Efficacy of Statin Therapy in the Prevention of Atrial Fibrillation in Patients after Coronary Artery Bypass Grafting

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BOCKERIA ET AL.: ***Efficacy of Statin Therapy in the Prevention of Atrial Fibrillation in Patients after Coronary Artery Bypass Grafting:*** Statin medication has shown good results in the prevention of the postoperative atrial fibrillation (AF) after coronary artery bypass grafting (CABG). ***Objective:*** To assess the role of statin medication in the prevention of AF after CABG. ***Material and Methods:*** A retrospective analysis of 225 medical records of the patients, aged 57.5±7.9 years (mean±SD), who underwent CABG. All patients was divided into two groups. The first group included those patients who did not received statin medication (n=93). We named this group as nSt-patients. Second group included patients who receive statin medication (n=132). We named this group as St-patients. Clinical data on all included patients were obtained in pre-, intra- and postoperative periods. The risk of occurrence of postoperative AF was evaluated using the Cox-regression model. Continuous variables were reported as medians (Me) with inter-quartile ranges (Q_1, Q_3). Categorical data were presented as percentages. ***Results:*** The rate of AF was 29% in nSt-patients and 9% in St-patients (P<0.001). On Day 4 after surgery, white blood cells (WBC) count was 10.9 (9.0, 13.0) $\times 10^9$ e/L in nSt-patients and 9.1 (7.6, 10.0) in St-patients (P<0.001). An analysis of WBC count day-to-day changes was performed in a subgroup of patients who developed postoperative AF. This analysis showed that the peak WBC numbers occurred on the day of arrhythmia manifestation. In this subgroup, WBC count increased from 10.4 (7.5, 12.3) on Day 1 after surgery to 10.9 (9.0, 13.0) $\times 10^9$ e/L on the day of onset of AF (P=0.008). According to the Cox-regression model, the risk of AF was 3.68 for prior AF and 0.31 for statin medication. ***Conclusion:*** In our study, we showed an association between the use of statin medication and AF in early postoperative period. *(J HK Coll Cardiol 2016;24:1-10)*

Atrial fibrillation, Coronary artery bypass grafting, Postoperative period, Risk factors, Statin medication

摘要

他汀類藥物治療在冠狀動脈旁路移植（CABG）後預防房顫（AF）一直表現出良好成效。**目的：**評估在冠狀動脈旁路移植後，他汀類藥物治療預防房顫的角色。**工具及方法：**回顧性分析225個曾經進行冠狀動脈旁路移植，年齡於57.5±7.9（平均值±標準差）病人的醫療記錄。所有病人分成兩組，第一組包括全部沒有接受他汀類藥物治療（n=93），這個組別病人被稱爲nSt-病人；第二組包括接受他汀類藥物治療（n=132），被稱爲St-病人。所得的病人臨床資料包括術前、術中及術後的所有時期。計算手術後發生房顫的風險使用 Cox 迴歸分析模型，連續變量報告中位數（Me）爲四分差範圍（Q_1, Q_3），分類數據顯示爲百分比。**結果：**nSt-病人的房顫發生率爲29%；St-病人爲

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9%（P<0.001），在手術第後四日，nSt-病人白血球細胞（WBC）讀數爲10.9（9.0, 13.0）×10⁹ e/L，St-病人爲9.1（7.6, 10.0）（P<0.001）。分析每日白血球值變化顯示亞組病人會發展手術後房顫。這分析顯示白血球量高峰值之時會發展心律失常的臨床表現。在這個亞組當中，白血球值手術第一天10.4（7.5, 12.3）增加至房顫發病的10.9（9.0, 13.0）×10⁹ e/L（P=0.008）。根據Cox迴歸分析模型，房顫的風險在優先AF爲3.68及他汀類藥物治療爲0.31。**結論**：在我們的研究發現，使用他汀類藥物治療與房顫發生在手術後初期有相關性。

關鍵詞：心房顫、冠狀動脈旁路移植、手術後期、風險因素、他汀類藥物治療

Introduction

Atrial fibrillation (AF) is the most common rhythm disorder occurring after coronary artery bypass grafting (CABG). AF occurs in 25 to 30% of patients after CABG.[1-4] The onset of AF is associated with a high risk of postoperative complications, such as hemodynamic instability, stroke and myocardial infarction. All these complications lead to prolonged hospital stay and large economic cost.[5-7]

Some researchers recommend amiodarone and beta-blockers to reduce the risk of postoperative AF.[8-10] However, it should be noted that such preventive therapy does not seem to be safe in all patients because of adverse effects of these drugs, such as hypotension and bradycardia associated with beta-blockers and proarrhythmogenic effect of amiodarone.[11] The difficulties in the prevention of AF after CABG is explained by a poor understanding of both the mechanisms of onset of AF in patients after the surgery and the impact of intraoperative and postoperative factors on the electrophysiological properties of the atria.[5,12]

Any cardiac surgery is associated with an inflammatory process that includes systemic and local inflammation.[13,14] CABG is associated with the increasing of the inflammatory markers, such as C-reactive protein and interleukin-6,[13] with a peak concentration on day 2 to 4 after the surgery, just when the postoperative AF morbidity achieves its highest rate.[13,15] Inflammation is supposed to be a cause of the AF by affecting as structural as electrophysiological properties of the atria.[16]

In a number of previous studies, statin therapy has been shown to be effective in prevention of the AF after CABG.[16-19] The reduction in CABG-related inflammatory markers was noticed when statins were used routinely prior and after the surgery.[13,20,21] However, other studies failed to demonstrate an antiarrhythmic affect of statins after open-heart surgery.[22-24]

The objective of this study is to assess the role of statin therapy in the prevention of the AF after GABG.

