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Atorvastatin for Reduction of Postoperative Atrial Fibrillation in Patients Undergoing Cardiac Surgery

Hossam Mansour[1,*], *Ramadan Galeb*[2]

[1]Department of Cardiology, Faculty of Medicine, October 6th University-Giza-Egypt.
[2]Department of Cardiology, Faculty of Medicine, Aswan University-Aswan-Egypt.

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Background: Post-operative atrial fibrillation (POAF) is the most common complication encountered after cardiac surgery. Atrial fibrillation (AF) after cardiac surgery is associated with increased risk of complications, length of stay, and cost of care. Observational evidence suggests that patients who have undergone previous statin therapy have a lower incidence of postoperative AF. We tested this observation in a randomized, controlled trial.
Methods and Results: patients undergoing elective cardiac surgery, without previous statin treatment or history of AF, were enrolled. Patients were randomized to atorvastatin (40 mg/d, n: 25) or placebo (n_±25) starting 7 days before operation. The primary end point was incidence of postoperative AF; secondary end points were length of stay, major adverse cardiac and cerebrovascular events, and postoperative C-reactive protein (CRP) variations. Atorvastatin significantly reduced the incidence of AF versus placebo (36% versus 64%, P=0.048). Accordingly, length of stay was longer in the placebo versus atorvastatin arm (7.5±1.5) versus (5.5±1.5) days, P=0.04). Peak CRP levels were lower in patients without AF (P=0.04). Multivariable analysis showed that atorvastatin treatment conferred a 61% reduction in risk of AF, whereas high postoperative CRP levels were associated with increased risk (P=0.04). The incidence of major adverse cardiac and cerebrovascular events at 30 days was similar in the 2 arms.
Conclusions: Treatment with atorvastatin 40 mg/d, initiated 7 days before surgery, significantly reduces the incidence of postoperative AF after elective cardiac surgery and shortens hospital stay. These results may influence pharmacological therapy before cardiac surgery
Keywords: cardiology, trials, statins, atrial fibrillation.

1 Introduction

Atrial fibrillation (AF) is a common postoperative complication after coronary artery bypass grafting (CABG), with a prevalence of 30–45%.(1–4) because of impaired atrial pump function and ventricular filling, AF following CABG may decrease cardiac output, hence causing unstable hemodynamics, prolonging the need for assisted ventilation and inotropic support, significant morbidity, and increased length of hospital stay and costs.(1,2)

Therefore, it becomes crucial for clinicians to prevent AF following CABG. The causes and pathogenesis of AF following CABG are multifactorial and may be related to surgical technical factors and a multitude of clinical factors; previous studies confirm that the inflammatory response plays an important role in the development of AF following CABG.(5,6) Statins, independent of their cholesterol-lowering property, are reported to reduce the risk of AF.

Recent clinical studies report that preoperative statin treatment significantly decreases the incidence of AF following CABG with cardiopulmonary bypass.(3-8). Numerous mechanisms have been proposed to explain a possible protective effect of statins in the prevention of postoperative AF after cardiac surgery including antioxidant effects, direct antiarrhythmic effects mediated through cell membrane stabilization, protection of ischemic myocardium, and anti-inflammatory effects (9-12). Although the precise mechanisms by which statins may prevent AF have not yet been identified, it is likely that the effects are multifactorial.

