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Review article

Statin therapy in the prevention of atrial fibrillation in the early postoperative period after coronary artery bypass grafting: A meta-analysis

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ABSTRACT

Background: Postoperative atrial fibrillation (POAF) is observed in the early postoperative period in approximately every third patient after coronary artery bypass grafting (CABG). The pathogenesis of POAF is multifactorial and is not yet fully studied. In many studies, postoperative inflammatory response has been extensively investigated as a potential basic factor of POAF. It is known that statins have anti-inflammatory properties. In some studies, pre- and perioperative use of statins has shown the decrease of incidence of POAF after CABG.

Objective: We conducted meta-analysis of randomized and observational studies of efficiency of statin therapy for the prevention of POAF after CABG.

Material and methods: The meta-analysis included 15 clinical trials of statins in 9369 patients with performed CABG during the past 10 years. 5598 patients (59.75%) were taking statins and 3771 patients (40.25%) were not taking statins. The following outcomes observed in the early postoperative period were studied: incidence of POAF, total mortality rate, total stroke rate, and total rate of myocardial infarction. The duration of hospitalization and levels of inflammatory markers before and after CABG were also assessed.

Results: The statin therapy reduced the incidence of POAF after CABG (OR = 0.48, 95% CI: 0.35–0.67, $P < 0.001$). Moreover, the statin therapy decreased the total length of hospital stay and levels of inflammatory markers in the blood serum.

Conclusion: The results of our meta-analysis leave no doubt in the presence of anti-inflammatory and anti-arrhythmic effect of statin therapy. We confirmed the overall positive role of using statins before CABG for POAF prevention.

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Contents

Introduction

Postoperative atrial fibrillation (POAF) is a fairly common complication of coronary artery bypass grafting (CABG). The frequency of POAF in the early postoperative period is 30–45% [1,2]. POAF after CABG is the major risk factor of stroke, myocardial infarction, prolonged hospitalization, and postoperative mortality [1,2]. Basic mechanism of POAF in the early postoperative period after CABG is multifactorial and not fully studied yet. However, several etiopathogenic mechanisms are undoubted. These mechanisms include the inflammation of pericardium, elevated catecholamine levels, autonomic dysfunction, and changes of blood volume and blood pressure. The emergence of the plurality of ''re-entry'' loops due to the dispersion of atrial refractoriness underlies the electrophysiological mechanisms of POAF after CABG [3,4]. Thus, the patients with structural changes in the atria before the CABG are more prone to the formation of ''re-entry'' tracks [5]. However, it should be noted that even in patients without structural changes, the physical damage of atrial myocardium in the result of the incision or perioperative ischemia can increase their arrhythmic potential [6,7].

The evidence of the important role of inflammation in the pathogenesis of POAF has been demonstrated in several studies. In particular, it was shown that the inflammation can change the atrial refractoriness by creating the ''re-entry'' loops and therefore giving rise to atrial fibrillation (AF) [8,9]. It is well known that operations with the cardio-pulmonary bypass are associated with a systemic inflammatory response, which may be partially the cause of POAF. According to the results of several studies, the leukocytosis which usually occurs in the first days after surgery with cardio-pulmonary bypass is an independent predictor of POAF [10,11].

The efficiency of statin therapy in the prevention of POAF in the early postoperative period after CABG has been actively studied in recent years. It is assumed that its beneficial effect in the prevention of POAF is associated with the pleiotropic (anti-inflammatory, antioxidant, and membrane-stabilized) properties of statins [12,13]. According to the results of many studies, the statin therapy reduces the level of markers associated with inflammation after CABG and other open-heart surgery [14–16].

A lot of clinical and experimental studies are devoted to the evaluation of the effectiveness of statins in the prevention of POAF after CABG, but their results are ambiguous. Many of these studies were carried out for a small number of patients. Moreover, different doses and types of statins were used in these studies. Besides, not all of them assess the role of inflammation in the POAF causing and effect of statin therapy on the duration of hospitalization.