Material and Methods

General Design of Study

Design of this study was approved by the Ethics Committee (Protocol no.9, 07 February 2014) of the Bakoulev Center for Cardiovascular Surgery in Moscow, Russia.

The data on the health status of all consecutive patients with CABG were gathered retrospectively in the Department of Surgical Treatment for Interactive Pathology, Bakoulev Scientific Center for Cardiovascular Surgery (Moscow, Russia). Informed consent was obtained from all participants.

The following inclusion criterion was established for the purposes of the study: isolated CABG performed in 2013.

The patients were not included in our study if they matched the following criteria:

i) Concomitant surgery (e.g. CABG with valve repair/prosthesis, CABG with aneurysmectomy, CABG with Maze-procedure, CABG with surgical correction of ventricular septal defect)
ii) Severe renal failure (creatinine clearance calculated by the Cockroft-Gault formula <50 mL/min)
iii) Hypo- or hyperkalaemia
iv) Left ventricle ejection fraction (LVEF) <35%
v) Thyroid dysfunction (hyper- or hypofunction)

vi) Other hormonal disorders
vii) Immunosuppressive and anti-inflammatory medications for the treatment of comorbid conditions
viii) Cancer
ix) Organic disorders of central nervous system
x) Psychological disorders

After selection, all patients were identified into two groups.

The first group was composed of patients without statin therapy neither prior nor after the CABG. We named this group as nSt-patients.

The second group was composed of patients who have statin therapy for at least 3 days prior to the CABG and continuously after the operation. We named this group as St-patients. Period 3 days was defined randomly according to the literature data. It is supposed that anti-inflammatory effect of statins begins to appear after 3 days of starting the therapy.[19] In our study only original atorvastatin and rosuvastatin were used. We made no reckoning of the dose of statins.

Patients

In 2013, 415 CABGs were performed in Department of Surgical Treatment for Interactive Pathology, Bakoulev Scientific Center for Cardiovascular Surgery (Moscow, Russia). Our retrospective study included medical records on 225 patients with coronary heart disease (CHD) (196 men and 29 women), aged 57.5±7.9 years (mean±SD), who underwent CABG in in 2013. Two hundred and sixteen patients were excluded from the study because of nonfulfilment of the enrollment criterions. Workflow of patients' selection is presented in Figure 1.

Healthy status of all included patients was confirmed by the results of clinical investigation.

Finally, we have identified 93 (41%) nSt-patients and 132 (59%) St-patients.

Data Collection

Clinical data (results with data physical examinations, instrumental and laboratory investigations) on all included patients were obtained during their hospital treatment in pre-, intra- and postoperative periods. The source of patient's data is a hospital chart.

Outcomes

AF event after CABG was endpoint of presented study.

A postoperative AF event was defined an AF episode lasting for more than 5 minutes occurred postoperatively in the period 7 days after CABG. In accordance with the study protocol and clinically appropriate, all patients were under 24-hour bedside electrocardiography and blood pressure (BP) monitoring for the first 96 hours after the surgery. AF episode was confirmed on the evidence of the above data.

