Indian Heart Journal 68 (2016) 792–797

Contents lists available at ScienceDirect

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj

Original Article

Statin therapy in the primary prevention of early atrial fibrillation after coronary artery bypass grafting

O.L. Bockeria [a,*], V.A. Shvartz [a], A.A. Akhobekov [a], A.R. Kiselev [a,*], M.D. Prokhorov [b], E.Z. Golukhova [c], L.A. Bockeria [d]

[a] Department of Surgical Treatment for Interactive Pathology, Bakoulev Scientific Center for Cardiovascular Surgery, Moscow, Russia
[b] Saratov Branch of the Institute of Radio Engineering and Electronics of Russian Academy of Sciences, Saratov, Russia
[c] Nonivasive Arrhythmology Department, Bakoulev Scientific Center for Cardiovascular Surgery, Moscow, Russia
[d] Bakoulev Scientific Center for Cardiovascular Surgery, Moscow, Russia

ARTICLE INFO

Article history:
Received 24 January 2016
Accepted 1 April 2016
Available online 13 April 2016

Keywords:
Atrial fibrillation
Statin therapy
Risk factors
Coronary artery bypass grafting
Early postoperative period

ABSTRACT

Objective: Assessment of the role of statin therapy in the prevention of postoperative atrial fibrillation (POAF) after coronary artery bypass grafting (CABG) in patients without prior atrial fibrillation.
Methods: A retrospective analysis of 206 patients, aged 57.2 ± 7.9 years (mean ± *SD*), who underwent isolated CABG is carried out. All patients are divided into two groups. The first group (nSt-patients) includes the patients who did not receive statin therapy prior to CABG ($n = 82$). The second group (St-patients) includes the patients who received statin therapy prior to CABG ($n = 124$). Both groups received the statin therapy from the first day after CABG. The risk of occurrence of POAF is evaluated using the Cox-regression model.
Results: The rate of POAF was 25.6% in nSt-patients and 6.5% in St-patients ($P = 0.020$). On the 4th day after CABG, white blood cells (WBC) count was 11.0 (9.0, 13.0) × 10^9/mL (medians with inter-quartile ranges) in nSt-patients and 9.0 (7.6, 10.2) × 10^9/mL in St-patients ($P < 0.001$). The peak WBC numbers occurred on the day of POAF onset. The Cox-regression analysis shows that only two factors (statin therapy and number of grafts) had significant influence on the POAF onset. Odds ratio of POAF event prediction by statin therapy was 0.20 (95%CI: 0.08–0.51), $P < 0.001$. Each subsequent graft increased the risk of POAF in 2.1 times.
Conclusion: Statin therapy carried out prior to the CABG is an effective approach to primary prevention of POAF in early postoperative period. Statin therapy after CABG in nSt-patients does not give prophylactic effect observed in St-patients.

1. Introduction

Atrial fibrillation (AF) is the most frequent postoperative complication after cardiac surgery. Postoperative atrial fibrillation (POAF) occurs in about 65% cases.[1–3] This complication leads to prolonged hospital stay and a large economic burden.[4,5]

Some researchers recommend amiodarone and beta-blockers to reduce the risk of POAF.[6–8] However, it should be noted that such preventive therapy do not seem to be safe in all patients because of side effects of these drugs, such as hypotension and bradycardia associated with beta-blockers and proarrhythmogenic effect of amiodarone.[9] It is assumed that one of the reasons of POAF may be the post-operative local and systemic inflammation.[10,11] For example, coronary artery bypass grafting (CABG) is associated with the increase of the inflammatory markers, such as C-reactive protein, leukocytes, interleukin-6, and interleukin-8.[12] Up to date, the reason of POAF remains controversial and it is actively studied by many researchers.[13] Some anti-inflammatory drugs (such as nonsteroidal anti-inflammatory drugs, glucocorticoids, colchicine, and statins) have shown promising results in the prevention of POAF.[14–17]

Statin therapy is recommended in patients with coronary heart disease (CHD), but not all patients are committed to this treatment. According to some previous studies, the statin therapy is efficient

* Corresponding authors at: 135, Rublevskoe shosse, Moscow 121552, Russia. Tel.: +7 4954147571; fax: +7 4954147571.
E-mail addresses: soleo2003@gmail.com (O.L. Bockeria), kiselev@cardio-it.ru (A.R. Kiselev).

http://dx.doi.org/10.1016/j.ihj.2016.04.002

in prevention of AF after CABG.[18–20] However, some other studies failed to demonstrate an antiarrhythmic affect of statins after open-heart surgery.[21]

The aim of our study is to assess the role of statin therapy in primary prevention of POAF in early postoperative period after GABG.

