ORIGINAL ARTICLE

Effects of perioperative statin treatment on postoperative atrial fibrillation and cardiac mortality in patients undergoing coronary artery bypass grafting: a propensity score analysis

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ABSTRACT

Aim To evaluate the effect of perioperative statin treatment on postoperative atrial fibrillation and cardiac mortality in patients undergoing coronary artery bypass grafting.

Methods A total of 1890 patients who underwent isolated coronary artery bypass were analyzed retrospectively, of which 425 patients (22.4%) older than 70 were included in the study. The demographic properties, preoperative, operative and postoperative data and other medications of these patients were recorded. Continuous preoperative and postoperative atorvastatin therapy were received by 124 (29.17%) patients; 301 (70.82%) patients were matched to a control group (no-statin group). The two groups were matched by propensity score analysis in terms of atrial fibrillation development and cardiac mortality.

Results Medical history, medical treatment, cardiovascular history, and operative characteristics demonstrated significant heterogeneity in both groups. Postoperative atrial fibrillation was similar in both groups. Before propensity score matching, the percentages of patients in postoperative atrial fibrillation with respect to Atorvastain-group and No-statin-group were 13.71 and 10.3 respectively; however, those were 13.71 and 14.51 after matching. In a multivariate regression analysis, five-vessel bypass (odds ratio OR, 2.354; 95% confidence interval CI, 0.99 to 5.57) was an independent predictor of postoperative atrial fibrillation in patients undergoing coronary artery bypass grafting. In-hospital mortality was higher in the Atorvastatin-group compared with the No-statin-group: 124 (8.9%) versus 301 (3.7%), respectively; p=0.027).

Conclusion Perioperative atorvastatin treatment is not found to be associated with reduced postoperative atrial fibrillation and cardiac mortality in patients undergoing isolated coronary artery bypass grafting above the age of seventy years.

Key words: preoperative statin therapy, coronary artery bypass grafting, postoperative atrial fibrillation, cardiac mortality, propensity score analysis

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Original submission:
20 January 2015;
Revised submission:
13 March 2015;
Accepted:
16 March 2015.

Med Glas (Zenica) 2015; 13(2):

INTRODUCTION

Atrial fibrillation (AF) occurs in 16% to 33% of patients undergoing coronary artery bypass grafting (CABG) (1,2). Patient age is one of the most important risk factors postoperative AF, more than 50% for patients older than 80 years undergoing CABG [3]. Moreover, a variety of pharmacological agents (4, 5) are thus commonly used to prevent AF after CABG. It is suggested that statins are associated with reduced risk of postoperative atrial fibrillation (6). In Atorvastatin for Reduction of Myocardial Dysrhythmia After Cardiac Surgery (ARMYDA-3) trial, preoperative atorvastatin treatment 7 days before CABG resulted in 61% decrease for the new-onset atrial fibrillation compared with placebo (35% vs 57%, respectively; p=0.003) (7). Postoperative AF increases hospital mortality (1, 8). Almassi and his colleagues first reported that 6-month survival after cardiac surgery decreased in patients affected by postoperative AF compared with patients without it (9.4% vs 4.2%, respectively) (9).

We retrospectively evaluated whether perioperative atorvastatin treatment was associated with effective prevention of postoperative atrial fibrillation and cardiac mortality in patients aged over seventy years after CABG, as well as two different doses and duration of atorvastatin treatment in this surgical cohort.

PATIENTS AND METHODS

Data collection and patient selection

We retrospectively evaluated consecutive 1890 patients (above the age of 70) attended to the Ankara Ataturk Education and Research Hospital, Cardiovascular Surgery Department from June 2004 to April 2012 and who underwent CABG.

A total of 425 eligible patients were selected for the study . All patients who would have the coronary bypass surgery and no AF before surgery were included in this study. Patients with documented preoperative AF and associated cardiac surgery were excluded from the study. Routine electrocardiograms were obtained before the operation, on admission to the intensive care unit, for the first 72 hours after the surgery and every day thereafter until hospital discharge.

