Primary prevention of cardiovascular mortality and events with statin treatments: a network meta-analysis involving more than 65,000 patients

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CRD summary

This review concluded that statin treatment used for the primary prevention of cardiovascular disease was effective in reducing cardiovascular death and other major cardiovascular events. The conduct and reporting of the review were good and the conclusions are likely to be reliable.

Authors' objectives

To assess the effects of statins in primary prevention of cardiovascular events.

Searching

MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, AMED, CINAHL, TOXNET, Development and Reproductive Toxicology, Hazardous Substances Databank, PsycINFO, ISI Web of Science and full text journal databases (Ovid, Science Direct, Ingenta) were searched from inception to May 2008. Searches were run in duplicate. No language restrictions were applied. Bibliographies of identified reviews and the authors' files were checked.

Study selection

Randomised controlled trials (RCTs) of at least 12 months duration that assessed the effects of atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin or simvastatin were sought. Studies on cerivastatin were excluded. Comparator groups were placebo, standard therapy or no treatment. Only studies on primary prevention were eligible, defined as most participants with no history of coronary heart disease (CHD). The outcomes of interest were all cause mortality, cardiovascular disease (CVD) mortality, fatal myocardial infarction (MI), nonfatal myocardial infarction and major coronary events. Other outcomes reported included incidence of cancer and rhabdomyolysis. Studies on high-risk diabetic people were excluded, as were those that assessed only surrogate outcomes (such as changes in cholesterol).

In the included studies, mean ages of participants ranged from 50 to 75 years. Most participants were men (range 22% to 100%). Some participants had average or low cholesterol; others had hypercholesterolemia, peripheral vascular disease, renal transplants, asymptomatic carotid artery plaque, treated or untreated hypertension or diabetes. Between 60% and 100% of participants were categorised as primary prevention. Mean follow up ranged from one year to 5.3 years.

Two reviewers independently selected papers for inclusion.

Assessment of study quality

Study quality was assessed using items such as blinding, use of intention to treat analysis and allocation concealment.

Quality was assessed by two reviewers independently.

Data extraction

Data were extracted on an intention to treat basis. Relative risks with 95% confidence intervals (CI) were calculated for outcomes in individual studies. Authors were contacted for additional information where necessary.

Data were extracted independently by two authors. Differences were resolved through discussion and consensus.

Methods of synthesis

Pooled relative risks (RR) with 95% confidence intervals (CI) were calculated using the Der Simonian and Laird random-effects method. Where there were no events in one arm of a trial, 0.5 was added to each arm.

The Lu-Ades method for combining direct and indirect evidence in mixed treatment comparisons was used to evaluate the relative effectiveness of each drug. Results were reported as posterior means with 95% credibility intervals (CrI).

Heterogeneity was assessed using the I^2 statistic. Logistic regression was used to assess the impact of study quality (allocation concealment) and percentage low density lipoprotein change between groups. Subgroup analysis investigated differences in study populations based on risk of cardiovascular disease death (low risk was categorised as no haemodynamically significant atherosclerosis or fewer than three cardiovascular disease risk factors).

Funnel plots were used to assess publication bias.

Results of the review

Twenty RCTs (n=65,261) were included: four assessed atorvastatin (n=15,907); three assessed fluvastatin (n=3,463); 11 assessed pravastatin (n=38,367); and two assessed lovastatin (n=7,524). No studies that assessed rosuvastatin or simvastatin were found. Study size ranged from 164 to 10,355 participants. All studies reported blinding of participants and assessors. Intention to treat (ITT) was reported in 19 studies. Allocation concealment was reported in 10 studies. Mean follow up ranged from one year to 5.3 years.

The authors stated that tests showed no indication of publication bias (data not reported).

Use of statins reduced all cause mortality (RR 0.93, 95% CI: 0.87 to 0.99, p=0.03, I^2=5%; 19 trials), cardiovascular disease deaths (RR 0.89, 95% CI: 0.81 to 0.98, p=0.02, I^2=0%; 17 trials), death from myocardial infarction (RR 0.46, 95% CI: 0.26 to 0.79, p=0.005, I^2=0%; nine trials), major cardiovascular events (RR 0.85, 95% CI: 0.77 to 0.95, p=0.004, I^2=61%; 17 trials) and myocardial infarction (RR 0.77, 95% CI: 0.63 to 0.95, p=0.001, I^2=59%; 17 trials).

When heterogeneity was investigated, studies that reported allocation concealment appeared to show increases in events for mortality, cardiovascular death, major cardiovascular events and myocardial infarction with statin treatment

Results for other cardiovascular outcomes were reported in the paper.

Statins had no effect on cancer incidence (RR 1.02, 95% CI: 0.94 to 1.11, p=0.59, I^2=0%; 10 trials) or on rhabdomyolysis (RR 0.97, 95% CI: 0.25 to 3.83, p=0.96, I^2=0%; 9 trials with 39,383 participants and only four cases of rhabdomyolysis).

Results from the mixed treatment comparison modelling estimated that atorvastatin was the most effective statin for reducing all cause mortality (probability of 48%) and lovastatin for reducing cardiovascular disease mortality (probability of 60%).

Authors' conclusions

Statins have a role in the primary prevention of cardiovascular disease mortality and other major cardiovascular events.

CRD commentary

The inclusion criteria for this review were clearly stated. The search was extensive and no language restrictions were applied, thus the possibility of missed studies and the introduction of publication and language biases was reduced. The authors stated that tests showed no evidence of publication bias. The methods used for study selection and data extraction were likely to reduce the introduction of errors or reviewer bias. The quality of included studies was assessed appropriately and this was used to inform investigations into heterogeneity between studies. Standard meta-analyses and mixed treatment comparison models were used and forest plots presented so that results could be compared. The analysis methods appeared to be appropriate. The conduct and reporting of the review was good and the conclusions are likely to be reliable.

Implications of the review for practice and research

Practice: The authors stated that the benefits, risks and costs of lifelong statin therapy should be considered in relation to individual patient risk and weighed against other preventative treatments such as aspirin.

Research: The authors stated that there was a need for head-to-head trials to assess the differing effects of individual statins. Future trials that report composite outcomes should also report separate results for each outcome to enable their inclusion in meta-analyses.

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