Intensive statin therapy in acute coronary syndromes and stable coronary heart disease: a comparative meta-analysis of randomised controlled trials

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CRD summary
This review concluded that intensive-dose statin therapy reduced all-cause mortality in patients with recent acute coronary syndrome but not in patients with stable coronary heart disease, compared with moderate-dose statin therapy. The review was well-conducted and these conclusions are likely to be reliable.

Authors' objectives
To compare the effect of intensive dose versus moderate dose statin therapy on all-cause mortality in patients with recent acute coronary syndrome or stable coronary heart disease.

Searching
EMBASE, Cochrane Central Register of Controlled Trials, Database of Reviews of Abstracts of Effects (DARE), the ACP (American College of Physicians) Journal Club and MEDLINE (including the PubMed ‘related articles’ feature) were searched from inception to March 2006. Search terms were reported. The following websites were searched: www.clinicaltrials.gov, www.clinicaltrialresults.org, www.cardiosource.com, www.medscape.com, www.theheart.org, and www.lipidsonline.org. References of retrieved articles were checked, abstracts from major cardiology conferences in North America and Europe were searched and investigators were contacted to seek further studies. There were no language restrictions.

Study selection
Randomised controlled trials (RCTs) comparing intensive versus moderate statin therapy among patients with documented recent acute coronary syndrome or stable coronary heart disease were eligible for inclusion. Included trials were required to report at least six months of follow up.

Intensive statin therapy was defined as simvastatin or atorvastatin 80 mg/day or rosuvastatin 20 to 40 mg/day. Moderate therapy was defined as pravastatin, lovastatin or fluvastatin ≤ 40 mg/day, simvastatin ≤ 20 mg/day, atorvastatin ≤10 mg/day, or rosuvastatin ≤ 5 mg/day.

The primary outcome was all-cause mortality. Secondary outcomes were: major adverse cardiovascular events (primarily cardiovascular death, acute coronary syndrome or stroke); hospital admissions for heart failure; adverse hepatic events (increase in alanine/aspartate aminotransferase over three times the upper limit of normal levels); and adverse muscular events (increase in rhabdomyolysis or creatine kinase over 10 times the upper limit of normal levels). Where trials included the need for revascularisation or resuscitated cardiac arrest in their definition of major adverse cardiovascular events, these were also included.

The mean age of trial participants was 56 to 64 years and 14% to 28% were women; 12% to 24% had diabetes mellitus and 17% to 100% had a history of myocardial infarction. Use of aspirin and β-blockers was similar in all trials, but use of angiotensin-converting enzyme inhibitors or angiotensin receptor blocker varied (range 24% to 84%), as did prior statin use (range 0% to 76%). All but one of the included trials evaluated atorvastatin in the intensive dose regime. One trial evaluated simvastatin. Mean duration of follow-up was two years in acute coronary syndrome studies and 4.7 years in stable coronary heart disease studies.

Three reviewers selected studies for inclusion.

Assessment of study quality
The following features of study validity were assessed: blinding, allocation concealment, completeness of follow-up, use of intention to treat analysis, similarity of groups at baseline, and equality of treatment apart from the intervention.

The authors did not state how the assessment was performed.
Data extraction
Odds ratios and 95% confidence intervals were calculated from the numbers of events in the control and intervention groups of each study. Data were extracted independently by two reviewers using a standardised protocol.

They were checked by a third reviewer, with disagreements resolved by consensus.

Methods of synthesis
Data were combined using a random-effects model to calculate pooled odds ratios and 95% confidence intervals. Numbers-needed-to-treat or numbers-needed-to-harm, and absolute rates for adverse events, were also reported. Most results were sub-grouped by patient diagnosis (recent acute coronary syndrome or stable coronary heart disease). Heterogeneity was assessed with the $I^2$ statistic ($I^2$ over 50% denoting significant heterogeneity). Sensitivity analyses were used to investigate whether results for mortality differed by cause (i.e. coronary heart disease/non-coronary heart disease) or when small trials were excluded.

Results of the review
Six randomised controlled trials (RCTs) were included in the review (n=28,505 participants). Five studies were double-blinded, four trials used intention-to-treat analysis, and four trials followed-up at least 97% of participants (range 77% to over 99%).

Intensive dose versus moderate dose statins for recent acute coronary syndrome (two RCTs, n=8,659 participants):
Intensive dose therapy significantly reduced all cause mortality (odds ratio 0.75, 95% confidence interval (CI): 0.61 to 0.93; p=0.010, number-needed-to-treat 90) and hospital admissions for heart failure (odds ratio 0.63, 95% CI: 0.46 to 0.86, p=0.004) among patients with recent acute coronary syndrome. Risk of major adverse cardiovascular events was not significantly reduced (odds ratio 0.86, 95% CI: 0.73 to 1.01; p=0.07), but there was significant heterogeneity for this outcome ($I^2=63\%$).

Intensive dose versus moderate dose statins for stable coronary heart disease (four RCTs, n=19,846 participants):
Intensive dose therapy did not significantly reduce all cause mortality (odds ratio 0.99, 95% CI: 0.89, 1.11; p=0.90, four RCTs) among patients with stable coronary heart disease. However, it did significantly reduce the risk of major adverse cardiovascular events (odds ratio 0.82, 95% CI: 0.75 to 0.91; p<0.0001, four RCTs) and hospital admission for heart failure (odds ratio 0.77, 95% CI: 0.64, 0.92, p=0.003, two RCTs).

When both groups were pooled, the numbers-needed-to-treat to prevent one major adverse cardiovascular event was 46 and to prevent one hospital admission was 112.

Adverse events:
When the acute coronary syndrome and coronary heart disease groups were pooled, intensive therapy significantly increased the risk of an adverse hepatic event (odds ratio 3.73, 95% CI: 2.11 to 6.58; p<0.00001, number-needed-to-harm 96, absolute risk 1.4%, five RCTs); but this analysis showed significant heterogeneity ($I^2=63\%$). Intensive therapy did not significantly increase the risk of an adverse muscular event (odds ratio 1.96, 95% CI: 0.50 to 7.63; p=0.33, absolute risk 0.11%, five RCTs). Sensitivity analyses indicated that intensive-dose statins reduced coronary heart disease mortality but not all-cause mortality, compared to moderate-dose statins. None of the sensitivity analyses substantially affected the main findings.

Authors' conclusions
Intensive-dose statin therapy reduced all-cause mortality in patients with recent acute coronary syndrome but not in patients with stable coronary heart disease, compared with moderate-dose statin therapy.

CRD commentary
The objectives and inclusion criteria of the review were clear. A wide range of relevant sources was searched without restriction by language or publication status. Relevant criteria were used to assess study validity. Steps were taken to minimise error and bias by having more than one reviewer involved in study selection and data extraction, but it was not stated whether this also applied to validity assessment. Suitable statistical methods appear to have been used to combine
studies, and to assess for heterogeneity and small-study bias. The authors discussed possible sources of bias and noted that their findings may not be generalisable to all statins. The review was well-conducted and the authors’ conclusions are likely to be reliable.

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

**Practice:** The authors stated that patients with recent acute coronary syndrome should receive intensive-dose statin therapy, while among those with stable coronary heart disease, its use should be determined on a case-by-case basis.

**Research:** The authors stated that a cost-effectiveness analysis of intensive-dose statin therapy for patients with recent acute coronary syndrome is needed.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.