Statin use and development of atrial fibrillation: a systematic review and meta-analysis of randomized clinical trials and observational studies

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CRD summary
The authors concluded that statins may be effective in preventing atrial fibrillation especially in postoperative patients, but there was insufficient evidence to recommend statins solely to prevent atrial fibrillation. Further research was required. This was generally a well-conducted review and the authors' cautious conclusions reflected the paucity of good-quality evidence.

Authors' objectives
To examine the association between statins and the development of atrial fibrillation.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials were searched from inception to November 2006 using reported search terms. No language restrictions were applied. Reference lists of reviews, primary studies and abstracts from scientific sessions of four specified societies were screened. Experts in the field and pharmacological companies were contacted for unpublished data.

Study selection
Parallel-group randomised controlled trials (RCTs) and prospective observational studies that compared statins with a control and reported the relationship between statins and new or recurrent atrial fibrillation were eligible for inclusion. Studies could have any duration of follow-up.

Included studies assessed a variety of statins. All but one of the RCTs evaluated atorvastatin (10 mg to 80 mg). Most of the observational studies evaluated more than one statin, including those with persistent and paroxysmal atrial fibrillation, acute coronary syndrome, post-cardioversion, postoperative and coronary artery disease. Studies used different methods to define atrial fibrillation (including new, recurrent and postoperative atrial fibrillation) and different methods to detect atrial fibrillation (including electrocardiograph, ambulatory and HOLTER monitoring). The duration of follow up ranged from less than one week to 6.5 years; follow up duration tended to be shorter for RCTs (one to six months).

Two reviewers independently scanned titles and abstracts and resolved disagreements on inclusions by consensus or with the aid of a third reviewer.

Assessment of study quality
Two reviewers independently assessed the validity of RCTs using the Jadad scale and the validity of observational studies using the checklist described by the Dutch Cochrane Centre, which was based on clear definition of study population, outcomes and outcome assessment, independent outcome assessment, adequate duration of follow up, no selective losses during follow up and identification of important confounders and prognostic factors.

Data extraction
For each study, the incidence of atrial fibrillation was extracted and used to calculate relative risks (RR) and 95% confidence intervals (CI). Authors were contacted for missing data, if required. One RCT with two types of patients was extracted as two separate trials. Two reviewers independently extracted data onto a standardised form. Discrepancies were resolved by consensus or with the aid of a third reviewer.

Methods of synthesis
RCTs and observational studies were analysed separately. Pooled RRs and 95% CIs were calculated using a random-effects model when significant heterogeneity ($X^2$ p<0.10 or $I^2$ squared >56%) was found and a fixed-effect model otherwise. Sensitivity analysis was performed by repeating the analyses after excluding each study in turn. Pre-specified
subgroup analysis was used to examine the influence of methods used to define and detect atrial fibrillation. Publication bias was assessed using a funnel plot.

Results of the review
Sixteen studies were included (n=7,041), comprising six RCTs (n=3,546) and 10 observational studies (n=3,495).

Two RCTs scored 5 on the Jadad scale, one scored 4, one scored 3 and two scored 2 points. One RCT was a post-hoc analysis. Most of the observational studies met five or six of the seven quality criteria.

For RCTs, there was no significant difference in the development of atrial fibrillation between statins and control, RR 0.76 (95% CI: 0.55, 1.05; p=0.09). Significant heterogeneity was observed (p=0.0008, I² =74%). The only sensitivity analyses to alter the main results was a significant decrease in atrial fibrillation when detected by Holter or continuous monitoring (RR 0.50, 95% CI: 0.93, 0.64; three studies, n=328; p<0.0000); no significant heterogeneity was observed (p=0.14, I² =49%).

Observational studies showed that statins were associated with a statistically significant reduction in the risk of developing atrial fibrillation compared to control, RR 0.77 (95% CI: 0.70, 0.85; p<0.00001). The reduction in risk of atrial fibrillation was greatest in postoperative in-hospital studies, RR 0.61 (95% CI: 0.49, 0.76; three studies; p<0.0001). No significant heterogeneity was observed for either analysis.

Funnel plots for both RCTs and observational studies appeared asymmetrical suggesting the potential for publication bias.

Authors’ conclusions
Statins may be effective in preventing atrial fibrillation especially in postoperative patients, but there was insufficient evidence to recommend the widespread use of statins solely to prevent atrial fibrillation. Further research was required.

CRD commentary
The review question and inclusion criteria were clearly stated. Several relevant sources were searched. Attempts were made to minimise publication and language bias, but funnel plots suggested that publication bias may have been present. Appropriate methods were used to minimise reviewer error and bias during much of the review process, but selection bias could not be ruled out when full papers were selected for inclusion. Study validity was assessed, although for RCTs only the composite score was presented making it difficult to comment independently on the reliability of the evidence presented. Control treatments were not described and this meant it was not clear with what statins were being compared. Studies were appropriately grouped by design. Studies were combined using meta-analysis. However, there were considerable differences between studies (for example, rates of atrial fibrillation in control groups of RCTs ranged from 1.6 per cent to 90 per cent) and pooling such clinically diverse studies may not have been appropriate. Heterogeneity was assessed and various predefined subgroup analyses conducted to examine potential sources of heterogeneity. Post-hoc sensitivity analyses were also conducted and results from these may be less reliable. About 87 per cent of patients in RCTs came from one study, hence findings from RCTs may not be generalisable. Some limitations of the review were discussed. This was generally a well-conducted review, but the reliability of results was limited by the paucity of good quality evidence. The cautious conclusions drawn by the authors and the recommendations for future research appeared appropriate.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that to define the role of statins in atrial fibrillation, large RCTs with long-term follow up were required. Studies should be conducted in different clinical situations and use more sensitive methods to detect atrial fibrillation. There was also a need to examine the effect of statins on atrial remodelling and the associated inflammatory and oxidative state.

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