Impact of gender in primary prevention of coronary heart disease with statin therapy: a meta-analysis

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CRD summary
This review concluded that statin therapy had no effect on mortality risk in men and women without prior cardiovascular disease, and that it reduced the risk of coronary heart disease events in men but not in women. There were some problems with the methodology of the review, so the authors' conclusions should be treated with some caution.

Authors' objectives
To compare the effects of statin therapy by gender for the primary prevention of cardiovascular disease.

Searching
MEDLINE, the Cochrane Library and DARE were searched from January 2002 to March 2008. Search terms were reported. No language restrictions were applied. Reference lists of retrieved papers were checked and colleagues were contacted.

Study selection
Randomised controlled trials (RCTs) of patients without known cardiovascular disease (primary prevention) that assessed lipid-lowering therapy, where data were available on women, and that reported on at least one clinical outcome, were eligible for inclusion. Clinical outcomes were total mortality, coronary heart disease mortality, nonfatal myocardial infarction, revascularisation or coronary heart disease events (defined as coronary heart disease mortality, nonfatal myocardial infarction, unstable angina, or sudden cardiac death). Trials that pre-screened patients for atherosclerosis using ultrasound, those that targeted patients with other conditions (e.g. dialysis, post-transplantation), or those where the proportion of patients being treated for primary prevention were not reported, were excluded.

Data for only two outcomes were available in included trials: total mortality and coronary heart disease events.

In the included trials the mean age of participants ranged between 55 and 75 years (where given). Blood lipid entry requirements were total cholesterol of more than 135 to 250mg/dL or low density lipoprotein of more than 100mg/dL to 159mg/dL or 190 mg/dL. The statins used for lipid-lowering therapy were atorvastatin, lovastatin, pravastatin and simvastatin. Control treatments were placebo, usual care or diet.

Two reviewers independently selected studies for inclusion. Discrepancies were resolved by discussion and consensus.

Assessment of study quality
Trial quality was assessed using the Jadad score that assessed reported method of randomisation, blinding, description of withdrawals and drop-outs, with a maximum score of 5 points.

The authors did not state how the validity assessment was performed.

Data extraction
Where necessary authors were contacted for additional information, although this was generally unsuccessful.

Data were extracted on an intention-to-treat basis. Participants could only contribute one event for each combined outcome. Relative risk (RR) and 95% confidence intervals (CI) were extracted or calculated for each outcome.

The authors did not state how the data were extracted for the review.
Methods of synthesis
Pooled relative risks and 95% confidence intervals were calculated using the inverse variance model. To avoid problems related to no events in study arms, 0.5 was added to all cells within the analysis.

Heterogeneity was assessed using the Q and I² statistics. Where heterogeneity was present, a random-effects analysis was also performed.

Sensitivity analyses were performed based on quality score (excluding trials scoring less than 3 points) and by excluding trials that appeared to be outliers (largest study with smaller than expected differential in total cholesterol and apparently different results; trials where some participants had cardiovascular disease).

Publication bias was investigated using methods of Begg and Mazumdar, and Egger.

Results of the review
Eight RCTs were included in the review (18,607 women and 35,771 men; numbers taken from tables); six trials were placebo controlled (8,200 women and 27,991 men), one trial compared statin therapy with diet (5,356 women and 2,476 men), and one trial compared statin therapy with usual care (5,051 women and 5,304 men). Three trials scored 5 points for quality, four trials scored 4 points, and one trial scored 2 points. The average length of follow-up was 3.9 years (range 2.8 to 5.3 years).

Tests showed no evidence of publication bias.

There was no association between statin use and mortality for men (RR 0.93, 95% CI 0.83 to 1.04; I²=0%; five trials) or for women (RR 0.96, 95% CI 0.81 to 1.13; I²=34.2%; four trials) when compared with control groups. Sensitivity analyses did not significantly alter the results.

There was a lower risk of coronary heart disease events with statin therapy for men (RR 0.59, 95% CI 0.48 to 0.74; I²=89.1%; seven trials) when compared with control groups. For women there was some reduction, but this did not reach statistical significance (RR 0.89, 95% CI 0.79 to 1.00; I²=17.9%; six trials).

After the exclusion of one study (with a Jadad score of less than 3 points), a statistically significant reduction in risk of coronary heart disease events was found with statin therapy among women (RR 0.84, 95% CI 0.73 to 0.97). All other results remained unchanged in sensitivity analyses.

Authors’ conclusions
Statin therapy reduced the risk of coronary heart disease events in men without prior cardiovascular disease, but no effect was found in women. There was no reduction in risk of mortality for either men or women.

CRD commentary
The review question was clearly stated in terms of study design and treatment. However, the included studies appeared to differ somewhat from the stated inclusion criteria in that some participants in some studies had evidence of prior coronary heart disease. The authors gave no criteria for a cut-off point related to selection of studies with mixed populations, or if other studies were rejected related to this. Although studies in any language were eligible, the sources searched were rather limited, so it was possible that studies were missed and that publication bias may have affected the results of the review. Methods of study selection were aimed at reducing reviewer error or bias, although the authors did not state what methods were used for data extraction and quality assessment.

Whilst quality was assessed, the use of a scoring system was not the most effective method. The methods of synthesis were appropriate and some attempts were made to investigate potential sources of heterogeneity. There was little information about the participants, dosages of statins and/or any concomitant treatments, which could have affected the generalisability of the results. There were some unexplained discrepancies between the numbers of participants in the text and in the tables. The authors acknowledged that follow-up may not have been long enough to identify any possible effect on mortality. The results were based on subgroup analyses of available trials.
In view of some limitations in the search procedure, unclear selection criteria and possible problems with the methodology of the review, the authors' conclusions should be treated with some caution.

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

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that clinicians would benefit from an individual patient data meta-analysis, taking account of gender-specific data from all completed trials of statins for primary prevention of coronary heart disease. They also implied that longer follow-up may be needed to assess the impact on mortality.

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