

# Efficiency of postoperative statin treatment for preventing new-onset postoperative atrial fibrillation in patients undergoing isolated coronary artery bypass grafting: A prospective randomized study

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## ABSTRACT

**Objective:** Recent studies have demonstrated that preoperative statin therapy reduces the incidence of postoperative atrial fibrillation (AF). The objective of this study was to assess the efficacy of statin therapy started in the early postoperative period for the prevention from new-onset AF after isolated coronary artery bypass grafting (CABG).

**Methods:** This prospective and randomized study consisted of 60 consecutive patients who underwent elective isolated CABG. Patients were divided into two groups to examine the influence of statins: those with postoperative statin therapy (statin group, n=30) and those without it (non-statin group, n=30). Patient data were collected and analyzed prospectively. In the statin group, each extubated patient was given 40 mg of atorvastatin per day, starting from an average of 6 hours after the operation.

**Results:** The overall incidence of postoperative AF was 30%. Postoperative AF occurred in 5 patients (16.7%) in the statin group. This was significantly lower compared with 13 patients (43.3%) in the non-statin group (p=0.049). According to the multivariate analysis, postoperative atorvastatin reduced the risk of postoperative AF by 49% [odds ratio (OR) 0.512, 95% confidence interval (CI) 0.005 to 0.517, p=0.012]. Also, age was an independent predictor of postoperative AF (OR 1.299, 95% CI 1.115 to 1.514, p=0.001).

**Conclusion:** Postoperative statin therapy seems to reduce new-onset AF after isolated CABG in our study. (*Anatol J Cardiol* 2015; 15: 491-5)

**Keywords:** statin, atrial fibrillation, coronary artery bypass grafting

## Introduction

Atrial fibrillation (AF) is the most common rhythm disturbance after coronary artery bypass grafting (CABG) and is reported to occur in 20% to 40% of patients (1-4). AF is associated with increased risk of mortality, postoperative thromboembolic stroke, and hemodynamic compromise and may require additional treatment that increases the hospital stay and costs (2-4). The precise pathophysiological mechanism of AF is unknown. However, most of the evidence suggests that it is multifactorial. Recently, increasing evidence shows that inflammation might play an important role in the pathophysiological mechanism of AF (2, 4-6). Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are a group of drugs used for the treatment of hyperlipidemia and are also known to be anti-oxidant and anti-inflammatory. Preoperative statin therapy is also shown to reduce the incidence of postoperative AF (1, 3, 7).

Recently, CABG has been performed frequently on the day after coronary angiography; therefore, preoperative statin therapy can not be administered to most of the patients. The objective of this study was to assess the efficacy of statin therapy started in the early postoperative period for the prevention of new-onset AF after isolated CABG.

## Methods

This prospective and randomized study consisted of 60 consecutive patients who underwent elective isolated CABG from January to December 2012. The exclusion criteria were as follows: preoperative statin therapy; emergency CABG; history of AF; elevated liver enzymes (aspartate aminotransferase/alanine aminotransferase); cardiac valvular dysfunction; chronic renal failure; functional thyroid deficiency; chronic obstructive pulmonary disease; and cerebrovascular or peripheral arterial dis-

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ease. This study was granted full approval of the institutional review board and ethical committee.

To assign patients to the statin or non-statin groups, a computer-generated randomization sequence was used. Randomization was performed in two blocks of 30 patients, without taking any of the patients' demographic characteristics into account. The assigned therapy was single-blinded; the individual subjects did not know whether they were included in the study or control group.

The randomization groups to examine the influence of statins consisted of patients with postoperative statin therapy (statin group, n=30) and those without it (non-statin group, n=30). In addition, patients were divided into two groups to determine independent predictors (apart from the exclusion criteria) of postoperative AF: those with postoperative AF (AF group, n: 18) and those without it (non-AF group, n: 42).

Standard anesthetic induction with intravenous propofol, fentanyl, and rocuronium bromide following standard [electrocardiography (ECG)], monitorization arterial catheterization, sPO<sub>2</sub>) was performed in all patients. The anesthetic management was made using inhalation of 60% oxygen and 6% desflurane. All of the patients were operated on with median sternotomy using cardiopulmonary bypass (CPB). CPB was obtained by cannulation of the ascending aorta and right atrium (double-stage single cannula) under moderate hemodilution (hematocrit of 22%-25%) and moderate systemic hypothermia (32°C). Myocardial protection was achieved by topical hypothermia and antegrade and retrograde cold blood cardioplegia (4°C).

