Chronic and Regular Use of Statin Prevents Atrial Fibrillation in Period after Cardiac Surgery

Renato Jorge Alves, Rodrigo Noronha Campos, Kenji Nakiri
Hospital Santa Cruz, Hospital Beneficência Portuguesa, São Paulo, SP - Brazil

Abstract

Background: Atrial fibrillation is a common complication after cardiac surgery. The previous use of statins may reduce the incidence of this arrhythmia.

Objective: To evaluate whether the chronic and regular use of statins, for a period of six months, prevents atrial fibrillation after elective cardiac surgery.

Methods: A study carried out with 107 patients that underwent cardiac surgery, including 66% of males and their mean age was 60.4 years (25 to 84). We evaluated the presence of atrial fibrillation among patients that used statins or not on a regular basis in the preoperative period. We excluded patients with urgent heart surgery, kidney failure, inflammatory diseases, previous atrial fibrillation, patients with thyroid disease and those using a permanent pacemaker.

Results: In the postoperative period, atrial fibrillation was present in 42 patients (39%) of the sample, including 11 (26%) people that had used statins on a regular basis in the preoperative period and 31 (74%) who had not. It was possible to observe that, in 22% of the patients that were using statin, there was no development of atrial fibrillation, while 45% of those who did not take statin had arrhythmia ($\rho = 0.02$). In the isolated myocardial revascularization, 47% of the patients that did not take statin and 23% of those that took statin developed atrial fibrillation ($\rho = 0.02$). There was no statistically significant difference in the analysis of groups with or without statin for the presence of risk factors for the development of atrial fibrillation ($\rho = 0.34$).

Conclusion: The regular use of statin, for six months or more in the preoperative period, reduced the incidence of atrial fibrillation after elective cardiac surgery. (Arq Bras Cardiol 2010; 95(5): 614-620)

Keywords: Arrhythmias, cardiac; atrial fibrillation; thoracic surgery; postoperative care; hydroxymethylglutaryl-CoA reductases inhibitors/therapeutic use.

Introduction

Atrial arrhythmias are frequent complications in the period after cardiac surgery, affecting from 11 to 40% of patients who undergo myocardial revascularization and 50% of patients who undergo valve replacement[1]. Despite the transient and benign character, their presence may have relevant consequences[2].

Atrial fibrillation is a common arrhythmia in the period after cardiac surgery, which prolongs the use of mechanical ventilation and vasoactive drugs, causing an increase in morbidity and hospitalization time, thereby overloading the health service[3-5]. Its pathogenesis is linked to variables such as: age, previous atrial arrhythmia, left ventricular end-diastolic pressure, intraoperative technical factors and inflammatory mechanisms[4,6,7].

Mailing address: Renato Jorge Alves •
Rua Santa Cruz, 398 - Hospital Santa Cruz - Diretoria - Vila Mariana - 04122-000, São Paulo, SP - Brazil
E-mail: rjorge@cardiol.br, renatoalves178@gmail.com
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Randomized studies have demonstrated efficacy in the use of statins for preventing atrial fibrillation in the postoperative period of patients that underwent cardiac surgery. However, these patients underwent prophylactic therapy only a few days before surgery and high dose of statin[4].

It is necessary to develop new strategies and to stratify patients to reduce postoperative clinical complications arising from cardiac surgery with extracorporeal circulation.

The primary endpoint that was evaluated was the possible beneficial effect of the chronic and regular use of statins to reduce the incidence of atrial fibrillation, after elective cardiac surgery. The secondary endpoint was to assess whether there was reduction in the hospitalization period of the group that was using statin.

Methods

Case-control study, carried out from February to October 2006, at São Joaquim Hospital (*Real e Benemérita Associação Portuguesa de Beneficência*) and at Santa Cruz Hospital in the city of São Paulo, São Paulo State, with a sample of 107 patients that underwent elective cardiac surgery, 75.7%

(81) of whom for myocardial revascularization and 24.3% (26) for aortic or mitral valve replacement, correction of interatrial communication or correction of interventricular communication. 66.4% (71) were male and 33.6% (36) were female. The age of subjects in the sample ranged from 25 to 84 years of age, with mean of 60.4 years of age.

