Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170,255 patients from 76 randomized trials


CRD summary
This review concluded that statin therapies offered clear benefits in reducing cardiovascular outcomes across broad populations. The review appeared generally well conducted. The authors’ conclusions appear likely to be reliable, although it should be borne in mind that subgroup analysis by population type was conducted only for the primary outcome of cardiovascular disease mortality.

Authors’ objectives
To assess the effects of statin therapy on cardiovascular mortality and other clinical outcomes and examine whether specific statins exerted different effects.

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), AMED, CINAHL, TOXNET, DART, HSDB, PsycINFO, Web of Science, Science Direct and Ingenta were searched to August 2010. Search terms were not reported, but were available from the authors. The authors’ files and bibliographies of identified reviews were checked and authors of trials were contacted for further studies. No language restrictions were applied.

Study selection
Randomised controlled trials (RCTs) that assessed the effects of atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin on cardiovascular events in people with or without prior cardiovascular disease were eligible for inclusion. Comparators had to be placebo, standard therapy or no treatment. Studies on cerivastatin were excluded. Studies had to report on all-cause mortality, cardiovascular disease mortality, fatal myocardial infarction, non-fatal myocardial infarction or major cardiovascular events (stroke, revascularisation). Adverse events were reported.

Twenty-six per cent of participants in the included studies were women. Mean age ranged from 38 to 75 years. Most studies included people with coronary heart disease. Some studies were of people with carotid stenosis, diabetes, renal disease, previous stroke, congestive heart failure, transplants or liver disease. Other studies investigated elderly people or primary prevention. Mean pre-treatment low-density lipoprotein ranged from 95 to 254mg/dL. Fifty-two trials were placebo controlled, 18 trials compared interventions to usual care, four to no treatment and two to conventional therapy. Twenty-five trials assessed pravastatin, 15 assessed atorvastatin, nine fluvastatin, nine simvastatin, eight lovastatin and five rosuvastatin. Follow-up ranged from 0.5 to 6.1 years.

Two authors independently assessed studies for inclusion.

Assessment of study quality
Quality was assessed on items such as sequence generation, allocation concealment, blinding, use of intention-to-treat analysis and percentage follow-up.

It appeared that two authors independently assessed study quality. Disagreements were resolved by consensus.

Data extraction
Data were extracted on an intention-to-treat basis and relative risks (RR) and 95% confidence intervals (CI) were calculated for cardiovascular outcomes and odds ratios (OR) and 95% CI were calculated for adverse events.

Two authors independently extracted data. Disagreements were resolved by consensus.

Methods of synthesis
Pooled relative risks and 95% CI were calculated using a random-effects model. Heterogeneity was assessed with $I^2$. 
Where there were no events in one arm in a trial, 0.50 was added to each arm to facilitate analysis. For adverse events, pooled odds ratios and 95% CI were calculated using the Peto method. Subgroup analyses investigated differences in cardiovascular disease mortality according to baseline risk (trials in people with coronary heart disease, atherosclerosis, diabetes, renal disease, transplants, previous stroke and congestive heart failure or elderly people or were trials of primary prevention people).

Meta-regression was used to investigate the impact of absolute low-density lipoprotein change, the proportion of men in trials, history of coronary heart disease, baseline diabetes, hypertension and current smokers. The Lu-Ades method for combining indirect evidence in mixed-treatment comparisons was used to investigate the relative effectiveness of each statin on cardiovascular disease mortality by calculating odds ratios and 95% credible intervals.

**Results of the review**

Seventy-six RCTs (170,255 participants, range 38 to 20,536) were included.

Study quality varied. Twenty-six trials reported on generation of randomisation sequence, 18 on allocation concealment, 64 on losses to follow-up and four reported that primary results were based on per protocol analysis rather than intention to treat. Sixty-one trials reported that at least one specific group was blinded (typically participants and caregivers).

Compared to controls, statins reduced all-cause mortality (RR 0.90, 95% CI 0.86 to 0.94, $I^2=17\%$), cardiovascular disease mortality (RR 0.80, 95% CI 0.74 to 0.87, $I^2=27\%$), fatal myocardial infarction (RR 0.82, 95% CI 0.75 to 0.91, $I^2=21\%$), non-fatal myocardial infarction (RR 0.74, 95% CI 0.67 to 0.81, $I^2=45\%$, 58 trials) and revascularisation (RR 0.76, 95% CI 0.70 to 0.81, $I^2=44\%$; 44 trials). Reductions in the relative risk of deaths from stroke and non-cardiovascular disease were not statistically significant. In meta-regression analyses, each 10% change in absolute low-density lipoprotein levels was associated with a 1.1% (95% CI 0.3 to 1.19) risk reduction in total mortality.

There was no difference between statin and control in the first incidence of cancer (34 trials) or of rhabdomyolysis (35 trials). Statins were associated with an increase in new incidence diabetes (OR 1.09, 95% CI 1.02 to 1.16, $I^2=26\%$; 17 trials) and in the incidences of elevated liver and muscle enzymes beyond normal.

Subgroup analyses that investigated the effects of baseline risk factors showed no importantly different direction of effect on cardiovascular disease mortality dependent on populations.

Mixed treatment comparison found statistically non-significant differences between the different statins. A Bayesian probability estimate suggested that certain statins exerted a minimally important difference over other statins.

**Authors’ conclusions**

Statin therapies offered clear benefits in reducing cardiovascular outcomes across broad populations.

**CRD commentary**

The aims of this review were clearly stated in terms of the inclusion criteria. The search covered several relevant sources and included studies in any language, which reduced the possibility of language bias. It was unclear whether unpublished studies were eligible for inclusion and so it was not possible to rule out publication bias. The review methods aimed to reduce reviewer error and bias. Study quality was assessed appropriately, but was not used to inform the analyses. Statistical heterogeneity was investigated. Subgroup analyses investigated differences between studies.

The authors conclusions appear likely to be reliable, although it should be borne in mind that subgroup analysis by population type was conducted only for the primary outcome of cardiovascular disease mortality.

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

**Practice:** The authors stated that as generic formulations of statins become available efforts to expand access should be a priority.

**Research:** The authors did not state any implications for research.

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