Statins for primary prevention of cardiovascular mortality in women: a systematic review and meta-analysis

Bukkapatnam RN, Gabler NB, Lewis WR

CRD summary
The review found that statin therapy combined with diet and exercise in moderately hyperlipidaemic women without a history of cardiovascular disease helped prevent coronary heart disease events, but was of no proven benefit in reducing all-cause mortality. These findings require cautious interpretation due to limitations in the review, including the authors’ failure to assess study validity.

Authors’ objectives
To assess the efficacy of statin therapy for the primary prevention of cardiovascular disease in women.

Searching
PubMed, The Cochrane Library, EMBASE and ClinicalTrials.gov were searched from 1985 to March 2009. Search terms were reported. The search was limited to articles published in English.

Study selection
Randomised controlled trials (RCTs) that compared statins with placebo for primary prevention of cardiovascular disease were eligible for inclusion. Studies were required to report sex-specific results and to have at least one year follow-up. Outcomes of interest were all-cause mortality, major cardiovascular disease events (fatal and non-fatal myocardial infarction, first revascularisation or cardiac surgery, unstable angina or any combination of these) and cancer.

All the eligible studies included both men and women; the proportion of women ranged from 15% to 69%. Only data relevant to women were included in the review. Mean age ranged from 58 to 64 years (where reported). Mean baseline low density lipoprotein cholesterol (LDL-C) ranged from about 127 to 160mg/dL. More than 99% of participants had no history of coronary heart disease. Lovastatin, pravastatin, atorvastatin, simvastatin and rosuvastatin were used at low to medium doses, combined with antihypertensives, diet, hormone replacement therapy and/or aspirin. Most primary studies reported various coronary heart disease events as a composite outcome. Outcomes reported in the review were all-cause mortality, coronary heart disease events (which included myocardial infarction, angina, stroke, revascularisation, congestive heart failure, cerebrovascular disease, symptomatic peripheral vascular disease and coronary heart disease mortality) and cancer. Median duration of follow-up ranged from 1.9 to 5.3 years. Most trials were multicentre and funded by pharmaceutical companies. Trials were conducted in USA, Europe, Japan and internationally (26 countries).

The authors did not state how many reviewers performed study selection.

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

Data extraction
Data were grouped by outcome. Few studies reported coronary heart disease mortality as a separate endpoint, so it was included with coronary heart disease events. Risk ratios (RRs) and 95% confidence intervals (CIs) or regression coefficients and standard errors were extracted from each study.

Two reviewers independently extracted data. Attempts were made to contact primary study authors to request sex-specific results where these were not reported in otherwise-eligible studies; no responses were received.

Methods of synthesis
Studies were combined to calculate pooled risk ratios and 95% CIs using the Wolfe method for fixed-effect and the DerSimonian and Laird method for random-effects. Results were similar and random-effects were reported in the review. Heterogeneity was assessed using the $\chi^2$ test. Publication bias was assessed using the Begg and Egger test. A sensitivity analysis was conducted to investigate the effect of including a seventh RCT that reported primary and secondary prevention data together.

**Results of the review**

Six RCTs were included (n=21,963). At least one study was of poor quality, with no blinding and a 30% crossover between study groups.

There was no statistically significant difference between statins and placebo in rates of all-cause mortality (three RCTs) and cancer (two RCTs). The risk of coronary heart disease events was significantly lower in the statin group (RR 0.78, 95% CI 0.64 to 0.96; six RCTs).

No evidence of significant heterogeneity or publication bias was found. Sensitivity analysis did not have a significant influence on the findings.

**Authors' conclusions**

Statin therapy combined with diet and exercise in moderately hyperlipidaemic women without a history of cardiovascular disease was of benefit in preventing coronary heart disease events, but of no proven benefit in reducing all-cause mortality.

**CRD commentary**

The objectives and inclusion criteria of the review were clear. Relevant sources were searched for studies. The language restriction meant that some studies may have been missed. It appeared that the search was limited by publication status. Tests for publication bias were conducted and none was found, but such tests are not very sensitive with so few studies. Steps were taken to minimise risks of reviewer bias and error by having more than one reviewer independently extract data; it was unclear whether such precautions applied to study selection. It appeared that study validity was not assessed. Concomitant therapies in the placebo group were not described. These factors made it difficult to determine the reliability of the results. Most studies were funded by pharmaceutical companies; the potential for this to create bias was unknown.

Appropriate statistical techniques were used to combine the studies and assess for heterogeneity; no significant heterogeneity was found. The authors noted that their review was limited by their inability to access sex-specific data from all relevant trials and by the non-uniformity of reported outcomes, which necessitated the use of composite endpoints in the review. Their concluding comments with respect to diet and exercise did not appear to reflect the evidence presented, as women in most studies received antihypertensives, only one study used diet therapy and exercise was not reported as an intervention in any study.

The authors’ findings require cautious interpretation due to limitations in the review, including their failure to assess study validity and inability to access all relevant data.

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

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

**Research:** The authors stated that more research was needed in the area of statin use for prevention of coronary heart disease in women. Research on modifiable coronary heart disease risk markers in women should extend beyond traditional markers (such as LDL-C) to include targets such as C-reactive protein.

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