The individuals included in the sample were divided into two groups: those who had used some type of statin, on a chronic and regular basis, for at least six months before the surgery and those who had not used statin in the six months prior to surgery. This period was adopted because the majority of patients selected for inclusion in the study had already been using the drug for more than six months.

The patients underwent cardiac surgery on the second day of hospitalization with the same team of cardiovascular surgeons, who used surgical techniques that were appropriate for each patient, in an individual way and with extracorporeal circulation. The team's chief surgeon decided on how the surgery and the procedures inherent in the surgery would be managed, in all cases. The induction and maintenance of anesthesia were similar for all patients. Beta-blockers, calcium channel blockers, angiotensin converting enzyme inhibitor and angiotensin receptor blockers were administered to patients, according to their individual needs. All patients that underwent myocardial revascularization received acetylsalicylic acid at doses of 100mg and intravenous nitroglycerin in the postoperative period, with the latter being replaced with isosorbide mononitrate (60mg divided in three daily doses), after the oral administration of medications began. All of them were monitored by three-lead electrocardiogram, during their stay at the intensive care unit, and by 12-lead electrocardiogram, on a daily basis during their stay at the hospital ward.

The exclusion criteria were: emergency cardiac surgery, history of previous non-reversed atrial fibrillation, renal insufficiency (creatinine > 3.0 mg/dl), inflammatory diseases, use of anti-inflammatory drugs, thyroid disease and the presence of a permanent pacemaker.

All patients that had atrial fibrillation after the cardiac surgery were given standard treatment with intravenous amiodarone, with initial bolus of 5 mg/kg and maintenance dose of 15mg/kg in 24 hours. In case of hemodynamic instability, electrical cardioversion was the procedure of choice. Atrial fibrillation was considered the episode that was longer than five minutes, recorded by 12-lead electrocardiogram, with or without hemodynamic instability.

The patients were stratified according to the clinical characteristics of the sample, and the data are shown in Table 1.

Statistics

The statistical analysis was conducted by using the Statistic 5.1 software. The mean and standard deviation were used for sample data such as age, risk factors and hospitalization time. The chi-square test was used to compare the endpoint of the study groups. The number needed to treat (NNT) was used to assess the average number of individuals who benefited from the use of statin, as a way to prevent acute atrial fibrillation after cardiac surgery. The charts were made in Excel XP. The data were presented in graphs and tables. The levels with $\rho<0.05$ were considered significant.

Table 1 - Clinical characteristics of the sample (total)

Risk factor	Total number (n)	%
Systemic Hypertension	79	73.8
Diabetes mellitus	41	38.3
Dyslipidemia	49	45.8
Smoking	38	35.5
Previous cardiac surgery	11	10.3
Previous atrial fibrillation reversed	04	3.7
Left atrial enlargement	51	47.7
Ventricular dysfunction	25	23.7
COPD	19	17.7
Previous valvular disease	22	20.6
Use of digitalis before surgery	04	3.7
Use of beta blockers before surgery	28	26.2

COPD - chronic obstructive pulmonary disease; hypertension if BP > 139 x 89 mmHg; dyslipidemia if LDL-c > 100 mg/dl, HDL-C < 40 mg/dl for males and < 50 mg/dl for women and diabetics, cholesterolemia > 200 mg/dl, triglyceridemia > 150 mg/dl.

Results

The incidence of atrial fibrillation in the sample was of 42 (39.3%) in 107 patients. Twenty-two point five percent (22.5%) of the patients that used some type of statin on a chronic and regular basis, as well as 44.7% of the patients that did not use statins ($\chi^2=5.37$ and $\rho=0.02$), had atrial fibrillation after cardiac surgery, as shown in Chart 1.