2. Material and methods

2.1. General design of study

Design of this study was approved by the Ethics Committee (Protocol No. 9, February 7, 2014) of the Bakoulev Center for Cardiovascular Surgery (Moscow, Russia).

The data on the health status of all 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 inclusion criteria in our study were the following:

i) CABG performed in 2013,
ii) Age from 40 to 80 years.

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

i) AF prior current CABG,
ii) Concomitant surgery (e.g. CABG with valve repair/prosthesis, CABG with aneurysmectomy, CABG with surgical correction of ventricular septal defect, etc.),
iii) Emergency CABG,
iv) Severe renal failure (creatinine clearance calculated by the Cockroft–Gault formula <50 mL/min),
v) Thyroid dysfunction (hyper- or hypofunction),
vi) Immunosuppressive and anti-inflammatory medications for the treatment of comorbid conditions,
vii) Cancer,
viii) Organic disorders of central nervous system,
ix) Psychological disorders,
x) Left ventricle ejection fraction (LVEF) <35%,
xi) Hypo- or hyperkalemia,
xii) Treatment with amiodarone,
xiii) Other hormonal disorders.

After selection, all patients were divided into two groups:

i) The first group was composed of patients without statin therapy prior to CABG. We named this group as nSt-patients. Note that all these patients began to receive the statin therapy from the first day after CABG.
ii) The second group was composed of patients who received the statin therapy for at least 3 days prior to the CABG and continuously after the operation. We named this group as St-patients. The period of 3 days was defined randomly according to data in the literature. It is supposed that anti-inflammatory effect of statins begins to appear after 3 days of starting the therapy.[22] In our study, only original atorvastatin (Pfizer Inc., USA) and rosuvastatin (AstraZeneca Pharmaceuticals LP, USA) were used. We did not take into account the dose of statins.

We did not influence on taking any drugs before CABG, due to the retrospective design of our study. Scarce use of statins in ambulatory practice in patients with CHD is the challenge in many countries, including Russia. According to population-based studies in Russia, statins are prescribed to CHD patients much rarely than other necessary drugs.[23,24] Moreover, the use of statins is often short. In a few months, the patients themselves stop the statin use, motivating it by normalization of cholesterol, economic aspects, and other reasons. This fact made it possible to carry out this retrospective study.

2.2. 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 includes medical records on 206 patients with CHD (173 men and 33 women), aged 57.2 ± 7.9 years (mean $\pm$ *SD*), who underwent isolated CABG in 2013. 209 patients were excluded from the study because of fulfillment of the above mentioned exclusion criteria. Clinical status of all included patients was confirmed by the results of clinical investigation.

Finally, we have identified 82 (40%) nSt-patients and 124 (60%) St-patients.

2.3. Data collection

Clinical data including the data of 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.

2.4. Outcomes

POAF event after CABG was the endpoint of the study. AF episode occurred in the 7-day period after CABG and lasting more than 5 min was defined as a POAF event. In accordance to the treatment protocol, all patients were under 24-h bedside electrocardiography (ECG) and blood pressure (BP) monitoring for the first 72 h after the surgery. After 72 h after the surgery, Holter monitoring of ECG was used every day until the day of discharge from the hospital.

2.5. Statistical analysis

We apply the Shapiro–Wilk test to check whether the data were approximately normally distributed. Continuous variables are 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 are presented as frequencies and percentages. To compare the variables between the patients' groups we use the Mann–Whitney test. The difference between the two samples is assessed by *t*-test. The risk of occurrence of POAF is evaluated using the Cox-regression model. Odds ratio is used for the assessment of risk-factors. The obtained estimations are considered statistically significant if $P < 0.05$.

We used the software package Statistica 8.0 (StatSoft Inc., Tulsa, Oklahoma, USA) for statistical analysis.

