Primary prevention of cardiovascular diseases with statin therapy: a meta-analysis of randomized controlled trials
Thavendiranathan P, Bagai A, Brookhart M A, Choudhry N K

CRD summary
This review evaluated statins in the treatment of patients without cardiovascular disease. It concluded that statins decrease the incidence of major coronary and cerebrovascular events and revascularisations, but not coronary heart disease and overall mortality. The authors’ conclusions seem reasonable, though they are based on few studies and there are factors that may have influenced the results that merit further investigation.

Authors’ objectives
To investigate the role of statins in the primary prevention of cardiovascular events.

Searching
MEDLINE, EMBASE the Cochrane CENTRAL Register, DARE, the Cochrane Database of Systematic Reviews and ACP Journal Club were searched up to June 2005 for studies reported in the English language; the search terms were provided. The reference lists of potentially relevant articles were also checked.

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

Specific interventions included in the review
Trials comparing a statin with a placebo, active control (except comparisons of high- and low-dose statins) or usual care control group were eligible for inclusion, provided that the only intervention difference between the groups was the use of statin. The included studies were of pravastatin (20 to 40 mg/day), lovastatin (20 to 40 mg/day), atorvastatin (10 mg/day) and simvastatin (40 mg/day). Apart from one study with a usual care control group, all of the studies compared statin with placebo.

Participants included in the review
Trials where at least 80% of participants were not known to have cardiovascular disease (defined as coronary artery disease, cerebrovascular disease and peripheral vascular disease) were eligible for inclusion. Studies targeted at patients with conditions that were not traditional risk factors for cardiovascular disease, such as dialysis patients, were excluded, as were studies that used ultrasound to pre-screen for atherosclerosis. In the included studies, 90% of patients had no evidence of cardiovascular disease. The mean low-density lipoprotein cholesterol (LDL-C) values ranged from 117 to 193 mg/dL. The mean age of the participants ranged from 55 to 75 years and in most studies the majority of participants were male. The participants were classified as being mainly at moderate or moderately high risk of a cardiovascular event.

Outcomes assessed in the review
Trials with a mean follow-up of at least one year and reporting at least 100 cardiovascular disease outcomes were eligible for inclusion. The primary outcomes of interest were major coronary events (nonfatal myocardial infarction and coronary heart disease death) and major cerebrovascular events (fatal and nonfatal strokes). The secondary outcomes were death from any cause, coronary heart disease death, nonfatal myocardial infarction, revascularisations and adverse outcomes. The mean length of follow-up in the included studies ranged from 3.2 to 5.2 years.

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
Study quality was assessed using the Jadad scale. Two reviewers independently assessed quality and any disagreements were resolved by consensus.

Data extraction
Two reviewers independently extracted the data and any disagreements were resolved by consensus. Authors of primary studies were contacted for additional data where necessary, but this was unsuccessful. Where necessary, data were calculated from papers subsequent to the main paper. Where there were mixed samples of patients with and without cardiovascular disease and the data were not presented separately for primary prevention patients (3 studies), the data were extracted for the primary and secondary prevention patients combined. Relative risks and 95% confidence intervals (CIs) were calculated using intention-to-treat data.

Methods of synthesis
How were the studies combined?
The studies were pooled using random-effects and fixed-effect models, with the conclusions based on the former.

How were differences between studies investigated?
Heterogeneity was investigated by visual inspection of a plot of the relative risk for the included studies and by calculation of the Q statistic. A univariate meta-regression was also performed to investigate the effect of statins in a range of patient subgroups.

Results of the review
Seven RCTs (n=42,848) were included.

Six of the 7 studies were described as double blind.

There was a 29.2% reduction (95% CI: 16.7, 39.8; based on 7 trials) in the relative risk of a major coronary event with statin therapy compared with control (924 events versus 1,219 events, respectively). There was a 14.4% reduction (95% CI: 2.8, 24.6; 6 trials) in the relative risk of major cerebrovascular events with statin therapy compared with control (440 events versus 517 events, respectively). There was statistically significant heterogeneity in the analysis of major coronary events (p<0.006).

In relation to the secondary outcomes, there was a 31.7% reduction (95% CI: 16.9, 43.9; 2 trials) in the relative risk of nonfatal myocardial infarction and a 33.8% reduction (95% CI: 19.6, 45.5; 4 trials) in the relative risk of having a revascularisation procedure with statin therapy compared with control. There was an 8% reduction in overall mortality and a 22.6% reduction in coronary heart disease mortality with statin therapy, but neither of these were statistically significant.

The use of statins was not associated with an increased risk of cancer or liver enzyme or creatine kinase levels, though there was variation between studies and not all studies assessed these adverse events. The meta-regression suggested that benefits from statins were associated with a greater risk of coronary artery disease risk at baseline, a smaller proportion of men in the study population, and with larger changes in LDL-C level after one year of treatment and at the end of follow-up.

Authors’ conclusions
Statin therapy decreases the incidence of major coronary and cerebrovascular events and revascularisations, but not coronary heart disease and overall mortality, in patients without cardiovascular disease.

CRD commentary
The review question and inclusion criteria were clearly stated and relevant databases were searched for studies.
However, studies might have been missed as only articles in English were included. Study quality was assessed but the findings were not reported. Appropriate methods were used to reduce error and bias in the data extraction and quality assessment, though it was unclear whether similar methods were applied to the study selection process.

The statistical pooling of studies appeared appropriate, but it was unclear whether the heterogeneity in the analysis of major coronary events was explained by the regression analysis. The authors' conclusions seem appropriate and they discussed how the inclusion of some patients with coronary heart disease, higher risk primary prevention patients, and studies using different statins might have influenced the results. The number of studies available was limited; this also prevented the exploration of the discussed factors.

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

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

Research: The authors stated that studies are required to clarify the cost-effectiveness of statins for people without cardiovascular disease who have an intermediate risk of developing the disease.

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