Statins for prevention of atrial fibrillation after cardiac surgery: a systematic literature review


CRD summary
This review concluded that preoperative statin therapy was associated with a reduction in the incidence of atrial fibrillation after cardiac surgery. This was a generally well-conducted study and the authors' conclusions appeared to reflect the evidence, but interpretation of their conclusions should take into account the limitations (such as generalisability of the findings) that were highlighted by the authors.

Authors' objectives
To assess the effects of preoperative statin therapy for prevention of atrial fibrillation, particularly new-onset atrial fibrillation, following cardiac surgery.

Searching
MEDLINE, EMBASE and The Cochrane Library were searched between 1966 and July 2008 for full text articles and abstracts. There were no language restrictions. The search strategy was reported to be available online, but could not be accessed. The following were searched over the previous three years for abstracts and presentations: American Heart Association, American College of Cardiology, European Society of Cardiology, American Association of Thoracic Surgery, Society of Thoracic Surgeons, European Association of Cardiothoracic Surgery and Society of Cardiovascular Anaesthesiology. References of relevant reports and reviews were searched.

Study selection
Randomised controlled trials (RCTs) and observational studies that reported the effect of preoperative statin therapy on incidence of postoperative atrial fibrillation in adults who underwent cardiac surgery were eligible for inclusion. Eligible studies were required to compare patients with or without preoperative statin therapy. Studies of atrial flutter or supraventricular tachycardia were excluded.

Included studies were of patients who underwent isolated coronary artery bypass grafting (CABG) (approximately 91% of included patients) and/or isolated valve surgery. Most procedures were elective. Mean ages ranged from 61 to 67 years. Some patients had diabetes, hypertension or hyperlipaemia. Statin types, dosage, and re-initiation regimens varied among studies. Exposure to perioperative statins ranged from the day of hospital admission to over two months preoperatively. Follow-up periods for postoperative atrial fibrillation varied from up to the day of discharge from hospital to 30-day post surgery. Some patients also received a β-blocker, angiotensin-converting enzyme inhibitor, or antiplatelet therapy (aspirin). Patients were similar for history of myocardial infarction, calcium channel blocker therapy, off-pump procedures and cardiopulmonary bypass and aortic cross clamp time.

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

Assessment of study quality
Two reviewers assessed the quality of RCTs using the Jadad Scale and scores ranged from 0 to 5 (5 indicated excellent quality). Downs and Black Checklist was used to assess RCTs and observational studies and scores ranged from 0 (poor) to 29 (excellent). Discrepancies were resolved by consensus.

Data extraction
Two reviewers independently extracted adjusted odds ratios (ORs) where reported. Where odds ratios were not reported, the incidence of any type of atrial fibrillation and new-onset atrial fibrillation were extracted to calculate unadjusted odds ratios and their 95% confidence intervals (CIs). The number needed to treat (NNT) to prevent one incident and relative risk reduction were calculated. Study authors were contacted if data were missing. The authors stated that the weighted mean difference was calculated for continuous variables, but no further details were reported and results were not presented in the review.
Discrepancies were resolved by consensus.

**Methods of synthesis**

Adjusted and unadjusted odds ratios were pooled using a fixed-effect model or (where there was evidence of statistical heterogeneity) a random-effects model. Statistical heterogeneity was assessed using the Cochran Q and $I^2$ statistics.

Meta-regression was undertaken to assess the impact of perioperative covariates of study characteristics (mean age of patients and percentage of females, non-elective type of surgery, hypertension, diabetes and preoperative use of β-blocker, angiotensin-converting enzyme inhibitor or antiplatelet therapy) on the summary estimates of effect.

Sensitivity analyses were undertaken to assess the effect of study design (prospective versus retrospective) and study quality on the results: high quality (Downs and Black score ≤21) versus low quality (Downs and Black score >21).

Publication bias was assessed using Egger's test and by visual inspection of funnel plots.

**Results of the review**

Thirteen studies with 17,643 participants (range 40 to 4,739) were included in the review: 10,304 (58.4%) who received preoperative statin therapy and 7,339 (41.6%) without statins. Three studies were RCTs, two were prospective observational studies and were eight retrospective studies. Two RCTs (one of which was not a placebo-controlled or blinded trial) scored 3 on the Jadad scale and one scored 5. The average Downs and Black score was 21.9 (range 18 to 28); four studies were rated low quality (scored <21).

The incidence of any type of atrial fibrillation was statistically significantly lower in patients who received preoperative statin therapy compared with controls (unadjusted OR 0.78, 95% CI 0.67 to 0.90; 13 studies). There was evidence of significant statistical heterogeneity ($p=0.0010, I^2=63\%$). The number needed to treat was 18.2. Reductions in new-onset atrial fibrillation were reported with statin therapy compared with controls (unadjusted OR 0.66, 95% CI 0.51 to 0.84; nine studies). There was evidence of statistical heterogeneity ($p=0.0002, I^2=73\%$). The number needed to treat was 25.1. The results did not alter significantly when only studies that reported adjusted odds ratios were included.

Relative risk reductions were reported in the review.

Investigation of statistical heterogeneity suggested that use of β-blocker and angiotensin-converting enzyme inhibitors were statistically significantly associated with improved statin treatment estimates for new-onset atrial fibrillation, but not for all types of atrial fibrillation. Sensitivity analyses of only studies of low quality significantly altered the results and showed no significant reduction for developing any type of atrial fibrillation (OR 0.82, 95% CI 0.57 to 1.16; four studies).

There was evidence of publication bias for both outcomes.

**Authors' conclusions**

Preoperative statin therapy was associated with a reduction in incidence of atrial fibrillation after cardiac surgery.

**CRD commentary**

The review question was clear and was supported by clearly defined inclusion criteria. The literature search was thorough, included attempts to locate unpublished literature and there were no language restrictions; which reduced potential for language and publication biases. However, assessment of publication bias showed some evidence of bias and the authors suggested that the magnitude of treatment effect may have been overestimated. The authors performed validity assessment and data extraction in duplicate; it was unclear whether this was the case for selection of studies and so reviewer error and bias could not be ruled out completely. Appropriate methods were used to synthesise data and investigate statistical heterogeneity and potentially confounding variables. The authors acknowledged heterogeneity among studies and highlighted potential limitations with the aims and methods of some of the studies. They also highlighted the potential limitations of including observational studies, but suggested this may have underestimated treatment effect. The authors also suggested that the results may not be generalisable to other populations as most
patients in the review had undergone CABG. This was a generally well-conducted study and the authors’ conclusions appeared to reflect the evidence, but interpretation of the conclusions should take into account the limitations highlighted by the authors.

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

**Practice:** The authors stated that use of intensified perioperative statin therapy followed current guidelines and evidence supported its use in patients with hyperlipaemia and multiple cardiac risk factors who were scheduled for coronary artery surgery.

**Research:** The authors stated that further RCTs were needed to investigate the effects of perioperative statins for prevention of atrial fibrillation, particularly in patients with normolipaeemia or valvular heart disease.

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