

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

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## Abstract

**Background :** Postoperative occurrence of AF has been associated with less favorable 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 literature published before April 2009 and earlier.

**Results :** This analysis identified 6 studies (observational studies) which examined the effect of preoperative use of statins on AF occurrence following cardiac surgery, involving 10165 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.

**Key Words :** Statins; Atrial Fibrillation; Cardiac Surgery; Postoperative; Meta-analysis

## Introduction

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%.<sup>1</sup> Moreover, recent studies have shown that postoperative AF is associated with increased morbidity and pro-

longed hospitalization, which requires additional medical and nursing time, even intensive care unit stay.<sup>2,3</sup>

The preoperative medication of amiodarone and  $\beta$ -Blocker are 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 comparatively.<sup>4,5</sup> Although the exact cause and mechanism of AF

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following cardiac surgery have not been testified, inflammatory component of this postoperative arrhythmia has been verified by several articles.<sup>6,7</sup> Statin drugs, which have both antioxidant and antiinflammatory properties, have showed efficacy in attenuating postoperative AF and may constitute a potential preventive approach<sup>8-10</sup> for postoperative arrhythmia. But there are several studies which showed different outcomes in the prophylactic use of statins.<sup>11-13</sup> Whether statins would maintain efficacy in preventing AF following cardiac surgery has not been verified.<sup>14</sup>

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.

## 1. Methods

We performed this analysis according to the guidelines of the MOOSE.<sup>15</sup>

### Inclusion criteria

Studies were considered eligible for this review if they met the following criteria: (1) the study 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 1990-2009 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 result is 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 heteroge-

**Table 1** | Quality assessment of included studies

<b>Cord</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>
Clear definition of study population?	+	+	+	+	+	+
Clear definition of outcomes?	+	+	+	+	+	+
Independent assessment of outcomes?	+	+	+	+	+	+
Follow-up of certain period of time?	.	.	.	.	+	+
No selective loss during follow-up?	.	.	.	.	.	.
Important prognostic factors identified?	+	+	+	+	+	+

+: eligible; .: not eligible.

The quality assessment showed that all the included articles had clear definition of study population, definition of outcomes, and assessment of outcome and identified prognostic factors. But 4 of them were lack of follow-up and none of them mentioned the selective loss during follow-up.

neity was tested a random-effects model was used, otherwise, with a fixed-effects model.<sup>16-21</sup> All the statistical strategies were performed by the professional statistical reviewer independently (LY). Disagreements were resolved by consensus with a second reviewer (XY).

## 2. Results

### 2.1 Articles

Fourteen records were identified by the primary literature search. However, finally 6 studies were included in this analysis, the other 8 studies were excluded because they were either laboratory studies, review articles, or irrelevant to the current analysis. There were altogether 10165 patients included, with the publication year ranging from 2006 to 2009. The characteristics of each study are depicted in Table 2.

In the 6 included articles, 4 of which favored that preoperative statins use may be protective against AF after cardiac surgery, especially in CABG. Marín<sup>13</sup> demonstrated that this protective effect was possibly due to alterations in the extracellular matrix and remodeling by statins. Also, in another report,<sup>22</sup> preoperative statins use was associated with a 42% reduction in risk of AF development after CABG surgery, and patients undergoing elective revascularization may benefit from a preventive statins approach. In favor of this result, Kourliouros's research<sup>45</sup> suggested that higher-dose statins had the greater preventative effect, whereas low-dose statins did not influence postoperative AF. Lertsburapa and his colleagues<sup>14</sup> also got the same result that higher-dose statins seemed to

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<sup>12</sup> 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<sup>36</sup> they even demonstrated that based on the similar baseline characteristics preoperative statins was associated with a significantly higher incidence of postoperative atrial fibrillation compared with no statins treatment in patients undergoing CABG.

### 2.2 Effect of statins on the AF occurrence following cardiac surgery

Of all the 6 studies, there were totally 10165 patients included, 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 6 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 to 1.09), and the z-score for overall effect was 1.30 ( $P = 0.19$ ) [Figure1].

