Effect of statins on atrial fibrillation after cardiac surgery: a duration- and dose-response meta-analysis

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CRD summary
This well-conducted review concluded that evidence suggested statins were associated with reduced risk of postoperative atrial fibrillation and shorter hospital stay after cardiac surgery, but as evidence came from small trials, proof was not definitive. The authors' conclusions, which acknowledge the limitations of the evidence, are likely to be reliable.

Authors' objectives
To assess the effects of statins on postoperative atrial fibrillation and hospital stay after cardiac surgery.

Searching
MEDLINE (1966 to August 2009) and the Cochrane Central Register of Controlled Trials (CENTRAL, 2009, Issue 2) were searched. Search terms were reported. No language restrictions were applied. Google Scholar and the reference lists of identified trials and reviews were checked.

Study selection
Randomised controlled trials (RCTs) that compared statins with placebo or open label in patients after cardiac surgery were eligible for inclusion. Trials had to report on the incidence of postoperative atrial fibrillation, length of hospital stay, or intensive-care unit stay. Incidence of atrial fibrillation was as defined in the included trials.

In the included trials, the mean age of participants ranged from 59 to 68 years; 61 to 86% were men. Some participants had diabetes or history of previous myocardial infarction. Most participants underwent on-pump coronary artery bypass grafting; one trial used off-pump CABG, and another included valve surgery. Perioperative treatment details were reported. Statins used included fluvastatin (80mg), pravastatin (40mg), rosuvastatin (20mg), atorvastatin (20 and 40mg) and simvastatin (20mg). Preoperative statin duration ranged from two days to four weeks. Some participants were also taking beta-blockers, coronary vasodilators (amiodarone) and/or angiotensin-converting enzyme inhibitors. Use of amiodarone and beta-blockers was inconsistently reported in included trials.

Three reviewers independently assessed studies for inclusion. Disagreements were resolved by consensus.

Assessment of study quality
Quality was assessed according to methods of randomisation, random allocation concealment, masking of treatment allocation, blinding, and reporting of withdrawals. The maximum Jadad score was 5 points.

Two reviewers assessed the quality of studies. Disagreements were resolved by consensus.

Data extraction
Relative risk (RR) and 95% confidence intervals (CI) were calculated for dichotomous data and mean differences and 95% confidence intervals for continuous data. The effect of using a fixed-effect method was also investigated.

Dosages were standardised to atorvastatin equivalent ratios (i.e. atorvastatin 10mg equivalent to simvastatin 5 to 20mg, pravastatin 10 to 40mg or fluvastatin 20 to 80mg; atorvastatin 20mg equivalent to simvastatin 40mg, pravastatin 80mg, or rosuvastatin 5mg; atorvastatin 40mg equivalent to simvastatin 80mg or rosuvastatin 10mg; atorvastatin 80mg equivalent to rosuvastatin 20mg). Authors were contacted for additional data.

Two reviewers independently extracted data. Disagreements were resolved by consensus.
Methods of synthesis
Pooled relative risks and 95% confidence intervals, and weighted mean differences (WMDs) and 95% confidence intervals were calculated using a random-effects model. Where there was no event in a single arm of a trial, 0.5 was added to each cell to facilitate analyses. Absolute risk reductions and numbers needed to treat (NNT) were calculated. Heterogeneity was assessed using the \( I^2 \) statistic.

Subgroup analyses were carried out based on type of surgery (involvement of valve surgery) and surgical technique (excluding those that used off-pump methods). Sensitivity analyses investigated differences in methodological quality (excluding those with a Jadad score below 3), and excluding those trials where the control rates of atrial fibrillation were at the extreme ends or outside the norm. Meta-regression was used to investigate the effects of preoperative statin duration and dosage intensity.

Publication bias was investigated by visual examination of funnel plots, Egger's weighted regression statistic, and the trim-and-fill method.

Results of the review
Eight RCTs (774 participants) were included in the review. Trial size ranged from 40 to 200 participants; all were published between 1999 and 2009. One trial scored 4 points for quality, four trials scored 3, one trial scored 2 and two trials scored 1.

Statins reduced the risk of postoperative atrial fibrillation compared with control (RR 0.57, 95% CI 0.45 to 0.72; \( I^2 = 0\% \); NNT=8; six trials). Meta-regression showed a statistically significant correlation between preoperative duration of statin use and reduction of relative risk for postoperative atrial fibrillation (p=0.008); there was no correlation between dosage and risk of atrial fibrillation.

Statins reduced total hospital stay (WMD -0.66 days, 95% CI -1.02 to -0.30; \( I^2 = 47\% \); six trials), but had no statistically significant effect on length of intensive-care unit stay (five trials). Results were not altered by various sensitivity analyses.

Tests suggested that publication bias was unlikely.

Authors’ conclusions
Evidence suggested that statins were associated with a reduced risk of postoperative atrial fibrillation and a shorter hospital stay after cardiac surgery. Earlier therapy was likely to have a greater benefit. However, as the meta-analysis included relatively small trials, proof of statins anti-fibrillatory benefit was not definitive, and optimal dose and duration were unclear.

CRD commentary
The aims of this review were clearly stated in terms of the inclusion criteria. The search covered several sources; no language restrictions were applied. However, no mention was made as to whether unpublished studies were eligible, so it was possible that publication bias could have affected the review. Although authors’ tests showed that publication bias was unlikely, the authors acknowledged that tests may have been unreliable given the limited number of included trials. The methods of study selection, data extraction and quality assessment were aimed at reducing reviewer error or bias.

Trial quality was assessed; the results were reported. The methods of synthesis appeared appropriate. Possible heterogeneity was investigated.

The review appeared to have been generally well conducted, but data came from small trials, some of which were of lower quality. The authors’ conclusions, which acknowledge the limitations of the included data, are likely to be reliable.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.
Research: The authors stated that large RCTs are required to assess clinical outcomes with the use of statins after cardiac surgery and to compare different dosing intensities and lengths of statin therapy.

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