JAFIB
Original Research
Journal of Atrial Fibrillation
www. jafib.com

Do Statins Reduce Atrial Fibrillation After Coronary Artery Bypass Grafting?

Anil Paturi, MD[a], Aman Shukla, MD[b], George Ebra, Ed.D[c], Viet Nguyen, DO[d], Steven Borzak, MD[e]

[a] Mayo Clinic, Rochester, Minnesota, USA.
[b] Cleveland Clinic, Cleveland, Ohio, USA.
[c] JFK Medical Center, Atlantis, Florida, USA.
[d] Cleveland Clinic, Weston, Florida, USA.
[e] University of Miami Miller School of Medicine, and Charles E. Schmidt College of Science, Florida Atlantic University, Boca Raton, Florida; Nova Southeastern College of Medicine, Ft. Lauderdale, Florida, USA.

Abstract

Background

Atrial Fibrillation (AF) is a common postoperative complication after coronary artery bypass grafting. There is contradictory evidence as to whether pre-operative statin use lowers the incidence of postoperative AF. This study aimed to assess whether pre operative statin therapy prevents the post-operative AF.

Methods

In this retrospective cohort study we used a propensity score–matching analysis to evaluate the effect of preoperative treatment with statins on postoperative atrial fibrillation. There were 427 matched pairs of patients. Primary outcome was the incidence of postoperative AF. Secondary outcomes were 30 day mortality, stroke, myocardial infarction and length of hospital stay

Results

The incidence of postoperative AF was not different in the statin users compared with the nonusers (123, 28.1%, versus 127, 29.7%, respectively; p = 0.764). The 30 day mortality (6, 1.4%, versus 8, 1.9%; p = 0.590), stroke (10, 2.3%, versus 8, 1.9%; p = 0.634), myocardial infarction (2, 0.5%, versus 0, 0.0%; p = 0.499) and length of hospital stay in days (11.8 ± 9.0, versus 11.9 ± 9.3; p = 0.544) did not differ significantly between the two groups.

Conclusions

In a propensity-matched cohort of patients undergoing coronary bypass surgery, we could not demonstrate that preoperative statins were protective for the development of post operative atrial fibrillation.

Introduction

Atrial Fibrillation (AF) is a common post operative complication after coronary artery bypass graft surgery. The incidence of post-operative AF is approximately 30% after isolated coronary artery bypass grafting (CABG), 40% after valve replacements or repair, and approximately 50% after combined procedures.[1-3] The etiology of postoperative AF is not well understood, although multiple mechanisms such as neurohormonal activation, volume overload, and inflammation have been proposed.4 Advanced age, history of AF or COPD, valve surgery, and withdrawal of beta-

Corresponding Address :Anil Paturi MD, Mayo Clinic, Old Marian Hall 2-115, 200 First Street SW, Rochester, MN, 55905, USA. Telephone No, MN 55112.

blockers or angiotensin-converting enzyme (ACE) inhibitors are other risk factors for AF after CABG surgery.[1-4] Post-operative AF has been shown to be associated with increased risk of mortality, morbidity, thromboembolic stroke, hemodynamic compromise, increased cost of care and prolonged length of hospital stay.[5-8] Many studies have investigated the benefits of pharmacologic prophylaxis to reduce post-operative AF, though AF remains a persistent problem and a worthwhile target to reduce morbidity and length of stay after open heart surgery.

The anti-inflammatory properties of statins may have a protective effect on the development of atrial fibrillation.[9] Several small observational studies investigated the role of prior statin use on the incidence of AF following open heart surgery10-11 and in other clinical settings.[9,12] These studies were limited in scope and size, and came to differing conclusions. A recent meta-analysis was published examining pre-procedural statin use in patients undergoing percutaneous coronary revascularization, CABG, or noncardiac surgery.[13] Six studies [14-19] randomized 748 patients before CABG and assessed postoperative atrial fibrillation, often as a secondary endpoint, and found that AF was significantly less in statin pretreated patients (73 of 376, 0.19) than control or placebo (137 of 372, 0.37, relative risk 0.54, 95% CI 0.43-0.68).[13]

Because of the limitations of observational data, as well as a meta-analysis of small trials with obvious heterogeneity, we sought to evaluate the hypothesis that preoperative statins reduce AF using propensity matching in a large, prospectively collected cohort of patients undergoing open heart surgery.