Patients were divided into two groups: Atorvastatin Group (n=124, 29.17%) and No-statin Group (n=301, 70.82%). Patients in the Atorvastatin group received two different doses (20 and 40 mg) of atorvastatin starting within several weeks before the operation and throughout the postoperative period. The two groups were matched by propensity score analysis in terms of atrial fibrillation development and cardiac mortality.

Primary and secondary end points

The primary end points were the development of postoperative AF and cardiac mortality during the hospital stay. Postoperative AF was indicated as lasting for more than 10 minutes with symptoms. Cardiac mortality was defined as in-hospital-mortality. Secondary end points were dose and duration of atorvastatin. Dose table for usage of atorvastatin was classified as four different categories: 10 mg, 20 mg, 40 mg and 80 mg. Time table for atorvastatin was analyzed according to the duration of the statin usage: $\leq$ 1 week, 1-2 weeks and > 2 week.

In our institution, we prefer to use amiodarone in the management of postoperative AF after coronary surgery, electrical cardioversion being reserved only in those patients unresponsive to amiodarone treatment or having hemodynamic compromise. Considering embolic events, our routine practice was to start anticoagulation treatment with enoxaparin in all patients postoperatively.

Operative procedure

All patients underwent isolated CABG surgery and performed using conventional procedures. Induction and maintenance of anesthesia were similar for all patients and consisted of fentanyl, midazolam and pancuronium bromide. All operations were done with a median sternotomy incision. Cardiopulmonary bypass was performed in a standard fashion with the use of a hollow fiber membrane oxygenator (Dideco; Sorin Group, Mirandola, Italy) and a roller pump (Stöckert; Sorin Group, Mirandola, Italy), with high ascending aortic cannulation added to right atrium cannulation. Cardioplegic arrest was achieved with cold blood cardioplegia infused into the ascending aorta. Moderate temperature was about 32 ºC. Distal anastomosis was performed under the cross-clamp and proximal anastomosis was completed under the side-clamp. Intra-aortic ballon counterpulsation was inserted into the patients who had hemodynamic instability in the perioperative period.

Statistical analysis

Variables with a significance level of less than 0.2 were entered into a multivariable logit regression model and predictors of atorvastatin-group membership were identified. The propensity score matching approach is an alternative approach to address the potential selection bias (endogeneity) in the treatment effects. Predictors for inclusion in the atorvastatin-group, as identified by multivariate regression analysis of co-variables, followed by logistic regression, were used to create the propensity score model to adjust outcomes. Univariate analysis of all patients was also done for the development (or not) of postoperative atrial fibrilation (PAF). Variables that were found to have a value of $p<0.20$ in the univariate analysis were examined by multivariate logistic regression to determine predictors of PAF. Logistic regression with forward elimination determined the most important denominators for the development of PAF or not.

Student t-test requires that the continuous variable should be normally distributed, but Mann-Whitney U test does not assume that the continuous variable is normally distributed. It only assumes that the variable is at least ordinal. Continuous and/or ordinal variables in our data do not satisfy the normality. Then, Mann-Whitney U test was used for continuous and/or ordinal variables to compare two groups. Chi-square test assumes the expected value of each cell is five or higher, but the Fisher's exact test has no such assumption and can be used regardless of how small the expected frequency is. Then, chi-square test was used for categorical variables if the expected value of each cell is five or higher in the data. In addition, Fisher's exact test was conducted in the case of violations of this assumption for some categorical variables in our data. Values of $p<0.05$ were considered statistically significant.

RESULTS

Patients' characteristics

The mean patient age was 74.4±3.2 years in Atorvastatin-Group versus 73.99±3.78 years in No-statin-Group at the time of surgery (p=0.056). Females surprisingly were higher in both groups; 86 (69.4%) patients in Atorvastatin-Group versus 189