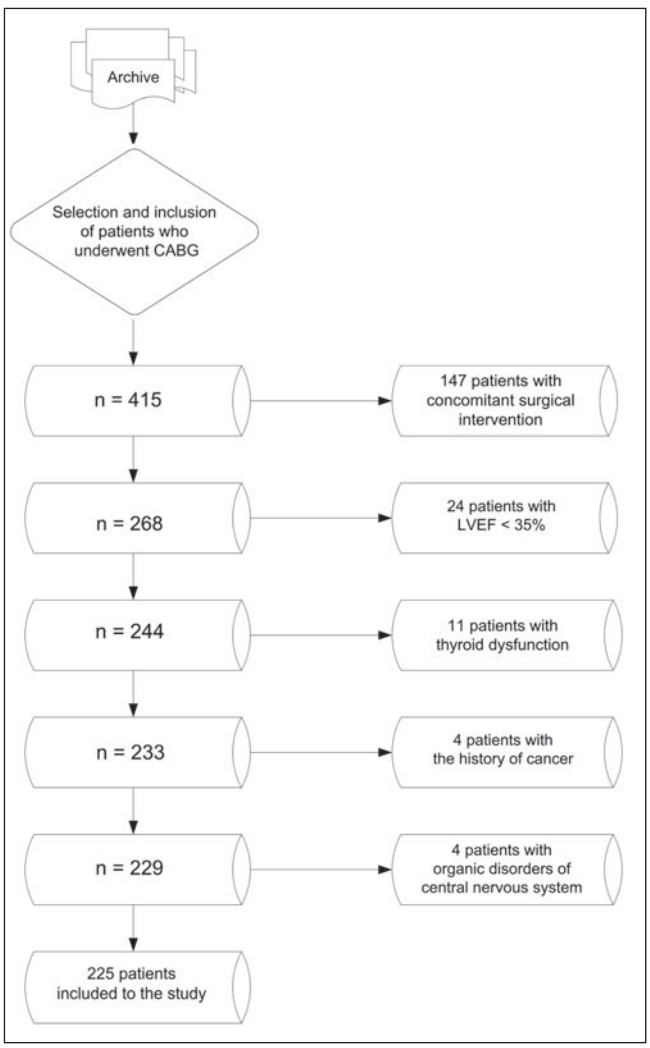

Figure 1. *Patients' selection in this study.*

Statistical Analysis

We apply the Shapiro-Wilk test to check whether the data were approximately normally distributed. Continuous variables were reported as medians (Me) with inter-quartile ranges (Q_1, Q_3) for non-normal data or mean (M) with standard deviation (SD) for normal data. Categorical data were presented as frequencies and percentages. To compare the variables between the patients' groups we used the Mann-Whitney test. The difference between the two proportions was assessed by t-test. Pared values were evaluated using Spearman's correlation (R). The risk of occurrence of postoperative AF was evaluated using the Cox-regression model. The obtained estimations were considered statistically significant if $P<0.05$.

We used the software package Statistica 10.0 (StatSoft Inc., Tulsa, Oklahoma, USA) for statistical analysis.

Results

The studied groups of St-patients and nSt-patients were comparable most anthropometric, clinical, instrumental and laboratory characteristics in pre-, intra- and postoperative periods. The relevant data for both groups are presented in Table 1. Significant differences between groups were found in the rate of AF and blood leucocytes in the early postoperative period. AF occurred in 29% of nSt-patients vs 9% in St-patients ($P<0.001$).

There was no significant difference in the length of hospital stay between groups: 9 (7, 11) in nSt-patients vs 9 (7, 11) in St-patients ($P=0.351$).

Also, there was a difference between groups in laboratory values: on Day 4 after surgery, white blood cells (WBC) count was 10.9 (9.0, 13.0) $\times 10^9$ e/L in nSt-patients and 9.1 (7.6, 10.0) $\times 10^9$ e/L in St-patients ($P<0.001$). On Day 1, WBC count was also lower in St-patients but the difference was insignificant ($P=0.391$) (Figure 2).

AF paroxysms occurred earlier in nSt-patients than in St-patients: Day 2 (2, 3) vs. Day 3 (3, 5), $P=0.039$.

An analysis of WBC count day-to-day changes was performed in a subgroup of patients who developed AF postoperatively. The analysis showed that peak WBC concentrations occurred on the day of onset of arrhythmia (Figure 3). In this subgroup, WBC count was 10.4 (7.5, 12.3) $\times 10^9$ e/L on Day 1 after surgery and 12.3 (10.0, 14.0) $\times 10^9$ e/L on the day of onset of AF ($P=0.008$). The difference remained significant.

The risk of occurrence of postoperative AF was evaluated using the Cox regression model (Table 2). The indicators with high correlation we not included together in the analysis. Such factors as «Prior AF» and «Antiarrhythmic therapy», «Prior MI» and «Therapy with beta-blockers» and «Therapy with ACE-Is» had high correlation ($R<0.7$). So only «Prior AF», «Prior MI» were included in the analysis.

Of these clinical variables included in Cox regression model, only prior AF and statin medication use were found to be statistically meaningful for the risk of AF after CABG. Results of the evaluation of the risk of AF in this study are given in Table 3.

Discussion

Blood WBC as inflammatory markers were chosen for our study as showing high prognostic value for the onset of AF.[25-27] Some previous studies have shown neutrophils level more specific as an independent predictor of postoperative AF.[26] It is known that during cardioplegia and bypassdue to ischemia and reperfusion, neutrophils are involved and secrete a wide variety of inflammatory biomarkers.

This study shows a strong correlation between blood WBC count and the risk of postoperative AF: the rate of AF was significantly higher in patients with a higher WBC count. Furthermore, peak WBC concentrations were observed on the day of onset of AF.