2 Material and Methods

Our study was a randomized, prospective trial performed at kasr al-aini hospitals. A total of 50 consecutive patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) from April 2012 to April 2013 were evaluated. All the study population will be subjected to Personal history, risk factors profile as:

Diabetes mellitus (DM), Hypertension (HTN), Dyslipidemia, Current cigarette smoking, Drug abuse and Alcohol intake, current medications administration of Beta-blockers (B blocker), Calcium channel blocker, Statins,

*Corresponding author e-mail: mansour.hossam@gmail.com

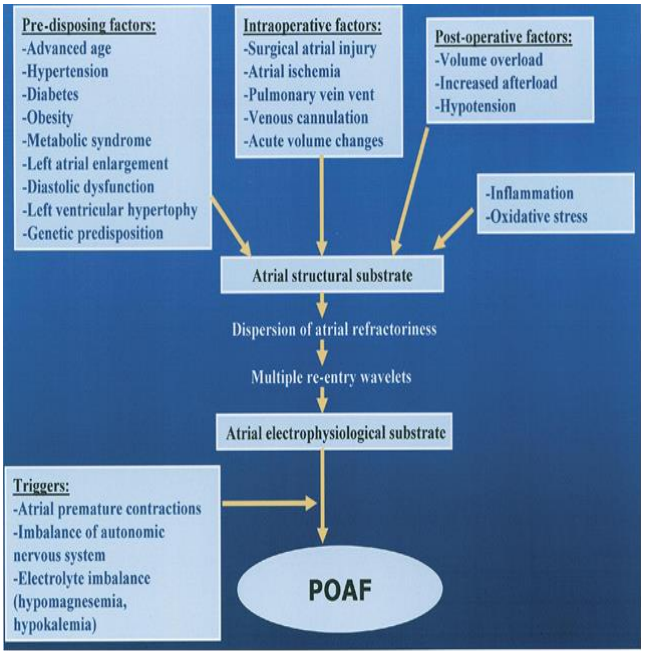

Fig. 1: Pathogenesis of atrial fibrillation.

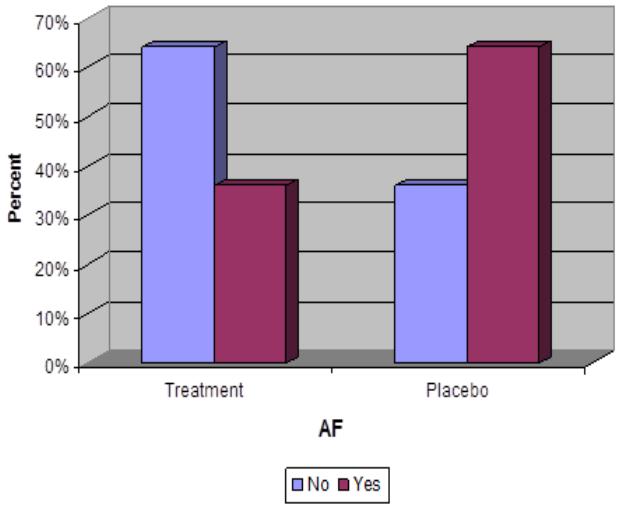

Fig. 2: Comparison between treatment and placebo group as regard AF occurrence.

Aspirin (acetyl salicylic acid), Fibrate, Clopidogrel, Angiotensin converting enzyme inhibitors (ACEIs), Angiotensin receptor blockers (ARBs) and Family history of Premature coronary artery disease and sudden cardiac death.

The study population was subjected to Assessment of the general condition and vital signs as Blood pressure, heart rate, temperature and respiratory rate, general examination and Local cardiac examination.

Laboratory investigations (CBC-renal functions, liver functions, serum electrolytes, lipid profile, post operative troponin and CRP level pre and post operative) were done to the study population

Patients will be randomized independent of their admission lipid levels and All patients will be divided into two groups, Group A: those who will receive atorvastatin 40mg daily one week before surgery and continued post operatively and group B : those who will not receive statins.