MATERIALS AND METHODS

Patient Population

All patients undergoing open-heart surgery at JFK Hospital, Atlantis, FL, are prospectively enrolled in the Society of Thoracic Surgeons Adult Cardiac Surgery Database (version 2.61). We identified all patients who underwent coronary artery bypass grafting (CABG) without any concomitant procedure between January 2005 and December 2009. There were 1,467 patients identified, of which 198 patients had a previous history of atrial fibrillation or flutter, or in which the surgery was performed off-pump, and were excluded from the study sample. The remaining 1,269 patients, of which 842 (66.3%) received preoperative statin therapy and 427 (33.6%) did not, constituted the clinical material for this comparative analysis. This study was presented to the Institutional Review Board and Waiver of Informed Consent was granted based on its retrospective nature and lack of identity disclosure.

Data Management and Statistical Analysis

Data were collected by trained abstractors concurrently or shortly after hospital discharge. Data were recorded in a standard manner using the Society of Thoracic Surgeons Adult Cardiac Surgery Database guidelines. Demographic and clinical data are presented as frequency distributions and simple percentages. Values of continuous variables are expressed as mean ± standard deviation. Univariate analysis of selected preoperative, intraoperative and postoperative discrete variables was accomplished by chi-square, the continuity-adjusted chi-square analysis or a 2-tailed Fisher exact test with the appropriate degrees of freedom to test for the equality of proportions in the case of categorical variables. Two-sample Student's t-tests (two-tailed) were used to test for the equality of means for continuous variables. A logistic regression model was used to calculate each patient's propensity score. [20] A score between 0 and 1 was generated and used to summarize a collection of covariates, indicating the likelihood of a patient receiving or not receiving statin therapy preoperatively. Using Rosenbaum's 21 optimal matching algorithms, patients who did not receive statin therapy were then matched to those who did. This approach minimizes the overall distance between observations and was conducted using Mahalanobis distance within propensity score calipers (no matches outside the calipers). The application of this matching technique controls for potential confounding variables. Data collected were analyzed using the biostatistical capabilities of the Number Cruncher Statistical Systems (NCSS), Kaysville, UT. A significant difference between measurements was defined as p less than or equal to 0.050.

RESULTS

IOf 1,269 patients undergoing isolated CABG surgery, 842 (66.3%) patients were receiving preoperative statin therapy and 427(33.6%) were not on statin therapy. Baseline characteristics of the study population are shown in Table 1. Compared with the control group, the patients receiving statins had a higher prevalence of hypertension and diabetes mellitus, angiotensin-converting enzyme (ACE) inhibitor and beta-blocker use. The incidence of postoperative atrial fibrillation (the period from arrival in the intensive care unit until hospital discharge) by univariate analysis was not statistically different in the statin users compared with the nonusers as shown in Table 3 (264, 31.4% versus 127, 29.7% respectively; p: 0.557).

To reduce the effect of treatment selection bias and potential confounding in this observational study, we used a propensity score–matching analysis to evaluate the pure effect of preoperative treatment with statins on end points. After propensity-score matching was performed for the entire population, there were 427 matched pairs of patients (Table 2). In the matched cohorts, there was no significant difference between the statin and the control group

Table 1 : Comparison of Preoperative Variables by Patient Group

Study Name	Statin	No Statin	p-value
No of Patients (%)	842(100.0) a	427 (100.0)	1
Male	668 (79.3)	317 (74.7)	0.061
TRENDS24	TRENDS24 50% Pacemaker 31% ICD 19% CRT	Allowed, but not required	≥5.5 hours
Biotronik25	100% CRT	Allowed, but not required	≥3.8 hours
Female	174 (20.7)	108 (25.3)	0.042
Age (mean years)	66.8	65.6	0.077
Hypertension	701 (83.3)	317 (73.3)	0.001
Diabetes Mellitus	333 (39.5)	123 (28.8)	0.001
Renal Dysfunction	41 (4.9)	15 (3.5)	0.266
COPD	76 (9.0)	46 (10.8)	0.319
Ejection Fraction (mean)=	50.4	48.6	48.6
Prior CABG	10 (1.2)	3 (0.7)	0.561
ACEI / ARB	341 (40.5)	123 (28.8)	0.001
Beta Blocker	681 (80.9)	312 (73.1)	0.001
Perfusion Time (min)	100.8	101.0	0.907
Graft to Right	178 (21.1)	88 (20.6)	0.826