Statin medication prior to CABG and in the postoperative period was associated with reductions in the rate of postoperative AF and blood WBC count. In St-patients, peak blood WBC count occurred later than in nSt-patients. In our study, the delay was 1 day. The anti-inflammatory effect of statins seems to be due to their pleiotropic properties. A considerable reduction of the activity of all inflammatory markers under exposure to 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA)

Table 1. Anthropometric and clinical characteristics of studied patients

Parameter	nSt-patients (n=93)	St-patients (n=132)	P-level
Age, years, M±SD	58.1±8.2	57.1±7.6	0.491
Male sex, no. (%)	81 (87.1)	114 (86.4)	0.872
Body weight, kg, M±SD	83.0±12.8	83.1±11.1	0.744
BMI, kg/m^2, M±SD	28,2±4.8	28,3±4.1	0.723
Smokers, no. (%)	30 (32.3)	53 (40.2)	0.221
Hypertension, no. (%)	72 (77.4)	94 (71.2)	0.299
Prior MI, no. (%)	58 (62.4)	74 (56.1)	0.166
Diabetes, no. (%)	9 (9.7)	11 (8.3)	0.537
Prior CVA, no. (%)	1 (1.1)	3 (2.3)	0.504
CRF, no. (%)	28 (30.1)	37 (28.0)	0.735
Prior AF, no. (%)	8 (8.6)	8 (6.1)	0.126
Euro SCORE II, Me (Q_1, Q_3)	1.87 (0.94, 2.15)	1.87 (0.94, 2.15)	0.754
Prior antiarrhythmic therapy, no. (%)	8 (8.6)	8 (6.1)	0.201
Prior PCI, no. (%)	3 (3.2)	7 (5.3)	0.453
Prior therapy with ACE-Is, no. (%)	91 (97.8)	129 (97.7)	0.951
Prior therapy with beta-blockers, no. (%)	92 (98.9)	129 (97.7)	0.773
LAD, cm, Me (Q_1, Q_3)	4.1 (3.9, 4.5)	4.1 (3.9, 4.4)	0.791
EDD, cm, Me (Q_1, Q_3)	5.4 (5.0, 5.7)	5.3 (4.9; 5.5)	0.111
EDV, mL, Me (Q_1, Q_3)	135 (124, 159)	134 (115, 154)	0.202
EFLV, %, Me (Q_1, Q_3)	60 (54, 63)	60 (56, 64)	0.411
Preoperative potassium, mmol/L, Me (Q_1, Q_3)	4,1 (3.7,4.3)	4,15 (3.8,4.3)	0.841
Preoperative WBC, x10^9/mL, Me (Q_1, Q_3)	9.9 (6.9, 10.1)	9.6 (7.3, 11.8)	0.412
Preoperative creatinine, mmol/L, Me (Q_1, Q_3)	93 (83, 103)	93 (86.5, 102.5)	0.958
Off-pump CABG, no. (%)	74 (79.6)	116 (87.9)	0.063
On-pump CABG, no. (%)	18 (20.4)	18 (12.1)	0.631
CPB time, min, Me (Q_1, Q_3)	99 (45, 123)	96 (65, 127)	0.342
Aortic cross-clamping time, min, Me (Q_1, Q_3)	56 (45, 66)	57 (45, 66)	0.715
APV time, h, Me (Q_1, Q_3)	7 (4, 9)	7 (4, 8)	0.854
Number of grafts, Me (Q_1, Q_3)	2 (2, 3)	2 (2, 3)	0.746
RCA bypass, no. (%)	51 (54.8)	77 (58.3)	0.603
Graft thrombosis, no. (%)	3 (3.2)	1 (0.8)	0.161
Cessation of cardiotonic support, days, Me (Q_1, Q_3)	3 (2, 3)	3 (2, 3)	0.055
Postoperative AF, no. (%)	27 (29.0)	12 (9.1)	**<0.001**
Day of AF onset, Me (Q_1, Q_3)	2 (2, 3), n=27	3 (3, 5), n=12	**0.039**
WBC count on Day 1, x10^9/mL, Me (Q_1, Q_3)	10.4 (7.5, 12.3)	9.5 (7.4, 12.0)	0.391
WBC count on Day 4, x10^9/mL, Me (Q_1, Q_3)	10.9 (9.0, 13.0)	9.1 (7.6, 10.0)	**<0.001**
WBC count on the day of AF onset, x10^9/mL, Me (Q_1, Q_3)	12.3 (10.0, 14.1), n=27	14.0 (10.0, 14.0), n =12	0.960
Postoperative pneumonia, no. (%)	3 (3.2)	7 (5.3)	0.452
Number of bed-days, Me (Q_1, Q_3)	9 (7, 11)	9 (7, 11)	0.351
Intensive unit bed-days, Me (Q_1, Q_3)	1 (1, 2)	1 (1, 3)	0.910
Antiarrhythmic therapy, no. (%)	8 (8.6)	8 (6.1)	0.201
Therapy with ACE-Is, no. (%)	93 (100)	132 (100)	1
Therapy with beta-blockers, no. (%)	92 (98.9)	130 (98.5)	0.943

BMI, body mass index; CVA, cerebral vascular accident; MI, myocardial infarction; CRF, chronic renal failure; ACE-Is, angiotensin-converting-enzyme inhibitors; LAD, left atrial diameter; EDD, end-diastolic dimension of left ventricle; EDV, end-diastolic volume of left ventricle; EFLV, ejection fraction of left ventricle; CPB, cardiopulmonary bypass; APV, artificial lung ventilation; RCA, right coronary artery; WBC, white blood cells.