3. Results

The studied groups of St-patients and nSt-patients did not differ in main anthropometric, clinical, instrumental, and laboratory characteristics in pre-, intra-, and postoperative periods. Also, there was no significant difference in the length of hospital stay. The relevant data for both groups are presented in Table 1. Significant differences between the groups are found in the rate of POAF and white blood cells (WBC) in the early postoperative period (Table 1). It should be noted that all St-patients in our study received the statin

Table 1
Anthropometric and clinical characteristics of studied patients.

Parameter	nSt-patients ($n=82$)	St-patients ($n=124$)	P-level
Age, years, $M \pm SD$	57.7 ± 8.3	56.9 ± 7.7	0.472
Male sex, no. (%)	71 (86.6)	105 (84.7)	0.893
Body weight, kg, $M \pm SD$	82.6 ± 12.4	82.7 ± 11.1	0.921
BMI, kg/m^2, $M \pm SD$	28.3 ± 4.7	28.5 ± 4.3	0.811
Smokers, no. (%)	26 (31.7)	46 (37.1)	0.223
Prior MI, no. (%)	52 (63.4)	68 (54.8)	0.225
Diabetes, no. (%)	8 (9.8)	11 (8.9)	0.911
COPD, no. (%)	2 (2.4)	5 (4.0)	0.516
Prior TIA, no. (%)	0 (0)	2 (1.6)	0.772
CRF, no. (%)	24 (29.3)	31 (25.0)	0.674
Euro SCORE II, *Me* (Q_1, Q_3)	1.87 (0.94, 2.15)	1.87 (0.94, 2.15)	0.901
Prior PCI, no. (%)	2 (2.4)	7 (5.6)	0.691
Prior statin therapy, no. (%)	0 (0)	124 (100)	<0.001
Prior therapy with ACE-Is, no. (%)	81 (98.8)	120 (96.8)	0.883
Prior therapy with beta-blockers, no. (%)	81 (98.8)	121 (97.6)	0.964
LAD, cm, *Me* (Q_1, Q_3)	4.1 (3.9, 4.4)	4.1 (3.9, 4.4)	0.665
EDD, cm, *Me* (Q_1, Q_3)	5.3 (5.0, 5.7)	5.3 (4.9, 5.6)	0.293
EDV, mL, *Me* (Q_1, Q_3)	135 (122, 156)	134 (115, 154)	0.397
EFLV, %, *Me* (Q_1, Q_3)	60 (52, 64)	60 (56, 64)	0.472
Off-pump CABG, no. (%)	16 (19.5)	29 (23.4)	0.542
CPB, no. (%)	66 (80.5)	110 (88.7)	0.154
CPB time, min, *Me* (Q_1, Q_3)	112 (80, 135)	105 (78, 136)	0.951
Number of grafts, *Me* (Q_1, Q_3)	2 (2, 3)	2 (2, 3)	0.590
RCA bypass, no. (%)	45 (54.9)	71 (57.3)	0.776
Graft thrombosis, no. (%)	1 (1.2)	1 (0.8)	0.962
POAF, no. (%)	21 (25.6)	8 (6.5)	0.020
Day of AF onset, *Me* (Q_1, Q_3)	2 (2, 3), $n=21$	3 (3, 4), $n=8$	0.164
Preoperative WBC, $\times 10^9$/mL, *Me* (Q_1, Q_3)	9.8 (7.0, 10.2)	9.7 (7.3, 11.7)	0.511
WBC count on the first day after CABG, $\times 10^9$/mL, *Me* (Q_1, Q_3)	10.0 (7.6, 13.0)	9.5 (7.3, 12.0)	0.290
WBC count on the 4th day after CABG, $\times 10^9$/mL, *Me* (Q_1, Q_3)	11.0 (9.0, 13.0)	9.0 (7.6, 10.2)	<0.001
WBC count on the day of POAF onset, $\times 10^9$/mL, *Me* (Q_1, Q_3)	12.1 (10.0, 14.2), $n=21$	14.0 (10.0, 14.5), $n=8$	0.511
Number of bed-days, *Me* (Q_1, Q_3)	9 (7, 11)	9 (7, 11)	0.465
Statin therapy after CABG, no. (%)	82 (100)	124 (100)	1
Therapy with ACE-Is after CABG, no. (%)	82 (100)	124 (100)	1
Therapy with beta-blockers after CABG, no. (%)	81 (98.8)	122 (98.4)	0.931

BMI, body mass index; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure (according to exclusion criteria of our study, the patients with moderately impaired renal function estimated by the Cockroft–Gault formula are taken into account); 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; RCA, right coronary artery; TIA, transient ischemic attack; WBC, white blood cells.

therapy in anamnesis. However, we did not assess the regularity of this treatment. As for the nSt-patients, they did not take statins in anamnesis.