Table 1. Demographic variables for atorvastatin and no statin groups

Variables*	Atorvastatin-Group (n=124)	No-statin-Group (n=301)	p
Age	74.4±3.2	73.99±3.78	0.056
Females	86 (69.4%)	189 (62.8%)	0.198
Diabetes Mellitus	42 (33.9%)	110 (36.5%)	0.601
Hypertension	80 (64.5%)	174 (57.8%)	0.200
Chronic obstructive pulmonary disease	30 (24.2%)	69 (22.9%)	0.778
Creatinine	1.21±0.7	1.39±2.9	0.331
Other medications			
ß-blockers	104 (83.9%)	210 (69.8%)	0.003
Angiotension converting enzyme inhibitors	66 (53.2%)	93 (30.9%)	<0.001
Calcium channel blockers	26 (21%)	32 (10.6%)	0.005
Cardiac status			
Class III-IV angina	69 (55.6%)	77 (25.6%)	<0.001
New York Heart Association class III-IV	21 (16.9%)	64 (21.2%)	0.311
Previous myocardial infarction	13 (10.5%)	51 (16.9%)	0.091
Ejection fraction <0.50	34 (27.4%)	50 (16.6%)	0.011
Body surface area	1.76±0.19	1.73±0.17	0.138
Emergency	3 (2.4%)	2 (0.7%)	0.151
Cross-clamp time (minutes)	48.23±12.8	45.7±14.1	0.020
Cardiopulmonary bypass time (minutes)	82.1±30.8	77.2±41.2	0.003
Inotropic support	80 (64.5%)	256 (85%)	<0.001
Intra-aortic balloon counter-pulsation	25 (20.2%)	24 (8%)	<0.001
Exitus	11 (8.9%)	11 (3.7%)	0.027

*Categorical data are numbers (percentage); continuous data are means ± standard deviation.

Table 2. Demographic variables for all patients with and without atrial fibrillation (AF)

Variables*	AF (n=48)	no-AF (377)	p
Age	74.67±3.77	74.04±3.60	0.209
Females	30 (62.5%)	245 (65%)	0.734
Diabetes Mellitus	11 (22.9%)	141 (37.4%)	0.049
Hypertension	32 (66.7%)	222 (58.9%)	0.301
Chronic obstructive pulmonary disease	13 (27.1%)	86 (22.8%)	0.510
Creatinine	1.29±0.77	1.35±2.57	0.963
Other medications			
ß-blockers	35 (72.9%)	279 (74%)	0.872
Angiotension converting enzyme inhibitors	18 (37.5%)	141(37.4%)	0.989
Calcium channel blockers	9 (18.8%)	49 (13%)	0.274
Cardiac status			
Class III-IV angina	21 (43.7%)	125 (33.2%)	0.145
New York Heart Association class III-IV	10 (20.8%)	75 (19.9%)	0.878
Previous myocardial infarction	7 (14.6%)	57 (15.1%)	0.922
Ejection fraction <0.50	12 (25%)	72 (19.1%)	0.334
Body surface area	1.73±0.16	1.74±0.18	0.479
Emergency	1 (2.1%)	4 (1.1%)	0.452
Cross-clamp time (minutes)	49.57 (11.14%)	46.06 (13.99%)	0.052
Cardiopulmonary bypass time (minutes)	80.23±17.57	78.42±40.4	0.054
Inotropic support	38 (79.2%)	298 (79.1%)	0.984
Intra-aortic balloon counterpulsation	8 (16.7%)	41 (10.9%)	0.237
Exitus	1 (2.1%)	11(2.9%)	0.082

*Categorical data are numbers (percentage); continuous data are means ± standard deviation

Table 3. Propensity score models for atorvastatin and atrial fibrillation: multivariate logistic regression, stepwise forward elimination