For the purpose of data compilation and analysis of literature, we conducted an updated meta-analysis of randomized and observational studies of the statin usage in the prevention of POAF after CABG.

Materials and methods

The search of literature was conducted over the last 10 years (from 2005 to 2014) in the following databases: MEDLINE via Pubmed, Embase, Cochrane Database, Medscape, Directory of Open Access Journals, and Russian Science Citation Index, as well as on the web-sites devoted to clinical research (Clinical Center, National Institutes of Health, ClinicalStudyResults.org, ClinicalTrials.gov, and TheHeart.org).

The search strategy included the following key words in Russian and English: atrial fibrillation, ischemic heart disease, coronary artery bypass grafting, statins, and 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors. All relevant studies were used for further analysis.

To evaluate the effectiveness of statins in the prevention of POAF after CABG we used for the meta-analysis the pro- and retrospective observational studies that included patients who have undergone the isolated CABG and examined the association of statins with POAF and other various clinical outcomes (acute cerebrovascular accident, myocardial infarction, and so on). The studies that included patients with concomitant CABG with the correction of the valve disease and/or structural defects (left ventricular aneurysm, ventricular septal defect, etc.) were excluded from the meta-analysis.

The endpoints of the study were selected as follows: the frequency of POAF, the overall mortality rate in the early postoperative period, the incidence of stroke, myocardial infarction rate, length of hospitalization, and the level of inflammatory markers before and after CABG. As a result, 5

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randomized and 10 observational studies were selected for the meta-analysis. These studies included 9369 patients in all. Among them, 5598 (59.75%) patients were taking statins and 3771 (40.25%) patients were not taking statins. The characteristics of studies included in the meta-analysis are presented in Table 1 [17–31].

Zheng et al. [32] and Elgendy et al. [33] meta-analyses are among recent reviews on this subject. Our meta-analysis covers several new original studies [26,30,31], two of which were published in 2014–2015, and were not mentioned in previous meta-analyses [32,33]. Therefore, presented meta-analysis is relevant to present day. Also, number of patients in

Table 1 – Brief characteristics of studies included in the meta-analysis.

