Statin therapy and atrial fibrillation: systematic review and updated meta-analysis of published randomized controlled trials

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CRD summary
This review concluded that statins reduced the risk of atrial fibrillation in patients with sinus rhythm; the greatest benefit was in prevention of postoperative atrial fibrillation and secondary prevention of atrial fibrillation. Given the variability across studies, limitations of the evidence available, and lack of reporting of the review process, reliability of the review's conclusions is uncertain.

Authors' objectives
To investigate whether statins can prevent atrial fibrillation.

Searching
MEDLINE and EMBASE were searched for studies published in English in peer-reviewed journals between 1980 and June 2012; search terms were reported. References from selected clinical trials, recent meta-analyses, review articles, and abstracts from major cardiology meetings (not specified) were also searched.

Study selection
Randomised controlled trials (RCTs) that either compared statins with a placebo or a control treatment, or compared different statin regimens were eligible for inclusion. Trials had to report incidence or recurrence of atrial fibrillation. Most studies evaluated atorvastatin; pravastatin, simvastatin and rosuvastatin were also investigated. The statin regimens varied across studies; most compared a statin with placebo. Mean age ranged from 54 to 76 years. Where reported, the proportion of patients with hypertension ranged from 15% to 100% and diabetes ranged from 1% to 50%. Where reported, left ventricular ejection fraction ranged from 33% to 66%, and the total cholesterol level at baseline ranged from 156 to 272mg/dL. The use of beta-blockers, digoxin, amiodarone and class 1 antiarrhythmics varied considerably across studies.

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

Assessment of study quality
Study quality was assessed using Jadad; a score out of five was presented. The authors did not state how many reviewers assessed study quality.

Data extraction
Outcomes data were extracted in order to calculate odds ratios and 95% confidence intervals. The authors did not state how many reviewers extracted data.

Methods of synthesis
Where studies were considered homogeneous, pooled odds ratios and 95% confidence intervals were calculated using fixed-effect Mantel–Haenszel model; otherwise a random-effects model was used. Heterogeneity was assessed using $I^2$ and $X^2$; homogeneity was defined as $p>0.10$ and $I^2$ less than 50%. Subgroup analyses were used to investigate populations with postoperative atrial fibrillation, primary and secondary prevention of atrial fibrillation, and more intensive versus standard statin regimens. Funnel plots were used to assess the presence of publication bias.

Results of the review
Thirty-two studies (71,005 patients; range 40 to 17,120) were included in the review; trial duration ranged from seven days to six years. Twenty-eight compared statins with no statins (61,773 patients) and four compared different statin regimens (9,232 patients). The Jadad score was 2 in six RCTs, 3 in six RCTs, 4 in five RCTs, and 5 in 15 RCTs.

Overall, the use of statins was significantly associated with a decreased risk of atrial fibrillation compared with controls.
Statin therapy was not beneficial for the primary prevention of atrial fibrillation (OR 1.00, 95% CI 0.86 to 1.15; nine RCTs; I² 52%), but was for secondary prevention (OR 0.57, 95% CI 0.36 to 0.91; 10 RCTs; I² 70%). There was no evidence of a reduction in the risk of atrial fibrillation more intensive statin regimens (OR 1.01, 95% CI 0.77 to 1.32; four RCTs; I² 31%).

The authors stated that they could not exclude the possibility of a publication bias.

Authors' conclusions
The use of statins was significantly associated with a decreased risk of atrial fibrillation in patients with sinus rhythm. The highest benefit was seen for the prevention of postoperative atrial fibrillation and in secondary prevention of atrial fibrillation, but heterogeneity was observed.

CRD commentary
The reviewers addressed a clear review question supported by reproducible inclusion criteria. An extensive search was conducted which included attempts to identify unpublished studies. Only studies in English were included. Publication and language bias could not be ruled out.

The authors did not report whether methods were used to reduce error and bias during the review process. Appropriate criteria were used to assess study quality although Jadad was not modified to include allocation concealment; the results were reported only as a summary score, therefore it is unclear which bias each trial was subject to. There was substantial clinical heterogeneity across the studies making the reliability and generalisability of the overall pooled results uncertain.

Given the variability across studies, methodological limitations of available evidence and imprecision of results from these studies, and the lack of reporting of the review process, the reliability of the review's conclusions is uncertain.

Implications of the review for practice and research
Practice: The authors stated: that it was possible that statin therapy only played an intermediate role in the risk of atrial fibrillation when there was acute inflammation, which could be effectively decreased; patients with low risk of atrial fibrillation or normal heart structure were unlikely to benefit from statin therapy for primary prevention of atrial fibrillation; statin therapy may only have a minor effect on patients highly prone to atrial fibrillation, with greater importance of mechanical or electrical remodelling; statin was unlikely to work very efficiently for patients with older and definitely established substrate, especially if patients were treated for a short period.

Research: The authors stated that large-scale RCTs were probably still needed to establish whether statins produce a similar benefit to some renin–angiotensin–aldosterone system blockers and provide an appropriate therapeutic option in some subgroups of patients for the management of atrial fibrillation.

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