Effect of different antilipidemic agents and diets on mortality: a systematic review

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CRD summary
This review assessed the effects of different lipid-lowering interventions on mortality. The authors concluded that statins and n-3 fatty acids both reduce cardiac and overall mortality, but that fibrates may increase noncardiovascular mortality. This was a well-conducted review and the authors’ conclusions are likely to be reliable.

Authors’ objectives
To assess the efficacy and safety of different lipid-lowering interventions using data on mortality.

Searching
MEDLINE, EMBASE, Pascal and the Cochrane Controlled Trials Register were searched for reports in any language published from 1965 to June 2003. The references from two previous reviews were included (see Other Publications of Related Interest nos.1-2).

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with a follow-up of at least 6 months were eligible for inclusion.

Specific interventions included in the review
Studies that compared any lipid-lowering intervention with placebo or usual care were eligible for inclusion. Studies using hormone therapy in men, postmenopausal hormone therapies, combinations of lipid-lowering interventions, or outdated interventions were excluded. The review classified lipid-lowering interventions in the included studies as statins, fibrates, resins, niacin, n-3 fatty acids and dietary interventions.

Participants included in the review
Studies restricted to heart transplant patients were excluded, as were studies of people with acute coronary syndromes or people undergoing coronary artery bypass grafts. The review included trials of primary prevention and secondary prevention. Primary prevention was defined as less than 10% of participants with coronary heart disease (CHD), while secondary prevention was defined as 100% of participants with CHD.

Outcomes assessed in the review
Studies that reported mortality were eligible for inclusion. The review assessed overall mortality, cardiac mortality (death from myocardial infarction, sudden death, or heart failure) and noncardiovascular mortality.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected studies and resolved any disagreements through consensus.

Assessment of study quality
Studies were assessed for allocation concealment, blinding of the patients, caregivers or outcome assessors, and completeness of follow-up. Where no information was provided, it was assumed that the quality criteria were not fulfilled. Two reviewers independently assessed validity and resolved any disagreements through consensus.

Data extraction
Two reviewers independently extracted the data. If required, the authors of the primary studies were contacted for further details. The percentage of total cholesterol reduction, percentage mortality per year in the control group, overall deaths, cardiac deaths and noncardiovascular deaths were extracted or calculated for each study.
Methods of synthesis
How were the studies combined?
Only interventions with at least 1,000 participants per treatment group were included in the analyses. The results for policosanol, probucol and garlic are reported on the Basel Institute for Clinical Epidemiology website (accessed 25/10/2005). See Web Address at end of abstract. Weighted average risk ratios (RRs) and 95% confidence intervals (CIs) were calculated separately for each of the six predefined intervention groups using a random-effects meta-analysis. The possibility of publication bias was explored using a funnel plot.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the Cochran Q test and I² statistic. A sensitivity analysis was undertaken by examining the influence on the results of study quality and type of trial (primary or secondary prevention). The number-needed-to-treat per year to prevent one death was calculated for patients with and without existing CHD. Inverse variance-weighted regression was used to explore the association between overall mortality and the extent of cholesterol reduction, study quality criteria, percentage of patients with established CHD, and type and duration of lipid-lowering intervention.

Results of the review
Ninety-seven RCTs (n=276,116) were included. Of these RCTs, 35 assessed statins, 17 assessed fibrates, 8 assessed resins, 2 assessed niacin, 14 assessed n-3 fatty acids and 17 assessed dietary interventions.

Overall mortality.
Overall mortality was significantly reduced with statins (RR 0.87, 95% CI: 0.81, 0.94; heterogeneity P=0.05, I²=30%) and n-3 fatty acids (RR 0.77, 95% CI: 0.63, 0.94; heterogeneity P=0.01, I²=53%; heterogeneity appeared to be due to one lower quality RCT). There was no statistically significant difference in mortality for the other interventions examined.

Statins significantly reduced overall mortality in primary and secondary prevention studies. Heterogeneity was reduced in both subgroup analyses (P=0.50 for primary prevention and P=0.42 for secondary prevention).

For n-3 fatty acids, there was insufficient evidence to assess the effects on mortality in primary prevention studies. The sensitivity analysis found that lower quality studies of statins and fibrates tended to report higher risk reductions, although these differences were not statistically significant.

Cardiac mortality.
Cardiac mortality was significantly reduced with statins (RR 0.78, 95% CI: 0.72, 0.84; heterogeneity P=0.42, I²=3%), resins (RR 0.70, 95% CI: 0.50, 0.99; heterogeneity P=0.83, I²=0%) and n-3 fatty acids (RR 0.68, 95% CI: 0.52, 0.90; heterogeneity P=0.001, I²=66%; heterogeneity appeared to be due to one lower quality RCT). Noncardiovascular mortality.

Only fibrates significantly increased noncardiovascular mortality compared with the control (RR 1.13, 95% CI: 1.01, 1.27; heterogeneity P=0.80, I²=0%). A post hoc analysis found no increase in deaths from neoplasia, but insufficient data precluded further examination.

A univariate meta-regression found that the percentage of patients with established CHD and trial duration explained a statistically significant amount of variability in overall mortality among studies.

Authors' conclusions
Statins and n-3 fatty acids both reduce cardiac and overall mortality. Fibrates may increase noncardiovascular mortality.

CRD commentary
The review addressed a clear question in terms of the intervention, outcomes and study design. Several relevant sources were searched, the search terms were stated, and attempts were made to minimise language and publication bias. Two reviewers independently selected the studies, assessed validity and extracted the data, thus reducing the potential for bias and errors. Validity was assessed using specified established criteria and adequate information was presented on the included studies. Data for each intervention type were combined in a meta-analysis and statistical heterogeneity was assessed. A sensitivity analysis were undertaken to explore the influence of various factors on the results. This was a well-conducted review and the authors' conclusions are likely to be reliable.

**Implications of the review for practice and research**
Practice: The authors did not state any implications for practice.
Research: The authors stated that future studies should assess the effects on CHD mortality of the combination of statins and n-3 fatty acids, particularly in patients with metabolic syndrome.

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