COPD: Chronic Obstructive Pulmonary Disease, ACEI: Angiotensin converting enzyme inhibitor, ARB: Angio- tensin receptor blocker.
[a] Numbers in parentheses are percentages

for any covariate. In this population, calculated overall incidence of postoperative atrial fibrillation was not different in the statin users compared with the nonusers (123, 28.1%, versus 127, 29.7%, respectively; p = 0.764) (Tables 3 and 4.) Secondary outcomes were not affected by prior statin use (table 5).

DISCUSSION

Despite the advance in cardiac anesthesia, myocardial protection, and surgical techniques, the incidence of postoperative AF remains high. Aside from established AF risk factors such as advanced age, COPD, low ejection fraction, and others, inflammation and oxidative stress might be involved in the development, recurrence, and persistence of atrial fibrillation. It has been shown that statin therapy, in addition to its antiatherosclerotic effects, may have antioxidant 22 and anti-inflammatory properties [23-24] and may reduce the incidence of AF.

The aim of our study was to evaluate the association between preoperative use of statins and postoperative incidence of atrial fibrillation in a large propensity score–matched group of patients who underwent isolated CABG. We found no statistically significant difference between the group on statin therapy preoperatively as compared to the patients not on statins in terms of post-operative incidence of atrial fibrillation. When we analyzed the independent predictors of postoperative incidence of atrial fibrillation using a multivariate logistic regression among the matched population, preoperative statin treatment had no relationship to the development of postoperative atrial fibrillation.

prospective observational study by Amar et al 12 showed that pre-operative statin use was associated with more than threefold reduction in the risk

Table 2 Comparison of Preoperative Variables by Patient Group Following Propensity Analysis and Matching.

Variables	Statin	No Statin	p-value
No of Patients (%)	427 (100.0) a	427 (100.0)	1
Male	329 (77.0)	317 (74.7)	0.424
Female	98 (23.0)	108 (25.3)	0.632
Age (mean years)	65.7	65.6	0.958
Hypertension	323 (75.6)	313 (73.3)	0.433
Diabetes Mellitus	125 (29.3)	123 (28.8)	0.880
Renal Dysfunction	15 (4.9)	15 (3.5)	1.000
COPD	43 (10.1)	46 (10.8)	0.737
Ejection Fraction	41 (4.9)	15 (3.5)	0.266
Prior CABG	2 (0.5)	3 (0.7)	1.000
ACEI / ARB	123 (28.3)	123 (28.8)	1.000
Beta Blocker	319 (74.7)	312 (73.1)	0.586
Perfusion Time	341 (40.5)	123 (28.8)	0.001
Graft to Right Coronary Artery	103.0	101.0	0.374

COPD: Chronic Obstructive Pulmonary Disease, ACEI: Angiotensin converting enzyme inhibitor, ARB: Angio- tensin receptor blocker.
[a] Numbers in parentheses are percentages

of AF after noncardiac thoracic surgery. Marin et al did show that the statin use was related to a lower incidence of AF after CABG (odds ratio 0.52, 95% confidence interval 0.28 – 0.96, p = 0.038) .10 but this study was limited due to relatively small sample size of 234 patients.

A large retrospective observational study by Miceli et al 11 however showed that preoperative statin use was associated with a significantly higher incidence of postoperative atrial fibrillation compared to no statin treatment in patients undergoing isolated coronary artery bypass grafting. Thus observational trials, despite their susceptibility to confounding, do not come to a consistent conclusion as to the prospective value of statins to reduce AF post CABG.