The risk of occurrence of POAF was evaluated using the Cox-regression model (Table 2). The indicators with high correlation ($R < 0.7$) were not included together in the analysis. Such factors as "prior myocardial infarction", "therapy with beta-blockers", and "therapy with angiotensin-converting-enzyme inhibitors (ACE-Is)" had high correlation ($R < 0.7$). Therefore, only "Prior myocardial infarction" was included in the multiple analysis.

From the clinical variables presented in Table 2, only the statin therapy and number of grafts are found to be statistically meaningful for the risk of POAF after CABG. Odds ratio of POAF event prediction by statin therapy was 0.20 (95%CI: 0.08–0.51), $P < 0.001$. Each subsequent graft increased the risk of POAF 2.1 times.

4. Discussion

Despite the numerous studies on the pathophysiology of POAF after cardiac surgery, there is still no definite answer to the question about the reasons of POAF event in patients without prior AF. Many factors have influence on AF, such as advanced age, hypertension, diabetes, obesity, the expansion of the left atrium, cardioplegia, surgical myocardial damage, oxidative stress, electrolyte imbalance, etc.

We investigated the role of statin therapy in the primary prevention of POAF after isolated CABG. We utilized WBCs as an

Table 2
Clinical variables used in the Cox-regression model for evaluation of the risk of occurrence of POAF in patients after CABG ($\chi^2 = 28.3$, $P = 0.008$).

Parameter	Regression coefficient (β)	Standard error	Risk index Exp (B)	Wald test	P-level
Statin therapy, yes/no	−1.600	0.434	0.201	13.63	<0.001
Number of grafts, no.	0.741	0.297	2.099	6.23	0.013
Therapy with beta-blockers, yes/no	−1.388	1.346	0.249	1.06	0.302
EDV, mL	0.007	0.007	1.007	0.976	0.323
Diabetes	−0.99	1.050	0.371	0.888	0.345
CRF	−0.414	0.464	0.660	0.79	0.372

EDV, end-diastolic volume of left ventricle; CRF, chronic renal failure.
Note that the statistically significant ($P < 0.05$) predictors of POAF and the first 4 non-significant factors are summarized and presented in the descending order of significance. Other indicators included in the multiple analysis (see Table 1) are not presented.

inflammatory marker, due to its high predictive value to AF.[25–27] Some studies have shown that neutrophils level is more specific independent predictor of POAF.[26] It is known that due to ischemia and reperfusion during cardioplegia (off-pump) and bypass, the neutrophils are involved in the secretion of a wide variety of inflammatory biomarkers. This study revealed the strong correlation between the WBC count and risk of POAF. The rate of POAF was significantly higher in patients with a higher WBC count on the 4th day after CABG (Table 1).

Understandably cardiopulmonary bypass and off-pump can cause inflammation by themselves. However, the study groups did not differ by these factors (Table 1). Therefore, in our opinion, the impact of these factors on the outcome was equal in both studied groups. In Cox-regression analysis, the bypass and off-pump did not show a significant predictive power for the risk assessment of POAF.

Furthermore, the WBC count was maximum on the day of POAF onset in the both study groups and the achieved maximal level was statistically comparable in both groups (Table 1). Note that only the patients with POAF event were taken into account, namely: 21 subjects from nSt-patients and 8 subjects from St-patients. In these patients, the inflammation degree was the same regardless of statin use. Probably it is due to genetic polymorphism affecting the variability of anti-inflammatory properties of statins. For example, a stronger lipid-lowering and non-lipid effects of atorvastatin are known in subjects with TrpTrp genotype of polymorphic marker Trp719Arg of KIF6 gene, AA genotype of polymorphic marker A(−290) of CYP3A4 gene, MM genotype of polymorphic marker Met455Thr of CYP3A4 gene, GG genotype of polymorphic marker G6986A of CYP3A5 gene, CC genotype of polymorphic marker C(−1947)A of YMGCR1 gene, etc.[28,29] In the world population, the immunity to this group of drugs varies widely depending on ethnic features.[30]

Statin therapy prior to CABG and in the postoperative period is associated with reductions in the rate of POAF and WBC count on the 4th day in patients without prior AF (according to comparison between nSt-patients and St-patients).

