Clinical benefit of statin pretreatment in patients undergoing percutaneous coronary intervention: a collaborative patient-level meta-analysis of 13 randomized studies

CRD summary
This individual patient data review concluded that high-dose statin pretreatment led to a significant reduction in periprocedural myocardial infarction and 30-day adverse cardiac events in patients undergoing planned percutaneous coronary intervention for heart disease. The authors’ conclusions reflect the evidence presented and, despite the potential for reviewer error and bias in review processes, are likely to be reliable.

Authors’ objectives
To assess the efficacy of high dose statin pre-treatment on cardiac events in patients undergoing percutaneous coronary intervention using individual patient data.

Searching
PubMed was searched from 1996 to 2010 for relevant studies; search terms were reported. Presentations at major cardiology conferences and official web sites were searched and meetings were attended to identify further studies. Cited references and reference lists of retrieved studies were also scanned.

Study selection
Prospective randomised controlled trials (RCTs) that compared high dose statin versus no statin or low dose statin pre-treatment in patients who were undergoing percutaneous coronary intervention were eligible for the review. The primary outcomes were periprocedural myocardial infarction and incidence of major adverse cardiac events at 30 days.

In the included trials, 28% of patients had diabetes mellitus. Approximately half of the patients were 65 years or older. The proportion of men ranged from 70% to 75%. Included patients had either chronic stable angina or acute coronary syndrome. Most included patients were naive to statins at the intervention. Antithrombotic therapy prior to percutaneous coronary intervention was mostly with unfractionated heparin but varied in dose and administration. Statin therapy included atorvastatin, simvastatin, pravastatin, fluvastatin and rosuvastatin; doses and duration of therapy varied. Control groups either had placebo, low doses of statins or no statin pre-treatment. Follow up was in hospital or at 30 days or at six months.

The authors did not state how many reviewers selected studies for the review.

Assessment of study quality
Trials were assessed for quality; criteria included adequacy of allocation concealment and use of intention-to-treat analyses.

All data were verified thoroughly for consistency using logical checking, with any disagreements resolved by the trial investigators.

The authors did not state how many reviewers assessed studies for quality.

Data extraction
Individual patient level outcome data were requested from the principal investigators of the included trials. Outcome data collected included: levels of creatine kinase (subtype MB) and troponin before and after intervention; periprocedural high-sensitivity C-reactive protein levels; and occurrence of death, stent thrombosis, unplanned target-vessel revascularisation, myocardial infarction up to 30 days or drug-related side effects. From 13 trials, investigators from 12 consented to provide data.

For each trial, percentages were extracted for discrete data, mean or medians with standard deviations were extracted for continuous data, and odds ratios (ORs), together with 95% confidence intervals (CIs), were calculated.
Standard definitions were applied for the primary outcomes, regardless of how they were defined in individual trials. Periprocedural myocardial infarction was defined as postintervention creatine kinase-MB increase three time or over the upper limit of normal or a 20% or more increase from the baseline value in creatine kinase-MB or troponin levels in the second sample drawn after three to six hours. Major adverse cardiac events was defined as death, myocardial infarction or target-vessel revascularisation by 30 days. Other related outcomes were assessed. Outcomes were evaluated according to how they were defined in the individual trial.

It appeared that least two reviewers were involved in data extraction, as disagreements were resolved by the trial investigator.

**Methods of synthesis**

Two types of analysis were performed: a patient-level pooled analysis and a trial-level meta-analysis. For the patient-level analysis, odds ratios and 95% confidence intervals were calculated according to an intention-to-treat strategy. Pooled means and medians were compared between groups in narrative format.

Differences in categorical variables between groups were compared with a $\chi^2$ test or Fisher exact test.

Subgroup analyses were undertaken for index event of stable angina versus acute coronary syndrome, use of glycoprotein IIb/IIIa inhibitors, age, sex, diabetes mellitus versus no diabetes, single vessel versus multivessel intervention, and presence or absence of elevated C-reactive protein.

