

## Review

# Effect of Statins in Preventing Postoperative Atrial Fibrillation Following Cardiac Surgery

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**Background:** Postoperative occurrence of AF has been associated with less favourable outcomes in patients undergoing cardiac surgery and may result in increased postoperative morbidity and mortality.

**Objectives:** A focused clinical question was designed and a meta-analysis of published studies was performed to identify the effect of preoperative use of statins on the occurrence of AF after cardiac surgery.

**Methods:** Using the Medline database, the Cochrane clinical trials database and online clinical trial databases, we reviewed all RCTs and observational studies examining the effect of statins on AF occurrence following cardiac surgery. We searched for the literature published before April 2009 and earlier.

**Results:** This analysis identified six studies (observational studies) which examined the effect of preoperative use of statins on AF occurrence following cardiac surgery, involving 10,165 patients. Contradictory to most of previous studies, the overall outcomes suggested that the statins group did not have a significant decrease in AF occurrence following cardiac surgery comparing to control group ( $P=0.19$ ).

**Conclusions:** The preoperative medication of statins showed no significant decrease in AF occurrence following cardiac surgery in this meta-analysis result. More prospective studies and researches are needed to explore and demonstrate the accurate mechanism and effect of statins on postoperative AF.

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**Keywords:** Statins; Atrial fibrillation; Cardiac surgery; Postoperative; Meta-analysis

AF is one of the most common complications following cardiac surgery, which has important clinical and economic implications. Patients undergoing cardiac operations are more likely to develop AF during their postoperative period with the incidence ranging from 25% to 50% [1]. Moreover, recent studies have shown that postoperative AF is associated with increased morbidity and prolonged hospitalisation, which requires additional medical and nursing time, even intensive care unit stay [2,3].

The preoperative medication of amiodarone and  $\beta$ -blocker is thought to be useful to prevent postoperative AF, though recently in an increasing number of studies, they showed no effect on AF occurrence following cardiac com-

paratively [4,5]. Although the exact cause and mechanism of AF following cardiac surgery have not been testified, the inflammatory component of this postoperative arrhythmia has been verified by several articles [6,7]. Statin drugs, which have both antioxidant and anti-inflammatory properties, have showed efficacy in attenuating postoperative AF and may constitute a potential preventive approach [8–10] for postoperative arrhythmia. But there are several studies which showed different outcomes in the prophylactic use of statins [11–13]. Whether statins would maintain efficacy in preventing AF following cardiac surgery has not been verified [14].

Therefore, we conducted a meta-analysis over the evidence obtained from observational studies to evaluate the effect of statins on AF occurrence following cardiac surgery, which we think can provide useful clinical evidence for the prophylactic medication of cardiac surgery to decrease the complications.

## Methods

We performed this analysis according to the guidelines of the MOOSE [15].

**Inclusion criteria:** Studies were considered eligible for this review if they met the following criteria: (1) the study

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**Abbreviations:** AF, atrial fibrillation; RCTs, randomised controlled trials; MOOSE, meta-analysis of observational studies in epidemiology group; CABG, coronary artery bypass graft; CRP, C-reactive protein; WBC, white blood cells; ACE-I, angiotension converting enzyme inhibitors.

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must have observational study design. Patients included were assigned into statins group and control group, (2) the study should describe the basic characteristics of patients involved in the study, and (3) evaluate the postoperative effect of statins on AF occurrence.

**Search strategies:** Published and unpublished studies from 1990 to 2009 without language restriction were included. The databases of MEDLINE, EMBASE and the Cochrane Controlled Trials Register were searched. The following keywords: “atrial fibrillation” “statins” “cardiac surgery” “effect” “outcome” were used to help find the articles. Titles and abstracts as well as the reference lists of all of the identified reports were also independently examined. The whole searching process was examined by two reviewers independently (YW and WW). Discussion was launched or consensus with the third reviewer (XY) was taken when disagreement occurs

**Quality assessment:** According to the checklist of the Dutch Cochrane Centre which was proposed by MOOSE, we assessed several key points of study quality of the included studies. The factors involved in assessment include: (1) whether there is clear definition of outcomes, (2) whether independent assessment of outcome is performed, (3) whether the author carries out a follow-up in a certain period of time, (4) whether there is elective loss during follow-up, and (5) whether important prognostic factors are identified for each study. The results are showed in Table 1.

