Use of lipid lowering drugs for primary prevention of coronary heart disease: meta-analysis of randomised trials

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Authors' objectives
To summarise the effect of primary prevention with lipid-lowering drugs on coronary heart disease (CHD) events, CHD mortality and all-cause mortality.

Searching
MEDLINE was searched from 1994 to 1999, using the MeSH terms 'hyperlipidemia', 'anti cholesteremic agents', individual drug names and 'randomised trials'. Additional material was obtained by searching the clinical trials register of the Cochrane Library (1999), reference lists of systematic reviews, and clinical practice guidelines. Studies published in languages other than English or in abstract form only were excluded.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) of at least one year in duration.

Specific interventions included in the review
Lipid-lowering drugs, namely colestyramine (24 g four times daily), gemfibrozil (600 mg twice daily), pravastatin (40 mg once daily) and lovastatin (20 to 40 mg once daily), compared with placebo.

Participants included in the review
Patients with no known CHD, cerebrovascular disease or peripheral vascular disease. Studies that included a mixture of primary and secondary prevention patients were excluded if the results could not be distinguished for each group.

Mean age of the participants (where reported) ranged from 47 to 58 years. In the stated inclusion criteria for patient selection there was no restriction by gender. However, in 3 trials included in the review all the participants were males, and in the other trial 85% were males. The mean level of cholesterol for the included patients was 5.7 mmol/L in one trial and 7.0 to 7.5 mmo/L in the other 3 trials.

Outcomes assessed in the review
The clinical end points studied in the review were: CHD mortality, all-cause mortality and nonfatal myocardial infarctions. Trials examining only the change in serum cholesterol concentrations or angiographic outcomes were excluded.

How were decisions on the relevance of primary studies made?
Two authors separately reviewed the abstracts for relevance. If the information provided by the abstract was insufficient to determine eligibility, or the reviewers disagreed about eligibility, the full paper was retrieved.

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

Data extraction
Relevant data were entered into evidence tables. Two authors independently performed the data extraction, and any disagreements were resolved by consensus.

Data were extracted for the categories of: study identification and year of publication, drug dose, study duration, number of participants, age and gender, mean initial total cholesterol, mean reduction in total cholesterol(%), incidence
of CHD, CHD mortality, and all-cause mortality.

**Methods of synthesis**

*How were the studies combined?*

A meta-analysis was performed to pool the results across studies. Pooled odds ratios (ORs) were calculated with 95% confidence intervals (CIs) using the Mantel-Haenszel fixed-effect model and the DerSimonian and Laird random-effects model for the outcomes of CHD events, CHD mortality and all-cause mortality.

*How were differences between studies investigated?*

Graphs of outcomes were examined visually and the chi-squared test for heterogeneity was performed to assess differences between studies. The authors also performed sensitivity analyses using the 4 additional studies that were possibly eligible for study inclusion, and looked at statins only, comparing these results with the overall results.

**Results of the review**

Four studies met all the inclusion criteria and were selected for the review (n=21,087). Another four, which were difficult to categorise as primary prevention or mixed primary or secondary prevention, were considered to be possibly suitable for inclusion.

The authors reported only the results of the fixed-effect analyses. The OR for CHD events, compared with placebo, was 0.70 (95% CI: 0.62, 0.79), and chi-squared was 3.23 (d.f.=3, P=0.36).

The OR for CHD mortality, compared with placebo, was 0.71 (95% CI: 0.56, 0.91), and chi-squared was 0.25 (d.f.=3, P=0.97).

The OR for all-cause mortality, compared with placebo, was 0.94 (95% CI: 0.81, 1.09), and chi-squared was 3.29 (d.f.=3, P=0.35).

Further analyses including the additional 4 studies possibly eligible:

The OR for CHD events, compared with placebo, was 0.72 (95% CI: 0.65, 0.80), and chi-squared was 5.55 (d.f.=7, P=0.59).

The OR for CHD mortality, compared with placebo, was 0.76 (95% CI: 0.61, 0.94), and chi-squared was 4.06 (d.f.=5, P=0.54).

The OR for all-cause mortality, compared with placebo, was 1.02 (95% CI: 0.89, 1.15), and chi-squared was 14.48 (d.f.=5, P=0.01).

Further analyses using statin trials (2 trials met original inclusion criteria and 1 was possibly eligible):

The OR for CHD events, compared with placebo, was 0.65 (95% CI: 0.55, 0.77), and chi-squared was 0.83 (d.f.=2, P=0.66).

The OR for CHD mortality, compared with placebo, was 0.65 (95% CI: 0.48, 0.89), and chi-squared was 1.47 (d.f.=2, P=0.48).

The OR for all-cause mortality, compared with placebo, was 0.89 (95% CI: 0.75, 1.06), and chi-squared was 6.45 (d.f.=2, P=0.04).

**Authors' conclusions**

Treatment with lipid-lowering drugs lasting 5 to 7 years reduces CHD events, but not all-cause mortality, in people with no known cardiovascular disease.
CRD commentary
The inclusion criteria were clearly stated. However, in terms of interventions, trials of one particular drug (clofibrate) were excluded and the reasons for this were not described. The search strategy was comprehensive but the start date of 1994 may have resulted in relevant earlier studies, which were not included in the systematic review mentioned, being missed. Relevant studies may also have been missed as only studies published in the English language were included, and those published as abstracts were excluded. Potentially important search terms were not used in the database search and not all keywords were not listed. Examination of bibliographies of included trials was not mentioned. No attempt was made to look for unpublished studies. There were no tests for publication bias. Nearly all study participants were white middle-aged males and findings may not be generalisable. No validity assessment was reported. Study details were not adequately reported and details regarding the reference population were not available. Methods of pooling seemed appropriate, but reasons for heterogeneity were not explored and inadequate account was taken of patient baseline characteristics. No information was given as to whether the individual trial results were calculated from intention to treat analyses.

The authors’ conclusions seem to follow from the results of the review, although it is unclear whether the treatment duration was the same as the study duration.

Implications of the review for practice and research
Practice: The authors state that risk assessment tools can be used to determine risk of individual patients, and to help providers and patients to decide about treatment.

Research: The authors state that future research should examine whether the effects of lipid-lowering treatments are similar for women and for people of non-European origin, i.e. groups that were not well represented in the trials included in the review. The effect of long-term treatment (5 to 10 years) should also be examined, to determine if it produces greater reductions in CHD events and possibly all-cause mortality.

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Other publications of related interest
This additional published commentary may also be of interest. Havranek EP. Review: lipid lowering drugs decrease coronary artery disease (CAD) events but not all cause or CAD mortality in men with no history of CAD. Evid Based Med 2001;6:85.

Indexing Status
Subject indexing assigned by NLM

MeSH
Cause of Death; Coronary Disease /mortality /prevention & control; Female; Humans; Hypolipidemic Agents /therapeutic use; Male; Middle Aged; Myocardial Infarction /prevention & control; Odds Ratio; Primary Health Care /methods; Randomized Controlled Trials as Topic; Risk
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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.