2.1 Surgical techniques and operative management

All operations were performed by experienced cardiac surgeons using standard techniques; type of surgery and procedural strategies were applied according to the surgeon's discretion. Induction and maintenance of anesthesia were similar for all patients and consisted of weight-related doses of fentanyl, midazolam, and pancuronium bromide. All operations were performed through exposure of the heart with a median sternotomy incision. CPB was performed in a standard fashion with the use of a hollow-fiber oxygenator and a roller pump, with ascending aortic cannulation added to right atrium cannulation in patients undergoing bypass grafting. During CPB, hematocrite was maintained between 20% and 25%, and pump flows were kept between 2.0 and 2.5 $L \cdot min^{-1} \cdot m^{-2}$ to maintain mean arterial pressure between 50 and 70 mm Hg. All patients were cooled to moderate hypothermia (mean 32°C), and cardioplegic arrest was achieved with cold blood cardioplegia (4°C) infused into the ascending aorta. No patient received retrograde cardioplegia. Heparin was given at a dose of 300 IU/kg to obtain an activated clotting time >400 seconds; on completion of anastomoses, heparin effects were reversed by intravenous protamine sulfate (1 mg/300 IU of heparin) to achieve an activated clotting time similar to preoperative values. All anastomoses were sutured by hand. Postoperative nonhemic volume expanders were routinely used. (70)A standardized protocol for early postoperative care was followed in the intensive care unit. Patients were extubated when the Tobin index [respiratory rate (spontaneous)/tidal volume (L)] was <105, PaO_2 was >60 mm Hg with FIO_2 <0.4, continuous positive airway pressure <5 mbar, $PaCO_2$ <50 mm Hg, and arterial pH >7.35. 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. Inotropic agents were used perioperatively in patients with a cardiac index <2.2 $L \cdot min^{-1} \cdot m^{-2}$, the target for cardiac index being 2.5 to 3.0 $L \cdot min^{-1} \cdot m^{-2}$. Non steroidal anti inflammatory drugs, β-blockers, calcium antagonists, and/or angiotensin converting enzyme inhibitors were given after surgery when clinically indicated. All patients receiving bypass grafting were treated with aspirin (162mg 24hours after surgery daily dose) and with intravenous nitroglycerin infusion for the first 24 hours, unless contraindicated. From the intensive care unit, patients were transferred to a monitored unit, where 3-lead telemetric monitoring was performed continuously for at least 2 days after the operation; in addition, patients had a 12-lead ECG daily until hospital discharge. The ECG data were reviewed on a daily

basis. Fluid intake and output were monitored hourly throughout the ICU stay.(70)

All patients continued the assigned treatment preoperatively (atorvastatin 40 mg/d or no statins) from the day after surgery until discharge. Open-label atorvastatin (40 mg/d) was given to all patients on discharge and prescribed indefinitely.

All patients who had in-hospital atrial fibrillation were treated according to protocol with intravenous amiodarone (bolus 5 mg/kg followed by infusion 15 mg · kg^{-1} · 24 h^{-1}) and were discharged with instructions to undergo oral amiodarone therapy for at least 30 days. Patients were scheduled for weekly visits in our outpatient clinic for the first month, where 12-lead ECGs were performed. Each patient gave informed consent to participate in the study.(10)

Postoperative AF was defined as any documented AF of >15 minutes in duration or AF episodes requiring intervention for symptoms or hemodynamic compromise after CABG surgery.

All deaths were regarded as cardiovascular deaths, unless there was documented evidence of a clear noncardiovascular cause. Postoperative stroke was defined as the development of stroke (a new focal neurologic deficit of vascular origin lasting >24 hours with confirmation by computed tomography or magnetic resonance imaging scan) after the surgery. The diagnosis of a perioperative myocardial infarction was based on the presence of 2 of the following criteria: new Q waves or disappearance of R waves in at least 2 contiguous leads on a postoperative ECG tracing; serum MB isoenzyme of creatine kinase (CK-MB) activity >100 IU/L 12 to 48 hours after surgery; and new akinetic-dyskinetic segments on the echocardiogram. Persistent AF was defined as documented AF confirmed by 12-lead ECG found at the 1-month follow-up. (10)

3 Results

Demographic, clinical, and preoperative variables were similar in the atorvastatin and placebo groups irrespective of the presence of HTN, DM, COPD, PVD, smoking, previous MI and stroke. Although there was a significant difference in age between the two groups with older age in the treatment group and unexpectedly in treatment group with older age the incidence of AF was decreased significantly (p =0 .018)

The echocardiography and angiographic characteristics shows no significant difference between the two groups however left atrium diameter was significantly larger in those who received atorvastatin (p = 0.04)

Statistical analysis of post-operative laboratory investigation in the form of electrolytes, hemoglobin and creatinine shows no significant difference between the two groups.