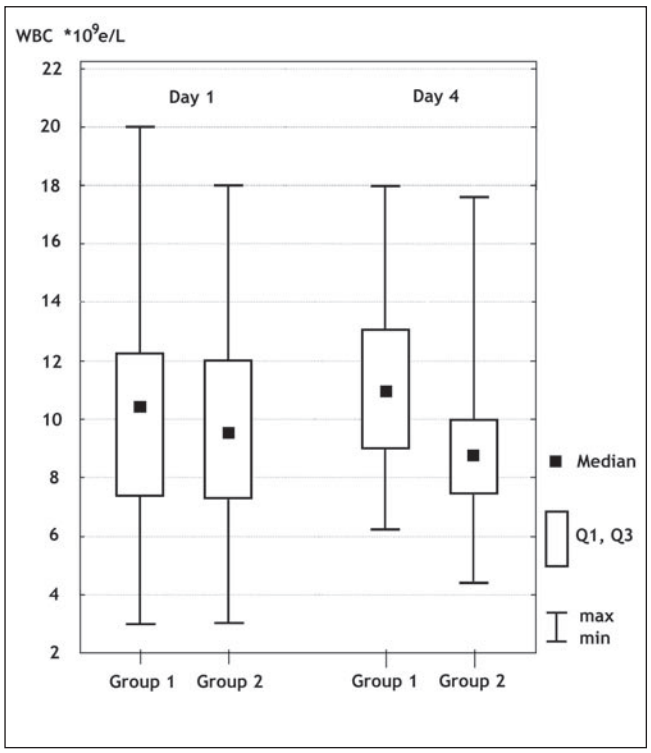

Figure 2. *Blood WBC count in studied groups on Day 1 after surgery and Day 4 after surgery.*

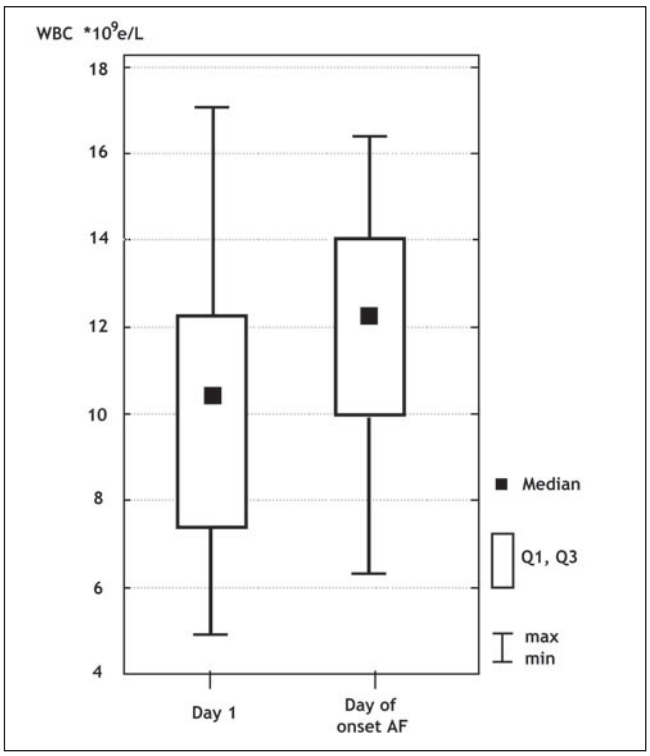

Figure 3. *Blood WBC count on Day 1 after surgery, and on the day of onset of AF.*

Table 2. Clinical variables used in the Cox model of regression for evaluation of the risk of occurrence of AF in patients after CABG (χ^2=38.42, P<0.001)

Parameter	Regression coefficient β	Standard error	Risk index Exp (B)	Wald test	P
Statins	**-1.145**	**0.357**	**0.318**	**10.24**	**0.001**
Prior AF	**1.251**	**0.396**	**3.493**	**9.96**	**0.002**
Number of grafts	0.419	0.231	1.520	3.28	0.070
Diabetes	-1.088	0.779	0.336	1.94	0.163
EDD	0.453	0.356	1.572	1.61	0.204
Preoperative creatinine	-0.017	0.014	0.982	1.38	0.238
Age	0.023	0.022	1.023	1.02	0.310
CRF	0.505	0.505	1.657	0.99	0.317
Prior MI	0.359	0.380	1.432	0.89	0.344
EF	0.014	0.021	1.014	0.43	0.510
Prior PCI	-0.462	1.037	0.629	0.19	0.655
CPB time	-0.001	0.003	0.999	0.14	0.706
Sex	0.012	0.520	1.012	<0.01	0.981
etc.					

Note. Statistically significant predictors (P<0.005) of postoperative AF and first 11 non-significant factors are summarized in Table 2 (presented in descending order of significance). Other indicators included in the multiple analysis (Table 1) are not presented in the Table 2.