Variables*	Logit coefficient	Std. error†	Exponential coefficient	95 % CI	p
For atorvastatin					
Age	0.024	0.031	1.025	0.97-1.09	0.424
Females	0.445	0.261	1.561	0.94-2.60	0.087
Hypertension	0.031	0.253	1.032	0.63-1.69	0.902
Previous cerebrovascular accident	0.421	0.487	1.524	0.59-3.96	0.387
Previous Urea	0.001	0.005	1.001	0.99-1.01	0.855
ß-blockers	0.927	0.316	2.527	1.36-4.69	0.003
Angiotension converting enzyme inhibitors	0.878	0.247	2.407	1.48-3.91	<0.001
Calcium channel blockers	0.84	0.334	2.321	1.20-4.47	0.012
Class III-IV angina	1.305	0.249	3.688	2.26-6.01	<0.001
Previous myocardial infarction	-0.235	0.374	0.791	0.38-1.65	0.531
Ejection fraction <0.50	0.156	0.295	1.169	0.66-2.08	0.598
Three vessel disease	-1.576	0.574	0.207	0.07-0.64	0.006
Bilateral carotid stenosis	0.864	0.437	2.373	1.01-5.58	0.048
Constant	-4.793	2.343	0.008		0.041
ACE inhibitors	0.876	0.243	2.402	1.49-3.87	<0.001
ß-blockers	0.820	0.309	2.271	1.24-4.16	0.008
Calcium channel blockers	0.780	0.311	2.182	1.19-4.02	0.012
Class III-IV angina	1.356	0.248	3.882	2.39-6.31	<0.001
Three vessel disease	-1.757	0.552	0.173	0.59-0.51	<0.001
Bilateral carotid stenosis	0.978	0.414	2.660	1.18-5.99	0.018
Constant	-2.497	0.347	0.0823		<0.001
For atrial fibrillation					
Three vessel disease	-1.553	0.738	0.212	0.05-0.90	0.035
Five-vessel bypass	0.856	0.439	2.354	0.99-5.57	0.050
Constant	-2.006	0.172	0.135		<0.001

*

†Robust standard errors.

(62.8%) patients in No-statin-Group (p =0.198)

Atorvastatin-40 mg was used in over half of the patients, used in 68 (54.83%) patients who took atorvastatin. Of the patients, postoperative AF occurred in 9 (13.2%) patients (Adjusted OR=0.82; confidence interval=0.32-2.06; p=0.669). Nearly half of the patients (n=58, 46.77%) used atorvastatin between 1-2 weeks before surgery. Of the patients, postoperative AF occurred in 6 (10.3%) patients in this period (Adjusted OR=0.53; confidence interval=0.18-1.56; p=0.238) (Table 2).

Postoperative atrial fibrillation

Patient characteristics, procedural variables, and postoperative characteristics for patients with and without were similar. Postoperative AF occurred in 48 (11.29%) patients in all patients. The mean patient age for AF was 74.67±3.77 years in Atorvastatin-Group versus 74.04±3.60 years in No-statin-Group at the time of surgery (p=0.209) (Table 3).

Propensity score analysis for atorvastatin and for AF has shown that three-vessel disease (Logit coefficient: -1.553, Exponential coefficient: 0.212, 95 % confidence interval: 0.05-0.90, p=0.035) and five-vessel bypass (Logit coefficient: 0.856, Exponential coefficient: 2.354, 95 % confidence interval: 0.99-5.57, p=0.050) were found as an independent predictor for the development of AF (Table 4).

Table 4. Dose and time of atorvastatin for Atorvastatin group

	Atorvastatin-Group (n=124)	AF	Adjusted OR*	CI*	p*
Dose					
10	23 (18.54%)	3 (10.3%)	0.89	0.29 - 2.79	0.854
20	31 (25%)	4 (12.9%)	0.90	0.23 – 3.52	0.884
40	68 (54.83%)	9 (13.2%)	0.82	0.32 - 2.06	0.669
80	2 (1.61%)	1(50%)	4.00	0.21 - 74.89	0.316
Time					
≤ 1 week	42 (33.87%)	6(14.3%)	0.87	0.34-2.20	0.765
1-2 weeks	58 (46.77%)	6 (10.3%)	0.53	0.18-1.56	0.238
> 2 weeks	24 (19.35%)	5 (20.8%)	Şub.66	0.78-9.13	0.106

*adjusted for propensity score; AF, atrial fibrillation; CI, confidence interval

Cardiac mortality

Cardiac death occurred in 22 (5.2%) patients. Although mortality was statistically significant in the no-statin-group comparing to statin group, the reasons of mortality were independent from the statin therapy. The reasons of the mortality were low cardiac output (1.4%), unable to wean cardiopulmonary bypass (0.7%), respiratory failure (0.7%), major cerebrovascular event (0.47%), gastrointestinal bleeding (0.47%), intestinal ischemia (0.47%), failure of left internal thoracic artery (0.47%), ventricular fibrillation (0.23%), and bleeding from the mediastinal space (0.23%).