Approximately one in five individuals that received statin benefited from the treatment to prevent atrial fibrillation in the postoperative period (NNT = 5 with IC of 95%, ranging from 2.5 to 21.3).

On average, atrial fibrillation was developed on day 2.70 ± 2.1 in the statin group and 2.83 ± 2.13 in the group without statin ($\rho = 0.43$). The mean number of risk factors for postoperative atrial fibrillation was 2.54 ± 1.8 in the statin group and 2.70 ± 1.80 in the group without statin ($\rho=0,40$). The average hospitalization time was 4.27 ± 0.47 days in the group that used statin and 5.97 ± 1.85 days in the group that did not use statin ($\rho<0.01$).

The analysis of the subgroup that underwent isolated myocardial revascularization surgery, the most frequent surgery in this study (73.8%), revealed that atrial fibrillation occurred in 23.2% of the patients that used some type of statin on a chronic and regular basis, and in 47.5% of those that did not use statin ($\chi^2=4.80$ and $\rho=0.02$), as shown in Chart 2. In this group, in every five patients that used the medication, one was successful in preventing atrial fibrillation (NNT = 5 with IC of 95%, ranging from 2.3 to 44.1).

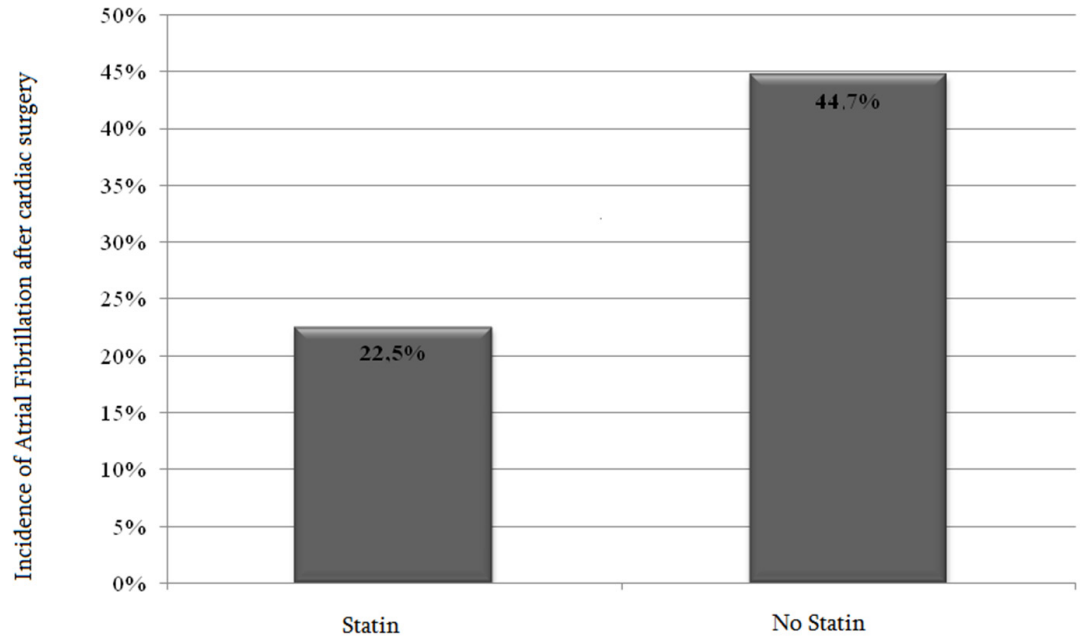

Chart 1 - Relationship between statin use and incidence of atrial fibrillation after cardiac surgery.

