Cholesterol reduction and non-illness mortality: meta-analysis of randomised clinical trials
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Authors' objectives
To investigate the association between cholesterol-lowering interventions and risk of death from suicide, accident or trauma (non-illness mortality).

Searching
MEDLINE was searched from 1966 to March 2000 using a strategy in which the term 'controlled clinical trial' was paired with each of the following: 'cholesterol', 'diet (fat restricted)' and 'anticholesterolemic drugs'. The reference lists of identified studies were examined.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials (RCTs) designed to measure treatment effects on clinical events and mortality were eligible. The median duration of follow-up ranged from 1.1 to 9.7 years.

Specific interventions included in the review
Comparisons of cholesterol-lowering interventions with a control intervention were eligible as long as other interventions to prevent coronary heart disease were not administered preferentially to the treatment group. The included interventions were diet, partial ileal bypass surgery, clofibrate, choletyramine, niacin, colestipol, gemfibrozil, pravastatin, lovastatin, simvastatin, clofibrate with niacin.

Participants included in the review
Studies of patients enrolled in primary or secondary prevention trials were included. Patients were eligible for primary prevention studies if there was no history of coronary artery disease (primary), and secondary prevention studies if there was clinical evidence of coronary artery disease. Studies were only included if there was a 5% or less variation in the mean serum cholesterol in the control group during the trial. Most of the participants were men aged between 40 and 70 years.

Outcomes assessed in the review
Non-illness related deaths (suicide, accident or trauma) were assessed.

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
No formal assessment of validity was undertaken.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. The data extracted (tables on the BMJ website) were participants (primary or secondary prevention), mean age, mean baseline cholesterol, cholesterol-lowering intervention, and cointerventions. The number of non-illness-related deaths and the number who did not die of non-illness causes were extracted for the treatment and control groups in each study.

Methods of synthesis
How were the studies combined?
A summary odds ratio (OR) and 95% confidence interval (CI) was calculated using the Mantel-Haenszel method, as modified by Yusuf et al. (see Other Publications of Related Interest no.1).

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared test. Subgroup analyses were conducted on the primary and secondary prevention trials separately, and on clinical trials using statins separate from other interventions. The association of non-illness mortality with the average amount of cholesterol reduction was assessed using a weighted regression model. A model was also fitted excluding studies with no deaths from non-illness-related causes in either or both the treatment and control groups.

Results of the review
Twenty-one RCTs were eligible, of which 19 provided data (70,704 patients).

The mean reduction in cholesterol varied considerably across studies (3.5 to 26%). There was no significant difference in non-illness mortality overall (OR 1.18, 95% CI: 0.91, 1.5, P=0.20). There was no evidence of heterogeneity (chi-squared P>0.05).

In the subgroup analyses of primary and secondary prevention trials, no significant increase was shown in non-illness-related mortality with cholesterol-lowering treatment. The OR was 1.28 (95% CI: 0.94, 1.74, P=0.12) for primary prevention trials (8 RCTs) and 1.00 (95% CI: 0.65, 1.55, P=0.98) for secondary prevention trials (11 RCTs).

The subgroup analysis of statin trials (5 RCTs) showed no significant increase in non-illness-related mortality (OR 0.84, 95% CI: 0.50, 1.41, P=0.50). Trials of non-statin treatment (13 RCTs) showed an increase in non-illness-related mortality, but this did not reach statistical significance (OR 1.32, 95% CI: 0.98, 1.77, P=0.06).

The regression analysis did not find an association between the mean cholesterol reduction and non-illness mortality (P=0.23).

Authors' conclusions
Currently available evidence does not indicate that non-illness mortality is increased significantly by cholesterol-lowering treatments. A modest increase may occur with dietary interventions and non-statin drugs.

CRD commentary
The review question was clear in terms of the study design, interventions and outcomes. Limiting the literature to only one database may have resulted in the omission of other relevant studies. It was not stated whether any language restrictions were applied. No details were presented of the methods used to select the studies or extract the data. Hence, the adequacy of the methods used to conduct these processes cannot be assessed. Validity was not formally assessed, and no comment was made on the validity of methods used to record and determine the cause of mortality in the individual studies. Relevant data were extracted and tabulated; the additional tables are available on the BMJ website (accessed 22/09/2003). See Web Address at end of abstract. The studies were appropriately combined in a meta-analysis and statistical heterogeneity was assessed for overall mortality. A subgroup analysis was used to explore the influence of various factors on the results. The evidence presented appears to support the authors' conclusion. This meta-analysis updates a previous review (see Other Publications of Related Interest no.2).

Implications of the review for practice and research
Practice: The authors report that statins do not adversely affect non-illness mortality, but the effect of other treatments is unclear.

Research: The authors did not report any implications for further research.
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Other publications of related interest

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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.