Patients were extubated with PaO<sub>2</sub> >60 mm Hg, 40% FIO<sub>2</sub>, continuous positive airway pressure <5 mbar, PaCO<sub>2</sub> <50 mm Hg, and arterial pH >7.35. The serum electrolyte (magnesium, calcium, potassium) level imbalances were properly stabilized. In the statin group, each extubated patient was given 40 mg of atorvastatin per day, starting from an average of 6 hours after the operation, to the end of the first month. The other routine postoperative medications were beta-blockers (metoprolol), nitroglycerine, famotidine, acetylsalicylic acid (300 mg/day), N-acetyl cysteine, and nonsteroidal anti-inflammatory drugs for both groups. Perioperative need for blood products was determined on an individual, patient-by-patient basis; in general, blood transfusions were given when hemoglobin was <9 g/dL.

C-reactive protein (CRP) levels were assessed in all patients before and 1, 7, and 14 days after CABG. From the intensive care unit, patients were transferred to a monitored unit, where 3-lead telemetric monitoring was performed continuously for at least 5 days after the operation; in addition, patients had a 12-lead electrocardiography (ECG) daily until hospital discharge. AF was defined as episodes lasting for more than 5 minutes detected by telemetry or requiring therapy due to hemodynamic instability. The outpatient ECG controls were done weekly. Detected AF was managed with intravenous amiodarone therapy protocol (5-mg/kg bolus intravenous infusion followed by 15-mg/kg infusion for 24 hours), and the patients were discharged with instructions to undergo oral amiodarone (2x200mg) therapy for at least 30 days.

**Table 1. Preoperative patient demographic and clinical features**

	Statin	Non-statin	P
Age, years	62.6±10.9	62.4±12.2	.938
Male	24 (80)	23 (76)	1.0
Body mass index ≥30	10 (33)	11 (36)	1.0
NYHA ≥III-IV	2 (6)	3 (10)	1.0
Unstable angina	3 (10)	4 (13)	1.0
Hypertension	16 (53)	18 (60)	.794
Hyperlipidemia	11 (36)	11 (36)	1.0
Diabetes mellitus	13 (43)	11 (36)	.792
Left ventricle hypertrophy	11 (36)	13 (43)	.792
Left ventricular EF≤50	7 (23)	9 (30)	.770
Left atrium enlargement	4 (13)	2 (6)	.671
LVEDD ≥5.7 cm	3 (10)	2 (6)	1.0
LVESD ≥3.5 cm	5 (16)	6 (20)	1.0
LMCA stenosis (≥50%)	6 (20)	5 (16)	1.0
Right coronary stenosis (≥70%)	24 (80)	25 (83)	1.0
Calcium channel blockers	8 (26)	6 (20)	.760
Beta-blockers	19 (56)	17 (63)	.792
ACE inhibitors	12 (40)	13 (43)	1.0

LMCA - left main coronary artery; LVEDD - left ventricular end-diastolic diameter; LVESD - left ventricular end-systolic diameter; values are given as number of patients (%) or mean±SD

Continuous variables were presented as mean ± standard deviation and were compared between groups using t-test. For comparison of quantitative data, student's t-test (parametric) or Mann-Whitney U test (nonparametric) was used as appropriate. Comparison of the qualitative data was performed using the chi-square test, applying the Yates correction to obtain the most conservative results. At first, univariate analysis was performed to examine the relationship between variables and statin therapy and the relationship between variables and the development of postoperative AF. Then, preoperative and perioperative variables that showed a univariate relationship (p<0.25) were entered into a multivariate logistic regression analysis model to determine the independent predictors for postoperative AF. All analyses were performed using SPSS statistical software, version 17.0 for Windows (SPSS Inc., Chicago, IL, USA). A p value of less than 0.05 was considered statistically significant.

## Results

The preoperative, perioperative, and postoperative variables between the statin and non-statin groups were similar (Table 1 and 2). No elevation in liver enzymes (aspartate aminotransferase/alanine aminotransferase) was detected in patients with atorvastatin; therefore, the drug was not stopped. Among the preoperative variables, there was no age difference between the statin and non-statin groups (p=0.938). Regarding postoperative factors, there were no significant differences between groups in

