The efficacy and safety of intensive statin therapy: a meta-analysis of randomized trials

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CRD summary
This review concluded that higher dose intensity statin therapy was safe, well-tolerated and provided incremental benefits over and above those of lower dose intensity statin therapy in the secondary prevention of myocardial infarction and stroke in patients with established coronary artery disease. This was a well conducted systematic review and the conclusions were likely to be reliable.

Authors' objectives
To assess the safety, efficacy and clinical effectiveness of different intensities of statin therapy for patients with coronary artery disease.

Searching
MEDLINE (from 1966), EMBASE (from 1988) and the Cochrane Central Register of Controlled Trials were searched for relevant studies in August 2006; searches were updated in July 2007. Search terms were reported in an appendix to the review. The authors also performed a cited-reference search in Web of Science, searched the reference lists of all included studies and relevant review articles, and contacted experts in the field for additional relevant studies. Studies published only as abstracts were not included in the review.

Study selection
Randomised controlled trials (RCTs) that compared different regimens of statin therapy intensity in adults with coronary artery disease and that reported cardiovascular events or mortality were eligible for inclusion in the review. Studies that used statin doses much lower than currently used in clinical practice were excluded from the review.

The included studies enrolled patients with chronic coronary artery disease or after acute coronary syndrome. Where stated, the average age of participants ranged from 56 to 72 years. Most participants were male (69 per cent to 86 per cent). A variable percentage of patients had undergone prior coronary artery bypass graft surgery and prior angioplasty. Most patients received aspirin and beta-blockers. Between 24 per cent and 71 per cent of patients also received ACE inhibitors. Mean baseline low-density lipoprotein (LDL) cholesterol ranged from 2.74 mmol/L to 3.9 mmol/L. All but one study compared pravastatin (40 mg), atorvastatin (10 mg), simvastatin (20 mg) or lovastatin (5 mg) with atorvastatin 80 mg; one study used simvastatin 80 mg as the higher-dose intervention. Follow-up ranged from one to 4.9 years.

Two reviewers independently assessed studies for inclusion in the review; disagreements were resolved by consensus.

Assessment of study quality
Two reviewers independently assessed the validity of the included studies using the Jadad scale; disagreements were resolved by consensus. In addition to items on the Jadad scale, the authors also reported: whether patients were recruited from a primary care setting; the proportion of all patients screened that were randomised to the study; whether duration of follow-up was adequate; whether the analysis was intention-to-treat; whether there was a run-in period before randomisation; and the proportion of patients receiving statins before being enrolled in the trial.

Data extraction
Data were extracted on outcomes that were objectively defined and common among studies (such as death, myocardial infarction and stroke) in an intention-to-treat format. Studies reported composite primary outcomes, but these differed between studies and so were not extracted. Two reviewers independently performed data extraction; disagreements were resolved by consensus.

Methods of synthesis
Odds ratios (OR) were synthesised using the DerSimonian and Laird random-effects model. The $I^2$ statistic was used to
assess heterogeneity. Subgroup analyses were used to examine the influence of presenting condition and quality variables.

**Results of the review**

Seven RCTs were included in the review (n=29,395). Jadad validity assessment scores ranged from 3 to 5 (out of 5).

LDL cholesterol was statistically significantly lower for patients receiving the higher dose intensity of statin compared with those receiving the lower dose intensity (weighted mean difference 0.72 mmol/L, 95% CI: 0.60, 0.84).

There was no significant difference in non-cardiovascular mortality or all-cause mortality between patients receiving the higher or lower dose intensities of statin, however, there was significant heterogeneity among trials for all-cause mortality ($I^2 = 42\%$). In a subgroup analysis of the two studies that enrolled patients after acute coronary syndromes (as opposed to those with chronic coronary artery disease), statin therapy was associated with a significant reduction in all-cause mortality (OR 0.75, 95% CI: 0.61, 0.93).

Myocardial infarction or coronary death was statistically significantly lower for patients receiving the higher dose intensity of statin compared with those receiving the lower dose intensity (OR 0.83, 95% CI: 0.77, 0.91), as was the incidence of stroke (OR 0.82, 95% CI: 0.71, 0.95). Four trials reported rates of major cardiovascular events (myocardial infarction, coronary death or stroke), which was also statistically significantly lower in patients receiving the higher dose intensity of statin (OR 0.80, 95% CI: 0.71, 0.90).

Aminotransferase levels were statistically significantly higher with more intensive statin therapy (six RCTs, OR 4.14, 95% CI: 2.30, 7.44).

Myopathic adverse events and discontinuation rates attributed to drug-related adverse events were not significantly different between the higher dose intensity and lower dose intensity groups. Sensitivity analyses assessing the effects of the quality variables showed that none of the assessed variables influenced the outcomes.

**Authors’ conclusions**

More intensive statin therapy was safe and well-tolerated, and provided incremental benefits over and above those of lower-intensity statin therapy in the secondary prevention of myocardial infarction and stroke in patients with established coronary artery disease.

**CRD commentary**

The objectives and inclusion criteria were clearly stated. A number of databases were searched for relevant studies and experts in the field were contacted to try to identify additional studies, thus reducing the potential for publication bias. The authors did not state whether any language restrictions were applied. Two reviewers independently assessed studies for inclusion in the review and performed data extraction and validity assessment, reducing the potential for reviewer bias and error. The validity of the included studies was assessed using appropriate criteria. The synthesis appears to have been appropriate. Heterogeneity was assessed and explored when significant. The authors acknowledged that although more intensive statin therapy was well-tolerated in the included studies, adverse events may be more common in clinical practice as the included studies excluded just over half of all screened patients due to comorbidities or use of concomitant medications. This was a well-conducted systematic review and the authors’ conclusions were likely to be reliable.

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

Practice: The authors stated that their review supported prescribing more intensive statin regimens for patients with established coronary artery disease, particularly those with acute coronary syndromes.

Research: The authors stated that large trials were needed to assess the clinical effectiveness and safety of combination therapy. They also stated that studies were required to define optimal LDL cholesterol targets, and that assessment of intensive statin therapy in patients without coronary artery disease, but with multiple atherosclerotic risk factors, was a priority area.
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