No.	Authors, year	Type of study	Groups of patients	Conclusion
1.	Marin et al., 2006 [17]	Observational retrospective study	Patients with statin therapy ($n = 144$) Patients without statin therapy ($n = 90$)	Statin therapy is associated with the decrease of POAF frequency after CABG (OR 0.52, 95% CI: 0.28–0.96, $P = 0.038$).
2.	Mariscalco et al., 2007 [18]	Observational retrospective study	Patients with statin therapy ($n = 218$) Control group ($n = 187$)	Statin therapy is associated with the decrease of POAF frequency ($P = 0.014$).
3.	Ozaydin et al., 2007 [19]	Observational retrospective study	Patients with statin therapy ($n = 267$) Control group ($n = 95$)	Statin therapy is associated with the decrease of POAF frequency ($P = 0.021$).
4.	Mannacio et al., 2008 [20]	Observational prospective study	Patients with statin therapy ($n = 100$) Control group ($n = 100$)	Statin therapy is associated with the decrease of POAF frequency ($P = 0.007$) and CRP level at the 4th day after CABG ($P < 0.001$).
5.	Song et al., 2008 [21]	Randomized prospective study	Patients with statin therapy ($n = 62$) Control group ($n = 62$)	Statin therapy is associated with the decrease of POAF frequency after CABG ($P = 0.048$).
6.	Ji et al., 2009 [22]	Randomized prospective study	Patients with statin therapy ($n = 71$) Control group ($n = 69$)	Statin therapy is associated with the decrease of POAF frequency ($P = 0.007$). At the 4th day after CABG, the CRP level is lower in patients with statin therapy ($P < 0.001$). CRP level is higher in patients with POAF than in patients without POAF ($P < 0.001$).
7.	Miceli et al., 2009 [23]	Observational retrospective study	Patients with statin therapy ($n = 2152$) Control group ($n = 2152$)	Statin therapy is associated with the increased risk of POAF ($P = 0.002$).
8.	Kinoshita et al., 2010 [24]	Observational retrospective study	Patients with statin therapy ($n = 360$) Control group ($n = 224$)	Statin therapy is associated with the decrease of POAF frequency after CABG ($P = 0.002$). Statin therapy has no influence on the CRP level at the 4th day after CABG ($P = 0.064$).
9.	Tamura et al., 2010 [25]	Observational retrospective study	Patients with statin therapy ($n = 84$) Control group ($n = 111$)	Statin therapy is not associated with the decrease of POAF frequency ($P = 0.337$).
10.	Gan et al., 2010 [26]	Observational retrospective study	Patients with statin therapy ($n = 320$) Control group ($n = 306$)	Statin therapy is not associated with the decrease of POAF frequency ($P = 0.080$).
11.	Sakamoto et al., 2011 [27]	Observational retrospective study	Patients with statin therapy ($n = 77$) Control group ($n = 126$)	Statin therapy is associated with the decrease of POAF frequency ($P = 0.007$). Statin therapy has no influence on the CRP level at the 4th day after CABG ($P = 0.2$). CRP level is higher in patients with POAF than in patients without POAF ($P = 0.007$).
12.	Sun et al., 2011 [28]	Observational retrospective study	Patients with statin therapy ($n = 49$) Control group ($n = 51$)	Statin therapy is associated with the decrease of POAF frequency ($P = 0.015$). Statin therapy decreases the CRP level at the 4th day after CABG ($P = 0.001$). CRP level is higher in patients with POAF than in patients without POAF ($P < 0.001$).
13.	Karimi et al., 2012 [29]	Observational retrospective study	Patients with statin therapy ($n = 1532$) Control group ($n = 75$)	Statin therapy is associated with the decrease of POAF frequency ($P = 0.015$).
14.	Bockeria et al., 2014 [30]	Observational retrospective study	Patients with statin therapy ($n = 132$) Control group ($n = 93$)	Statin therapy is associated with the decrease of POAF frequency ($P < 0.001$).
15.	Aydin et al., 2015 [31]	Randomized prospective study	Patients with statin therapy ($n = 30$) Control group ($n = 30$)	Statin therapy is associated with the decrease of POAF frequency ($P = 0.029$). Statin therapy does not decrease the CRP level at the 4th day after CABG ($P = 0.153$). CRP level is higher in patients with POAF than in patients without POAF ($P < 0.001$).

TIMR-1/MMR-1, index of remodeling of extracellular matrix.

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added studies increased up to 911 people. Therefore, data validity is considerably higher, which rose statistical significance of conducted meta-analysis. Another important feature of our meta-analysis is that in earlier reviews inflammatory marker analysis was not represented, while in present article we systematized 4 studies of this problem.

Statistical analysis

For binary data (the incidence of POAF, overall mortality, myocardial infarction, and stroke) we calculated the odds ratio (OR) and 95% confidence intervals (95% CI). For continuous variables (length of stay and the level of inflammatory markers) the standardized mean difference (SMD) and 95% confidence intervals (95% CI) were determined. To calculate the statistical parameters and construct the meta-graphs we used the Meta-Analysis Comprehensive v.2.0.

Results

In general, the statins significantly reduced the incidence of POAF after CABG compared to the control group (OR = 0.48, 95% CI: 0.35–0.67, $P < 0.001$; Fig. 1).

Among the inflammatory markers, the serum C-reactive protein (CRP) was the most investigated one. It was analyzed in four studies. The baseline CRP levels were not significantly different in the group of statin therapy and the control group (SMD = −0.34, 95% CI: −0.96 to −0.28, $P = 0.278$; Fig. 2A). On the 4th day after the surgery, the CRP was significantly higher in the control group compared to the patients treated with statins (SMD = 0.43, 95% CI: 0.204–0.648, $P < 0.001$; Fig. 2B). In the group of patients with POAF, the CRP was significantly higher than that in patients without POAF in the postoperative period (SMD = 1.74, 95% CI: 0.520–2.96, $P = 0.005$; Fig. 3).