Table 3. Evaluation of the risk of AF depending on statin medication and prior AF variables (χ^2=16.14, P<0.001)

Risk factors		Risk of AF in accordance with the Cox model of regression	Level of AF risk	Rate of AF in this study
Statins	Prior AF			
Yes	No	0.31	Low	6.5%
No	No	1.00	Moderate	25.6%
Yes	Yes	1.15	High	50.0%
No	Yes	3.68	Very high	54.5%

reductase inhibitors seems to be due to their effect on neutrophils: increasing apoptosis and enhancing cytokine secretion. Chello et al. in their blind placebo-controlled study showed that using simvastatin 40 mg/daily during 7 days after surgery reduced peak anti-inflammatory markers count (interleukin 6 an 8).[28] The anti-inflammatory effect of statins begins to appear before their hypolipidemic effect. In our study, statin medication started just in 3 days before the intervention led to significant results in terms of prevention of postoperative AF.

In our study, the regression analysis showed that only two factors could have significant influence on the onset of postoperative AF, which are prior AF and statin medication. Moreover prior AF increases the risk of postoperative AF significantly due to arrhythmogenic cardiomyopathy while the statin medication significantly decreased the risk of postoperative AF (P=0.001). In accordance with the Cox model of regression, the risk of AF was lowest (6.5%) in St-patients without a history of AF, moderate (25.6%) in nSt-patients without a history of AF, high (50%) in St-patients with prior AF and very high (54.5%) in nSt-patients with a prior AF.

Marìn et al. obtained similar results in a study on 234 patients.[29] In the multivariant analysis, statin therapy was found to be associated with a reduction of the rate of AF after GABG (HR 0.52, 95% CI 0.28; 0.96, P=0.038). The TIMP-1/MMP-1 ratio (TIMP-1 is tissue inhibitor matrix metalloproteinase-1, MMP-1 is matrix metalloproteinase-1) in 24 h after GABG was higher in patients without a history of AF (P=0.043). Statin medication was associated with increases of both the TIMP-1 level and TIMP-1 / MMP-1 ratio (P=0.027 and P=0.036, respectively). It should be noted that, unlike us, Marìn used TIMP-1 and MMP-1 as inflammatory markers.

Kimura et al. showed experimentally that fluvastatin could inhibit the activities of leukotriene B_4 and platelet activation factor.[30] The lipid-independent anti-inflammatory effect was confirmed in an experimental study performed by Scalia et al.[31] who observed an inhibiting effect of simvastatin and cerivastatin on actin-mediated membrane polymerization and integrin-binding molecules of CD 11a, CD 18 and VLA-4.

As far back as 1999, Ikeda et al. found that fluvastatin and simvastatin exert a considerable inhibiting effect on angiotensin 2-induced secretion of interleukin-6 in the culture of human SMCs. This effect was accompanied by a reduction in the level of C-reactive protein.[32]

In a few studies, it was shown that statin therapy could lead to the decrease in the length of hospital stay due to a reduction of the AF.[5-7] We have not seen this in our study.

No significant association between several clinical characteristics (chronic renal failure, prior myocardial infarction, etc.) and risk of AF after CABG was shown. It was also shown in previous studies.[33-35] Whereas there is different data on the influence of chronic renal failure on the onset of postoperative AF showing as significant association[36,37] as well as no association.[38,39]

Otherwise other studies have shown significant association between postoperative AF after CABG and left atrial parameters,[40] perioperative intra-aortic balloon pump use,[41] which was not shown in our study. The reason may be due to the design of our study, which is reflected in the Limitations section.

Postoperative pneumonia according to some authors was also associated with postoperative AF.[42] In our study it was a rare complication. Moreover the

statistical analysis was presented for pre- and intraoperatively characteristics, so the influence of post-operative pneumonia could not be evaluated according to the design of the study.

Conclusion

AF is one of potential complications that can cause hemodynamic instability in patients after GABG and increase the risk of stroke and postoperative mortality. In our study, we showed an association between the use of statin medication and AF in early postoperative period. Anti-inflammatory properties demonstrated by statins are one of the factors that may explain why their beneficial effects on the clinical course and prognosis of the atherosclerotic vascular disease are more pronounced than could be expected.

Limitations

There are some limitations of our study. The main one is related to the design. As it was retrospective trial, there was no randomization and placebo-control.

It is known that all the patients with coronary artery disease should get statin medication according to the updated ESC/ACC/AHA guidelines. And if conduct prospective randomized trial half of the patients are supposed to discontinue the lipid-lowering therapy. In our opinion it is impossible from the ethical position according to the modern recommendations. In a retrospective design of the study we were able to enroll the patients who were not taking statins for other reasons (social factors, economic factors, etc.).

It should be noticed that the authors did not analyze the reasons for not receiving statin therapy prior to the surgery. The study was retrospective and to perform CABG there is no need for patients to receive statin therapy. Statin medication and lipid levels control is usually within the outpatient cardiologists cognizance. In addition, it is known, that outpatient treatment compliance is still unsolved problem.