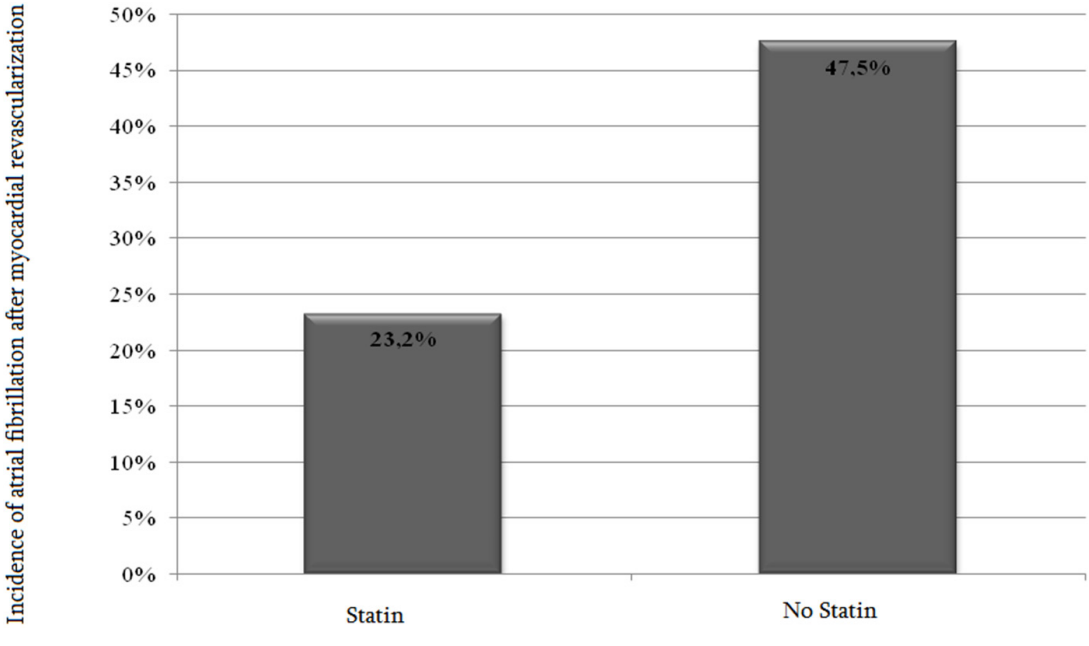

Chart 2 - Relationship between statin use and incidence of atrial fibrillation after myocardial revascularization surgery.

In addition to the clinical characteristics of the sample, we evaluated the presence of risk factors for development of atrial fibrillation among patients who used statins or not on a regular basis in the preoperative period. Laboratory data were evaluated on the first day after surgery (Table 2). The preceding table showed the clinical characteristics and risk factors for development of atrial fibrillation in the group that used some type of statin on a chronic regular basis, compared to the group that did not use statin in the preoperative period of the elective cardiac surgery. There was a statistically significant difference between the groups only in atherosclerotic risk factors, hypertension, dyslipidemia and *diabetes mellitus*, with the highest prevalence among the ones that took statins. It was also shown that there was no difference among the other variables. The correlation of three or more risk factors between groups was not statistically significant (χ^2=0.55 and ρ=0.34).

Table 3 demonstrates the relationship of the clinical characteristics between the subgroups of patients who developed or not atrial fibrillation after cardiac surgery.

Among the patients that developed atrial fibrillation, there was no difference between the groups that used statins or not, with respect to baseline clinical characteristics, thereby demonstrating a similarity between the groups.

The use of digitalis and beta-blockers preoperatively, as well as the presence of atrial enlargement and ventricular dysfunction, were similar in both groups analyzed. On the other hand, 87% of hypertensive patients who did not develop atrial fibrillation were using statin, while 64.8% of hypertensive patients who did not develop the arrhythmia did not use statin (ρ = 0.03). Among patients in the subgroup of previous myocardial revascularization, 96.8% of those that used statin had no atrial fibrillation, whereas 70.4% of those who did not use statin did not have the arrhythmia (ρ<0.01). The other clinical characteristics were statistically similar.