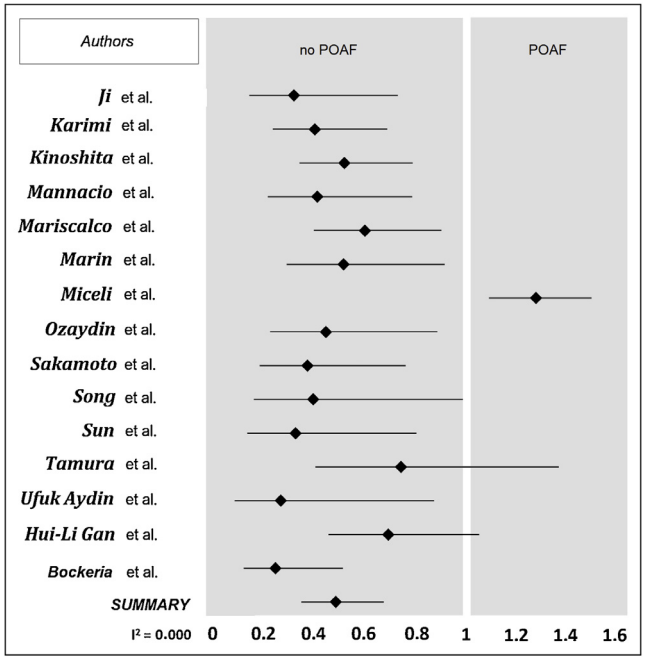

Fig. 1 – Effect of statin therapy on the occurrence of POAF in the early postoperative period after CABG. Data are presented as odds ratios with 95% confidence intervals.

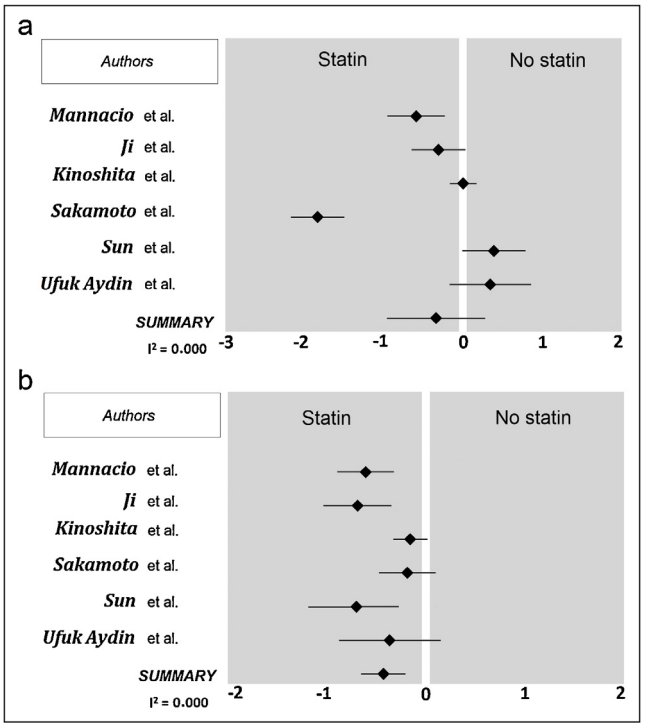

Fig. 2 – Effect of statin therapy on the baseline CRP levels (A) and CRP on the 4th day after CABG (B). Data are presented as standardized mean differences with 95% confidence intervals.

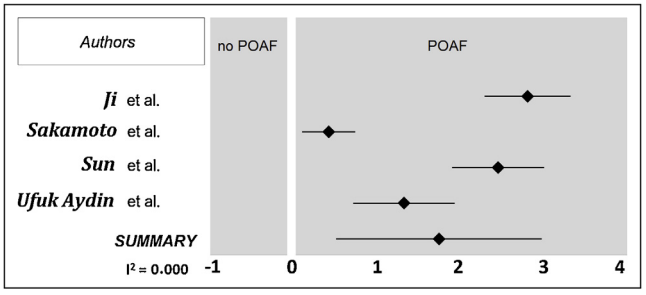

Fig. 3 – Differences between the patients with POAF and without POAF basing on CRP level. Data are presented as standardized mean differences with 95% confidence intervals.