In the presented study we have not evaluated the influence of different doses and duration of statin therapy due to lack of retrospective information. Chen et al.[43] evaluated the correlation between statin therapy effectiveness in postoperative AF prevention and different doses and duration of the therapy. Analysis has shown statistically significant association between the duration of preoperative statin therapy and risk of postoperative AF, but no significant association was show between statin doses and lower risk of postoperative AF.

The main limitation of the study was no information about serum lipid profile before the operation, so the information was not included into the analysis. So we have no statistically significant data to propose that the anti-fibrillatory effect of statin extend beyond its lipid lowering action.

Such factors as «Prior AF» and «Antiarrhythmic therapy», «Prior MI» and «Therapy with beta-blockers» and «Therapy with ACE-Is» had high correlation between each other ($R<0.7$) and so were excluded from the analysis.

Conflict of interest

None declared.

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References

1. Hogue CW Jr, Creswell LL, Gutterman DD, et al; American College of Chest Physicians. Epidemiology, mechanisms, and risks: American College of Chest Physicians guidelines for the prevention and management of postoperative atrial fibrillation after cardiac surgery. Chest 2005;128:9S-16S.
2. Zaman AG, Archbold RA, Helft G, et al. Atrial fibrillation after coronary artery bypass surgery: a model for preoperative risk stratification. Circulation 2000;101:1403-8.
3. Echahidi N, Pibarot P, O'Hara G, et al. Mechanisms, prevention, and treatment of atrial fibrillation after cardiac surgery. J Am Coll Cardiol 2008;51:793-801.
4. Bockeria OL, Akhobekov AA. The efficiency of statins in the prevention of atrial fibrillation after cardiac operations. Annaly

