Use of statins in primary and secondary prevention of coronary heart disease and ischemic stroke: meta-analysis of randomized trials

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CRD summary
This study assessed the effects of statins on preventing clinical events associated with cardiovascular disease (CVD). The authors concluded that there was a considerable reduction in risk of CVD morbidity and mortality in people with CVD, and a small reduction in risk in those without CVD.

Authors' objectives
The objective was to estimate the relative risk reduction of clinical outcomes associated with statin therapy in the primary and secondary prevention of coronary heart disease (CHD) or ischaemic stroke.

Searching
MEDLINE was searched from 1985 to July 2002; the search terms were given. In addition, the Cochrane Library was searched and the reference lists of identified studies and reviews were checked. The authors also implied that they searched Ringdoc. Only studies in English, German, French or Italian were eligible for inclusion.

Study selection
Study designs of evaluations included in the review
Only randomised placebo-controlled trials, with more than 30 participants with hypercholesterolaemia per group, were eligible for inclusion.

Specific interventions included in the review
Only studies of statins compared with placebo were eligible for inclusion. The duration of treatment had to be one year or more. The statins used in the included studies were simvastatin, pravastatin or lovastatin. The treatments ranged from 1 to 6.1 years in duration. In one of the included studies some of the participants also received antioxidant vitamins.

Participants included in the review
The inclusion criteria stated that studies on people with no evidence of cardiovascular disease (CVD) (primary prevention), or on those with CVD (secondary prevention), were eligible for inclusion. In one included study some participants had CVD whilst others did not (mixed primary and secondary prevention). In the included studies, the majority of the participants were male (52 to 100%) and the mean ages ranged from 53 to 62 years. Some participants had hypertension, diabetes, angina or myocardial infarction, or were smokers.

Outcomes assessed in the review
Only primary and secondary prevention studies with clinical outcomes (i.e. CHD mortality, all-cause mortality, stroke, stroke mortality, coronary disease event) were eligible for inclusion. The results were grouped by treatment objective (primary, secondary, or combined or mixed studies). Changes in cholesterol levels were also reported: total cholesterol, low- and high-density lipoprotein cholesterol (LDL and HDL, respectively) and triglycerides.

How were decisions on the relevance of primary studies made?
Two authors independently selected papers for inclusion.

Assessment of study quality
The authors did not state that they assessed validity.
Data extraction
Two authors independently extracted the data. Any differences were resolved by discussion or by a third author. The results for each end point in each study were tabulated. The relative risk (RR) and 95% confidence interval (CI) were calculated for each outcome in each study.

Methods of synthesis
How were the studies combined?
The RRs were pooled using a fixed-effect model if there was no evidence of heterogeneity, otherwise a random-effects model was used. For the meta-analysis, where no event was recorded 0.5 was added to the tables.

How were differences between studies investigated?
Heterogeneity was assessed using the chi-squared test, where a P-value of less than 0.05 was taken to indicate statistical significance. Sensitivity analyses were performed by removing individual studies from the analyses.

Results of the review
Fifteen studies (63,410 participants) were included. Of these 4 studies (14,566 participants) were primary prevention, 10 studies (28,308 participants) were secondary prevention and one study (20,536 participants) was mixed (primary and secondary prevention).

Tests for heterogeneity showed little variability between studies so fixed-effect analyses were reported. Not all studies reported on all outcomes.

Primary prevention.
The use of statins reduced the risk of cardiovascular mortality (RR 0.66, 95% CI: 0.49, 0.90, P=0.0082) and of having a coronary event (RR 0.67, 95% CI: 0.58, 0.77, P<0.0001). There was no difference in non-cardiovascular mortality between the statins and placebo groups (RR 1.03, 95% CI: 0.80, 1.33, P=0.8026). There was no evidence of an effect on fatal stroke, nonfatal stroke or total stroke. The effect on all-cause mortality was non significant (RR 0.86, 95% CI: 0.72, 1.04, P=0.1303).

Secondary prevention.
The use of statins reduced the risk of a coronary event (RR 0.74, 95% CI: 0.69, 0.79, P<0.0001), CVD mortality (RR 0.76, 95% CI: 0.69, 0.84, P<0.0001) and all-cause mortality (RR 0.80, 95% CI: 0.74, 0.87, P<0.0001). The risks of nonfatal stroke and total stroke (fatal and nonfatal) were also reduced. There was no evidence of an effect on non-CVD mortality (RR 0.88, 95% CI: 0.75, 1.02, P=0.1677) or fatal stroke (RR 0.99, 95% CI: 0.67, 1.48, P=0.9832). Statin use was associated with a 22% reduction in total cholesterol, a 29% reduction in LDL cholesterol, a 12% reduction in triglycerides and a 6% increase in HDL cholesterol. Different statins appeared to have similar effects on cholesterol levels. The results were not altered when individual studies were removed from the analyses.

Primary, secondary and mixed studies analysed together.
The use of statins reduced CVD mortality (RR 0.78, 95% CI: 0.73, 0.84, P<0.0001) and coronary events (RR 0.73, 95% CI: 0.68, 0.77, P<0.0001), nonfatal stroke (RR 0.74, 95% CI: 0.67, 0.82, P=0.0001), total stroke (fatal and nonfatal) (RR 0.94, 95% CI: 0.86, 1.03, P=0.1677) and all-cause mortality (RR 0.77, 95% CI: 0.70, 0.84, P<0.001). The effect on non-CVD mortality or fatal stroke did not reach statistical significance (P=0.1677 and P=0.1912, respectively). Statin use was associated with a 22% reduction in total cholesterol, a 29% reduction in LDL cholesterol, a 12% reduction in triglycerides and a 6% increase in HDL cholesterol. Different statins appeared to have similar effects on cholesterol levels. The results were not altered when individual studies were removed from the analyses.

Authors' conclusions
The evidence indicated that statin therapy reduces the RR of recurrence of coronary events, CVD mortality, nonfatal strokes and all-cause mortality. The studies showed that secondary prevention provides considerable improvement in CVD mortality and morbidity, while primary prevention provides only a small, and clinically hardly relevant, improvement in CVD morbidity and mortality.
CRD commentary
The aims of this review were clearly stated. While MEDLINE and the Cochrane Library were searched, searches of other databases (such as EMBASE) might have identified other studies. The methods of the review (i.e. study selection, data extraction) were described. No quality assessment of the included studies was reported, but only randomised placebo-controlled studies were included. The meta-analysis was appropriate and some information on the individual studies (e.g. participant characteristics) was included. The authors said that they included one large study that did not meet the inclusion criteria because it was performed on mixed (primary and secondary prevention) participants and the participants were also given antioxidants. This is problematic since it is unclear whether there were any similar studies that were not included in the review.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice

Research: The authors stated that updates of this review should establish the efficacy of different (newer) statins.

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