**Table 2. Perioperative and postoperative features**

	Statin	Non-statin	P
Cross-clamp duration, min	67.5±16.3	63.7±13.6	.337
CPB duration, min	98.6±22.5	93.7±19.3	.376
Distal anastomoses	2.8±0.7	2.6±0.6	.456
Intra-aortic balloon pumping	1 (3)	0 (0)	1.0
Postoperative use of inotropic agents	4 (13)	5 (16)	1.0
Perioperative myocardial infarction	1 (3)	0 (0)	1.0
Ventilation, hours	5.5±1.3	5.8±1.6	.674
Postoperative body temperature ≥38°C	8 (26)	6 (20)	.760
Deep sternal wound infection	1 (3)	0 (0)	1.0
Blood transfusion	5 (16)	4 (13)	1.0
Cerebrovascular disease	2 (6)	1 (3)	1.0
Postoperative potassium ≤3.5 mEq/L	7 (23)	6 (20)	1.0
Postoperative magnesium ≤2 mg/dL	6 (20)	4 (13)	.729
Postoperative hemoglobin ≤9 g/dL	5 (16)	4 (13)	1.0
ICU stay, days	2.3±1.05 (2-7)	2.4±1.5 (2-9)	.966
Hospital stay, days	6.9±2.6 (5-18)	7.4±3.5 (5-20)	.750
Atrial fibrillation	5 (16)	13 (43)	.049
Onset of AF (postoperative day)	3.4±3.08 (2-6)	4.2±1.9 (1-13)	.703
30-day mortality	1 (3)	0 (0)	1.0

CPB - cardiopulmonary bypass; values are given as number of patients (%) or mean±SD (min-max)

postoperative ventilation time, intensive care unit stay, and incidence of operative complications.

The results of the univariate analysis of the AF and non-AF groups are shown in Table 3. The AF group was significantly older compared to the non-AF group ( $p=0.001$ ). Regarding preoperative oral medication, calcium blockers, angiotensin receptor blockers, and beta-blockers did not appear to influence the development of postoperative new-onset AF. The usage rate of beta-blockers between the AF group and the non-AF group was similar (61% versus 59%,  $p=1.0$ ) (Table 3).

The overall incidence of postoperative new-onset AF was 30%. Postoperative new-onset AF occurred in 5 patients (16.7%) in the statin group. This was significantly lower compared with 13 patients (43.3%) in the non-statin group ( $p=0.049$ ). The time between surgery and AF development was similar in the statin group compared with the non-statin group ( $3.40±3.08$  days versus  $4.23±1.94$  days,  $p=0.703$ ). Intravenous infusion of amiodarone restored normal sinus rhythm in all patients. No patient had recurrence of the arrhythmia after cessation of the first episode. During the first month of follow-up, all patients remained in normal sinus rhythm, and no episodes of atrial fibrillation occurred in either group.

**Table 3. Univariate analysis of the AF group and non-AF group**

	AF (n:18)	Non-AF (n:42)	P
Age, years	72.1±7.8	58.4±10.3	.001
Male	17 (94)	30 (71)	.084
Body mass index ≥30	10 (56)	11 (26)	.059
NYHA ≥III-IV	1 (5)	4 (9)	1.0
Unstable angina	3 (16)	4 (9)	.419
Hypertension	7 (38)	27 (64)	.125
Hyperlipidemia	8 (44)	14 (33)	.599
Diabetes mellitus	6 (33)	18 (42)	.687
Left ventricular hypertrophy	10 (56)	14 (33)	.186
Left ventricular EF≤50	9 (50)	7 (16)	.012
Left atrium enlargement	2 (11)	4 (9)	1.0
LVEDD ≥5.7 cm	4 (22)	1 (2)	.025
LVESS ≥3.5 cm	6 (33)	5 (11)	.049
LMCA stenosis (≥50%)	3 (16)	8 (19)	1.0
Right coronary stenosis (≥70%)	15 (83)	34 (81)	1.0
Calcium channel blockers	4 (22)	10 (23)	1.0
Beta-blockers	11 (61)	25 (59)	1.0
ACE inhibitors	8 (44)	17 (40)	1.0
Cross-clamp duration, min	68.6±10.5	64.3±16.5	.323
CPB duration, min	101.4±12.5	93.9±23.4	.356
Distal anastomoses	2.8±0.4	2.6±0.7	.253
Intra-aortic balloon pumping	1 (5)	0 (0)	.300
Postoperative use of inotropic agents	5 (27)	4 (9)	.111
Perioperative myocardial infarction	1 (5)	0 (0)	.300
Ventilation, hours	5.4±0.9	5.7±1.7	.822
Postoperative body temperature ≥38°C	6 (33)	8 (19)	.319
Deep sternal wound infection	1 (5)	0 (0)	.300
Blood transfusion	3 (16)	6 (14)	1.0
Cerebrovascular disease	1 (5)	2 (4)	1.0
Postoperative potassium ≤3.5 mEq/L	4 (22)	9 (21)	1.0
Postoperative magnesium ≤2 mg/dL	6 (33)	4 (9)	.052
Postoperative hemoglobin ≤9 g/dL	4 (22)	5 (11)	.431
ICU stay, days	2.5±1.7 (2-9)	2.2±1.08 (2-7)	.804
Hospital stay, days	7.8±3.8 (5-18)	6.9±2.8 (5-20)	.620
30-days mortality	1 (5)	0 (0)	.300

