Drug treatment of hyperlipidemia in women
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CRD summary
This review looked for evidence on the use of drugs to reduce hyperlipidaemia in women. The authors found that for women without cardiovascular disease (CVD), lipid lowering did not affect total or coronary heart disease (CHD) mortality. However, for women with existing CVD, lipid-lowering treatment appears to be effective in reducing CHD events.

Authors’ objectives
To assess evidence, from clinical trials, on drug treatments for hyperlipidaemia for the prevention of coronary heart disease (CHD) events and death in women with or without prior cardiovascular disease (CVD).

Searching
MEDLINE, the Cochrane Library and DARE were searched from 1966 to December 2003; the search terms were given. Studies reported in English and other languages were sought. In addition, bibliographies were reviewed and experts were contacted. Authors were contacted for further information when the studies included women but did not report the outcomes by gender.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials (RCTs), where separate outcome data were reported for women, were eligible for inclusion.

Specific interventions included in the review
Studies that compared any lipid-lowering drug treatments, where treatment lasted at least one year, were eligible for inclusion. The drugs assessed in the included studies were statins (lovastatin, simvastatin, pravastatin, atorvastatin), colestipol, clofibrate and cholestyramine. The control group in one study received 'usual care', whilst placebo was used in all others. The mean duration of treatment ranged from 2.8 to 6.1 years.

Participants included in the review
Studies on out-patients with or without known CVD (secondary or primary prevention), and which provided separate data on women, were eligible for inclusion. The studies had to report on primary and secondary prevention separately. In the included studies, the mean ages of the participants ranged (where given) from 54 to 62 years. The eligibility criteria in some studies included blood cholesterol levels considered 'mild hyperlipidaemia' or in the 'normal range'. The participants in most of the primary prevention studies were at increased risk of CHD. In two of the primary prevention studies 14% and 20% of the participants had CHD.

Outcomes assessed in the review
Studies were eligible for inclusion if they reported at least one clinical outcome: CHD events, CHD mortality, total mortality, nonfatal myocardial infarction (MI), or revascularisation. Coronary events included ischaemic coronary syndromes and nonfatal MI. Revascularisation included coronary artery bypass graft, percutaneous coronary angioplasty and stenting.

How were decisions on the relevance of primary studies made?
Two reviewers reviewed titles and excluded those that did not meet the inclusion criteria. Two reviewers, who were blinded to the authors’ names and journal titles, independently reviewed eligible articles.

Assessment of study quality
Quality was assessed by factors such as clear and appropriate inclusion criteria, concealment of allocation, use of placebo, participants and research staff blinded to the treatment group, and more than 75% completing follow-up. Studies that met all quality criteria were considered 'good quality', while those that did not were classed as 'fair quality'. At least two independent reviewers performed the quality assessment. All disagreements about quality were resolved by discussion and consensus.

**Data extraction**
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Relative risks (RR) were calculated for each outcome for each study.

**Methods of synthesis**
How were the studies combined?
Summary estimates of RR and 95% confidence intervals (CIs) were calculated using fixed-effect (Mantel-Haenszel) and random-effects (DerSimonian and Laird) models. Since the findings from these were similar, the results for the random-effects model were presented. Where there were no events, 0.5 was added to tables for calculations. The significance level was set at a P-value of less than 0.05.

Publication bias was investigated by calculating the correlation between individual study weight and RR.

How were differences between studies investigated?
The chi-squared test and Q statistic were used to assess heterogeneity. The critical value was set at 0.10. Subgroup analyses were conducted according to the type of drug (statins and non-statins) and the quality of the studies ('good' and 'fair'). A sensitivity analysis was performed by including an additional study (of mixed primary and secondary prevention) in both primary and secondary prevention analyses.

**Results of the review**
Thirteen studies met the inclusion criteria, 6 studies on primary prevention (11,435 women) and 8 studies on secondary prevention (6,456 women); one study reported on primary and secondary prevention separately. One further study of mixed primary and secondary prevention was included in some analyses. Nine of the studies assessed statin treatment (16,458 women), one colestipol (1,184 women), two clofibrate (221 women) and one cholestyramine (28 women). Only data for women were analysed. The percentage of women in the overall participants within individual studies ranged from 14 to 52%.

Nine of the studies were rated 'good quality' and 4 were rated 'fair'. There was no statistical evidence of heterogeneity in any of the summary estimates. There was no evidence of publication bias.

Primary prevention (6 studies).

When the studies were pooled, treatment with lipid-lowering drugs showed no effect on total mortality (4 studies); the summary RR was 0.95 (95% CI: 0.62, 1.46) and the RR for CHD mortality was 1.07 (95% CI: 0.47, 2.40). The results for nonfatal MI or revascularisation also showed no effect. One study of diabetic women showed a significant reduction in CHD events. However, when the studies were pooled, the RR was 0.87 (4 studies; 95% CI: 0.69, 1.09).

One study was considered to have different characteristics to the others. When this study was removed, the results for total mortality were similar whereas those for CHD events favoured treatment (RR 0.77, 95% CI: 0.64, 0.94).

The summary RR were similar when only studies of statins were combined (5 studies).

Secondary prevention (8 studies). Treatment with lipid-lowering agents showed no effect on total mortality (4 studies; RR 1.00, 95% CI: 0.77, 1.29). However, there was a reduction in risk with treatment for the other outcomes: the RR was 0.74 (7 studies; 95% CI: 0.55, 1.00) for CHD mortality, 0.71 (7 studies; 95% CI: 0.58, 0.87) for nonfatal MI, 0.70 (3 studies; 95% CI: 0.55, 0.89) for revascularisation, and 0.80 (4 studies; 95% CI: 0.71, 0.91) for total CHD events.
One additional study, on people with or without CVD, was included in separate analyses of both the primary and the secondary studies. The effect of this study was similar to the main analyses.

**Authors’ conclusions**
For women without CVD (primary prevention), lipid-lowering therapy does not affect total or CHD mortality. However, it may reduce CHD events, although current evidence is insufficient to determine this conclusively. For women with existing CVD (secondary prevention), treatment is effective in reducing CHD events, CHD mortality, nonfatal MI and revascularisation. Total mortality is not affected.

**CRD commentary**
This was a detailed and clear paper with clearly stated aims. The search was adequate, although it is possible that additional studies would have been identified if other databases (e.g. EMBASE) had been searched. The methods of the review were described and the quality of the included studies was assessed. The meta-analysis was appropriate, although it is unclear why the authors reported the results for random-effects pooling when they said there was no statistical heterogeneity. In a secondary analysis, the authors included the results of one study that did not meet the inclusion criteria because data were not available separately for primary and secondary prevention. This may be problematic since the authors did not mention whether any similar studies were available. The authors also commented that the number of women in the studies, and subsequent limited number of events available for analysis, may limit the value of some results. The authors’ conclusion are supported by the results presented.

**Implications of the review for practice and research**
Practice: The authors implied that decisions about lipid-lowering therapy should take into account a woman's overall CHD risk factor.

Research: The authors stated that future studies should include adequate numbers of women, with a range of CHD risk levels, and the results should be stratified by gender and primary or secondary prevention. They also suggested that it would be helpful to undertake an individual patient data meta-analysis using data from all existing studies where the participants included women.

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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.