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-methylglutaryl-CoA (HMG-CoA) reductase inhibitors seems to be due to their effect on neutrophils, i.e. in increase of apoptosis and enhancement of cytokine secretion. Chello et al. reported that using of simvastatin 40 mg/day during 7 days after surgery reduced the peak anti-inflammatory markers count (interleukin 6 and interleukin 8) and WBC count.[31] The anti-inflammatory effect of statins begins to appear before their hypolipidemic effect. In our study, the statin therapy started just in 3 days before CABG led to significant results in terms of prevention of POAF.

In our study, the Cox-regression analysis showed that only two factors (statin therapy and number of grafts) have significant influence on the POAF onset. Moreover, the number of grafts increased the risk of POAF significantly, while the statin therapy significantly decreased the risk of POAF (Table 2).

Anti-inflammatory properties of statins have been shown in several studies. Ikeda et al. have 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] Marìn et al. obtained similar results in a study on 234 patients.[33]

Kimura et al. have shown experimentally that fluvastatin can inhibit the activities of leukotriene B_4 and platelet activation factor.[34] The lipid-independent anti-inflammatory effect was confirmed in the experimental study performed by Scalia et al.[35] 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.

The ARMYDA-3 study revealed that treatment with atorvastatin 40 mg/day, initiated 7 days before surgery, significantly reduced the incidence of POAF after elective cardiac surgery with cardiopulmonary bypass. Our results agree with the main results of Patti et al. and considerably complement them. However, there is some difference between our results and those of Patti et al. In our study, all nSt-patients began to receive the statin therapy from the first day after CABG. The criterion for inclusion in the group of St-patients was the use of statin therapy for at least 3 days prior to the CABG that was continued after the operation. Note that all St-patients in our study received the statin therapy in anamnesis, but we did not assess the regularity of this treatment. The nSt-patients did not receive the statins in anamnesis. Thus, all patients in our study received the statin therapy after CABG. As for Patti et al., they compared the statin therapy with placebo. We have shown that prescription of statins after the operation (without the preceding statin therapy) did not give effect in primary prevention of POAF unlike in patients receiving the regular statin therapy at least 3 days prior to the operation. This peculiarity of our study allows us to supplement the results of the known meta-analysis carried out by Liakopoulos et al.,[37] in which the authors have shown that evidence of supporting perioperative statin use for prevention of AF remains inconclusive.

In a few studies, it was shown that statin therapy can lead to the decrease in the length of hospital stay due to a reduction of the AF.[2,36] We have not seen this effect in our study. Several studies have shown similar results.[38–42] It should be noted that some of these studies were carried out for a small number of patients. Furthermore, different doses and types of statins were used in these studies.

At the same time, other studies have shown significant association between POAF after CABG and left atrial parameters[43] and between POAF and perioperative use of intra-aortic balloon pump.[44] In our study, we did not observe any such association. The reason may be due to the design of our study mentioned in Section 6.

5. Conclusion

Statin therapy carried out prior to the isolated CABG is an effective approach to primary prevention of POAF in early postoperative period. The prescription of statin therapy after CABG in nSt-patients did not give any prophylactic benefit as observed in St-patients. The positive effect of statins may be explained by their anti-inflammatory properties.

6. Limitations

There are some limitations of our study. The main being the retrospective nature of the study, precluding any randomization with placebo-control.

It is known that all the patients with coronary artery disease should receive statin medication according to the clinical guidelines.[45] When a prospective randomized trial is conducted, a half of the patients are supposed to discontinue the lipid-lowering therapy. In our opinion, it is impossible from the ethical viewpoint according to the contemporary 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 noted that we did not analyze the reasons why the patients did not receive the statin therapy prior to the surgery. Our study was retrospective and to perform CABG there was no need

for patients receiving the statin therapy. Statin medication and lipid level control is usually within the cognizance of outpatient cardiologist. In addition, it is known that outpatient treatment compliance is still the unsolved problem.