## 3. 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

Table 2

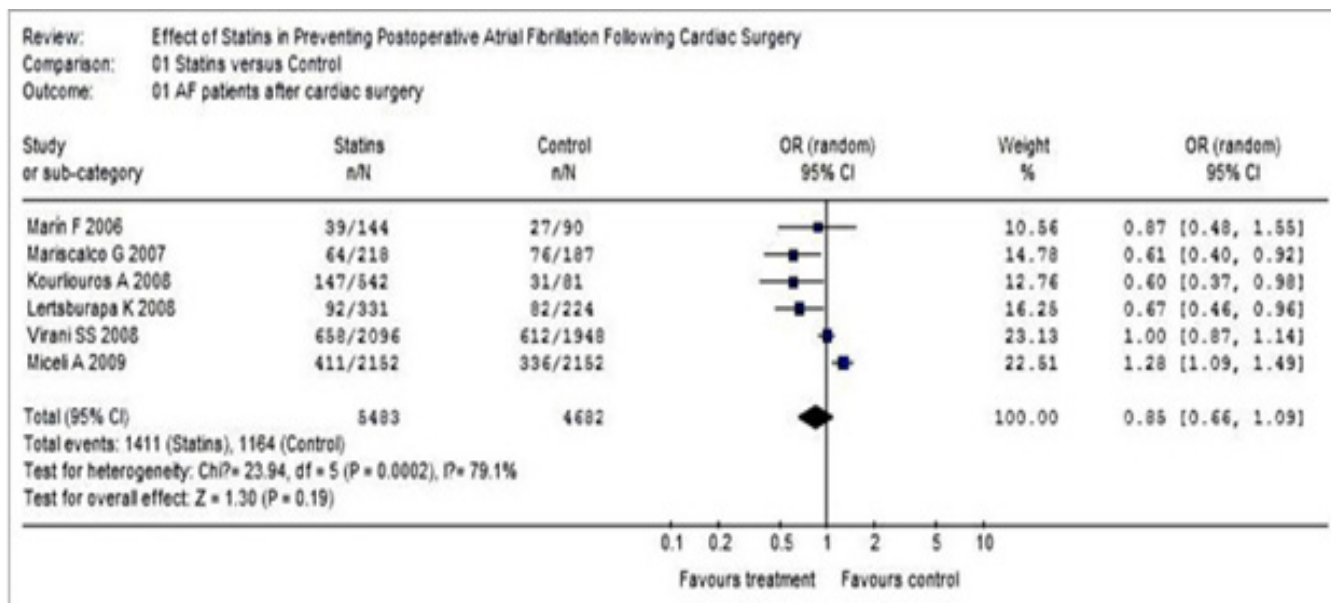
Baseline Characteristics

Cord	Author	Year	Groups		Male Gender (%)		Mean age	
			Statins	Control	Statins	Control	Statins	Control
1	Marín F <sup>13</sup>	2006	144	90	NM	NM	NM	NM
2	Mariscalco G <sup>22</sup>	2007	218	187	182 (83.4)	148(79.0)	65.1±9.1	65.5±9.7
3	Kourliouros A <sup>45</sup>	2008	542	81	427(79)	56(69)	67±9	65±13
4	Lertsburapa K <sup>14</sup>	2008	331	224	256(73.8)	172(77.3)	66.7±8.4	69.4±8.7
5	. Virani SS <sup>12</sup>	2008	2096	1948	348(17)	1289(66)	NM	NM
6	Miceli A <sup>36</sup>	2009	2152	2152	1774(82.4)	1769(82.2)	64.5±9.1	64.6±9

NM-not mentioned; All data are expressed as mean value ± SD or number (%) of patients.

The baseline characteristics of each article were showed above, including author, publication year, groups, sample size, age, and gender.

**Figure 1:** Meta-analysis result of the included 6 articles on AF occurrence following cardiac surgery. Compared with the control group, the statins group did not have a significant decrease in AF occurrence. The overall odds ratio (OR) was 0.85 units (95% confidence interval 0.66 to 1.09), and the z-score for overall effect was 1.30 (P = 0.19).



heart failure and stroke, the risk of thromboembolic complications also increases in patients with AF after cardiac surgery.<sup>1,13,32</sup> But the mechanisms underlying remains 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.<sup>7,23-25</sup> 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.<sup>26-27</sup> In a recent study, Manuel L and his colleagues demonstrate that a rise in the WBC count immediately after surgery has been recognized 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.<sup>27</sup>