CPB - cardiopulmonary bypass; LMCA - left main coronary artery; LVEDD - left ventricular end-diastolic diameter; LVESS - left ventricular end-systolic diameter; values are given as number of patients (%) or mean±SD (min-max)

According to the multivariate analysis, postoperative atorvastatin reduced the risk of postoperative AF by 49% [odds ratio (OR) 0.512, 95% confidence interval (CI) 0.005 to 0.517,  $p=0.012$ ]. Also, age was an independent predictor of postoperative AF (OR 1.299, 95% CI 1.115 to 1.514,  $p=0.001$ ).

**Table 4. Time-dependent change of CRP levels (mg/L)**

	Statin	Non-statin	P	AF	Non-AF	P
Preoperative CRP	2.9±1.4	2.5±0.9	.25	2.7±1.7	2.7±1.2	.98
Postoperative CRP Day 1	63±17.6	69.8±20.1	.17	81.7±14.6	59.8±16.9	.001
Postoperative CRP Day 7	33.7±13.7	35.3±14.9	.67	50.8±10.3	27.5±9.07	.001
Postoperative CRP Day 14	12.4±10.1	22.6±11.3	.001	31.9±9.3	11.3±5.9	.001
CRP- C-reactive protein						

As for the relation with inflammation, preoperative CRP levels showed no significant differences between the statin and the non-statin groups or between the AF and the non-AF groups. However, CRP levels on postoperative Day 14 were significantly lower in the statin group compared with the non-statin group (12.46±10.14 mg/L versus 22.60±11.39 mg/L,  $p=0.001$ ). CRP levels were significantly lower in patients without AF versus those with AF ( $p=0.001$ ). The detailed results are shown in Table 4.

## Discussion

The present prospective and randomized study with statin therapy regimen in the early postoperative period showed a statistically significant decrease in postoperative new-onset AF and a significant decrease in CRP levels in patients undergoing isolated CABG.

Prevention or minimization of new-onset AF after cardiac surgery either pharmacologically or non-pharmacologically is a reasonable goal. Treatment strategies for the prevention of postoperative AF have been mainly focused on antiarrhythmic medications, such as amiodarone, digitalis,  $\beta$ -blockers, and calcium channel blockers which have potential cardiovascular side effects, such as hypotension, bradycardia, atrioventricular block, torsades de pointes, and others (1, 3, 6, 8, 9). Statins have anti-inflammatory, antioxidant, coronary plaque regressive and antiarrhythmic effects and also play a role in extracellular matrix modulation (1, 2, 4, 5). Moreover, recent studies have revealed that statins have preventive effects on postoperative new-onset AF (1, 2, 7, 10-13). In these studies, statin therapy was started in the preoperative period or the patients were already receiving statin therapy preoperatively. With the fact that, nowadays there are more patients undergoing CABG very early after coronary angiography; in this study, statin therapy was initiated in the early postoperative period in patients who were not receiving statins preoperatively. As a result, statin reduced the risk of postoperative AF, with an incidence of 16% in the statin group versus 43% in the nonstatin group.

ARMYDA-3 was the first randomized, controlled trial to evaluate the impact of preoperative statin therapy on postoperative AF (2). This was the largest randomized study; 200 patients were randomized to either preoperative 40 mg/day of atorvastatin or placebo starting 7 days before heart surgery. As a result,

preoperative atorvastatin reduced the risk of postoperative AF by 61%, with an incidence of 35% in the atorvastatin group versus 57% in the placebo group. In this study, peak CRP levels were not different between the placebo and atorvastatin groups, but CRP levels were significantly higher in the AF-developing group compared to those who did not develop AF.

In another retrospective study, Sakamoto et al. (1) evaluated the effects of statins on postoperative AF in 203 patients (77 of whom received preoperative statins) who underwent isolated coronary artery bypass grafting. They concluded that preoperative statin treatment reduced the risk of postoperative AF by 67%, with an incidence of 16% in the statin group versus 33% in the non-statin group.

