Effectiveness of statin therapy in adults with coronary heart disease

CRD summary
The review assessed the effectiveness of statins in treating coronary heart disease (CHD) and in preventing CHD in those at high risk. The authors found that the use of statins reduced mortality and other cardiovascular events. The evidence presented supports the conclusions. This was a well-conducted systematic review, but the authors did not discuss the quality of individual included studies.

Authors' objectives
To assess the effectiveness of statin therapy in adults with coronary heart disease (CHD).

Searching
MEDLINE (from January 1966 to January 2003) and the Cochrane Library (January 2003) were searched; the search terms were reported. The bibliographies from identified studies and reviews were also checked for additional relevant studies. Only studies published in full and in the English language were eligible for inclusion.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials with at least 100 participants per intervention arm were eligible for inclusion. The mean or median follow-up ranged from 0.3 to 6.1 years.

Specific interventions included in the review
The statins assessed in the included studies were pravastatin, simvastatin, lovastatin and fluvastatin. Nearly 90% of the participants randomised to statin were given simvastatin or pravastatin. All placebo-controlled trials used moderate to high doses of statins (20 to 80 mg), most of which were fixed doses. Where placebo was not used as the comparator, the comparators included 'usual care' (not defined), 'aggressive' versus 'moderate dose', an alternative statin, or angioplasty. Some studies used titrated doses aimed at achieving a specific low-density lipoprotein cholesterol (LDL-C), whilst others used a fixed dose. Further details of the doses used were given.

Participants included in the review
Adults with CHD, or at high risk of CHD, were eligible for inclusion. The participants were predominantly male (77%) and white (88 to 100%). The mean age of the participants was 63 years. The weighted mean baseline LDL-C concentration was 149 mg/dL (3.85 mmol/L; range: 126 to 198 mg/dL, 3.26 to 5.12 mmol/L). Most study participants had overt CHD; the 20% who did not were at high risk (i.e. had vascular disease, diabetes or hypertension, or smoked). Individuals without CHD were excluded from the main analyses. Between 23 and 24% of the participants had previous revascularisation procedures, i.e. percutaneous coronary intervention (PCI) or coronary artery bypass surgery.

Outcomes assessed in the review
Studies that reported clinical outcomes were eligible for inclusion. The primary outcome measure was CHD death or nonfatal myocardial infarction (MI). The secondary outcome measures were all-cause mortality, serum LDL-C and total cholesterol concentration.

How were decisions on the relevance of primary studies made?
Two authors independently assessed studies for relevance according to stated inclusion criteria.

Assessment of study quality
Study quality was evaluated according to Schulz's scale. Two authors may have independently assessed the studies for validity, but the authors did not state how any disagreements were resolved.
Data extraction
Two authors independently extracted the data for each study using a prospectively defined proforma, but the authors did not state how any disagreements were resolved. Data from studies in which participants did not have overt CHD were excluded. The authors estimated the number of events, using event rates for all participants, in studies where the numbers of events for statin and placebo arms were not given.

Methods of synthesis
How were the studies combined?
Data from studies using comparators of usual care, placebo and active control were pooled and reported separately. The data were pooled using a fixed-effect model to calculate the relative risk (RR) if heterogeneity was not detected.

No methods were used to describe publication bias.

How were differences between studies investigated?
The chi-squared test and scatterplots were used to investigate heterogeneity. Sensitivity analyses were carried out to assess any variability caused by different study characteristics: i.e. study duration; the inclusion of people without overt CHD; trials with CHD death or MI as the primary outcome; enrolled participants limited to those undergoing PCI; and patients with ACS. Subgroup analyses were used to assess the differing effects of statins according to statin type, and by gender, age (i.e. the elderly, although the definition of elderly varied according to individual study), occurrence of a PCI and the presence of ACS. The associations between the outcomes and statin dose, reductions in LDL levels and concomitant cardiovascular medications were investigated. Also investigated was the effect of pre-treatment LDL-C concentration on the effectiveness of statins; the effects of aggressive versus moderate LDL-C reduction regimens; and the effect of statin therapy in individuals with a baseline LDL-C concentration of less than 2.59 mmol/L. A meta-regression was used to investigate the relationship between LDL-C levels and CHD outcomes.

