statins reduced the incidence of stroke (RRR 0.82, 95% CI: 0.75, 0.90).

When the additional study was included in analyses for coronary events and for mortality, the effect of statins was still beneficial.

**Subgroup analyses.**

There was no evidence of a difference in benefit from statins for men or women (P=0.37), or for hypertensives or normotensives (P=0.15). Although the data were limited, both diabetics and non-diabetics benefited from statins. Smokers appeared to benefit more than non-smokers (P=0.048).

Five studies used pravastatin. For coronary events and mortality the effects of pravastatin and other statins were similar. However, for stroke, the reduction with pravastatin was about half of that of other statins (P=0.039).

**Authors’ conclusions**
Statins reduced coronary events and all-cause mortality, with no increase in non-coronary mortality. There were benefits for men and women, hypertensives and normotensives, diabetics and non-diabetics and, in particular, for smokers. Pravastatin appeared to have less impact on stroke.
CRD commentary
The aims of this review were clearly stated and the results were based on large randomised studies. The searching was rather limited and studies could have been missed, although the strategy of seeking only long-term large studies probably minimised this. The methods of the review (study selection, data extraction, quality assessment) were not described, and decisions made at these stages could have introduced bias. The meta-analyses appeared appropriate. Whilst the main results were based on studies that met all the inclusion criteria, the authors included one study that was not placebo-controlled in some analyses. It was unclear if other similar studies were identified and, if so, how they would have been dealt with. However, the evidence given in the review appears to support the authors’ conclusions.

Implications of the review for practice and research
The authors did not state any implications for practice or further research.

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