The possibility of effect modification produced by technique of operations, number of anastomosis, inotropic support and use of pacing and other post-operative data were investigated and showed no significant modification was detected

As regards to the effect of the drugs which may affect the incidence of post-operative AF in both groups, it was nil, because there was no significant difference between the two groups as regard receiving beta blockers, calcium channel blockers , digoxin , amiodarone , ACE inhibitors.

Statistical analysis showed there was no significant difference between the two groups in there lipid profile, although unexpectedly there was a significant decrease in LDL post operatively in patients who did not receive atorvastatin (p=0.001). In addition, this goes with that the effect of atorvastatin in decreasing AF not related to its affection on lipid profile but to its pleiotropic effect.

Comparing the effect of beta blockers on the incidence of atrial fibrillation between the patients receiving it in both arms to the patients who don't receive it, there was a significant reduction in the incidence of atrial fibrillation in favor to the patients receiving beta blockers (p <0.05)

Statistical analysis showed a significant reduction in atrial fibrillation occurrence in the treatment group comparing with non-treatment group demonstrated a significant clinical benefit, with a 61% reduction in risk of postoperative atrial fibrillation (p=0.048).

The duration of atrial fibrillation episodes were significantly reduced in treatment group in comparison to non-treatment group, similarly the ventricular response was less in treatment group (p=0.045), (p= 0.046) respectively. These results show clinical benefits in favor to the treatment.

In addition, we had found that Baseline preoperative CRP levels were not different

(3.8±2.4mg/L in the statin group versus 4.3±1.5mg/L in the placebo group, P_0.06), nor were peak CRP levels after the operation (170±30 versus 165.5±45mg/L, P_0.07); CRP levels were significantly lower in patients without versus those with atrial fibrillation (P_0.04). Patients with atrial fibrillation had the highest postoperative peak levels of CRP, irrespective of the randomization assignment (atorvastatin 190±2 mg/L, placebo 187±5 mg/L).

The mean postoperative hospital stay was significantly lower in the atorvastatin versus placebo arm (5.5±1.5versus 7.5±1.5days, P_0.04). Occurrence of major adverse cardiac and cerebrovascular events was as follows: 5patients (2 in the atorvastatin and 3in the placebo arm) died after the operation;

Cause of death was ischemic stroke in two patients, respiratory failure in 1, and multiorgan failure in 2 patients. The incidence of postoperative myocardial infarction was 4% in patients in the atorvastatin arm (1/25) and 4% in those randomized to placebo (1/25); all had troponin I elevation _3.1 _g/L at 12 hours, without ST segment elevation on the ECG or new wall-motion abnormalities on the echocardiogram. No correlation was found between

Table 1: Comparison between treatment and placebo group as regard personal characteristics and risk factors

