The effect of early, intensive statin therapy on acute coronary syndrome: a meta-analysis of randomized controlled trials

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CRD summary
This review investigated the effects of early intensive statin therapy for acute coronary syndrome. It concluded that early treatment reduces cardiovascular events with benefits observed after 6 months, but an analysis of individual patient data is needed to confirm these findings. The pooled results should be regarded with some caution because of limitations such as the variation between study results.

Authors' objectives
To determine the effectiveness of early intensive statin therapy for acute coronary syndrome (ACS).

Searching
PubMed, EMBASE, BIOSIS Previews, SciSearch, Pascal, International Pharmaceutical Abstracts and the Cochrane Controlled Trials Register were searched from January 1974 to November 2005 without any language restrictions; the search terms were reported. In addition, the references of reviewed articles were screened. Studies published only as abstracts were excluded.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible; all of the included studies were parallel trials.

Specific interventions included in the review
Studies on intensive statin therapy initiated within 14 days of hospitalisation, compared with control, were eligible for inclusion; intensive therapy was defined as a medication regimen begun at a higher than usual dose than recommended by routine treatment following National Cholesterol Education Panel guidelines. The included studies compared atorvastatin, pravastatin, simvastatin or fluvastatin with placebo, usual care, another statin or the same statin in a lower dose. Doses varied between 10 and 80 mg and in most patients treatment was initiated 1 or 2 days following hospitalisation, with a maximum of 14 days. In one study the patients also underwent a percutaneous coronary intervention.

Participants included in the review
Studies of adults (older than 18 years) with ACS were eligible. Where reported, the mean age of the patients in the included studies was 51 to 68 years.

Outcomes assessed in the review
The studies had to report clinical outcomes; trials that measured only inflammatory markers, angiogram data or atherosclerotic plaque volume were excluded. The primary outcome in the included studies was a combined end point of death, hospitalisation for recurrent ischaemia, or recurrent myocardial infarction (MI); these events were also analysed individually. Other outcomes were cardiovascular death, revascularisation by percutaneous coronary intervention or coronary artery bypass graft, reduction in low-density lipoprotein (LDL) cholesterol, and adverse events.

How were decisions on the relevance of primary studies made?
Two reviewers independently screened the papers and any disagreements were resolved by consensus.

Assessment of study quality
Two reviewers independently applied the Jadad scale and any disagreements were resolved by consensus.
Data extraction
Two reviewers independently extracted the data and any disagreements were resolved by consensus. Hazard ratios (HRs) of the combined as well as the individual outcomes of death, MI and hospitalisation for recurrent ischaemia were extracted and reported at 1, 4, 6, 12 and 24 months' follow-up. The numbers of patients at risk and events in each time period were used to estimate an overall HR using a published method.

Methods of synthesis
How were the studies combined?
The HRs were combined using a random-effects model, weighted by the inverse of the variance, and reported together with the 95% confidence interval (CI). Pooled survival curves were calculated for each outcome using the number of eligible patients and the number of events during the relevant period; the variance was calculated using exact binomial methods. The pooled survival curves were compared using log rank tests. Publication bias was assessed using linear regression with the log HR as the dependent variable and the inverse of the total sample size as the independent variable.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the I-squared statistic. A stratified analysis was used to investigate the effects of the following study characteristics: study duration, change in LDL cholesterol, time to initiation of statin therapy and study quality. Meta-regression, using the restricted maximum likelihood method, was also applied to assess the effect of these factors on the pooled results. Sensitivity analyses used a components analysis to assess each individual quality domain and each study was also excluded one at a time to see if they influenced the pooled results.

Results of the review
Thirteen RCTs (n=17,963) were included in the review.

The median Jadad score was 6 (range: 3 to 8). There was no evidence of publication bias (Peters' chi-squared test, p=0.22).

Early intensive statin therapy for ACS decreased the rate of cardiovascular events (death, MI, ischaemia) over 2 years' follow-up (HR 0.81, 95% CI: 0.77, 0.87; based on 4 studies). During the first 4 months of treatment there was no reduction in overall cardiovascular events; the benefit of early intensive statin therapy was not seen until the sixth month when there was a significant reduction in cardiovascular events (HR 0.76, 95% CI: 0.70, 0.84; 7 studies). All analyses showed evidence of statistical heterogeneity: I-squared was 94.9% at the 2-year follow-up and 92.4% at the 6-month follow-up. The meta-regression and stratified analyses did not identify any sources of heterogeneity.

When cardiovascular events were analysed as separate outcomes, similar results were seen for cardiovascular deaths and ischaemia after 24 months and significant reductions were observed for the early intensive statin therapy group. There was no reduction in MI. Those receiving early intensive statin therapy had a significantly greater reduction in LDL-cholesterol compared with the control (mean values of 34 and 6 mg/dL, respectively, p<0.001).

Safety data showed comparable tolerability for both groups. With regard to severe adverse events, three patients receiving atorvastatin were hospitalised for hepatitis, whilst rhabdomyolysis occurred in three patients receiving simvastatin.

Authors' conclusions
Early intensive statin therapy reduced death and cardiovascular events after 4 months of treatment, but a meta-analysis using individual patient data would strengthen the validity of this finding.

CRD commentary
This review addressed a clear question and stated clear inclusion criteria. The search was not restricted to English language publications, which helps prevent language bias. Studies published only as abstracts were excluded, but the
authors assessed publication bias and concluded that there was no evidence of any. Steps were taken throughout the review process to reduce errors and bias by having two reviewers independently screen articles and perform the quality assessment and data extraction. The quality of the studies was assessed, although full details were not reported; this makes it difficult for readers of the review to assess study quality. The assessment also did not seem to follow the usual scoring of the Jadad scale, and it was unclear whether the quality assessment encompassed issues relevant to RCTs such as allocation concealment.

The analyses were based on HRs but were performed using estimated values, rather than actual values as reported in the studies. There was also considerable statistical heterogeneity that could not be fully explained. Therefore, the pooled results may be unreliable, a fact which the authors acknowledge as a limitation of this meta-analysis. The evidence presented supports the authors' conclusions but the pooled results 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 a pooled analysis using patient-level data should be performed to investigate the effects of early intensive statin therapy for ACS.

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