In the present study, we did not evaluate the dose of statin therapy, because of the complexity of the retrospective collection of such data. Previously, the meta-analysis of Chen et al.[46] has shown the importance of the duration of preoperative therapy with statins for reducing the risk of POAF, that somewhat limits the results of our study. However, these authors found no relationship between the dose of statins and reduced risk of POAF.

Another limitation of our study was the absence of information about serum lipid profile before the operation. Therefore, this information was not included in the analysis. Thus, we have no statistically significant data to propose that the anti-fibrillatory effect of statin extends beyond their lipid lowering action.

Beta-blockers could also affect the frequency of POAF. However, the ethical rules did not allow us to deny the patients the medication with proven efficacy. This limitation is typical for other studies.[47]

It is noteworthy that all patients included in this study had relatively high values of ejection fraction of left ventricle. It can be explained by the fact that patients with left ventricular dysfunction are often subjected to combined interventions (e.g., correction of valve apparatus, etc.) that was the exclusion criterion for our study. It is obvious that such selection of patients could influence the study results.

Conflicts of interest

The authors have none to declare.

Acknowledgement

This study was supported by the Russian Science Foundation, Grant No. 15-15-30040.

References

1. Villareal RP, Hariharan R, Liu BC, et al. Postoperative atrial fibrillation and mortality after coronary artery bypass surgery. *J Am Coll Cardiol.* 2004;43:742–748. http://dx.doi.org/10.1016/j.jacc.2003.11.023.
2. Mathew JP, Fontes ML, Tudor IC, et al. A multicenter risk index for atrial fibrillation after cardiac surgery. *JAMA.* 2004;291:1720–1729. http://dx.doi.org/10.1001/jama.291.14.1720.
3. Archbold RA, Curzen NP. Off pump coronary artery bypass graft surgery. The incidence of postoperative atrial fibrillation. *Heart.* 2003;89:1134–1137. http://dx.doi.org/10.1136/heart.89.10.1134.
4. Filatov AG, Tarashvili EG. Epidemiology and social significance of atrial fibrillation. *Annaly Aritmologii.* 2012;9:5–13.
5. Bockeria LA, Zelenikin MA, Golukhova EZ, Batov SM. Heart rhythm and conduction disturbances in early postoperative period after surgical correction for congenital heart defects in infants. *Annaly Aritmologii.* 2012;9:24–32.
6. 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;27:2846–2857. http://dx.doi.org/10.1093/eurheartj/ehl272.
7. 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. http://dx.doi.org/10.1378/chest.128.2_suppl.39S.
8. 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;38:2012–2016.
9. Lertsburapa K, White CM, Kluger J, et al. Preoperative statins for the prevention of atrial fibrillation after cardiothoracic surgery. *J Thorac Cardiovasc Surg.* 2008;135:405–411. http://dx.doi.org/10.1016/j.jtcvs.2007.08.049.
10. Gravlee GP. Update on cardiopulmonary bypass. *Curr Opin Anesthesiol.* 2001;14:11–16.
11. Melikulov AK., Maglakelidze DA. Possible ways and strategies for prevention of atrial fibrillation after off-pump surgeries. *Annaly Aritmologii.* 2012;9:13–19.
12. Jarett C, Kwame A. Postoperative atrial fibrillation: role of inflammatory biomarkers and use of colchicine for its prevention. *Pharmacotherapy.* 2014;34:1167–1173. http://dx.doi.org/10.1002/phar.1485.
13. Bockeria LA, Shengelia LD. Mechanisms of atrial fibrillation: from ideas and hypotheses to effective understanding of the problem. *Annaly Aritmologii.* 2014;11:5–9. http://dx.doi.org/10.15275/annaritmol.2014.1.1.
14. Bockeria OL, Akhobekov AA. The efficiency of statins in the prevention of atrial fibrillation after cardiac operations. *Annaly Aritmologii.* 2014;11:14–23. http://dx.doi.org/10.15275/annaritmol.2014.1.2.
15. Worden JC, Asare K. Postoperative atrial fibrillation: role of inflammatory biomarkers and use of colchicine for its prevention. *Pharmacotherapy.* 2014;34:1167–1173. http://dx.doi.org/10.1002/phar.1485.
16. Liu C, Wang J, Yiu D, Liu K. The efficacy of glucocorticoids for the prevention of atrial fibrillation, or length of intensive care unite or hospital stay after cardiac surgery: a meta-analysis. *Cardiovasc Ther.* 2014;32:89–96. http://dx.doi.org/10.1111/1755-5922.12062.
17. Raiten JM, Ghadimi K, Augoustides JG, et al. Atrial fibrillation after cardiac surgery: clinical update on mechanisms and prophylactic strategies. *J Cardiothorac Vasc Anesth.* 2015;29:806–816. http://dx.doi.org/10.1053/j.jvca.2015.01.001.
