Statins and all-cause mortality in high-risk primary prevention: a meta-analysis of 11 randomized controlled trials involving 65229 participants

CRD summary
The authors concluded that statin therapy for an average period of 3.7 years did not significantly reduce all-cause mortality in a high-risk primary prevention population. The authors acknowledged certain limitations with the included trials and statistical analyses. Despite the potential for bias in the review, the authors' conclusions appear to reflect the evidence, based on a large sample population.

Authors' objectives
To assess whether statins reduce the risk of all-cause mortality in intermediate to high-risk individuals without a history of cardiovascular disease.

Searching
MEDLINE and the Cochrane Library were searched between 1970 and May 2009 for published articles. Key search terms were reported. In addition, reference lists of relevant publications were searched. Primary authors of identified studies were contacted for unpublished data.

Study selection
Randomised controlled trials (RCTs) that compared statins versus placebo/control in individuals without prevalent cardiovascular disease at baseline, and that reported all-cause mortality, were eligible for inclusion.

Included trials enrolled patients from every continent, representing a wide range of countries. Most trials included a greater proportion of males (range 32 to 100%). Included patients’ mean age ranged from 51 to 75 years. The percentage of patients with diabetes ranged from 0 to 100%, and the percentage of patients who smoked ranged from 13 to 44%. Statin therapy used in the included trials was rosuvastatin calcium, pravastatin sodium, atorvastatin calcium, lovastatin and fluvastatin sodium, with doses ranging from 10 to 40mg per day; the average treatment period was 3.7 years. At baseline, mean systolic blood pressure of patients ranged from 130 to 164mmHg; their weighted mean baseline low-density lipoprotein cholesterol level was 138mg/dL.

The association between change in low-density lipoprotein cholesterol levels from baseline to follow-up and all-cause mortality were reported as an outcome.

The authors did not mention how many reviewers screened studies for inclusion.

Assessment of study quality
The authors did not state that they assessed study validity.

Data extraction
Two reviewers extracted baseline and follow-up low-density lipoprotein cholesterol levels to calculate the percentage reduction. Where possible, the number of deaths in each treatment group or effect estimates and their 95% confidence intervals (CIs) were also extracted. Where data were not available, trial authors were contacted for further details, and risk ratios (RRs) and their 95% confidence intervals were calculated. Discrepancies were referred to a third reviewer.

Methods of synthesis
Random-effects and fixed-effect models were used to pool risk ratios and their 95% confidence intervals.

Statistical heterogeneity was assessed using the $X^2$ test and $I^2$ statistic. Meta-regression was used to investigate potential sources of heterogeneity, and unless specified otherwise, adjustments were not made for other covariates.

Sensitivity analyses were conducted to remove trials recruiting only individuals with diabetes.
Publication bias was assessed using the Egger's test and funnel plots.

Results of the review
Eleven RCTs (n=65,229 patients, range 568 to 17,802) were included in the review. The mean follow-up duration ranged between 2.2 and 5.2 years.

There were no statistically significant differences in the risk of all-cause mortality between the two treatment groups (RR 0.91, 95% CI 0.83 to 1.01; random-effects model). There was no evidence of significant statistical heterogeneity ($I^2=23\%$). Sensitivity analyses did not significantly alter the results.

There was no evidence of publication bias.

The weighted mean baseline low-density lipoprotein cholesterol level was 138mg/dL, 134mg/dL in the placebo group compared with 94mg/dL in the intervention group. The relationship between low-density lipoprotein cholesterol levels and reduction in all-cause mortality were reported in the review.

Authors’ conclusions
Statin therapy for an average period of 3.7 years did not significantly reduce all-cause mortality in a high-risk primary prevention population.

CRD commentary
The review question and supporting inclusion criteria were clearly defined. The literature search was limited to two electronic databases, but attempts were made to locate unpublished data for trials included in the review. There was no evidence of publication bias. It was unclear whether any language restrictions were in place during the search, so it was unclear whether language bias was introduced. The authors undertook the data extraction in duplicate, but as it was unclear whether this was true for study selection, reviewer error and bias could not be ruled out.

The authors did not appear to have assessed validity, which meant that the quality of the included trials was unclear and that the reliability of the subsequent conclusions was also unclear. A large data set was included. Appropriate methods were used to pool the results and assess for statistical heterogeneity. The authors did acknowledge certain limitations with the included trials, such as differences in population characteristics and treatment methodology, and suggested that the findings should be interpreted with caution. The authors also acknowledged certain limitations with performing further statistical analyses due to insufficient data.

There was potential for bias in the review, but the authors’ conclusions appear to reflect the evidence, which included a large sample population, and they acknowledged certain limitations with the included trials and statistical analyses.

Some of the authors disclosed financial links with various companies that market or manufacture lipid-lowering agents.

Implications of the review for practice and research
Practice: The authors stated that due consideration is needed before using statins in lower-risk primary prevention populations.

Implications: The authors did not state any implications for further research.

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