Table 2 - Clinical characteristics of the sample and presence of risk factors

Clinical characteristics	With statin	No statin	ρ
Age	62.7 ± 13.3	59.2 ± 16.1	0.26
Male	69.8%	66.2%	0.96
Diabetes mellitus	52.4%	32.3%	0.03
Systemic hypertension	78.2%	66.2%	0.02
Dyslipidemia	97.1%	16.1%	0.01
Smoking	40.4%	36.7%	0.64
Previous cardiac surgery	1.0%	30.5%	0.17
Previous atrial fibrillation reversed	36.4%	22.6%	0.37
Left atrial enlargement	19.0%	33.3%	1.11
Ventricular dysfunction	27.3%	25.8%	0.92
COPD	57.1%	21.8%	0.41
Anemia (hb < 10 mg/dl)	22.2%	37.5%	0.76
Water-electrolyte imbalance (K < 3.6 or > 5.5 mEq/l)	100%	24.4%	0.09
Hypoxemia	33.3%	25.6%	0.77
Previous valvular disease	20.0%	29.6%	0.49
Digitalis before surgery	1.0%	28.2%	0.17
Beta-blocker before surgery	33.3%	24.2%	0.58
> 03 risk factors for AF	23.0%	31.2%	0.34

COPD - chronic obstructive pulmonary disease; AF - atrial fibrillation; hypertension, if BP > 139 x 89 mmHg; dyslipidemia, if LDL-c > 100 mg/dl, HDL-C < 40 mg/dl for men and < 50 mg/dl for women, cholesterolemia > 200 mg/dl, triglyceridemia >150 mg/dl. Anemia, electrolyte imbalance and hypoxemia were evaluated on the first day after surgery. Statistical significance - p<0.05.

Discussion

Our study demonstrated that the chronic and regular treatment with statins prevents atrial fibrillation and shortens the hospitalization time in the period after cardiac surgery, especially for those patients that underwent myocardial revascularization surgery. The use of statins to prevent atrial fibrillation after cardiac surgery was described in the study ARMYDA-3 (Atorvastatin for Reduction of Myocardial Dysrhythmias After Cardiac Surgery), in which the administration of atorvastatin was started on the seventh day before the surgery, demonstrating a significant reduction in the incidence of atrial fibrillation[4]. This study, which used atorvastatin at high doses and for a short period of time, significantly reduced not only the incidence of atrial fibrillation (p = 0.017, CI = 95%, 0.18 to 0.85, OR = 0.39), but also the length of hospital stay (p = 0.001).

The benefit was also noted in subjects with coronary artery disease[8] and in patients who underwent non-cardiac surgery[9].

In our study, we did not adopt as inclusion criterion some specific type of statin, but only the regular use and for a period of not less than six months. However, most patients (69%) used simvastatin, at moderate doses (20 to 40 mg/day, with mean of 35 mg). The remaining part of the sample used atorvastatin (20 mg/day) and rosuvastatin (10 mg/day), with 26% and 5%, respectively.

Several factors may contribute to the development of atrial fibrillation after cardiac surgery such as surgical trauma, increase in atrial pressure due to postoperative ventricular stunning, abrupt increase in temperature after cardioplegia with cooling, atrial distension caused by atrial enlargement, the proarrhythmic effect of vasoactive drugs, water-electrolyte imbalance, reflex sympathetic activation, hypoxemia and histological changes[10,11].

Old age, mitral stenosis and atrial manipulation were described as independent factors for development of atrial fibrillation in other studies[5,12].

The presence of postoperative atrial fibrillation is associated with a higher incidence of complications, such as congestive heart failure, cerebrovascular accidents, renal dysfunction, infections and cognitive disorders[5,13]. These complications increase the length of hospital stay, thereby increasing the hospitalization costs[14,15]. Thus, the identification of preventive strategies is clinically and economically relevant, which encourages the continuation of investigations.