A recent meta-analysis performed a structured literature review from the mid 1960s until February, 2010, to disclose all studies that examined AF following coronary intervention, CABG and noncardiac surgery.[13] This review identified 8 trials of statins of which 6 reported the outcome of postoperative AF.[14-19] While the combined outcomes favored statins, the trials were heterogeneous with respect to size (40-200 patients) as well as type of surgery (off-pump or not specified). Only 3 trials identified postop AF as a primary aim.[14,16,18] While prospective randomized trials represent the highest level of evidence, circumspection is warranted because of past experience with pooled small trials of nitrates and magnesium showing mortality reduction for acute MI, while a larger randomized trial came to a different and definitive conclusion.25 We therefore suggest that a meta-analysis of 6 small heterogeneous trials may not yield definitive conclusions with certainty.

Study Limitations:

Propensity score analysis, while a useful method for reducing bias in observational studies when randomization to treatment groups is not possible, is not a substitute for a large and prospectively randomized group of patients to directly test the hypothesis. The study is limited by its design because it provides associations, but not cause and effect. Only a randomized, controlled trial could permit a conclusion that statins protect against post operative AF. Nevertheless, our study is based on a large sample size and therefore reflects the general population of patients undergoing CABG.

Another limitation of our study is the lack of information about left atrial enlargement, timing and dose of preoperative statin treatment, duration of preoperative statin treatment, or postoperative variables such as volume overload or electrolyte imbalance (hypomagnesemia, hypokalemia) which are independent risk factors for atrial fibrillation and are necessarily limited in scope in a database analysis. A selection bias might be present because there was no uniform indication for the use of statins and thus clinical indexes (e.g., hypertension, diabetes mellitus, and ejection fraction) were associated with statin use The occurrence of atrial fibrillation was monitored for the duration of hospitalization, but this dura- tion was variable depending on the post-op length of stay of the patients, though observation bias is likely to have influenced both groups similarly.

Conclusions

Table 3 Comparison of Preoperative Variables by Univariate Analysis.

Variables	Statin	No Statin	p-value
No of Patients (%)	842 (100.0) a	427 (100)	1
Atrial Fibrillation	264 (31.4)	127 (29.7)	0.557

[a] Numbers in parentheses are percentages

Table 4 Comparison of Preoperative Atrial Fibrillation after Propensity Analysis and Matching

Variables	Statin	No Statin	p-value
No of Patients (%)	427 (100.0) a	427 (100)	1
Atrial Fibrillation	123 (28.1)	127 (29.7)	0.764

[a] Numbers in parentheses are percentages

In a propensity-matched cohort of patients undergoing open heart surgery, we could not demonstrate that preoperative statins were protective for the development of postoperative atrial fibrillation. Since our findings differ from a meta-analysis of fewer than 900 patients in 6 heterogeneous trials, a firm conclusion must await a large, prospective trial.

Disclosures

None of the authors has a financial conflict of interest to report. There are no other disclosures for any of the authors. There was no grant support for the study. The authors acknowledge the support and guidance of Ms. Jamie Kosik whose assistance was invaluable.

References

1. Lauer MS, Eagle KA, Buckley MJ, DeSanctis RW. Atrial fibrillation following coronary artery bypass surgery. Prog Cardiovasc Dis 1989; 31:367–78.
2. Vecht RJ, Nicolaides EP, Ikweuke JK, Liassides CH. Cleary J, Cooper WB. Incidence and prevention of supraventricular tachyarrhythmias after coronary bypass surgery. Int J Cardiol 1986; 13:125–34.
3. Cox JL. A perspective of postoperative atrial fibrillation in cardiac operations. Ann Thorac Surg 1993; 56:405–9.
4. Baker WL, White CM. Post-Cardiothoracic Surgery Atrial Fibrillation: A Review of Preventive Strategies. The Annals of Pharmacotherapy 2007; 41:587-598.
5. Hogue CW Jr, Hyder ML. Atrial fibrillation after cardiac operation: risks, mechanisms, and treatment. Ann Thorac Surg. 2000; 69:300 –306.
6. Weintraub WS, Jones EL, Craver J, Guyton R, Cohen C. Determinants of prolonged length of hospital stay after coronary bypass surgery. Circulation 1989; 80:276–84.
7. Tamis JE, Steinberg JS. Atrial fibrillation independently pro-

