Meta-analysis of drug-induced adverse events associated with intensive-dose statin therapy

CRD summary
The authors concluded that intensive-dose statin therapy significantly reduced the risk of a serious cardiovascular event but increased the risk of a statin-induced adverse event, compared with moderate dose therapy. The reliability of these conclusions is uncertain due to methodological weaknesses in the review such as failure to assess study validity or check for heterogeneity between the studies.

Authors' objectives
To quantify the incremental risks associated with intensive-dose statin therapy, compared with moderate-dose statin therapy.

Searching
MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials were searched from 1995 to 2006. Search terms were reported. The reference lists of studies identified and of the National Cholesterol Education Program Adult Treatment Panel III guidelines were hand searched.

Study selection
Prospective randomised controlled trials (RCTs) that compared intensive-dose statin therapy with moderate-dose therapy for the reduction of secondary cardiovascular (CV) events, among patients with acute coronary syndrome (ACS) or stable coronary artery disease (CAD), were eligible for inclusion. Studies were required to report CV death, fatal or non-fatal myocardial infarction (MI), stroke or all-cause mortality (ACM). They were also required to report adverse events.

The following outcomes were reported in the review: ACM, CV death, non-fatal MI, stroke, creatine kinase (CK) levels at or in excess of ten times the upper limit of normal (ULN) (with or without myalgia), alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels at or in excess of three times the ULN, rhabdomyolysis and any drug-induced adverse events (including those requiring discontinuation).

The mean age of participants in the included studies ranged from 58 to 62 years and 75% to 81% were male. All studies enrolled patients with either recent ACS or stable CAD, but clinical characteristics differed widely across all studies. Overall 17% to 58% of participants had a history of MI, 15% to 54% had a history of angioplasty, 4% to 46% had had coronary artery bypass surgery, 33% to 54% were hypertensive, 12% to 23% had diabetes and 13% to 41% were current smokers. Most participants were receiving aspirin and beta-blockers. All studies prohibited concomitant lipid-lowering therapy and statin use at baseline. Two studies reported previous statin use by participants (25% and 75%). The high dose group received atorvastatin or simvastatin 80 milligrams (mgs) and the moderate dose group received atorvastatin 10 mg, simvastatin 20 mg or pravastatin 40 mgs. Mean follow-up was 3.4 years (range 2- 4.9 years).

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 did not state that they assessed validity.

Data extraction
Odds ratios (ORs) were calculated from the numbers of events in the control and intervention groups of each study, with 95% confidence intervals (CIs). Data were extracted independently by two reviewers. It was unclear how discrepancies were resolved.

Methods of synthesis
Data were combined using a DerSimonian and Laird random effects model to calculate pooled ORs and 95% CIs, absolute risk differences and number needed to treat (NNT) or number needed to harm (NNH, i.e. the number of
patients needing to be treated with higher dose statins in order to cause one additional beneficial or harmful event.
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rials were subgrouped by patient diagnosis (CAD or ACS) for CV outcomes.

Results of the review
Four RCTs were included in the review (n=27,548); sample sizes ranged from 4,162 to 10,001.

There was a significant increase in risk in the intensive-dose versus moderate-dose statin group for the following outcomes: drug-induced adverse event (OR 1.44, 95% CI: 1.33, 1.55, p<0.001; NNH 30, 95% CI: 24, 37), drug-induced adverse event requiring discontinuation of therapy (OR 1.28, 95% CI: 1.18, 1.39, p≤0.001; NNH 47, 95% CI: 35, 69), AST or ALT elevation ≥3 times ULN (OR 4.84, 95% CI: 3.27, 6.16, p≤0.001; NNH 86, 95% CI: 72, 106), and CK elevation ≥10 times ULN (OR 9.97, 95% CI: 1.28, 77.92, p=0.028; NNH 1,532, 95% CI: 890, 5,528).

There was no significant difference between the groups in risk of rhabdomyolysis or ACM.

There was a decreased risk in the intensive-dose versus moderate-dose statin group for the following: CV death (OR 0.86, 95% CI: 0.75, 0.99, p=0.031; NNT 229, 95% CI: 119, 2844), MI (OR=0.84, 95% CI: 0.76, 0.93, p<0.001; NNT 99, 95% CI: 63, 224) and stroke (OR 0.82, 95% CI: 0.72, 0.94, p=0.004; NNT 166, 95% CI: 98, 526).

The findings suggested that treating 1000 patients with intensive-dose rather than moderate-dose therapy would prevent 4 additional CV deaths, 10 MIs and 6 strokes, while causing 33 additional adverse events (21 requiring drug discontinuation). For every CV event prevented by intensive-dose compared to moderate-dose therapy, eight patients could be expected to have an adverse event of any type, five a potentially serious adverse event and three an AST or ALT elevation ≥3 times ULN.

Other results were reported in the review.

Authors’ conclusions
Intensive-dose statin therapy significantly reduced the risk of a serious cardiovascular event but increased the risk of a statin-induced adverse event, compared with moderate dose therapy.

CRD commentary
The authors’ objectives and inclusion criteria were clear and relevant sources were searched for studies. However, no specific attempts were made to locate unpublished studies, so the review was prone to publication bias. No formal test for publication bias was conducted. It was unclear whether the search was restricted by language, thus language bias cannot be ruled out. Steps were taken to minimise error and bias by having more than one reviewer extract data but it is unclear whether this also applied to study selection. It does not appear that study validity was systematically assessed and no methodological details about the studies were presented. This makes it difficult to assess the reliability of the evidence presented. Suitable statistical techniques appear to have been used to pool the studies and subgroup analysis was used to identify differences between the studies in CV outcomes. However no formal tests for heterogeneity were reported and the effect measures for individual study results were not reported, so it was unclear whether findings were consistent across studies. CIs were wide for some study outcomes and there were clinical differences between the studies in baseline characteristics, which suggest potential heterogeneity. The reliability of the authors’ conclusions is uncertain due to methodological weaknesses in the review such as failure to assess study validity or check for heterogeneity between the studies.

Implications of the review for practice and research
Practice: the authors stated that most patients receiving statin therapy should receive moderate-dose therapy, while intensive-dose therapy should be used only for the highest-risk patients. Providers and pharmacists should be vigilant for adverse events in patients on high-dose statins and should reduce the dose, change the statin or discontinue the therapy if such events occur.
Research: the authors did not state any implications for research.

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