The effects of statin on atrial fibrillation: a meta-analysis of published data from randomized controlled trials

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CRD summary
The review concluded that statins significantly reduced risks of atrial fibrillation compared to controls in both short- and long-term trials. There was no evidence of a reduction in risk in long-term trials that compared more intensive versus standard statins. Potential limitations in the review process and differences between study participants make the reliability of the authors’ conclusions unclear.

Authors’ objectives
To evaluate the efficacy of statins in reducing atrial fibrillation.

Searching
PubMed, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to November 2010. There were no time or language limitations. Search terms were reported. Bibliographies of selected clinical trials, recent meta-analyses and review articles were handsearched.

Study selection
Randomised controlled trials (RCTs) that compared a statin against control treatment or a more intensive versus a less intensive statin treatment were eligible for inclusion. Trials needed to have a follow-up time of at least 30 days and have incidence or recurrence of atrial fibrillation (atrial fibrillation) as an outcome. A study published in Chinese and a study that was not specific to statins were excluded.

Most trials used Atorvastatin (range 10mg to 80mg daily). Other statins used included Pravastatin (20mg or 40mg daily), Rosuvastatin (10mg daily) and Simvastatin (20mg or 80mg daily). Short-term duration ranged from 30 days to six months and long-term duration ranged from one to 4.8 years. Participant eligibility characteristics were very varied. Most commonly patients with atrial fibrillation or persistent atrial fibrillation for more than 48 hours or after electrical cardioversion or with paroxysmal atrial fibrillation were eligible. Other eligibility criteria were: patients scheduled for electrical cardioversion, cardiac surgery, coronary artery bypass surgery or grafting; patients with acute coronary syndrome, chronic heart failure or Brady arrhythmias and implantation of a pacemaker; patients with hypertension; and patients with no history of coronary artery disease.

Mean age of participants ranged from 54 to 71 years. The percentage of participants with hypertension ranged from 30% to 96% and with diabetes ranged from 7% to 50%. Details of drugs other than statins taken by patients were reported. The endpoint was atrial fibrillation occurrence/incidence in 62% studies and atrial fibrillation recurrence in the other studies. In all studies except one, atrial fibrillation was monitored with electrocardiogram (ECG); the exception was a study that used 48-hour ambulatory monitoring. A few studies used 24 hour Holter monitoring and ECG.

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

Assessment of study quality
Methodological quality was assessed using the Jadad and CONSORT scoring system with a maximum score of 7. Criteria included sample size, random allocation, random sequence, random allocation concealment, blinding, use of double-blinding and follow-up.

The authors did not report how many reviewers assess study validity.

Data extraction
Numbers of events for each outcome were extracted. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.
One reviewer extracted data. These were checked by a second reviewer and any disagreements were resolved by discussion.

**Methods of synthesis**

Pooled odds ratios and 95% CIs were calculated using a fixed-effect model (no significant heterogeneity) and a random-effects model (significant heterogeneity, p≤0.1). Between-study heterogeneity was determined with the $X^2$ and $I^2$ statistics. Publication bias was assessed using the fail-safe number ($N_{fs}$). A sensitivity analysis was carried out for study quality.

**Results of the review**

Sixteen relevant RCTs were identified (22,628 participants reported in the tables, range 48 to 8,582). Study quality scores ranged from 2 to 7 (eight scored 7, four scored 4 or 5 and four scored 2 or 3).

Endpoints for the nine short-duration studies were atrial fibrillation recurrence (five studies, two after cardioversion) and postoperative atrial fibrillation (three studies) and atrial fibrillation after cardioversion (one study).

Endpoints for the seven long-duration studies were atrial fibrillation occurrence or incidence (five studies, one also included atrial flutter), paroxysmal atrial fibrillation or atrial high rate episodes (one study) and atrial fibrillation recurrence after cardioversion (one study).

Statins significantly decreased the risk of atrial fibrillation recurrence versus controls in short-term trials (OR 0.43, 95% CI 0.25 to 0.73; $I^2$=71.0%, nine studies). There was a greater decrease in risk (OR 0.32, 95% CI 0.18 to 0.54; $I^2$=63.7%, seven studies) when lower quality studies (Jadad score <3) were excluded from the analysis.

Nfs for short-term trials was 142, for long-term trials 8.74 and for trials of more intensive versus less intensive statins 0.52 (lower numbers mean a higher likelihood of publication bias).

**Authors' conclusions**

The meta-analysis suggested that statin use may be associated with preventing atrial fibrillation in short- and long-term trials, but there was no evidence of a reduction in atrial fibrillation risk in long-term trials of more intensive versus standard statin.

**CRD commentary**

The review addressed a well-defined question in terms of interventions, study design and relevant outcomes. The authors did not define relevant participants and the participants in the included studies were very diverse. Relevant databases were searched in any language. It appeared that unpublished studies were not considered and so some relevant studies may have been missed. Publication bias was assessed. One Chinese study was excluded. Study quality was assessed using suitable criteria and relevant data were provided. Half of the studies were of high quality. Data extraction was carried out with efforts to reduce error and bias; it was unclear whether similar processes were applied to other aspects of the review. The total number of participants differed between tables and text.

Relevant study details were reported but there were no details of loss to follow-up and little information about controls. Statistical heterogeneity was assessed and evidence of it was found for some outcomes. The statistical method used for meta-analysis of the RCTs seemed appropriate, but the differentiation made between incidence/occurrence and recurrence was not clear. One relevant sensitivity analysis was performed.

Potential limitations in the review process and differences between study participants make the reliability of the authors' conclusions unclear.

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

**Practice:** The authors did not state any implications for practice.
Research: The authors identified a need for large-scale randomised double-blind statin trials with atrial fibrillation occurrence as the main endpoint in order to finally confirm the benefits of statins in atrial fibrillation patients. Trials of all kinds of statins were required. The effects of statins on atrial remodelling and inflammatory and oxidative conditions should be evaluated. Further research was required to find the most effective methods of preventing postoperative atrial fibrillation. The authors recommended use of 24 hour Holter monitoring to detect atrial fibrillation.

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