18. Hung CY, Hsieh YC, Huang JL, et al. Statin therapy for primary prevention of atrial fibrillation: guided by CHADS2/CHA2DS2VASc score. *Korean Circ J.* 2014;44:205–209. http://dx.doi.org/10.4070/kcj.2014.44.4.205.
19. Zheng H, Xue S, Hu ZL, et al. The use of statins to prevent postoperative atrial fibrillation after coronary artery bypass grafting: a meta analysis of 12 studies. *J Cardiovasc Pharmacol.* 2014;64:285–292. http://dx.doi.org/10.1097/FJC.0000000000000102.
20. Samadikhah J, Golzari S, Sabermarouf B, Karimzadeh I. Efficacy of combination therapy of statin and vitamin C in comparison with statin in the prevention of post CABG atrial fibrillation. *Adv Pharm Bull.* 2014;4:97–100. http://dx.doi.org/10.5681/apb.2014.015.
21. 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;155:541–546. http://dx.doi.org/10.1016/j.ahj.2007.10.027.
22. Jacob KA, Nathoe HM, Dieleman JM, van Osch D, Kluin J, van Dijk D. Inflammation in new-onset atrial fibrillation after cardiac surgery: a systematic review. *Eur J Clin Investig.* 2014;44:402–428. http://dx.doi.org/10.1111/eci.12237.
23. Martsevich SY., Gaisenok OV, Tripkosh SG, et al. Real practice of statins use and its dependence on follow-up in the specialized medical centre in patients with high cardiovascular risk (according to the PROFILE register). *Ration Pharmacother Cardiol.* 2013;9:362–367.
24. Malay LN. Statins in the treatment and prevention of cardiovascular diseases: repetition of the past and optimism for the future. *Ration Pharmacother Cardiol.* 2014;10:513–524.
25. Lamm G, Auer J, Weber T, et al. Postoperative white blood cell count predicts atrial fibrillation after cardiac surgery. *J Cardiothorac Vasc Anesth.* 2006;20:51–56. http://dx.doi.org/10.1053/j.jvca.2005.03.026.
26. Gibson PH, Cuthbertson BH, Rae D, et al. Usefulness of neutrophil/lymphocyte ratio as predictor of new onset atrial fibrillation after coronary artery bypass grafting. *Am J Cardiol.* 2010;105:186–191. http://dx.doi.org/10.1016/j.amjcard.2009.09.007.
27. 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. http://dx.doi.org/10.1093/ejcts/ezt181.
28. Vishnuprabu D, Geetha S, Bhaskar LV, et al. Genotyping and meta-analysis of KIF6 Trp719Arg polymorphism in South Indian Coronary Artery Disease patients: a case–control study. *Meta Gene.* 2015;5:129–134. http://dx.doi.org/10.1016/j.mgene.2015.07.001.
29. Korhonova M, Doricakova A, Dvorak Z. Optical isomers of atorvastatin, rosuvastatin and fluvastatin enantiospecifically activate pregnane X receptor PXR and induce CYP2A6, CYP2B6 and CYP3A4 in human hepatocytes. *PLOS ONE.* 2015;10:e0137720. http://dx.doi.org/10.1371/journal.pone.0137720.
30. Peng P, Lian J, Huang RS, et al. Meta-analyses of KIF6 Trp719Arg in coronary heart disease and statin therapeutic effect. *PLoS ONE.* 2012;7:e50126. http://dx.doi.org/10.1371/journal.pone.0050126.
31. Chello M, Anselmi A, Spadaccio C, et al. Simvastatin increases neutrophil apoptosis and reduces inflammatory reaction after coronary surgery. *Ann Thorac Surg.* 2007;83:1374–1380. http://dx.doi.org/10.1016/j.athoracsur.2006.10.065.
32. Ikeda U, Shimada K. Statin and monocytes. *Lancet.* 1999;353:2070. http://dx.doi.org/10.1016/S0140-6736(05)77885-5.
33. 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. http://dx.doi.org/10.1016/j.amjcard.2005.07.124.
34. Kimura M, Kurose I, Russell J, Granger DN. Effects of fluvastatin on leukocyte–endothelial cell adhesion in hypercholesterolemic rats. *Arterioscler Thromb Vasc Biol.* 1997;17:1521–1526. http://dx.doi.org/10.1161/01.ATV.17.8.1521.
35. Scalia R, Gooszen ME, Jones SP. Simvastatin exers both anti-inflammatory and cardioprotective effects in apolipoprotein E-deficient mice. *Circulation.* 2001;103:2598–2603. http://dx.doi.org/10.1161/01.CIR.103.21.2598.
36. Patti G, Chello M, Candura D, et al. Randomized trial of atorvastatin for reduction of postoperative atrial fibrillation in patients undergoing cardiac surgery: results of the ARMYDA-3 (Atorvastatin for Reduction of MYocardial Dysrhythmia After cardiac surgery) study. *Circulation.* 2006;114:1455–1461. http://dx.doi.org/10.1161/CIRCULATIONAHA.106.621763.
37. Liakopoulos OJ, Choi YH, Kuhn EW, et al. Statins for prevention of atrial fibrillation after cardiac surgery: a systematic literature review. *J Thorac Cardiovasc Surg.* 2009;138:678–686. http://dx.doi.org/10.1016/j.jtcvs.2009.03.054e1.
38. Sakamoto H, Watanabe Y, Satou M. Do preoperative statins reduce atrial fibrillation after coronary artery bypass grafting? *Ann Thorac Cardiovasc Surg.* 2011;17:376–382. http://dx.doi.org/10.5761/atcs.oa.10.01588.

