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

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Objective: To determine the strength of evidence of preoperative statin therapy for prevention of atrial fibrillation after cardiac surgery.

Methods: A meta-analysis was performed of randomized controlled trials and observational trials reporting the impact of preoperative statin therapy on the incidence of any type and new-onset atrial fibrillation after cardiac surgery. Unadjusted and adjusted treatment effects (odds ratio, 95% confidence intervals) were pooled using a random-effects model, and publication bias was assessed.

Results: Thirteen studies were identified (3 randomized controlled trials, 10 observational trials) that reported the incidence of postoperative atrial fibrillation in 17,643 patients having cardiac surgery with (n = 10,304; 58%) or without (n = 7339; 42%) preoperative statin use. New-onset atrial fibrillation was reported in a total of 7855 patients. Postoperative incidence rates for any or new-onset atrial fibrillation were 24.6% and 29.9%, respectively. Preoperative statin use resulted in a 22% and 34% unadjusted odds reduction for any atrial fibrillation (odds ratio, 0.78; 95% confidence interval, 0.67–0.90) or new-onset atrial fibrillation (odds ratio, 0.66; 95% confidence interval, 0.51–0.84) after surgery ($P < .001$). Relevant publication bias and an unequal distribution of confounding variables favoring patients treated with statins were identified. Nevertheless, the beneficial actions of statins on atrial fibrillation persisted after pooled analysis of risk-adjusted treatment effects from randomized controlled trials and observational trials (any atrial fibrillation—odds ratio, 0.64; 95% confidence interval, 0.48–0.87; new-onset atrial fibrillation—odds ratio, 0.66; 95% confidence intervals, 0.48–0.89; $P < .01$).

Conclusion: Our meta-analysis provides evidence that preoperative statin therapy is associated with a reduction in the incidence of atrial fibrillation after cardiac surgery.

Supplemental material is available online.

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Atrial fibrillation (AF) is a common complication after cardiac surgery and is associated with increased morbidity and prolonged hospitalization with significant economic implications.[1,2] Although perioperative predictors of AF are identified and various preventive pharmacologic and surgical strategies have been introduced,[3,4] the incidence of AF after cardiac surgery remains high, occurring in 20% to 40% of patients.[1,2] Beyond the involvement of a multitude of perioperative factors including alterations in the autonomic and metabolic response and oxidative myocardial stress, inflammation has been suggested recently to play a pivotal role in the pathogenesis of AF after cardiac surgery.[5,6]

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Received for publication Oct 11, 2008; revisions received March 4, 2009; accepted for publication March 29, 2009; available ahead of print June 8, 2009.

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J Thorac Cardiovasc Surg 2009;138:678-86
0022-5223/$36.00

doi:10.1016/j.jtcvs.2009.03.054

Statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) exert multiple pleiotropic actions independently of their lipid-lowering properties. We and others have demonstrated that preoperative statin therapy decreases markers of inflammation[7,8] and attenuates myocardial reperfusion injury after cardiac surgery.[9] Thus, use of statins prior to heart surgery may contribute to improved perioperative cardiac protection with a favorable impact on the incidence of AF. Consistent with this, the ARMYDA-3 trial demonstrated a 61% reduction in the odds for new-onset AF in patients randomly allocated to 7-day atorvastatin treatment before elective heart surgery.[6] However, conclusions drawn from this study were limited by the relatively small sample size (n = 200) and unusually high incidence rates of AF reported in the placebo group (57%). Moreover, evidence from previous reviews investigating the potential benefits of statins on postoperative AF in cardiac surgery is inconclusive,[10-12] as controversial data from recent reports with more patients have become available.[13-17] Limited clarity of available data underscores the need for an updated comprehensive review of this potentially relevant therapeutic strategy.

The primary objective of the present meta-analysis was to determine the strength of evidence for preoperative statin therapy for prevention of AF after cardiac surgery, with special focus on new-onset AF. As a secondary objective, we sought to identify possible confounding factors that may limit the observed treatment effects of statins on AF.

Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
AF = atrial fibrillation
CABG = coronary artery bypass grafting
OR = odds ratio
RCT = randomized controlled trial

METHODS

Selection Criteria and Search Strategy

A systematic review of the literature was performed following the guidelines for quality of reporting of meta-analysis.[18,19] Randomized controlled trials (RCTs) and observational studies published between 1966 and July 2008 that reported the effects of preoperative statin therapy on the incidence of postoperative AF in adult patients having cardiac surgery were identified and analyzed using a priori defined inclusion criteria: (1) studies reporting the use of any commercially available statin before cardiac surgery for any given duration and dose, and (2) studies comparing patients with or without preoperative statin therapy. Postoperative AF was defined as occurrence of any type of postoperative AF. New-onset AF was recorded when studies indicated exclusion of patients with a history of preoperative AF from their studies, including permanent (chronic), persistent, or paroxysmal AF. We disregarded atrial flutter or supraventricular tachycardia and accepted the authors' postoperative monitoring modalities and definitions for AF.