Results of the review
There were 69,511 participants in the 25 studies included in the review. There were 19 placebo-controlled studies (n=52,782), 3 studies of statin versus usual care (n=12,181), one of aggressive versus moderate dose of lovastatin, one of statin versus statin (simvastatin versus atorvastatin), one of statin versus PCI, and one of statin for participants with acute coronary syndromes (ACS) (n=3,076). There were 42,173 participants with overt CHD and 10,389 participants at high risk of CHD.

Statins versus placebo.
The pooled analyses showed statins reduced CHD mortality or nonfatal MI by 25% (RR 0.75, 95% confidence interval, CI: 0.71, 0.79) with an absolute risk reduction (ARR) of 3.8%. Statins also reduced all-cause mortality by 16% (RR 0.84, 95% CI: 0.79, 0.89; ARR 1.8%) and CHD mortality by 23% (RR 0.77, 95% CI: 0.71, 0.83; ARR 1.4%). The reduction in risk for these outcomes was consistent in sensitivity analyses of studies of patients with ACS, patients with PCI, and patients with high versus low use of concomitant cardiovascular medications. The authors reported that there were similar reductions in risk for outcomes of revascularisation, cerebrovascular events, and major coronary or vascular events, although no data were presented.

In women (6 studies, 7,920 participants), statins reduced CHD mortality or nonfatal MI by 25% (RR 0.75, 95% CI: 0.65, 0.86; ARR 2.8%). All-cause or CHD mortality was only reported for women in 2 studies, and no significant difference was seen.

In older people (6 studies), statins reduced CHD death or nonfatal MI (16,785 participants) by 24% (RR 0.76, 95% CI: 0.71, 0.81; ARR 4.2%), all cause mortality (4,941 participants) by 15% (RR 0.85, 95% CI: 0.73, 0.99; ARR 1.8%) and CHD death (3,942 participants) by 35% (RR 0.65, 95% CI: 0.49, 0.86; ARR 2.1%).

There were no results presented according to race as few studies provided data.

In studies of people with previous revascularisation (3,206 participants), statins reduced CHD mortality or nonfatal MI
by 33% (RR 0.67, 95% CI: 0.48, 0.93; ARR 1.7%).

Further results were presented in the paper.

Statins versus usual care (3 studies, 12,081 participants).

Compared with usual care, statins reduced CHD mortality by 31% (RR 0.69, 95% CI: 0.47, 1.01). There were no significant reductions in CHD mortality and nonfatal MI (1 study, 1,475 participants) or all-cause mortality (2 studies, 3,075 participants).

**Authors' conclusions**
The use of statins in moderate doses decreased mortality, CHD events, cerebrovascular events and cardiovascular procedures in adults with CHD by 16 to 24%. The benefits occurred within 2 years of initiating statin therapy and were found in people with pre-treatment levels of LDL-C of 100 mg/dL (less than 2.59 mmol/L), women, the elderly, and independently of concomitant CHD medication use.

**CRD commentary**
This was a detailed review with clearly stated aims and inclusion criteria. Two relevant electronic bibliographic databases were searched and the search terms were provided. However, the authors did not include unpublished studies, or studies published in abstract form only or in languages other than English. It was possible that studies were missed. Publication bias was not investigated. The methods of the review were described: the study selection, data extraction and, possibly, quality assessment processes were conducted independently. This helped reduce errors and reviewer-related bias. Some details of individual studies were given. Details of quality were not provided and did not appear to have been used to assess the effect of study quality on treatment effect. The authors assessed the statistical heterogeneity of the outcome data, and their conclusions accurately reflected the evidence presented.

The authors' overall conclusion that statins reduced morbidity and mortality did reflect the data reported. However, no data were presented for cardiovascular events or procedures, or on the impact of length of follow-up on treatment effect.

**Implications of the review for practice and research**
The authors did not state any implications for practice or further research.

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