Aritmologii 2014;11:14-23.
5. Mathew JP, Fontes ML, Tudor IC, et al. A multicenter risk index for atrial fibrillation after cardiac surgery. JAMA 2004;291: 1720-9.
6. Creswell LL, Schuessler RB, Rosenbloom M, et al. Hazards of postoperative atrial arrhythmias. Ann Thorac Surg 1993;56:539-49.
7. Shuvaev IP, Asymbekova EU, Tugeeva EF, et al. Cardiac arrhythmias in patients with coronary heart disease and metabolic syndrome after surgery. The Bulletin of A.N. Bakoulev Scientific Center for Cardiovascular Surgery of Russian Academy of Medical Sciences. Cardiovascular Diseases 2014; 15:53-60.
8. Burgess DC, Kilborn MJ, Keech AC. Interventions for prevention of post-operative atrial fibrillation and its complications after cardiac surgery: a meta-analysis. Eur Heart J 2006;27:2846-57.
9. Bradley D, Creswell LL, Hogue CW, et al. Pharmacologic prophylaxis: American College of Chest Physicians guidelines for the prevention and management of postoperative atrial fibrillation after cardiac surgery. Chest 2005;28:39S-47S.
10. Coleman CI, Perkerson KA, Gillespie EL, et al. Impact of prophylactic postoperative beta-blockade on post-cardiothoracic surgery length of stay and atrial fibrillation. Ann Pharmacother 2004;38(12):2012-6.
11. Lertsburapa K, White CM, Kluger J, et al. Preoperative statins for the prevention of atrial fibrillation after cardiothoracic surgery. J Thorac Cardiovasc Surg 2008;135:405-11.
12. Benjamin EJ, Chen PS, Bild DE, et al. Prevention of atrial fibrillation: report from a national heart, lung, and blood institute workshop. Circulation 2009;119:606-18.
13. Bruins P, te Velthuis H, Yazdanbakhsh AP, et al. Activation of the complement system during and after cardiopulmonary bypass surgery: postsurgery activation involves C-reactive protein and is associated with postoperative arrhythmia. Circulation 1997; 96:3542-8.
14. Gravlee GP. Update on cardiopulmonary bypass. Curr Opin Anesthesiol 2001;14:11-6.
15. Chung MK, Martin DO, Sprecher D, et al. C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. Circulation 2001;104:2886-91.
16. Kumagai K, Nakashima H, Saku K. The HMG-CoA reductase inhibitor atorvastatin prevents atrial fibrillation by inhibiting inflammation in a canine sterile pericarditis model. Cardiovasc Res 2004;62:105-11.
17. Jialal I, Stein D, Balis D, et al. Effect of hydroxymethyl glutaryl coenzyme a reductase inhibitor therapy on high sensitive C-reactive protein levels. Circulation 2001;103:1933-5.
18. Ridker PM, Rifai N, Pfeffer MA, et al. Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events (CARE) Investigators. Circulation 1998;98:839-44.
19. Jacob KA, Nathoe HM, Dieleman JM, et al. Inflammation in new-onset atrial fibrillation after cardiac surgery: a systematic review. Eur J Clin Invest 2014;44:402-28.
20. Liakopoulos OJ, Dorge H, Schmitto JD, et al. Effects of preoperative statin therapy on cytokines after cardiac surgery. Thorac Cardiovasc Surg 2006;54:250-4.
21. Brull DJ, Sanders J, Rumley A, et al. Statin therapy and the acute inflammatory response after coronary artery bypass grafting. Am J Cardiol 2001;88:431-3.
22. Pan W, Pintar T, Anton J, et al. Satins are associated with a reduced incidence of perioperative mortality after coronary artery bypass graft surgery. Circulation 2004;110:II45-9.
23. Powell BD, Bybee KA, Valeti U, et al. Influence of preoperative lipid-lowering therapy on postoperative outcome in patients undergoing coronary artery bypass grafting. Am J Cardiol 2007; 99:785-9.
24. Virani SS, Nambi V, Razavi M, et al. Preoperative statin therapy is not associated with a decrease in the incidence of postoperative atrial fibrillation in patients undergoing cardiac surgery. Am Heart J 2008;155:541-6.
25. Kuhn EW, Liakopoulos OJ, Stange S, et al. Preoperative statin therapy in cardiac surgery: a meta-analysis of 90,000 patients. Eur J Cardiothorac Surg 2014;45:17-26.
26. Gibson PH, Cuthbertson BH, Croal BL, et al. Usefulness of neutrophil/lymphocyte ratio as predictor of new-onset atrial fibrillation after coronary artery bypass grafting. Am J Cardiol 2010;105:186-91.
27. Lamm G, Auer J, Weber T, et al. Postoperative white blood cell count predicts atrial fibrillation after cardiac surgery. J Cardiothorac Vasc Anesth 2006;20:51-6.
28. Chello M, Anselmi A, Spadaccio C, et al. Simvastatin increases neutrophil apoptosis and reduces inflammatory reaction after coronary surgery. Ann Thorac Surg 2007;83:1374-80.
29. Marin F, Pascual DA, Roldán V, et al. Statins and postoperative risk of atrial fibrillation following coronary artery bypass grafting. Am J Cardiol 2006;97:55-60.
30. Kimura M, Kurose I, Russell J, et al. Effects of fluvastatin on leukocyte – endothelial cell adhesion in hypercholesterolemic rats. Arterioscler Thromb Vasc Biol 1997;17:1521-6.
31. Scalia R, Gooszen ME, Jones SP, et al. Simvastatin exers both anti-inflamatory and cardioprotective effects in apolipoprotein E-deficient mice. Circulation 2001;103:2598-603.
32. Ikeda U, Shimada K. Statin and monocytes. Lancet 1999;353: 2070.
33. Mathew JP, Fontes ML, Tudor IC, et al. A multicenter risk index for atrial fibrillation after cardiac surgery. JAMA 2004;291: 1720-9.
34. Auer J, Weber T, Berent R, et al. Risk factors of postoperative atrial fibrillation after cardiac surgery. J Card Surg 2005;20: 425-31.
35. Helgadottir S, Sigurdsson MI, Ingvarsdottir IL, et al. Atrial fibrillation following cardiac surgery: risk analysis and long-term survival. J Cardiothorac Surg 2012;7:87.
36. Villareal RP, Hariharan R, Liu BC, et al. Postoperative atrial fibrillation and mortality after coronary artery bypass surgery. J Am Coll Cardiol 2004;43:742-8.
37. Ananthapanyasut W, Napan S, Rudolph EH, et al. Prevalence of atrial fibrillation and its predictors in nondialysis patients with chronic kidney disease. Clin J Am Soc Nephrol 2010;5: 173-81.
38. Shirzad M, Karimi A, Tazik M, et al. Determinants of postoperative atrial fibrillation and associated resource

utilization in cardiac surgery. Rev Esp Cardiol 2010;63:1054-60.
39. Hashemzadeh K, Dehdilani M, Dehdilani M. Postoperative atrial fibrillation following open cardiac surgery: predisposing factors and complications. J Cardiovasc Thorac Res 2013;5:101-7.
40. Verdejo HE, Becerra E, Zalaquet R, et al. Atrial function assessed by speckle tracking echocardiography is a good predictor of postoperative atrial fibrillation in elderly patients. Echocardiography 2016;33:242-8.
41. Mirhosseini SJ, Forouzannia SK, Ali-Hassan-Sayegh S, et al. On pump versus off pump coronary artery bypass surgery in patients over seventy years old with triple vessels disease and severe left ventricle dysfunction: focus on early clinical outcomes. Acta Med Iran 2013;51:320-3.
42. Phan K, Ha HS, Phan S, et al. New-onset atrial fibrillation following coronary bypass surgery predicts long-term mortality: a systematic review and meta-analysis. Eur J Cardiothorac Surg 2015;48:817-24.
43. Chen WT, Krishnan GM, Sood N, et al. Effect of statins on atrial fibrillation after cardiac surgery: a duration- and dose-response meta-analysis. J Thorac Cardiovasc Surg 2010;140: 364-72.