Discussion

The prevention of POAF in the early postoperative period after CABG is the most urgent problem because of the annual increase of the number of these procedures performed in the world. The adverse effect of POAF on the outcome of surgical treatment of ischemic heart disease leads to the increased interest to the problem of its prevention. Amiodarone, β-blockers and sotalol have been proposed to reduce the

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incidence of POAF. However, it should be noted that many patients continue to experience paroxysmal POAF in the early postoperative period, despite the ongoing preventive therapy with the above-mentioned drugs.

There are also a large number of patients susceptible to such adverse effects of these drugs as proarrhythmic effect, bradycardia, sinoatrial and atrioventricular block, and hypotension. Moreover, the patients with reduced left ventricular function, chronic obstructive pulmonary disease, asthma, and kidney failure are often left without prevention due to the contraindications, despite the fact that these patients are in the high-risk group of POAF incidence.

In our meta-analysis, only in 3 of 15 studies the positive role of statins in the prevention of POAF was not found. For example, the study performed by Miceli et al. has revealed the negative effect of statins on the risk of POAF after CABG [23]. However, this study had several limitations including the absence of information about the number of patients taking β-blockers and other anti-arrhythmics in each group and lack of data on electrolyte balance, the structural anatomy of the heart (left atrium), and the duration and dose of preoperative treatment with statins. Also the authors did not give the information about the presence/absence of chronic inflammatory and infectious diseases in patients involved in their study.

Tamura and Gan have found a tendency for decreasing the risk of POAF by statins, but this result was not statistically significant [25,26]. The lack of data about the presence of atrial fibrillation in patients prior to CABG, which is one of the most important factors in the development of atrial fibrillation in the early postoperative period, could affect the results of this study.

All other studies have shown a statistically significant reduction in the incidence of POAF in the early postoperative period after CABG. The meta-analysis of data from 6 studies has shown that statins lead to CRP level decreasing in the postoperative period. The CRP concentration is found to be higher in patients with POAF than in patients without it. It is also necessary to mention the results of two studies which investigated the leukocytes and extracellular matrix as inflammatory markers. Index of remodeling of extracellular matrix (TIMR-1/MMP-1) was higher in patients without atrial fibrillation within 24 h after CABG. The statin therapy was accompanied by the increased levels of TIMP-1 and TIMP-index 1/MMP-1. The level of leukocytes on the 4th day after CABG decreased in the statin group and leukocyte count was higher in patients with atrial fibrillation than in patients without it [17,30].

According to numerous epidemiological studies, there is a close relationship between the CRP levels and risk of cardiovascular complications in patients with previously diagnosed ischemic heart disease. The necessity of decreasing the CRP levels is demonstrated by the results of PROVE-IT TIMI 22 and REVERSAL. In these studies, for the case of equal target level of low-density lipoprotein cholesterol achieved by the statin therapy, the patients with low CRP concentrations had better outcomes and less progression of atherosclerosis according to intravascular ultrasound [34]. The statins are the prospective and actively studied drugs for the medical decreasing of CRP levels in the serum. The exact mechanism responsible for the reduction of CRP and risk of atrial fibrillation under the influence of statins is not known yet.

Conclusion

The available research data leave no doubt in the presence of anti-inflammatory and anti-arrhythmic effects of statins [35]. The meta-analysis of 15 clinical studies confirmed the important role of using statins in patients prior to CABG and demonstrated the influence of statins on the decrease of POAF frequency in the early postoperative period.

Limitations

We understand that there is a relatively large heterogeneity of associations of CRP levels, statin use, and the risk of POAF in the subset of studies assessing the problem. Our meta-analysis summarizes several known studies. However, new studies are necessary to clarify this problem.

Conflict of interest

None declared.

Ethical statement

Authors state that the research was conducted according to ethical standards.

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