An electronic literature search was performed by two investigators (O.J.L. and M.B.) in Medline, EMBASE, and The Cochrane Library using a predefined keywords list (See Supplemental data S1—search strategy). All studies published in full-text or abstract forms were eligible for inclusion without applying any language restrictions. In addition, abstracts and oral presentations from the past 3 years' scientific meetings of the 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 Anesthesiology were screened. Studies not including a control group, animal studies, in vitro studies, prevention trials, editorials, letters, review articles, or trials that exclusively reported other clinical outcomes were excluded after initial abstract review. All potentially relevant studies were identified and full-text publications retrieved for detailed evaluation. References of relevant reports and reviews were screened to identify other eligible studies. When more than 1 publication from the same patient cohort existed, then the study with the most complete data set was included in the systematic review.

Data Extraction and Quality Assessment

All data with regard to authorship, year of publication, type of publication (abstract, full-text), study design, patient population (sample size, age, preoperative risk factors, type of surgery), length of preoperative statin exposure, applied statin regimen, length of follow-up, preoperative medications (antiarrhythmic medication), and type of AF (any AF vs new-onset AF) were extracted. Methodologic quality of the included studies was assessed by two independent investigators (O.J.L. and Y.-H.C.) using the Jadad Score (total score from 0 [poor] to 5 [excellent]) for RCTs[20] and the Downs and Black Checklist (total score from 0 [poor] to 29 [excellent]) for both RCTs and observational trials, respectively.[21] Disagreements were resolved by consensus.

Statistics

Statistical analyses were performed using Review Manager (Version 5.0.1.4; The Nordic Cochrane Centre, Købehavn, Denmark) and StatsDirect statistical software package, version 2.6.8 (StatsDirect Ltd., Chelsire, UK). For each individual study, the raw incidence data were used to calculate the unadjusted ''crude'' odds ratio (OR). Adjusted OR resulting from multivariate analysis or propensity score matching of treatment groups were extracted from included studies. To control for confounding covariates, an estimated summary OR was generated by combining all studies reporting adjusted and unadjusted OR (combined OR) and summarized by Forest plots. Furthermore, an overall adjusted OR was calculated after considering only RCTs and observational trials reporting adjusted treatment effects. Q-statistics and I^2-statistics were performed to test for heterogeneity between included studies.[22] In the presence of heterogeneity (Q-statistics $P < .10$ or $I^2 > 50\%$), the DerSimonian and Laird random-effects model was used. Pooled treatment effect estimate was calculated as a weighted average of the treatment effects so that an OR of less than 1 favored statin treatment over control. For continuous variables, the weighted mean difference was calculated. In 1 case, missing information on the type of AF was retrieved by contacting the primary author of the study.[23] A meta-regression analysis of summary statistics was conducted to investigate the impact of perioperative covariates of study characteristics on the statin effect estimates (logarithmic OR) on AF, including mean age of patients and percentage of female patients, nonelective type of surgery, hypertension, diabetes and preoperative use of ß-blocker, angiotensin-converting enzyme (ACE) inhibitor, or antiplatelet therapy (ie, aspirin).

A funnel plot was constructed to visually assess the presence of publication bias. The treatment effects, given as the OR on a logarithmic scale, were plotted against a measure of precision expressed as the standard error. Additionally, publication bias was assessed by applying the Egger's weighted regression statistic. Sensitivity analysis was performed to estimate differences of treatment effects between prospective and retrospective trials and to account for low- and high-quality studies (Downs and Black score ≤ 21 or >21, respectively).

RESULTS

Selection and Characteristics of Included Studies

A search of the literature retrieved 1142 studies of which 1106 (96.9%) were excluded after initial abstract review for reasons explained in Figure 1. Of the remaining 36 studies, 23 studies were excluded after full-text evaluation either due to insufficient reporting of desired clinical end points (n = 21) or due to inclusion of the same patient population in more than 1 publication (n = 2). (See supplemental data S2—references.)

After critical appraisal, 13 unique full-text studies published between the years 2004 to July 2008 fulfilled our inclusion criteria, reporting the influence of preoperative statin therapy on the incidence of postoperative AF in a total of 17,643 patients having heart surgery. Three studies were RCTs,[6,7,17] and 2 studies used a prospective observational[15,24] and 8 a retrospective design.[13,14,16,23,25-28] One study examined the effects of preoperative lipid-lowering therapy rather than statin therapy on postoperative outcomes.[27] Because the vast majority of these patients received statins (86%) compared with other lipid-lowering agents (14%) before surgery, this report was included in our systematic review. Moreover, a recently published, nested patient cohort analysis from the Atrial Fibrillation Suppression Trials I, II and III (AFIST) was also included, despite approximately 45% of enrolled patients being randomized to a prophylactic oral amiodarone therapy before surgery.[14]

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