	Treatment		No treatment		P		Sig
	N	%	N	%			
Age group	<60 Yrs	13	52.0%	19	76.0%	.077*	NS
	=>60 Yrs	12	48.0%	6	24.0%		
Age	Mean ±SD	59.12	4.84	56.00	4.16	.018‡	S
Sex	Male	19	76.0%	16	64.0%	.355*	NS
	Female	6	24.0%	9	36.0%		
BMI	Mean ±SD	27.96	2.46	28.54	2.38	.398‡	NS
DM	No	13	52.0%	15	60.0%	.569*	NS
	Yes	12	48.0%	10	40.0%		
HTN	No	3	12.0%	5	20.0%	.702**	NS
	Yes	22	88.0%	20	80.0%		
SMOKER	No	13	52.0%	14	56.0%	.777*	NS
	Yes	12	48.0%	11	44.0%		
Previous MI	No	9	36.0%	11	44.0%	.564*	NS
	Yes	16	64.0%	14	56.0%		
Previous stroke	No	23	92.0%	24	96.0%	1.00**	NS
	Yes	2	8.0%	1	4.0%		
PVD	No	19	76.0%	21	84.0%	.725**	NS
	Yes	6	24.0%	4	16.0%		
COPD	No	18	72.0%	19	76.0%	.747*	NS
	Yes	7	28.0%	6	24.0%		
Dyslipidemia	No	15	60.0%	16	64.0%	.771*	NS
	Yes	10	40.0%	9	36.0%		
CAD	Stable COD	23	92.0%	24	96.0%	1.00**	NS
	Unstable COD	2	8.0%	1	4.0%		

*Chi-Square Tests
**fisher exact
‡Student t test
BMI: body mass index, DM: diabetes mellitus, HTN: hypertension, MI: myocardial infarction, PVD: peripheral vascular disease, COPD:chronic obstructive pulmonary disease, CAD: coronary artery disease.

Table 2: Comparison between treatment and placebo group as regard Change in lipid profile.

	Treatment		**No treatment**		**P**	**Sig**
	Mean	**±SD**	**Mean**	**±SD**		
Cholesterol change	-18.40	6.86	-16.08	7.09	.245*	NS
TG change	-13.40	4.79	-16.28	7.36	.108*	NS
LDL change	-12.92	5.35	-16.12	11.30	.209*	NS
HDL change	.60	2.08	.96	2.03	.346**	NS

***Student t test**
****Mann Whitney test**
TG: triglycerides, LDL: low density lipoprotein, HDL: high density lipoprotein.

Table 3: Comparison between treatment and placebo group as regard AF occurrence:

		Treatment		**No treatment**		**P**	**Sig**
		N	**%**	**N**	**%**		
AF	**No**	16	64.0%	9	36.0%	.048*	S
	Yes	9	36.0%	16	64.0%		

AF: atrial fibrillation

postoperative peak levels of troponin I or CK-MB and occurrence of atrial fibrillation (P_0.41)

4 Discussion

Atrial fibrillation (AF) is one of the most common postoperative arrhythmias in patients who undergo coronary artery bypass grafting (CABG). Additionally, AF may affect the hemodynamic stability resulting in much morbidities after cardiac surgery; hence, prophylactic against AF should be optimized carefully in those going to CABG.

It is well known that incidence of atrial fibrillation was significantly lower in nonsmoking patient whose underwent CABG. However many reports presented the Statin irrespective to its cholesterol lowering effect, is potentially and effectively the drug of choice to decrease the risk of AF by its pleiotropic effects such as anti-inflammatory and anti-oxidant effect, modification of extracellular matrix remodeling property and its direct or indirect anti-arrhythmic effect. (10-14).

In the current study we evaluated the valuable Atorvastatin for those undergoing cardiac surgery to reduce AF risks post operatively, as regard to age difference between two groups we had found there was a significant difference in age between the two groups with older age in the treatment group and unexpectedly in treatment group with older age, the incidence of AF was decreased significantly suggesting the beneficial role of statin in decreasing incidence of Atrial fibrillation.

However some reports were controversial that suggested the incidence of post-operative atrial fibrillation was significantly lower in the younger age group 62.2 Vs 69.1 (15). Furthermore, Salima Mithani and his group found that atrial fibrillation was significantly lower in the treatment group with the lower mean age (16).

The echocardiographic features of the patients in both groups in our study revealed that there is significant difference in the left atrium size between the arms.