Trial-level meta-analyses were performed using the event rates in the high-dose statin and control arms for each trial with a fixed-effect model.

Heterogeneity was assessed using $\chi^2$ and $I^2$.

Publication bias was assessed by funnel plot analysis.

**Results of the review**

Thirteen RCTs (3,341 patients) were included in the review. One trial (200 patients) did not contribute data to the patient-level meta-analyses.

**Periprocedural outcome:** In patient-level analysis, high-dose statin pretreatment of patients undergoing percutaneous coronary intervention was associated with a significant reduction in the rate of periprocedural myocardial infarction (OR 0.54, 95% CI 0.42 to 0.70; 12 RCTs) compared with control. This result was consistent in trial-level analysis (OR 0.56, 95% CI 0.44 to 0.71; 13 RCTs). There was no significant heterogeneity.

**Adverse events at 30 days:** In trial-level analysis, high-dose statins were associated with a significant reduction in major adverse cardiac events (including periprocedural myocardial infarction) at 30 days follow-up (OR 0.56, 95% CI 0.44 to 0.71; 13 RCTs) compared with control; there was no significant heterogeneity. When only spontaneous myocardial infarctions were counted, there was a non-significant trend favouring high-dose statins (OR 0.44, 95% CI 0.19 to 1.01; 13 RCTs).

**C-reactive protein levels:** In subgroup analyses, the reduction in the incidence of periprocedural myocardial infarction with high-dose statins was greater in patients with elevated C-reactive protein levels (OR 0.32, 95% CI 0.18 to 0.58) than in patients with normal C-reactive protein levels (OR 0.69, 95% CI 0.50 to 0.95) (p value for quantitative interaction was 0.025).

Periprocedural myocardial infarction protection with high-dose statins was generally maintained across other subgroups of patients. However, for patients older than 65 years, patients with acute coronary syndrome, multivessel percutaneous coronary intervention, and patients receiving IIb/IIIa inhibitors, the benefit with high-dose statins was not statistically different between groups.

The results of other related outcomes were presented in the review.

There was no evidence of publication bias.
Authors' conclusions
High-dose statin pretreatment significantly reduced periprocedural myocardial infarction and 30 day adverse cardiac events in patients undergoing percutaneous coronary intervention.

CRD commentary
The review addressed a clear research question, supported by appropriate inclusion criteria. A range of relevant sources, including attempts to find unpublished studies, were used to identify studies. The authors did not report using methods designed to reduce reviewer bias and error (independent duplicate checking) at any stage of the review process.

Limited quality assessment of the included trials was performed; the results of the analysis were not reported, so it was difficult to assess the reliability of results and whether these varied according to quality. It was not clear how standard IPD data checking and cleaning procedures were performed. Although the included trials used different definitions of myocardial infarction, the authors applied standard definitions to categorise the primary outcomes to enhance comparability between trials.

Patient-level data were sought from trial investigators. In all but one trial, trialists provided data for patient-level meta-analysis, so the reliability of the patient-level findings was unlikely to have been markedly compromised. Both patient-level and trial-level meta-analyses were performed and their results were similar. Assessment of heterogeneity and publication bias were appropriate; no evidence of either was found. Variation in the clinical presentation of participants, doses of statins, time points for measurement of outcomes, and antithrombotic prophylaxis varied between trials; this did not appear to influence overall results. Subgroup and sensitivity analyses were undertaken to test the stability of the results. The benefits of high-dose statins generally persisted, but some of these analyses were underpowered because of low event rates.

The authors' conclusions reflect the evidence presented and, despite the potential for bias in review processes, are likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that a strategy of high-dose statin pretreatment (such as atorvastatin 80mg or rosuvastatin 40mg) should be used routinely in patients undergoing percutaneous coronary intervention, irrespective of clinical presentation and chronic statin therapy.

Research: The authors stated that further research was required with larger numbers of patients to assess potential benefits in subgroups of patients, such as those with acute coronary syndrome.

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