39. Sun Y, Ji Q, Mei Y, et al. Role of preoperative atorvastatin administration in protection against postoperative atrial fibrillation following conventional coronary artery bypass grafting. *Int Heart J.* 2011;52(1):7–11. http://dx.doi.org/10.1536/ihj.52.7.
40. Karimi A, Bidhendi LM, Rezvanfard M, et al. The effect of a high dose of atorvastatin on the occurrence of atrial fibrillation after coronary artery bypass grafting. *Ann Thorac Surg.* 2012;94(1):8–14. http://dx.doi.org/10.1016/j.athoracsur.2012.01.054.
41. Aydın U, Yılmaz M, Düzyol Çcdl, et al. Efficiency of postoperative statin treatment for preventing new-onset postoperative atrial fibrillation in patients undergoing isolated coronary artery bypass grafting: a prospective randomized study. *Anatol J Cardiol.* 2015;15(6):491–495. http://dx.doi.org/10.5152/akd.2014.5531.
42. Gan HL, Zhang JQ, Bo P, Wang SX, Lu CS. Statins decrease adverse outcomes in coronary artery bypass for extensive coronary artery disease as well as left main coronary stenosis. *Cardiovasc Ther.* 2010;28(2):70–79. http://dx.doi.org/10.1111/j.1755-5922.2009.00098.x.
43. 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;33:242–248. http://dx.doi.org/10.1111/echo.13059.
44. 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;51:320–323.
45. Reiner Z, Catapano AL, De Backer G, et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur Heart J.* 2011;32:1769–1818. http://dx.doi.org/10.1093/eurheartj/ehr158.
46. Chen WT, Krishnan GM, Sood N, Kluger J, Coleman CI. Effect of statins on atrial fibrillation after cardiac surgery: a duration- and dose-response meta-analysis. *J Thorac Cardiovasc Surg.* 2010;140:364–372. http://dx.doi.org/10.1016/j.jtcvs.2010.02.042.
47. Golzari SE, Mahmoodpoor A. Care bundles in intensive care units. *Lancet Infect Dis.* 2014;14:371–372. http://dx.doi.org/10.1016/S1473-3099(14)70731-5.