Impact of statin dosing intensity on transaminase and creatine kinase

Dale K M, White C M, Henyan N N, Kluger J, Coleman C I

CRD summary
The authors concluded that higher intensity statin therapy significantly increases the incidence of transaminase and creatine kinase elevations. Higher intensity hydrophilic statins appear more likely to be associated with increases in transaminase, whereas higher intensity lipophilic statins appear more likely to be associated with increases in creatine kinase. Overall, the review was well-conducted and these conclusions are likely to be reliable.

Authors' objectives
To compare the effect of higher versus lower intensity statin therapy on liver and muscle toxicity.

Searching
MEDLINE (from 1966), EMBASE (from 1990), CINAHL (from 1982), the Web of Science (from 1994) and the Cochrane Library were searched to January 2006; the search terms were reported. The U.S. Food and Drug Administration website was also searched, and the references of relevant articles were reviewed. The search was limited to studies published in English.

Study selection
Randomised controlled trials (RCTs) comparing higher versus lower intensity statin therapy were eligible for inclusion, provided they included at least 100 participants. The interventions in the included studies comprised atorvastatin, pravastatin (hydrophilic agents), simvastatin and lovastatin (lipophilic agents). The studies compared different doses of the same drug, or high doses of atorvastatin with moderate doses of simvastatin or pravastatin. The following doses (higher/lower) were used: atorvastatin (80/10 mg), simvastatin (40 to 80 mg/20 to 40 mg), lovastatin (76/4 mg), pravastatin (only used in lower intensity arm, 40 mg). The study size varied from 161 to over 10,000 participants. Eligible studies were required to report hepatic or muscle toxicity as a primary or secondary outcome, measured by rates of elevation in aspartate aminotransferase, alanine aminotransferase or creatine kinase (CK), and to have a mean or median follow-up of at least 48 weeks. The duration of follow-up ranged from 1 to 5 years in the included studies. The included studies defined elevated transaminases as more than two or three times the upper limit of normal, while CK elevations were defined as more than three times or more than ten times the upper limit of normal. There were no specific inclusion criteria with respect to the participants. The participants in the included studies were predominantly male (78%) with a mean age of 48 to 62 years. Where stated, 3 to 100% of the participants had a history of myocardial infarction and 2 to 24% had diabetes.

Three reviewers independently selected studies for inclusion.

Assessment of study quality
Study quality was evaluated using the Jadad scale, which measures adequacy of randomisation, blinding, and the management of withdrawals and drop-outs. Each study was awarded a score out of a maximum of 5 points.

The authors did not state clearly how the validity assessment was performed.

Data extraction
Risk ratios (RRs) with 95% confidence intervals (CIs) were calculated for all outcomes. Where there were no events in the control group, a nominal value (0.5) was added to all 2x2 cells to enable calculation of an effect estimate. Statistical heterogeneity was assessed using the Q statistic (with p<0.1 denoting statistical significance) and by visual inspection of L'Abbe plots. Funnel plots and Egger's weighted regression test were used to assess publication bias (with p<0.05 denoting statistical significance).

Three reviewers independently extracted the data, with any discrepancies resolved by consensus.
Methods of synthesis

The RRs were pooled using the random-effects model of DerSimonian and Laird. Sensitivity analyses were conducted to assess the effect of using a fixed-effect model and of excluding studies with a Jadad score of less than 3 (denoting a higher risk of bias). Additional analyses were conducted, stratifying the studies by the type of statin used (hydrophilic or lipophilic).

Results of the review

Nine RCTs were included (n=30,653; based on the table of studies, which differs from the text). Three RCTs had Jadad scores of 5, one scored 4, three scored 3 and two scored 2.

All statins (9 RCTs, n=30,653): transaminase elevations were significantly higher in the higher intensity group than in the lower intensity group, at 1.5% versus 0.4% (RR 3.10, 95% CI: 1.72, 5.58). This finding had significant statistical heterogeneity as measured by the Q test (p=0.002), though none was evident on the L'Abbe plot. There was no evidence of publication bias for this finding with Egger's test, but it could not be ruled out on viewing the funnel plot. No statistically significant difference was found between the groups in the incidence of CK elevations when a random-effects model was used. The sensitivity analysis using a fixed-effect model did not change the statistical significance of the findings for transaminase elevations, but resulted in a statistically significant difference between the groups in the incidence of CK elevations (RR 3.20, 95% CI: 1.17, 8.74).

Hydrophilic statins (5 RCTs, n=15,592): transaminase elevations were significantly higher in the higher intensity group than in the lower intensity group (RR 3.54, 95% CI: 1.83, 6.85). There were no CK elevations in either group.

Lipophilic statins (2 RCTs, n=5,848): CK elevations were significantly higher in the higher intensity group than in the lower intensity group (RR 6.09, 95% CI: 1.36, 27.35), but no significant difference was found between the groups in transaminase elevations.

Sensitivity analysis by Jadad score: the exclusion of studies with a score of less than 3 did not change the statistical significance of the results.

Authors' conclusions

Higher intensity statin therapy significantly increases the incidence of transaminase and CK elevations. It appears that higher intensity hydrophilic statins are more likely to be associated with increases in transaminase, whereas higher intensity lipophilic statins are more likely to be associated with increases in CK.

CRD commentary

The objectives and inclusion criteria of the review were clear and relevant sources were searched, although the restriction to studies published in English means that there is the possibility of publication and language bias. Steps were taken to minimise the potential for error and bias in the review process, by having more than one reviewer independently select studies and extract the data. It is unclear whether this also applied to the assessment of study validity. Relevant criteria were used to assess study validity, though it is possible that other differences in validity which were not assessed, such as allocation concealment, may be significant predictors of outcome. Appropriate statistical methods were used to pool the studies and to assess heterogeneity, and potential publication bias and possible reasons for variations in findings were addressed in the text. Overall, 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 where there are potential safety concerns with statins, clinicians may be able to maintain higher dose therapy by switching between classes of the drug. When prescribing statins for a patient at risk of muscle toxicity (e.g. with a small frame), a higher intensity therapy with a hydrophilic statin could be considered because it does not increase the risk of muscle toxicity compared with a modest intensity statin. For patients experiencing a transaminase elevation with higher intensity hydrophilic statins, it may be worth trying a higher intensity lipophilic statin once the elevation has resolved, before opting for lower intensity therapy.
Research: The authors did not state any implications for research.

**Funding**
Not stated.

**Bibliographic details**

**PubMedID**
17679130

**DOI**
10.1016/j.amjmed.2006.07.033

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Atorvastatin Calcium; Creatine Kinase /blood; Heptanoic Acids /administration & dosage; Humans; Hydroxymethylglutaryl-CoA Reductase Inhibitors /administration & dosage; Liver Function Tests; Lovastatin /administration & dosage; Pravastatin /administration & dosage; Pyrroles /administration & dosage; Randomized Controlled Trials as Topic; Simvastatin /administration & dosage; Transaminases /blood

**AccessionNumber**
12007002885

**Date bibliographic record published**
09/08/2008

**Date abstract record published**
03/11/2008

**Record Status**
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.