Left atrial dilatation was significantly higher in the treatment group and unpredictably the incidence of atrial fibrillation was significantly lower in the treatment group. As regards peripheral vascular disease the results of our study had demonstrated that the incidence of atrial fibrillation was similar in both groups and it has no statistically

In addition, we had found that baseline preoperative CRP levels were not different (3.8+2.4mg/L in the statin group versus 4.3+1.5mg/L in the placebo group, P_0.06), nor were peak CRP levels after the operation (170+30versus 165.5+45mg/L, P_0.07); CRP levels were significantly lower in patients without AF versus those with atrial fibrillation (P_0.04). Patients with atrial fibrillation had the highest postoperative peak levels of CRP, irrespective of the randomization assignment (atorvastatin 190±2mg/L, placebo 187±5mg/L). These results accordance with Giuseppe Patti (10).

Historical evidence to support an association between AF and inflammation can be extracted from the frequent association of AF with inflammatory conditions of the heart, such as myocarditis and pericarditis. (17,18)

Bruins and colleagues (19) were the first to propose the inflammation–AF hypothesis, following their observations of an increased frequency of AF after coronary artery bypass surgery. They noted that the peak incidence of AF occurred

On the second and third postoperative days, this coincided with the peak elevation of CRP levels.

In an interesting study by Maixent and colleagues, (20) the authors demonstrated the Presence of circulating autoantibodies against myosin heavy chain in a significant percentage of patients with idiopathic paroxysmal AF, which raises the possibility of an inflammatory autoimmune process in some patients with paroxysmal AF

Recent clinical studies have also explored the possible role of inflammatory mechanisms in the pathogenesis of atrial fibrillation after cardiac surgery.(21–23,19) it had been reported that cytokine release, leukocyte-endothelial adhesion, and levels of circulating adhesion molecules after cardiac surgery with CPB are attenuated in patients receiving statins.(24,25) In the present study, postoperative peak CRP levels were higher in patients who developed atrial fibrillation in either arm, and on multivariable analysis, CRP levels above the median were associated with increased risk.

This appears to confirm that higher inflammatory status is an important factor in the development of postoperative atrial fibrillation. Other mechanisms might contribute to the clinical benefit of atorvastatin, such as antioxidant effects, (26) direct antiarrhythmic effects by cell membrane ion channel stabilization, (27)

In addition, we had found that Mean postoperative hospital stay was significantly lower in the atorvastatin versus placebo arm (5.5+1.5versus 7.5+1.5days, P=0.04). Occurrence of major adverse cardiac and cerebrovascular events was as follows: 5patients (2 in the atorvastatin and 3in the placebo arm) died after the operation; Cause of death was ischemic stroke in 2 patients, respiratory failure in 1, and multiorgan failure in 2 patients. The incidence of postoperative myocardial infarction was 4% in patients in the atorvastatin arm (1/25) and 4% in those randomized to placebo (1/25); all had troponin I elevation at 12 hours, without ST segment elevation on the ECG or new wall-motion abnormalities on the echocardiogram. No correlation was found between postoperative peak levels of troponin I or creatine kinase-MB and occurrence of atrial fibrillation

Occurrence of major adverse cardiac and cerebrovascular events was as follows: 4 patients (2 in the atorvastatin and 2 in the placebo arm) died after the operation; cause of death was ischemic stroke in 1 patient, respiratory failure in 1, and multi organ failure in 2 patients. The incidence of postoperative myocardial infarction was 3% in patients in the atorvastatin arm (3/101) and 3% in those randomized to

placebo (3/99). No correlation was found between postoperative peak levels of troponin I or creatinine kinase-MB and occurrence of atrial fibrillation (P=0.41). Additionally our study emphasized that that Demographic, clinical, and preoperative variables were similar in the atorvastatin and placebo groups in the present study, the treatment effect occurred irrespective of age, sex, presence of diabetes mellitus, hypertension, peripheral vascular disease, smoking, previous MI, stroke, and chronic obstructive pulmonary disease.

