Pleiotropic effects of statins: benefit beyond cholesterol reduction? A meta-regression analysis

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CRD summary
The review sought to determine whether statins reduced the risk of coronary heart disease more than other low-density lipoprotein cholesterol-lowering interventions. The authors concluded that pleiotropic effects of statins did not seem to contribute an additional cardiovascular risk reduction benefit beyond that expected from non-statin interventions. The conclusion has to be regarded with caution.

Authors' objectives
To determine whether statins reduce the risk of coronary heart disease (CHD) more than other interventions primarily aimed at lowering low-density lipoprotein cholesterol (LDL-C).

Searching
The reviewers searched MEDLINE (1966 to October 2004), unspecified English language journals, reference lists of original articles, reviews and meta-analyses, and the authors' own article collections on the topic.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. These had to employ concealment allocation, except for dietary interventions. The follow-up periods in the included studies ranged from 3 to 6.1 years.

Specific interventions included in the review
Studies that compared a single predominantly LDL-C-lowering treatment given for over 2 years with placebo were eligible for inclusion. The included studies investigated the effects of specific diets, bile acid sequestrants, surgery and statins. The statins used were simvastatin, pravastatin, lovastatin, fluvastatin and atorvastatin.

Participants included in the review
The review did not state any inclusion criteria for the participants. The patients in the included studies were CHD patients, high- or moderate-risk patients, and patients with other cardiovascular diseases (stroke, transient ischaemic attack, peripheral arterial disease), renal transplants or diabetes. Many samples were male only.

Outcomes assessed in the review
Studies that reported clinical effects and used nonfatal myocardial infarction (MI), CHD death, and fatal and nonfatal ischaemic stroke as primary or secondary outcomes were eligible for inclusion. The review focused on relative risk reductions and the percentage change in LDL-C. Percentage reductions in LDL-C, nonfatal MI or CHD and/or death, and stroke (fatal or nonfatal) were reported.

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 review restricted most intervention types to concealed allocation studies, but the authors did not state that they assessed the validity of the included studies.

The authors did not state how the papers were assessed for validity, or how many reviewers performed the validity assessment.
Data extraction
Two reviewers extracted the data independently using a standardised protocol and reporting form. Any discrepancies were resolved by consensus. The reviewers extracted information on treatment type and duration, sample size and characteristics at baseline, reduction in lipids and the specified outcomes. The mean percentage LDL-C reduction was calculated from the LDL-C level in the intent-to-treat group compared with the placebo group after 1 or 2 years' follow-up. Relative risks and associated standard errors were estimated from the reported total number of participants and incident cases in the treatment and control groups for nonfatal MI and CHD death and fatal and nonfatal ischaemic stroke.

Methods of synthesis
How were the studies combined?
A Bayesian random-effects model was applied. The relative risk was modelled as a linear function of the mean change in LDL-C and the mean length of follow-up in the individual studies. The estimated effect of LDL-C reduction on the 5-year risk of CHD death or nonfatal MI for the statin trials was plotted along with the 95% probability interval. In addition, a regression line with the slope of one was depicted; this might have been derived from the non-statin trials only or all trials combined. Also depicted were the point estimate and the 95% confidence interval of most, but not all, individual studies. A similar plot was presented for the stroke outcome, but this showed only the individual results of 8 statin trials. The null hypothesis for the main analysis was that the effect of LDL-C is the same between statin and non-statin trials.

How were differences between studies investigated?
Differences between the individual studies, such as diagnostic criteria, were discussed in the text. The results of the included studies were compared with studies that did not meet the inclusion criteria. Statin trials were compared with non-statin trials (including diet, bile acid sequestrant and surgical interventions).

Results of the review
Nineteen RCTs (n=81,859) met the inclusion criteria.

The Bayes factor comparing the estimated effect of LDL-C on MI or CHD death between the statin and non-statin trials was 0.0000073, indicating that there was no difference between statin and non-statin trials. Nineteen trials provided data on this outcome.

The 95% probability interval for the estimated regression line for the stroke data contained the line representing a one-to-one relationship between LDL-C reduction and percentage risk reduction. All but one individual trial also included the one-to-one line. This analysis was based on 9 statin trials.

The authors summarised that the regression lines for non-statin and statin trials were similar and consistent with a one-to-one relationship between LDL-C lowering and CHD and stroke reduction over 5 years of treatment.

Authors' conclusions
The pleiotropic effects of statins did not seem to contribute an additional cardiovascular risk reduction benefit beyond the expected degree observed in other LDL-C lowering interventions.

CRD commentary
This was a review with a clear question and inclusion criteria, but the inclusion criteria did not necessarily follow from the research question. The research question was to compare statin and non-statin interventions. However, trials were only eligible for inclusion in the review if they compared an intervention with a placebo intervention, hence excluding all potentially existing direct comparisons of the effects of statin and non-statin treatments. The review was therefore based on an indirect comparison only.

It is unclear why diet trials were exempt from the inclusion criteria of concealment allocation: this should be possible.
even if blinding was not. The searches were limited and concentrated on English language publications, hence it was unclear whether relevant studies had been missed and a biased selection of studies was reviewed. The authors did not state that any measures to reduce errors and bias were taken in the study selection process, as was the case for the data extraction. The review used complex analyses to derive the conclusions but the description of the methodology was limited. It is, for example, unclear how a comparative statement could be made that included the stroke outcome, while none of the non-statin interventions appear to have reported this outcome. The review was restricted to high-level evidence studies but did not critically appraise the included studies, so the quality of the included RCTs is not known.

The chosen composite outcomes included fatal and nonfatal incidences. Given the different impact these incidences have on patients, a stratified comparison would have been useful to compare the two different treatment approaches. Furthermore, it is unclear whether the pooling of the included studies was clinically meaningful, especially since the non-statin trials encompassed a variety of very different interventions. Overall, the conclusion should be regarded with caution.

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

**Practice:** The authors stated that the focus should remain on achieving LDL-C goals as recommended by current guidelines.

**Research:** The authors stated that further research is needed before the choice of cholesterol-lowering therapy is influenced by effects other than the degree of LDL-C reduction.

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