Though preoperative medication of  $\beta$ -blocker and amiodarone are thought to be effective to prevent postoperative AF, recent studies challenged this idea<sup>28-29</sup> Statins, a type of lipid-lowering agents, which is also known for its effect of attenuation of inflammation, shows great effect in prevention AF following cardiac surgery by some previous reports. It used to be considered as lipid-lowering agents but more studies demonstrate a pleiotropic effect rather than lipid-lowering<sup>[30]</sup>. The an-

ti-inflammatory property of statins has been suggested as one of the mechanisms by which they exhibit their protective role in parthenogenesis and possibly in the development of AF.<sup>30</sup> And the anti-inflammatory role of statins as a regulatory mechanism for AF has been used preoperatively to reduce the occurrence of AF following cardiac surgery, which showed great efficacy.<sup>31-33</sup> This beneficial effect of statins on AF has been described in different reports. Two recent studies observed a significant reduction in AF risk following cardiac surgery on patients with preoperative statins use. In a study published by Patti and his colleagues, a randomized 200 patients with preoperative atorvastatin use starting 7 days before operation showed a significant decrease in postoperative AF than placebo.<sup>34</sup> But there are studies by other researchers which argued that preoperative statins therapy is not associated with a decrease in the incidence of postoperative AF in patients.<sup>12,35,36</sup> So the exact efficacy of statins in preventing AF occurrence following cardiac surgery needs more studies to be verified. And we searched related articles to give a Meta-analysis and to provide clinical evidence for the prophylaxis of AF in cardiac surgery.

Our study is a Meta-analysis, we searched published studies related to the effect of statins on the occurrence of AF following cardiac surgery to conduct this analysis. In the 14 studies, 6 met our criteria and are included in this analysis. Finally we include a total of 10165 patients, 5483 of which had

used statins preoperatively and showed no significant decrease in the occurrence of AF compared to the control group, which is contradictory to most previous studies' demonstration that statins could decrease the postoperative AF occurrence greatly. In a recent Metaanalysis conducted by Saso and his team,<sup>46</sup> they reviewed the same purpose with mixed RCTs and retrospective reports, by which they got the result that statins administration results in a reduction in the incidence of AF in patients who undergo cardiac surgery. Since there are a number of factors causing AF in patients undergoing cardiac surgery, including the age, weight, history of hypertension, obesity, use of  $\beta$ -Blocker and ACEI, diabetes, coronary diseases and others, which may have important impact on the AF occurrence after surgery.<sup>37-40</sup> In our study, the two groups were reasonably balanced in the preoperative baseline characters, but their effect was thought to be inevitable. More prospective studies and researches are needed to explore and demonstrate the exact effect of statins on postoperative AF occurrence.

In a recent study, Dimitrios and his colleagues found that therapy with statins in patients with coronary artery disease and AF was associated with an increase in collagen degradation and cholesterol lowering.<sup>30</sup> And previous studies have also shown that atrial fibrosis with collagen deposition is the underlying substrate in AF, Kumagai also reported that a decreased fibrosis was found in all atrial regions in the atorvastatin group compared with the control group in a prospective study.<sup>6,41,42</sup> This evidence may imply that the anti-remodeling effect of statins may play an important role in preventing the occurrence of AF following cardiac surgery in some cases. In some cases whose AF occurrence did not decreased more than the control group, a decreased fibrosis was also found. In other reports the most researches found the decreased AF occurrence after electrical cardioversion by the use of statins, and most studies are observational designed. Until now the indication and mechanism are still not well known exactly, so further research is need to be done.<sup>43,44</sup> The contradictory result of our analysis is absolutely a support for the further research.

#### 4. Study limitations

Our study adds to the prevention effect of statins

on AF occurrence following cardiac surgery. However, some potential limitations may be apparent. Firstly, because of the lack of prospective published studies, the analysis based on 6 observational articles, which definitely would affect the final outcomes. Secondly, our included studies are not enough and it requires more related studies, which may be subjected to the potential biases of such studies. Thirdly, in converting non-normally distributed statistics to normally distributed statistics, there may be a cause of bias in this analysis. But in conclusion, our studies may be useful for clinical evidence.

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