DISCUSSION

Meta-analyses have demonstrated that some pharmacological agents and biatrial pacing reduced postoperative AF (10,11). Only amiodarone and beta-blockers have shown to be effective for the management of postoperative AF as advised recently by the American College of Cardiology/ American Heart Association/European Society of Cardiology guidelines. Subsequently, some studies reported that there is a relationship between preoperative statin use and reduced postoperative AF (12-14).

Relationship between preoperative statin use and rates of reduced postoperative was first reported by ARMYDA-3 trial (7). Two hundred patients who underwent coronary bypass were randomized to either atorvastatin (40 mg/d, n=101) or placebo (n=99) starting 7 days preoperatively. There was a 61% reduction in postoperative AF in patients who received statins; AF occurred in 35% of patients with statins and 57% of patients with placebo (p=.017). However, some authors have suggested that a dose–response relationship with statins and postoperative AF may also exist (15-17). Lertsburapa et al (15) conducted a nested case–control study with data from the randomized, controlled Atrial Fibrillation Suppression Trials I, II, and III and found that higher statin doses (atorvastatin 40 mg/d) were associated with greater reduction in postoperative AF than were lower doses. This finding was later corroborated by observational studies conducted by Kourliouros (16) and Mathani (17) et al. One of the findings of our study was that preoperative statin treatment was not associated with the reduction of postoperative AF in the patients. The other one was that there was no relationship between dose and duration of statin therapy for the development of postoperative AF in this specific surgical cohort.

As it is known, advanced age is a major risk factor for the development postoperative AF after cardiac surgery (3,18,19). Levy and colleagues (20) suggested that age is a very powerful predictor of postoperative AF. Actually, there is limited data whether statin treatment has beneficial effects in advanced age on postoperative AF after the coronary surgery. The Multicenter Study of Perioperative Ischemia Research Group and investigators of the Ischemia Research and Education Foundation have published the prospective study performed in 70 hospitals on 4 continents (1) including more than 5,000 patients undergoing CABG operations with or without valve surgery on cardiopulmonary bypass: patients with postoperative AF were significantly older (67.8 years versus 61.8 years), and a significantly larger number had a history of AF (14.6% versus 6.0%). The incidence of postoperative AF was 11.29% in the present study population after coronary artery bypass grafting.

Postoperative AF is thought to be mostly benign (21,22), it increases late mortality after isolated coronary surgery only (23). Kalavrouziotis and coworkers (24) concluded the same in a large study on postoperative AF in cardiac surgery patients after multivariate analysis and propensity score matching. When considering early cardiac mortality, it is really hard to combine the effects of these two clinical positions on cardiac death: preoperative statin therapy and postoperative AF. In the study of Villareal and colleagues (25), postoperative AF was a significant predictor of early death after adjusting risk factors. A large number of studies (3,8,9,22,24) show significantly higher incidence of early death in patients with postoperative AF after coronary bypass surgery or cardiac operations, but none of these studies identified postoperative AF as an independent predictor of early mortality. In the present study we have reported in-hospital cardiac mortality of 8.9% in the Atorvastatin-Group versus 3.7% in the No-statin-Group (p=0.027); cardiac death in patients with and without AF occurred at approximately 2.1% in the Atorvastatin-Group versus 2.9% in the No-statin-Group.

Despite a small number of patients in the present study, we cannot rule out widespread use of statins in patients undergoing coronary artery bypass grafting to prevent postoperative atrial fibrillation. We cannot exclude the possibility that ß-blockers and ACE inhibitors attenuated the benefits in our study or that the results were due to chance or population differences. Two groups were not homogenous. No-statin-Group had higher patient population compared to Atorvastatin-Group. Over a half of the patients were females in contrast to standard population of coronary surgery.

Postoperative atrial fibrillation is a frequent complication of cardiac operations and may result in serious cardiac adverse events including cardiac mortality. Although further work is necessary before any definitive recommendation, omitting statin drugs is not found to be associated with reduced postoperative atrial fibrillation and cardiac mortality in patients undergoing isolated coronary artery bypass grafting above the age of seventy years in the perioperative period.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATION

Competing interests: None to declare.

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