Long-term benefit of statin therapy initiated during hospitalization for an acute coronary syndrome: a systematic review of randomized trials


CRD summary
This review concluded that statin therapy slowly produces benefit in patients with acute coronary syndromes, such that all-cause mortality, cardiovascular mortality, unstable angina and revascularisation are all reduced at around 24 months. Despite the poor reporting of some methods of the review process, the review seems generally well-conducted and the authors' conclusions are likely to be reliable.

Authors' objectives
To assess whether the initiation of statin (HMG-CoA reductase inhibitor) therapy during acute coronary syndrome (ACS) reduces long-term mortality and other adverse cardiac outcomes.

Searching
MEDLINE and the Cochrane CENTRAL Register were searched from 1996 to March 2006; the search terms were reported. Eligible studies were also cross-referenced with the Science Citation Index, and experts in the field were consulted.

Study selection

Study designs of evaluations included in the review
Randomised clinical trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies comparing statin therapy, commenced during the index hospitalisation for ACS, with less intensive lipid reduction therapy were eligible for inclusion. Studies comparing two statin therapies were included if there was a significant difference in low-density lipoprotein-cholesterol at the final follow-up. Studies in which statins were used as primary prevention were excluded. The statins reviewed were pravastatin, atorvastatin, fluvastatin and simvastatin, compared with each other, usual care or placebo.

Participants included in the review
Studies of patients with an ACS were eligible for inclusion. Studies primarily of stable patients were excluded. In the included studies, the mean age of the participants ranged from 52 to 69 years and the proportion of males from 58 to 86%. Between 0% and 85% of the participants had a prior myocardial infarction (MI), and most had an MI at the time of randomisation.

Outcomes assessed in the review
It was not clear whether the outcomes of interest were applied as inclusion criteria, but all included studies reported all-cause mortality, cardiovascular mortality, nonfatal MI, revascularisation, stroke and unstable angina requiring hospitalisation.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors assessed study validity using the Jadad checklist, a 5-point quality scale. It was unclear how many reviewers performed the validity assessment.

Data extraction
Three reviewers independently extracted the data and any discrepancies were resolved through a fourth reviewer. The numbers of events for outcomes in each arm of the trial were extracted from each study, and odds ratios (ORs) with
95% confidence intervals (CIs) were calculated.

**Methods of synthesis**

How were the studies combined?

A Mantel-Haenszel model was used to calculate a summary OR with 95% CIs. From this the number-needed-to-treat (NNT) was calculated. Publication bias was investigated through a Begg funnel plot. Mean follow-up was weighted relative to the sample size of the trial.

How were differences between studies investigated?

Statistical heterogeneity between the studies was assessed using the Q statistic. A paired t-test was used to compare mean values.

**Results of the review**

Seven RCTs (n=9,553) were included in the analysis. The sample size ranged from 70 to 4,497 patients. The duration of follow-up ranged from 6 to 24 months and completeness of follow-up from 98 to 100%.

All seven studies scored 4 or 5 on the Jadad scale, implying that they were of a high quality.

The incidence of all-cause mortality was 3.4% in the statin group versus 4.6% in the less intensive lipid reduction group at the mean follow-up of 23 months (OR 0.74, 95% CI: 0.61, 0.90, p=0.003; NNT=84). There was no significant difference in all-cause mortality at 6 and 12 months.

The incidence of cardiovascular mortality was 2.4% in the statin group versus 3.3% in the less intensive lipid reduction group at the mean follow-up of 23 months (OR 0.74, 95% CI: 0.58, 0.93, p=0.010; NNT=115). There was no difference in cardiovascular mortality at 6 and 12 months.

In the statin versus the less intensive lipid reduction group, the incidence of MI was 6.6% versus 7.0% (OR 0.94, 95% CI 0.81, 1.09, p=0.41), unstable angina that required hospitalisation 4.1% versus 5.0% (OR 0.81, 95% CI: 0.68, 0.98, p=0.027; NNT=100), revascularisation 11.2% versus 12.9% (OR 0.86, 95% CI: 0.78, 0.96, p=0.006; NNT=56) and stroke 1.1% versus 1.2% (OR 0.90, 95% CI: 0.62, 1.30, p=0.56). The only analysis to show statistical heterogeneity was that of the incidence of unstable angina that required hospitalisation.

There was no evidence of publication bias.

**Authors’ conclusions**

Initiation of statin therapy during ACS slowly produces benefit, such that all-cause mortality, cardiovascular mortality, unstable angina and revascularisation are all reduced at around 24 months.

**CRD commentary**

This review had clearly stated inclusion criteria with respect to the study design, participants and intervention, but not outcomes. Several relevant sources were searched and the potential influence of publication bias was evaluated through appropriate methods, with no evidence of publication bias detected. It was unclear whether language restrictions were applied, therefore language bias may have been introduced. The data extraction was conducted in duplicate, but it was unclear whether similar methods were used to reduce reviewer error and bias during the study selection and validity assessment processes. Validity was assessed according to published criteria. Details presented on the included studies suggest that the decision to combine some of the studies statistically was appropriate. However, the main analyses were for a weighted mean follow-up of 23 months, combining two studies with 6 months, two with 12 months, and three with 24 months’ follow-up; separate analyses were given for combining the three studies with 24 months’ follow-up. Statistical heterogeneity was assessed. Despite the lack of reporting of some parts of the review process, the review appears generally well conducted. The authors’ conclusions seem reliable based on the evidence presented.

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

The authors did not state any implications for practice or further research.
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