Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins


CRD summary
This prospective meta-analysis of individual patient data concluded that statin therapy can safely reduce the 5-year incidence of major coronary events, coronary revascularisation and stroke by about 20% per mmol/L reduction in cholesterol, largely irrespective of lipid profile or other characteristics. The authors' conclusions reflect the evidence presented and are likely to be reliable.

Authors' objectives
To perform a prospective meta-analysis to assess the efficacy and safety of interventions to modify blood lipid levels.

Searching
Potentially eligible studies were identified prospectively, before any results were known, by computer-aided literature searches, manual searches of journals, examination of reference lists of trials and review articles, examination of abstracts and conference proceedings, by collaboration with the trial register of the International Committee on Thrombosis and Haemostasis, and by contacting colleagues, collaborators and drug manufacturers.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with at least 1,000 patients and a treatment duration of at least 2 years were eligible for inclusion.

Specific interventions included in the review
Interventions whose main effect was to modify lipid levels were eligible for inclusion. The main intervention in the included studies was a statin (simvastatin, lovastatin, pravastatin, fluvastatin or atorvastatin) compared with placebo, low-dose statin, usual care or no treatment.

Participants included in the review
No specific inclusion criteria were stated for the participants. Most of the included studies had a wide age range for participants. The proportion of women ranged from 0 to 52%, the proportion of participants with diabetes from 1 to 100%, and the proportion with a previous myocardial infarction (MI) from 0 to 100%.

Outcomes assessed in the review
The main pre-specified outcomes were all-cause mortality, coronary heart disease (CHD) mortality and non-CHD mortality. Other outcomes assessed in the review included major coronary and vascular events and the incidence of rhabdomyolysis and cancer.

How were decisions on the relevance of primary studies made?
The authors did not state explicitly how trials were selected for the prospective meta-analysis.

Assessment of study quality
The secretariat of the Cholesterol Treatment Trialists' Collaboration was established to coordinate the prospective meta-analysis. Individual patient data (IPD) were checked for internal consistency and completeness of individual patient records, for balance of group sizes overall and by prognostic categories, and for other indicators of possible anomalies. Queries were referred to the principal investigator of the trial concerned. Detailed summary tabulations and consistency checks based on the IPD provided were returned to each collaborator for review and confirmation. Summary data from each trial were also sought and checked for consistency with the IPD and any published reports.

Data extraction
Data on deaths from vascular and non-vascular causes, major coronary and vascular events, and incidence of cancer were extracted by treatment group, year of follow-up and presence of various baseline prognostic factors. For each trial, the log rank observed-minus-expected statistic (o-e) and its variance were calculated from the results during every year of follow-up. These values were weighted by the absolute low-density lipoprotein (LDL) cholesterol difference at the end of the first year of follow-up in each trial.

**Methods of synthesis**

How were the studies combined?
The meta-analysis used an 'assumption-free' Mantel Haenszel method. Weighted values of o-e and its variance from individual trials were used to produce pooled estimates of the event rate ratio (RR) per 1 mmol/L reduction in LDL cholesterol, with associated 95% or 99% confidence intervals (CIs).

How were differences between studies investigated?
Heterogeneity between trials for effect per mmol reduction in LDL cholesterol was assessed using a chi-squared test. Subgroup analyses were performed to assess the effects of baseline prognostic factors (previous disease, age, gender, treated hypertension history of diabetes, blood-pressure, triglycerides and total, low- and high-density cholesterol).

**Results of the review**

Fourteen RCTs with 90,056 participants were included.

Across all the RCTs, statin treatment was associated with a statistically significant 12% reduction in all-cause mortality (RR 0.88, 95% CI: 0.84, 0.91, p<0.0001). Deaths from vascular causes were significantly reduced, but those from non-CHD vascular and non-vascular causes were not. Major vascular events (including nonfatal MI, CHD death, coronary revascularisation and stroke) were reduced by 21% in the statin group (RR 0.79, 95% CI: 0.77, 0.81, p<0.0001). Effects on major vascular events were statistically significant in the first year but were greater in subsequent years. Reductions in major vascular events were similar across all subgroups examined. There was no evidence that statins increased the incidence of cancer (RR 1.00, 95% CI: 0.95, 1.06, p=0.9). The risk of rhabdomyolysis was not significantly higher in the statin group.

**Authors' conclusions**

Statin therapy can safely reduce the 5-year incidence of major coronary events, coronary revascularisation and stroke by about 20% per mmol/L reduction in LDL cholesterol, largely irrespective of lipid profile or other characteristics.

**CRD commentary**

This prospective meta-analysis had a clear objective. Appropriate methods were used to locate relevant trials before the results were known. A secretariat was established to coordinate the meta-analysis. IPD from included RCTs were checked for consistency and queried with the principal investigators if necessary. Investigators were provided with detailed summary tabulations. The authors did not state explicitly how trials were selected for the meta-analysis, so it is unclear whether any trials were excluded. The methods used for the meta-analysis seem appropriate and heterogeneity was investigated by means of a range of pre-specified subgroup analyses. The authors' conclusions reflect the evidence presented and are likely to be reliable.

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

Practice: The authors stated that prolonged statin treatment should be considered for patients at high risk of any type of major vascular event, and that the aim of treatment should be to achieve substantial absolute reductions in LDL cholesterol rather than to achieve particular target levels.

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

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