Table 5 Secondary Outcomes after Propensity Analysis and Matching

Variables	Statin	No Statin	p-value
No of Patients (%)	427 (100.0) a	427 (100)	1
Death (30 days)	6 (1.4)	8 (1.9)	0.590
Stroke	10 (2.3)	8 (1.9)	0.634
Myocardial Infarction	2 (0.5)	0 (0.0)	0.499
Length of hospital stay	11.8 ± 9.0	11.9 ± 9.3	0.544

[a] Numbers in parentheses are percentages

longs hospital stay after coronary artery bypass surgery. Clin Cardiol 2000; 23:155–9.
8. Villareal RP, Hariharan R, Liu BC, Kar B, Lee VV, Elayda M, Lopez JA, Rasekh A, Wilson JM, Massumi A . Postoperative Atrial Fibrillation and Mortality after Coronary Artery Bypass Surgery. J Am Coll Cardiol 2004; 43:742– 8
9. Adam O, Neuberger HR, Bohm M, Laufs U. Prevention of Atrial Fibrillation with 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Inhibitors. Circulation. 2008; 118:1285-1293.
10. Marin F, Pascual DA, Roldan V, Arribas JM, Ahumada M, Tornel PL, Oliver C, Gómez-Plana J, Lip GY, Valdés M.. Statins and postoperative risk of atrial fibrillation following coronary artery bypass grafting. Am J Cardiol. 2006; 97:55– 60.
11. Miceli A, Fino C, Fiorani B, Yeatman M, Narayan P, Angelini GD, Caputo M.. Effects of Preoperative Statin Treatment on the Incidence of Postoperative Atrial Fibrillation in Patients Undergoing Coronary Artery Bypass Grafting. Ann Thorac Surg. 2009 Jun; 87(6):1853-8.
12. Amar D, Zhang H, Heerdt PM, Park B, Fleisher M, Thaler H. Statin use is associated with a reduction in atrial fibrillation after noncardiac thoracic surgery independent of C-reactive protein. Chest. 2005; 128: 3421–3427.
13. Winchester DE, Wen X, Xie L, Anthony AB. Eficence of preprocedural statin therapy: a meta-analysis of randomized trials. J Am Coll Cardiol 2010; 56:1099-109.
14. Patti G, Chello M, Candura D, Pasceri V, Ambrosio A, Covino E, Sciascio GD. 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.
15. Mannacio VA, Iorio D, De Amicis V, Di Lello F, Musumeci F. Effect of rosuvastatin pretreatment on myocardial damage after coronary surgery: a randomized trial. J Thorac Cardiovasc Surg 2008; 136:1541-8.
16. Ji Q, Mei Y, Wang X, Sun Y, Feng J, Cai J, Xie S, Chi L. Effect of preoperative atorvastatin therapy on atrial fibrillation following off-pump coronary artery bypass grafting. Circ J 2009; 73:2244-49.
17. 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; 34:660-7.
18. Song YB, On YK, Kim JH, Shin DH, Kim JS, Sung J, Lee SH, Kim WS, Lee YT. The effects of atorvastatin on the occurrence of postoperative atrial fibrillation after off-pump coronary artery bypass grafting surgery. Am Heart J 2008; 156:373.e9-373.e16.
19. Tamayo E, Alonso O, Alvarez J, Castrodeza J, Flórez S, di Stefano S. Effects of simvastatin on acute-phase protein levels after cardiac surgery. Med Clin (Barc.) 2008; 130:773-5.
20. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika 1983; 70:41-55.
21. Rosenbaum PR. Optimal matching for observational studies. J Am Stat Assoc 1989;
84(408):1024-1032.
22. Rosenson RS. Statins in atherosclerosis: lipid-lowering agents with antioxidant capabilities. Atherosclerosis 2004; 173:1–12.
23. Strandberg TE, Vanhanen H, Tikkanen MJ. Effect of statins on C-reactive protein in patients with coronary artery disease. Lancet 1999; 353:118 –9.
24. Albert MA, Danielson E, Rifai N, Ridker PM. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/ CRP evaluation (PRINCE): a randomized trial and cohort study. JAMA 2001;286:64 –70.
25. Borzak S. Ridker PM. Discordance between meta-analyses and large-scale randomized, controlled trials: examples from the management of acute myocardial infarction. Ann Internal Med 1995; 123(11):873-877.