It was shown in meta-analyses that the use of statins significantly decreases the risk of incidence or recurrence of AF in patients in sinus rhythm with a history of previous AF, in those who have undergone cardiac surgery, or after acute coronary syndrome (7).

In the studies mentioned above, patients who were administered statin preoperatively or under previous statin treatment were evaluated comparing different types and differential doses of statin therapies. Moreover, there was no significant difference between the effect of a higher (80 mg/d) and a lower dose (40 mg/d) of statin therapy in reducing postoperative AF, and 40 mg of statin had the greatest preventative effect, whereas 10 mg of statin did not influence postoperative AF (12). In our study, the effect of a standard dose of statin therapy (40 mg of atorvastatin), started in the early postoperative period, on the incidence of postoperative AF was sought after. Also, the univariate and multivariate analysis revealed that postoperative statin therapy had a significant preventative effect on the development of AF after CABG in our study.

Recent clinical studies have also explored the possible role of inflammatory mechanisms in the pathogenesis of AF after cardiac surgery (2, 5-7). In our study, CRP levels were significantly lower in patients without AF versus those with AF. CRP levels on the 14th postoperative day were significantly lower in the statin group compared with the non-statin group. These findings appear to confirm the suggestion that higher inflammatory status is an important factor in the development of postoperative AF.

Sakamoto et al. (1) detected a delay of approximately 2 days in the occurrence of AF in patients with preoperative statin therapy versus without statin therapy. This fact is meaningful for postoperative care, as it indicates that preoperative statin therapy can avoid AF development in unstable hemodynamics immediately after surgery. The patients did not have preoperative statin therapy in our study, and we also did not detect any difference between the onset of the first postoperative AF. Therefore, we suggest that statin therapy should be started preoperatively if available.

Atrial fibrillation is a common complication after CABG and is reported to occur in 20%-40% of patients (1-4). Such a great range of difference in the incidence of AF was reported to possibly occur due to the increased duration of usage and availability of postoperative monitors (4). In our study, the incidence of AF was 30%, which is similar to the reports.



Previous studies also revealed that beta-blockers have AF-preventive effects (1, 3, 14-16). In our study, 36 patients were administered beta-blockers preoperatively, but there was no significant difference in preoperative beta-blocker usage between the AF and the non-AF groups. In our study, the usage of beta-blockers preoperatively in most of the patients and the routine administration of postoperative beta-blockers in all of the patients may explain this situation.

Advanced patient age has been repeatedly reported as an independent predictor of AF after CABG (1, 2, 17, 18). Previously, many studies of postoperative AF have been done and described that predictors of postoperative AF were older age, previous history of AF, male gender, decreased left ventricular ejection fraction, valvular heart surgery, left atrial enlargement, chronic obstructive pulmonary disease, chronic renal failure, and diabetes mellitus (1, 3, 14, 16). Similarly, multivariate analysis showed advanced age to be an independent preoperative predictor of postoperative AF in our study.

## Study limitations

There are some limitations of our study. We studied only CRP in our study as a marker of inflammation; however, other proinflammatory markers could have been studied. Exclusion of patients with preoperative statin therapy, emergency CABG, history of AF, elevated liver enzymes (aspartate aminotransferase/alanine aminotransferase), cardiac valvular dysfunction, chronic renal failure, functional thyroid deficiency, chronic obstructive pulmonary disease, cerebrovascular or peripheral arterial disease, and off-pump CABG might have reduced the patient population in our study. However, we think that this condition provided a uniform distribution.

## Conclusion

In conclusion, postoperative statin therapy seemed to reduce AF development after CABG in our study. We suggest that routine administration of statins seems to be useful in patients undergoing elective CABG for the prevention of postoperative AF.

**Conflict of interest:** None declared.

**Peer-review:** Externally peer-reviewed.

**Authorship contributions:** Concept - U.A., C.U.K., A.L.O.; Design - U.A., T.T., C.U.K., Ç.D.; Supervision - U.A., C.U.K.; Resource - U.A., M.Y., Ç.D., Y.A., T.T., A.L.O., C.U.K.; Materials - U.A.; Data collection &/or processing - U.A., Ç.D., M.Y., C.U.K., A.L.O., Y.A., T.T.; Analysis &/or interpretation - U.A., M.Y., Y.A., T.T., C.U.K.; Literature search - U.A., T.T., A.L.O., Ç.D.; Writing - U.A., M.Y., T.T.; Critical review - U.A., M.Y., Ç.D., Y.A., T.T., A.L.O., C.U.K.

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