Clinical outcomes in statin treatment trials: a meta-analysis

Authors' objectives
To determine the risk of cardiovascular events and death in patients receiving statin treatment for cholesterol regulation.

Searching
The authors searched MEDLARS using the search terms: 'anticholesterolemic agents', 'pravastatin', 'lovastatin', 'fluvastatin', atorvastatin', 'cerivastatin', 'simvastatin', and 'human trials'. The authors also searched Current Contents (1994 to 1997) and manually searched the bibliographies of retrieved studies. The authors attempted to contact several investigators to identify any new trials or the availability of results for ongoing unpublished trials. The publication cut-off date was April 15, 1997 and the retrieval cut-off date was May 1, 1997. Study languages included were: English, French, German, Spanish or Italian.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with parallel design and duration of at least one year. Eligible studies had to have at least 10 participants per group and one group receiving a monotherapy statin agent versus at least one concurrent control arm that used placebo or no pharmacologic treatment for cholesterol regulation.

Specific interventions included in the review
Statin treatment (lovostatin 20/40 mg(n=5), pravastatin 15/20/40 mg(n=10) and simvastatin 20 mg (n=3)) versus placebo.

Participants included in the review
Patients with hypercholesterolemia. The average age of participants was 57 years of age and men outnumbered women by 7 to 1. Hypertension and/or cigarette smoking was reported in one-third of the patients; prior MI was noted in one-half of the patients in 10 of the studies; angina was noted in 7 of the studies and ranged from 84% of patients in the regression trials to 10% of patients in the mixed population studies; and diabetes mellitus was noted in approximately 5% of patients in 7 studies. The occurrence of prior stroke was not reported.

Outcomes assessed in the review
Primary outcomes were all-cause mortality, sudden or non-sudden death, fatal myocardial infarction (MI) or stroke, nonfatal MI or stroke, and angina (with coronary artery bypass graft (CABG) surgery and percutaneous transluminal angioplasty (PCTA). A secondary outcome was the total number of withdrawals from the studies.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The authors used the 0 to 5 point Jadad scale to score studies for randomisation, blinding and withdrawals (see Other Publications of Related Interest no.1). The authors do not state how the papers were assessed for validity, or how many of the reviewers performed the validity assessment.

Data extraction
Two of the authors performed the data extraction using pre-designed data extraction forms. Reviewers were blinded as to the source of financial support, authors, and treatment group assignments. Completed data extraction forms were
cross-checked against one another and differences were resolved by referring to the original papers or to a third reviewer.

Data were extracted for the categories of: study characteristics, patient characteristics, treatment characteristics, and clinical outcomes.

The risk of major cardiovascular events and mortality for all patients receiving statin treatment versus controls was tabulated prior to the statistical pooling. The efficacy in patient subgroups, the impact of prognostic factors and the relationship between the risk of events and the degree of cholesterol reduction was assessed as data permitted.

**Methods of synthesis**

How were the studies combined?
Pooled log odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using both random-effects and fixed-effect models, and the random-effects calculations were reported in the results. The number needed to treat (NNT) was also calculated when appropriate.

How were differences between studies investigated?
The authors used the Cochran Q statistic to test for statistical heterogeneity.

Sensitivity analyses tested the impact of the study type and duration, statin treatment type, and control arm event rates. The authors also performed multivariate regressions to incorporate all significant prognostic variables and their treatment interaction terms.

**Results of the review**

Seventeen RCTs were included in the review with 21,303 participants (2 secondary prevention studies, 5 mixed primary-secondary prevention population studies, and 10 regression trials). Of the 21,303 participants, 10,754 received statin treatment and 10,525 received placebo.

In all studies, for all-cause mortality (n = 14), the OR was 0.76 (95% CI: 0.67, 0.86) in favour of receiving statin treatment. NNT = 67.

In all studies, for fatal MI (n = 14), the OR was 0.61 (95% CI: 0.48, 0.78) in favour of receiving statin treatment. NNT = 166.

In all studies, for non-fatal MI (n = 13), the OR was 0.66 (95% CI: 0.57, 0.77) in favour of receiving statin treatment. NNT = 43.

In all studies, for fatal stroke (n = 10), the OR was 0.77 (95% CI: 0.57, 1.04) which was not statistically significant. NNT = 500.

In all studies, for non-fatal stroke (n = 7), the OR was 0.69 (95% CI: 0.54, 0.88) in favour of receiving statin treatment. NNT = 143.

In all studies, for angina (n = 12), the OR was 0.70 (95% CI: 0.65, 0.76) in favour of receiving statin treatment. NNT = 24.

In all studies, for withdrawals (n = 11), the OR was 0.80 (95% CI: 0.61, 1.04) which was not statistically significant. NNT not reported.

Sensitivity analyses revealed no significant differences in results.

**Authors' conclusions**
The authors state that patients who received statin treatment demonstrated a 20% to 30% reduction in death and major
cardiovascular events compared with patients who received placebo. This advantage was generally present across study types and statin treatment types and for patients with less severe dyslipidemias. The benefit in clinical outcomes was noticeable as early as 1 year.

CRD commentary
The authors have clearly stated the research question and inclusion and exclusion criteria. The literature search appears to be thorough. The authors also include searches for unpublished and grey literature. The quality of the included studies was formally assessed. The authors have not reported how the articles were selected, or who performed the selection, however they do report who performed the validity assessment and data extraction.

The data extraction is reported in tables and discussed in the text of the review. The studies were combined in a statistical meta-analysis using both fixed-effect or random-effects models. There were tests for heterogeneity, and further sub-group analyses and meta-regression were performed to investigate the influence certain study, participant and treatment characteristics had on the results.

The conclusions stated by the authors appear to follow from the results. It should also be noted that this study was funded by the Bayer Corporation and two of the reviewers are employees of the company.

Implications of the review for practice and research
Practice: The authors do not state any implications for practice.

Research: The authors state that until head-to-head comparisons are done for different statins it is not possible to draw conclusions about differences in effectiveness. They also state that future reviews of cholesterol-lowering effects of various treatments should assess drug-specific or class-specific effects. Frequent updates to this review would also be valuable since the literature on statin treatment is growing quickly. New reviews would be especially helpful to establish efficacy in subgroups that are still under-represented in individual trials, such as women and the elderly.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.