5 Conclusion

the present study shows that treatment with atorvastatin 40 mg/d, initiated 1 week before elective cardiac surgery with CPB and continued in the postoperative period, significantly decreases postoperative atrial fibrillation with a 61% reduction in risk of postoperative atrial fibrillation and a significant reduction in length of hospital stay, thus, the low cost and low risk of this therapy may support the routine early initiation of atorvastatin treatment in such patients.

6 Limitation of the Study

1-Given the small sample group included within the study we suggest a further large number study would clarify much scientific approaches.

2-Clinical experience played the major role in all information mentioned in the study, hence multi-center studies may show more statistical variations that support the scientific guidelines.

References

[1] Go A, Hylek E, Phillips K, Henault L, Selby J, Singer D. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001; 285:2370–5.

[2] Benjamin E, Wolf P, D'Agostino R, Silbershatz H, Kannel W, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 1998; 98:946–52.

[3] Fuster V, Ryden L, Cannom D, Crijns HJ, Curtis AB, Ellenbogen KA, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: full text: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 guidelines for the management of patients with atrial fibrillation) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. J Am Coll Cardiol 2006; 48:854–906.

[4] Shiroshita-Takeshita A, Brundel B, Nattel S. Atrial fibrillation: basic mechanisms, remodeling and triggers. J Interv Card Electrophysiol 2005; 13:181–93.

[5] Boos C, Anderson R, Lip G. Is atrial fibrillation an inflammatory disorder? Eur Heart J 2006; 27:136–49.

[6] Engelmann M, Svendsen J. Inflammation in the genesis and perpetuation of atrial fibrillation. Eur Heart J 2005; 26:2083–92.

[7] Boos C, Lip G. The role of inflammation in atrial fibrillation. Int J Clin Pract 2005; 59:870–2.

[8] Dorian P. The future of atrial fibrillation therapy. J Cardiovasc Electrophysiol 2006; 17:S11–6.

[9] Marin F, Pascual DA, Roldàn V, Arribas JM, Ahumada M, Tornel PL, Oliver C, Gòmez-Plana J, Lip GYH, Valdés M. Statins and postoperative risk of atrial fibrillation following coronary artery bypass grafting. *Am J Cardiol*. 2006;97:55–60.

[10] Patti G, Chello M, Candura D, et al. Randomized trial of atorvastatin for reduction of post-operative atrial fibrillation in patients undergoing cardiac surgery: results of the ARMYDA-3 (Atorvastatin for Reduc tion of MYocardial Dysrhythmia After cardiac surgery) study. Circulation 2006;114:1455– 61.

[11] M.S. Kostapanos, E.N. Liberopoulos, J.A. Goudevenos, D.P.Mikhailidis, M.S. Elisaf. Do statins have an antiayyhythmic activity? Doi:10.1016/j.cardiores.2007.02.029.

[12] Chello M, Patti G, Candura D, Mastrobuoni S, Di Sciascio G, Agrò F, Carassiti M, Covino E. Effects of atorvastatin on systemic inflammatory response after coronary bypass surgery. *Crit Care Med*. 2006;34: 660–667.

[13] Yunqing Mei, MD, PhD; Xisheng Wang, MD, PhD; Yifeng Sun, MD; Jing Feng, MD; Jianzhi Cai, MD, PhD; Shiliang Xie, MD; Liangjie Chi, PhD. Effect of Preoperative Atorvastatin Therapy on Atrial Fibrillation Following Off-Pump Coronary Artery Bypass Grafting. the Japanese Circulation Society. 2015

[14] Statins and Postoperative Risk of Atrial Fibrillation Following Coronary Artery Bypass Grafting Francisco Marín, MD, PhDa,*, Domingo A. Pascual, MD, PhDd, Vanessa Roldán, MD, PhDc, José María Arribas, MD, Miguel Ahumada, MD, Pedro Luis Tornel, MD, Clara Oliver, MD, Jesús Gómez-Plana, MD, Gregory Y.H. Lip, MD, and Mariano Valdés, MD, PhD 2006 Elsevier Inc.