**Statistical analysis:** The data extraction was performed using a well-designed data extraction form to determine eligibility for inclusion and extract data. The data elements include: (1) publication details: first author’s name, and publication year, (2) characteristics of the studied population: sample size, age, gender, and operation performed, and (3) end-point evaluation: AF occurrence during the same period of time for each group. All studies were conducted using Review Manager Version 4.2 (Revman, The Cochrane Collaboration). If significant heterogeneity was tested a random-effects model was used, otherwise, with a fixed-effects model [16–21]. All the statistical strategies were performed by the professional statistical reviewer independently (LY). Disagreements were resolved by consensus with a second reviewer (XY).

## Results

### Articles

Fourteen records were identified by the primary literature search. However, finally six studies were included in this analysis, the other eight studies were excluded because they were either laboratory studies, review articles, or irrelevant to the current analysis. There were altogether 10,165 patients included, with the publication year ranging from 2006 to 2009. The characteristics of each study are depicted in Table 2.

In the six included articles, four of which favoured that preoperative statins use may be protective against AF after cardiac surgery, especially in CABG. Marín et al. [13] demonstrated that this protective effect was possibly due to alterations in the extracellular matrix and

remodeling by statins. Also, in another report [22], preoperative statins use was associated with a 42% reduction in risk of AF development after CABG surgery, and patients undergoing elective revascularisation may benefit from a preventive statins approach. In favour of this result, Kourliouros’s research [45] suggested that higher dose statins had the greater preventative effect, whereas low-dose statins did not influence postoperative AF. Lertsburapa et al. [14] also got the same result, that higher dose statins seemed to be more protective than the low-dose statins. But the other two articles refused to support this idea. In a total of 2096 patients study, Virani et al. [12] found that preoperative statins therapy was not associated with decreased incidence of postoperative AF in patients undergoing cardiac surgery (OR = 1.13). Furthermore, in the study reported by Miceli et al. [36] they even demonstrated that, based on the similar baseline characteristics, preoperative statins were associated with a significantly higher incidence of postoperative atrial fibrillation compared with no statins treatment in patients undergoing CABG.

### Effect of Statins on the AF Occurrence Following Cardiac Surgery

In all six studies, there was a total of 10,165 patients with 5483 patients in the statins group and 4682 for the control. Using the software of Review Manager Version 4.2 it was found that there was significant heterogeneity within the six articles ( $P = 0.0002$ ), so random-effects model was used. Compared with the control group, the result showed that the statins group did not have a significant decrease in the AF occurrence following cardiac surgery. The overall statistical result is that the OR was 0.85 units (95% confidence interval 0.66–1.09), and the z-score for overall effect was 1.30 ( $P = 0.19$ ; Fig. 1).

## Discussion

Postoperative AF following cardiac surgery remains a problem, especially in CABG which is associated with an increasing hospital stay. Furthermore, it may result in hypotension, congestive heart failure and stroke, the risk of thromboembolic complications also increases in patients with AF after cardiac surgery [1,13,22]. But the mechanisms underlying remain unknown and are thought to be multifactorial. Recently there are reports which demonstrate the role of inflammation in the initiation of AF, especially in postoperative AF following cardiac surgery [7,23–25]. The association between CRP and AF in non-postoperative patients has been reported by many studies, which aroused new exploration into the mechanism of AF. These reports suggested that levels of CRP are higher in patients with AF and are significantly associated with unsuccessful cardioversion to sinus rhythm [26,27]. In a recent study, Manuel and his colleagues demonstrate that a rise in the WBC count immediately after surgery has been recognised and attributed to inflammatory reaction in postoperative AF patients and they also suggested that preoperative leukocytosis was a significant predictor of AF independent of CRP [27].

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