Table 3 - Relationship between the clinical characteristics of subgroups of patients who developed atrial fibrillation or not

Clinical characteristics	Presence of AF after surgery (p)			Absence of AF after surgery (p)		
	Statin use (%)	No statin (%)	ρ	Statin use (%)	No statin (%)	P
Age	66.4 ± 8	63.5 ± 12	00.23	61.5 ±14.6	55.4 ± 18.3	00.07
Male	63.6	63.3	00.98	74.2	62.2	00.29
Diabetes mellitus	55.0	30.0	00.15	52.1	35.0	00.17
SH	82.1	63.3	00.26	87.1	64.8	00.03
Smoking	35.8	60.0	00.55	41.9	29.7	00.29
MR	82.0	60.0	00.19	96.8	70.3	00.004
LAE	36.0	52.8	00.33	48.3	43.2	00.67
Ventricular dysfunction	27.3	23.3	00.79	16.1	27.0	00.28
COPD	36.4	1.0	00.04	29.0	43.2	00.11
Anemia (hb < 10 mg/l)	18.2	2.0	00.89	9.7	16.2	00.59
Water-electrolyte imbalance (k < 3.6 or > 5.5 mEq/l)	9.1	1.0	00.09	9.7	10.8	00.88
Hypoxemia	9.1	6.7	00.79	12.9	8.1	00.43
Previous valvular disease	27.3	40.0	00.45	8.6	18.9	00.08
Digitalis before surgery	1.6	6.7	00.38	3.2	1.3	00.27
Beta-blocker before surgery	27.3	16.7	00.45	41.9	21.6	00.07

SH - systemic hypertension; LAE - left atrial enlargement; COPD - chronic obstructive pulmonary disease; MR - myocardial revascularization; AF - atrial fibrillation.

In this study, the use of statin reduced the hospitalization period by 1.7 day, without increasing the risk of side effects linked to the treatment, such as the proarrhythmic effect of antiarrhythmic agents, which can prolong hospital stay[16]. Moreover, the benefit of statin use was noted regardless of age, sex, number of risk factors and preoperative use of beta-blockers and digitalis.

It is known that the presence of three or more risk factors should be considered an important predictor of atrial fibrillation after cardiac surgery[17,18].

In our case selection, most patients with hypertension and undergoing myocardial revascularization, who did not develop atrial fibrillation after surgery, took statins on a chronic and regular basis.

Recent clinical studies have explored the role of inflammatory mechanisms in the pathogenesis of postoperative atrial fibrillation[7,19,20]. The relationship of higher levels of C-reactive protein in the postoperative period of patients who developed atrial fibrillation can confirm the presence of inflammation as an important factor in the development of postoperative atrial fibrillation[4,21,22].

The mechanisms that may explain the clinical benefit of the chronic and regular use of statins in the prevention of atrial fibrillation after cardiac surgery are its antioxidant effect and direct antiarrhythmic power, stabilizing the ion channels of cell membrane and the direct anti-ischemic protection[23,24]. This is due to the etiology of this arrhythmia in cardiac surgery, including activation of the neurohormonal system, exacerbation of inflammatory response and other factors already described above. However, a strong predictor, responsible for triggering atrial fibrillation, has not yet been identified[25].

The use of statins would attenuate the release of cytokines, endothelial adhesion of leukocytes and elevated levels of circulating adhesion molecules, such as P-selectin and ICAM-1, after cardiac surgery[26-28].

However, there are still a limited number of studies to assess the real benefits of using statins before the surgical procedure. In addition, in the studies available, there is a lot of variation in the type and dose of statins, as well as in treatment duration. Therefore, the results should be analyzed with caution, and further studies should be encouraged to further elucidate the prevention of atrial fibrillation after cardiac surgery[29].

Conclusion

Our study showed that the chronic and regular treatment with statins, started at least six months before elective cardiac surgery, particularly myocardial revascularization, significantly reduces the incidence of atrial fibrillation in the postoperative period. These results may influence the pharmacological management of patients undergoing cardiac surgery.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any post-graduation program.

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