[15] Giovanni Filardo, Cody Hamilton, Robert F. Hebeler, Jr, Baron Hamman and Paul Grayburn 2009;*Circ Cardiovasc Qual Outcomes* 2009;2;164-169; originally published online April24,DOI: 10.1161/CIRCOUTCO New-Onset Postoperative Atrial Fibrillation After Isolated Coronary Artery Bypass Graft Surgery and Long-Term Survival.

[16] Dose dependent effect of statins on postoperative atrial fibrillationafter cardiac surgery among patients treated with beta blockersSalima Mithani, Muhammad S Akbar, Deborah J Johnson,Michael Kuskowski, Katherine K Apple, Jana Bonawitz-Conlin, Herbert B Ward, Rosemary F Kelly, Edward O McFallsHanna E Bloomfield, Jian-Ming Li and Selcuk Adabag*Journal of Cardiothoracic Surgery* 2009, 4:61 doi:10.1186/1749-8090-4-61.

[17] Spodick DH. Arrhythmias during acute pericarditis: a prospective study of 100 consecutive cases. *JAMA*. 1976;235:39–41.

[18] Morgera T, Di Lenarda A, Dreas L, et al. Electrocardiography of myocarditis revisited: clinical and prognostic significance of electrocardiographic changes. *Am Heart J*. 1992;124:455–467.

[19] Bruins P, Velthuis H, Yazdanbakhsh A, 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;1997:3542–3548.

[20] Maixent JM, Paganelli F, Scaglione J, et al. Antibodies against myosin in sera of patients with idiopathic paroxysmal atrial fibrillation.*J Cardiovasc Electrophysiol.* 1998;9:612–617.

[21] Gaudino M, Andreotti F, Zamparelli R, Di Castelnuovo A, Nasso G, Burzotta F, Iacoviello L, Donati MB, Schiavello R, Maseri A, Possati G. The -174G/C interleukin-6 polymorphism influences postoperative interleukin-6 levels and postoperative atrial fibrillation: is atrial fibrillation an inflammatory complication? *Circulation.* 2003;108:195–199.

[22] Abdelhadi RH, Gurm HS, Van Wagoner DR, Chung MK. Relation of an exaggerated rise in white blood cells after coronary bypass or cardiac valve surgery to development of atrial fibrillation postoperatively. *Am J Cardiol.* 2004;93:1176 –1178.

[23] Fontes ML, Mathew JP, Rinder HM, Zelterman D, Smith BR, Rinder CS; Multicenter Study of Perioperative Ischemia (McSPI) Research Group. Atrial fibrillation after cardiac surgery/cardiopulmonary bypass is associated with monocyte activation. *Anesth Analg*. 2005;101:17–23.

[24] Bucerius J, Gummert JF, Borger MA, et al. Stroke after cardiac surgery: a risk factor analysis of 16,184 consecutive adult patients. Ann Thorac Surg 2003;75:472– 8.

[25] Chello M, Carassiti M, Agrò F, Mastroroberto P, Pugliese G, Colonna D, Covino E. Simvastatin blunts the increase of circulating adhesion moleculesafter coronary artery bypass surgery with cardiopulmonary bypass. *J Cardiothorac Vasc Anesth*. 2004;18:605– 609.

[26] Bonetti PO, Lerman LO, Napoli C, Lerman A. Statin effects beyond lipid lowering: are they clinically relevant? *Eur Heart J*. 2003;24:225–248.

[27] Pound EM, Kang JX, Leaf A. Partitioning of polyunsaturated fatty acids, which prevent cardiac arrhythmias, into phospholipid cell membranes. *J Lipid Res*. 2001;42:346 – 351.